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Socioeconomic determinants of respiratory health in patients with cystic fibrosis: implications for treatment strategies

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Abstract

Introduction: Great variation exists in the progression and outcomes of cystic fibrosis (CF) lung disease, due to both genetic and environmental influences. Social determinants mediate environmental exposures and treatment success; people with CF from socioeconomically disadvantaged backgrounds have worse health and die younger than those in more advantaged positions.

Areas covered: This paper reviews the literature on the mechanisms that are responsible for generating and sustaining disparities in CF health, and the ways by which social determinants translate into health advantages or disadvantages in people with CF. The authors make recommendations for addressing social risk factors in CF clinical practice.

Expert opinion: Socioeconomic factors are not dichotomous and their impact is felt at every step of the social ladder. CF care programs need to adopt a systematic protocol to screen for health-related social risk factors, and then connect patients to available resources to meet individual needs. Considerations such as daycare, schooling options, living and working conditions, and opportunities for physical exercise and recreation as well as promotion of self-efficacy are often overlooked. In addition, advocacy for changes in public policies on health insurance, environmental regulations, social welfare, and education would all help address the root causes of CF health inequities.

Keywords

cystic fibrosis; respiratory outcomes; social determinants of health; social risk factors; socioeconomic position

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1. INTRODUCTION

Cystic fibrosis (CF), the second most common autosomal recessive genetic disorder in the United States, is characterized by abnormal secretions in multiple organ systems and eventual respiratory failure [1]. Although the disease is caused by mutations in a single gene – the cystic fibrosis transmembrane conductance regulator (CFTR) – there is a substantial variation in disease progression and outcomes among individuals with identical CFTR genotypes [2–4].

While it is hypothesized that variants in several non-CFTR genes are influential, a number of non-genetic factors also have been implicated in this variability [2, 5–7]. These non-genetic factors are, for the most part, associated with social determinants of health, and contribute substantially to individual and group differences in health status [8–12]; it has been estimated that they account for approximately 50% of the clinical variation in CF [2].

The current paper summarizes the evidence of social determinants in relation to respiratory decline in CF, assesses implications for CF treatment strategies, and makes recommendations for clinical and population-based care and research to address the role of social determinants in CF lung health.

2. SOCIAL DETERMINANTS OF HEALTH

The World Health Organization (WHO) has defined social determinants of health as “the circumstances in which people are born, grow up, live, work, and age,” which are “shaped by the distribution of money, power, and resources locally, nationally, and globally [13].” In the WHO framework (Figure 1) [14], the high-level socioeconomic and political context (e.g., the labor market, the educational system, political institutions, and cultural and societal values) generate social stratification according to income, education, occupation, gender, race/ethnicity, and other factors. The socioeconomic and political context and the resultant social stratification are “structural determinants” that act as determinants *of health inequity*. One’s standing in the resulting social hierarchy shapes one’s material circumstances (living and working conditions, housing, food, transportation), environmental exposures, and associated behavioral and psychosocial factors, which may be conceptualized as proximal or intermediary determinants of an individual’s health. In this context, the health system may be seen as an intermediary determinant that mediates the differential consequences of illness, whereas social cohesion and social capital cut across the structural and intermediary dimensions.

As seen in the WHO framework, the social determinants of health inequities, such as macroeconomic policy and policies on education, housing, and labor, impact the variation in the more proximal social determinants, such as food access and living conditions. Therefore, social determinants have both direct and indirect effects on health.

It is important to note that the term “social determinants of health” encompasses factors that, depending on their manifestation, can promote or undermine health. For example, as a structural determinant, income can affect health positively or negatively through either granting or limiting access to food, housing, educational opportunities, and health care.

In other words, the social determinants of health affect everyone, not just the poor and vulnerable. In their adverse manifestation (e.g., poverty, housing instability, food insecurity), they may be classified as social risk factors, but the effect of social determinants is typically that of a non-binary gradient [15].

3. STRUCTURAL DETERMINANTS OF CF RESPIRATORY OUTCOMES

3.1 Social policies

The socioeconomic and political context, which encompasses the structural and functional aspects of the social system, is a powerful determinant of health, although its impact cannot be directly measured at the individual level. In general, there is a paucity of studies that quantify the effect of the economic, social, and political context on human health, with even fewer attempts in the field of respiratory health. Recently, an analysis of data from the U.S. CF Foundation Patient Registry (CFFPR) showed that both area-level socioeconomic characteristics and state-level child health play a role in the health of children with CF. Importantly, the residual association of state child health with CF outcomes after controlling for area-level socioeconomic deprivation reflects the ability of state policies and programs to mitigate the effect of poverty [16]. For example, policies regarding Supplemental Nutrition Assistant Program (SNAP) and Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) vary considerably by state in terms of eligibility, income limits, asset limits, benefit levels, and medical nutrition. Similarly, there is a significant state-level variation in health insurance policies, including expansion of Medicaid eligibility under the Affordable Care Act. Such differences in public policy have a major impact on health outcomes [17], and likely a significant impact on CF lung health. On a global level, analysis of data from 13 European countries in the European Cystic Fibrosis Society Patient Registry showed that, after adjusting for confounders, countries with higher health care spending had a 46% lower hazard of mortality than countries with lowest health care spending [18].

3.2 Socioeconomic position

As a powerful structural determinant of health, socioeconomic position, manifested though indicators such as income, education, and occupation, is linked in a stepwise manner to health outcomes across disease conditions at every point of the life course [19–25]. Below we present evidence for the role of social stratification in CF respiratory health.

3.2.1 Income.—CFFPR data from 1986 to 2011 showed that patients residing in zip codes with lower income had 3–10% lower ppFEV$_1$ than those residing in higher-income zip codes [26]. Another study with zip code income data reported a 5.5% difference in first spirometry at 6 years of age between the lowest quintile (<$20,000/year) and the highest quintile (>$50,000/year) zip codes; the disparity persisted until 18 years of age without increasing significantly over time [27]. The authors also found a 44% increased risk of death for CF patients residing in the most deprived compared to the least deprived income quintiles [27]. Taylor-Robinson et al.[28] assessed the correlation between area-level social deprivation and CF outcomes in a longitudinal study of the UK CF population (1996–2009). The results showed that, compared with CF patients residing in the least deprived areas, those in the most deprived areas had 4% lower ppFEV$_1$ and nearly twice the odds

of having chronic *P. aeruginosa* infection. The lung function disparity was present at 5 years of age and remained constant over time. More recently, in longitudinal analysis of household income data from the CFFPR (2006–2016), Oates et al. reported a dose-response relationship between annual household income and lung function, where every additional $10,000 is associated with a 0.2% increase in $ppFEV_1$ after controlling for demographic and clinical covariates [29]. Additionally, a retrospective analysis of single-center data from Mexico (2000–2020) revealed that, compared with high-income counterparts, low-income patients with CF are four times more likely to have shortened survival; median survival age for the low-income group was 15 years compared to 30 years in the high-income group [30].

3.2.2 Education.—Maternal education of high school or less was associated with 4.2% lower $ppFEV_1$ at age 6–7 in a U.S. multicenter cohort of children with CF enrolled in the Early Pseudomonas Infection Control (EPIC) Observational Study [31]. A retrospective longitudinal analysis of CFFPR data (2006–2016) showed that lower paternal education is associated with a 4.9% lower $ppFEV_1$ after adjusting for demographic and clinical covariates[29]; the disparity was present at age 6 and remained constant through age 18. A lung function deficit by paternal educational attainment has been observed as early as 12 months of age in infants diagnosed with CF through newborn screening [32]. In Denmark, a retrospective longitudinal study with data from the Danish CF patient registry (1969–2010) linked to the national administrative register showed that low parental education was associated with a 0.5% greater annual decline in $ppFEV_1$ after adjusting for demographic, genetic, and clinical factors, resulting in approximately 4% gap between the most and least disadvantaged by 17 years of age [33]. In contrast to US data, however, the lung function deficit was not present at 6 years of age but developed over time. The authors opined that “the Danish welfare system, coupled with lower levels of child poverty, and universal access to high quality healthcare may reduce social differences in outcomes in early childhood [33].” They further acknowledged the potential contribution of monthly follow-up and aggressive treatment of infections in Denmark, which may protect the most disadvantaged in the early years.

3.2.3 Occupation.—One of the first CF studies that demonstrated the independent effect of socioeconomic position was conducted by Britton [34]. Using mortality data for England and Wales (1959–1986), he found that the odds of death from CF above the median age were 2.75 higher among individuals in non-manual occupations than among those in manual occupations. Updated with data through 2008, a subsequent analysis showed that individuals in the highest socioeconomic group had 2.5 higher odds of dying above the median age of death from CF than those in the lowest socioeconomic group [35].

3.2.4 Health insurance.—In the United States, Medicaid is a network of Statewide programs administered by State governments following broad national guidelines established by Federal statutes, regulations, and policies. It specifically provides health care coverage for low-income adults and children, using age-related eligibility criteria and benefits that vary from state to state. Schechter et al.[36, 37] used Medicaid coverage as an indicator for low socioeconomic position and found that the adjusted risk of death was 3.65 times higher for patients on Medicaid than for those not on Medicaid. In addition, the lung

function ($ppFEV_1$) of Medicaid patients was 9% lower than that of non-Medicaid patients. The lung function disparity was present at 5 years of age and widened only slightly up to 20 years of age [36]. More recently, Dickinson et al. reported that in the 2000–2011 CF birth cohort, children with intermittent private insurance and exclusively public insurance had, respectively, 3.3% and 6.6% lower $ppFEV_1$ at age 6 compared to those with always private insurance [38].Transition from pediatric to adult CF care is a high-risk period for losing health insurance [39], and the group of 18–25 year olds have the highest uninsured rate of any CF patient age group [1]. During the transition to adulthood, public insurance coverage was associated with accelerated lung function decline among patients with CF: 3.1% and 2.4% per year among those with among patients with continuous and intermittent public insurance, respectively, compared to 2.1% per year among patients with continuous private coverage. These differences were not explained by differences in outpatient care [40]. Therefore, universal health coverage is critical for improving access to CF care.

3.3 Race and ethnicity

Members of racial or ethnic minorities make up a growing proportion of U.S. patients with CF. Between 2004 and 2019, the CFFPR reported an increase in minorities from 3.9 to 4.7% for African Americans, from 6.1 to 9.4% for Hispanics/Latinos, and from 1.9 to 3.8% for other designations [1]. When interpreting reports of racial/ethnic differences in CF respiratory outcomes, it is important to recognize that race and ethnicity are social constructs with little genetic basis [41–43]. As such, the association of race and ethnicity with CF outcomes is to a great extent attributable to unequal social conditions and long-standing structural inequalities. For example, both African Americans and Hispanics/Latinos with CF reside in neighborhoods with lower median household income[44] and have higher Medicaid coverage (52.2% and 41.8%, respectively) than non-Hispanic white counterparts [44]. The adverse effects of lower income, education, and public health insurance were described earlier.

CF patients from racial/ethnic minority backgrounds experience greater disease burden and worse outcomes that parallel the disparities by race/ethnicity in the general population. For example, African Americans with CF have lower lung function than Whites [45], and in the Southern U.S. they also have a higher risk of future hospitalization compared with Whites [46]. Similarly, after adjusting for demographic and clinical covariates, Hispanics/Latinos with CF have approximately 6% lower FEV_1 than non-Hispanic/Latino counterparts [47], and in the Western U.S. they have lung function deficit as high as 9.0% [48]. Significant differences in CF mortality by race and ethnicity have also been reported [44,49].

It is notable that disparities in CF outcomes by Hispanic ethnicity occur in spite of higher BMI and a larger proportion of residual function pancreatic sufficient CFTR mutations in the Hispanic/Latino population [43, 50]. Understanding the racial/ethnic disparities in CF respiratory decline requires careful consideration of the effects of socioeconomic position as well as intermediary determinants, including environmental exposures, psychosocial factors, health literacy and acculturation, and the effects of stress and racism [51]. For example, African American and Hispanic patients report worse emotional and social functioning after controlling for disease severity and socioeconomic position [52].

4. INTERMEDIARY DETERMINANTS OF CF RESPIRATORY OUTCOMES

People's position in the social hierarchy shapes their material circumstances (living and working conditions, housing, food, transportation), environmental exposures, and psychosocial context and greatly influences their health-related behaviors.

4.1 Material circumstances

4.1.1 Food access.—Measured on a household level, food insecurity is defined as limited or uncertain availability of nutritionally adequate foods, with either disrupted eating patterns or reduced food intake [53]. In 2016, 12.3% of all U.S. households experienced food insecurity, with higher prevalence in certain populations and geographic areas. Among people with CF, about 30% are food insecure [54]. Limited access to full-service supermarkets and farmers markets, as well as difficulty getting to grocery stores due to lack of transportation or unsafe neighborhoods are important environmental correlates of nutritional intake and food insecurity [55, 56]. There is ample evidence that the nutritional status of CF patients is closely associated with their socioeconomic status [28, 36, 57–59]. Because food insecurity has profound implication for the health of people with CF [60], the CF Foundation has recommended screening for food insecurity and linking individuals to programs and community resources for food assistance. Studies that evaluate the role of food access for CF respiratory outcomes are yet to be conducted.

4.1.2 Housing and living conditions.—Molds, particularly the filamentous fungus *Aspergillus fumigatus*, have been implicated in the pathogenesis of allergic bronchopulmonary aspergillosis (ABPA) and CF bronchiectasis [61, 62]. Housing instability has been associated with more severe chronic asthma and greater risk of emergency and hospital readmissions in pediatric patients [63]. In general, however, the role of housing and living conditions for CF respiratory outcomes remains underexplored.

4.1.3 Neighborhood characteristics.—Residential neighborhoods are often divided across socioeconomic and racial/ethnic lines [64]. Low-income and minority neighborhoods are typically characterized by limited access to healthy food, green spaces, and other health-promoting resources[65–68] and have higher rates of crime and violence [69–72]. There are also regional disparities: for example, states with the highest share of neighborhoods that are both low-income and have low access to food are mostly in the South [73].

The neighborhood social and physical environments, including residential segregation, social cohesion, blight, walkability, and food access, are a powerful determinant of health [74, 75]. Important health indicators have been shown to improve with moving people to areas of less concentrated poverty [76]. Specifically, neighborhood crime has been associated with worse respiratory outcomes [77–79], likely through stress [80–82], and with negative health behaviors such as smoking and poor adherence to medications [83]. Exposure to green space has shown protective effects against asthma hospitalizations[84] and bronchitis [85], after accounting for noise and air pollution. Residential segregation predicts asthma burden better than race/ethnicity[86] and has been adversely associated with dyspnea, lung function, emphysema, and air trapping in Black people with chronic obstructive pulmonary disease [87].

Currently, there is a paucity of research on the effect of neighborhood characteristics for CF respiratory outcomes. Area socioeconomic deprivation, calculated at the level of residential zip codes, has been associated with worse respiratory outcomes in pediatric patients with CF in the CFFPR. After adjusting for demographic and clinical covariates, children with CF residing in the worst tertile for area deprivation had 2.8% lower $ppFEV_1$, 1.2 more intravenous treatment nights annually, and 20% higher odds of two or more pulmonary exacerbations [16]. The individual and cumulative impact of specific neighborhood characteristics is yet to be investigated.

4.1.4 Environmental exposures.—Exposures from the natural and built environment, such as outdoor and indoor air quality, allergens, and infectious agents, are important social determinants on CF lung health. A summary of current knowledge about the role of environmental exposures for CF outcomes was presented in a recent review by Szczesniak et al [88]. The mechanisms of this association include both direct damage to the lung tissue and indirect pathways via reactive oxygen species and systemic inflammation [89, 90]

Tobacco smoke exposure.: Aside from direct use of tobacco products, tobacco smoke exposure includes exposure to burning tobacco products or exhaled by a smoker (second-hand), as well as exposure to the residue from tobacco smoke that accumulates in dust, objects, and on surfaces and is reemitted into the air, ingested, or absorbed via skin contact (third-hand) [91]. Approximately one-third of U.S. children and adolescents with CF are regularly exposed [29, 92].

Compelling evidence from animal and human studies indicates that cigarette smoke reduces the expression of the CFTR gene and impairs anion transport and [93–102] and could result in acquired CFTR dysfunction among people without CF [97, 103]. Smoke exposure also increases airway inflammation and impairs pathogen clearance people with CF [104–106]. Because of associations in the prevalence of tobacco use with socioeconomic status, tobacco smoke exposure has been proposed as one of the mechanisms of the link between socioeconomic position and CF lung health [4, 107].

A dose-dependent association between tobacco smoke exposure and overall CF disease severity was first reported by Rubin [108]. These early findings have been corroborated in subsequent studies. A retrospective assessment of the U.S. Cystic Fibrosis Twin and Sibling Study reported a 6.1% decrease in mean $ppFEV_1$ at age 20 attributable to smoke exposure [4]. More recently, analysis of data from the Early Pseudomonas Infection Control (EPIC) Observational Study found a 4-year decrease in mean $ppFEV_1$ associated with smoke exposure (6.0% if mother smoked after birth, 4.6% if mother smoked during pregnancy, 3.2% if child ever around smokers, 2.6% if a household member smokes) [92]. A longitudinal study of CFFPR data (2006–2016) evaluated the contributions of tobacco smoke exposure and socioeconomic factors on initial spirometry at age 6 and change in $ppFEV_1$ through age 18 years [29]. At age 6, $ppFEV_1$ of smoke-exposed children was nearly 5% lower than among unexposed, and the deficit persisted through age 18. Smoke exposure and socioeconomic factors had independent, additive associations with lung function, with the effect of smoke exposure on $ppFEV_1$ being larger in disadvantaged children compared to privileged counterparts (3.2% vs 1.2%) [29]. Routine assessments may

present an opportunity to identify socio-environmental risk factors and prioritize children who are both low-income and smoke-exposed for targeted interventions [109].

Important recent evidence points to an interaction of smoke exposure with novel, highly effective modulator therapies for CF. A retrospective longitudinal analysis of encounter-based data from the CFFPR (2016–2018) showed that among individuals with CF aged 12–20 years old, tezacaftor/ivacaftor provided no benefit to smoke-exposed patients although it was associated with improved $ppFEV_1$ among unexposed counterparts [110]. To maximize the therapeutic opportunity presented by highly effective CFTR modulators, every effort must be taken to eliminate environmental exposure to smoke for people with CF. The benefits of removing smoke exposure were demonstrated in a recent study of CFFPR data for children and adolescents with CF (2006–2018). The authors found that removing smoke exposure reduces the odds of having a pulmonary exacerbation by 17% in the first year and by another 6% in each additional year of non-exposure [111]. Stopping of exposure is also associated with respiratory and nutritional improvements: 0.7% $ppFEV_1$ increase in the first year and 0.4% increase in each additional year of non-exposure; 1% increase in BMI percentile in the first year and 0.4% increase in each additional year. After three years of not being exposed to tobacco smoke, children and adolescents with CF have 8% lower predicted probability of an exacerbation and 2% higher $ppFEV_1$ and BMI than counterparts who remain exposed [111]. These results provide further support for the need to prioritize smoking cessation and exposure prevention in CF care.

Ambient air pollution.: In general, residents of socioeconomically disadvantaged communities are exposed to greater short- and long-term air pollution [112–115], which compromises lung growth [116] and leads to increased mortality [115, 117]. These effects are ever stronger among populations with increased susceptibility, such as people with CF and other lung diseases [118]. For example, longitudinal CF studies outside of the US show that ozone is associated with an increased risk of pulmonary exacerbations [119] in people with CF, whereas higher concentrations of ozone, particulate matter, and nitrogen dioxide are associated with more prescriptions of IV antibiotics [120]. Analysis of CFFPR data shows similar results: higher exposure to ozone and particulate matter ($PM_{2.5}$ and PM_{10}) is linked to increased exacerbations and decreased lung function [121]. In addition, fine particulate matter ($PM_{2.5}$) increases the risk of *P. aeruginosa* acquisition in young children with CF [122].

Infectious agents.: Socioeconomically disadvantaged communities are exposed to greater health risks through a disproportionate exposure to infectious agents. In the UK, people with CF residing in poor areas were nearly twice more likely to have chronic *P. aeruginosa* infection than counterparts in affluent areas [30]. In the US, the likelihood of *P. aeruginosa* acquisition among children with CF is also increased with low maternal education [123]. Similar disparities have been reported in Methicillin-resistant Staphylococcus aureus (MRSA) infection. In the US, private health insurance has been associated with 13% lower risk of having MRSA [124]. Neighborhood socioeconomic deprivation has been linked to more than 2-fold increase in the odds of having MRSA after adjusting for demographic and clinical covariates [125]. Multiple mechanisms may be contributing to this association.

Collective and concentrated poverty may affect exposure to indoor and outdoor air quality and pathogens. Further study of potential mediators of the link between socioeconomic deprivation and infectious agents is warranted.

4.2 Behavioral factors

Due to high treatment burden in CF, maintenance of daily therapies is a challenge for all people with CF [126]; suboptimal adherence and associated adverse effects for disease outcomes have been reported across the entire CF population [127, 128]. Parental educational level is correlated with chronic disease self-management in the general population [129–132], and studies suggest that knowledge of the treatment regimen and an understanding of its rationale are a prerequisite for adherence in CF as well [133, 134]. Anthony et al.[135] reported that maternal nutritional knowledge specific to CF is a predictor of caloric intake and growth in children with CF, while Quittner et al.[136] found that nonadherence was explained by misunderstanding of the prescribed regimen. CF treatment adherence also correlates with optimism, family functioning [137, 138], and parental stress [139], discussed below. Thus, worse adherence is a likely contributor to poorer outcomes among disadvantaged children with CF [140, 141]

4.3 Psychosocial factors

4.3.1 Family structure.—Closely related to socioeconomic status, family structure is implicated in a range of health-related outcomes. For example, children with CF who are cared for by single mothers have worse respiratory and nutritional outcomes than children with dual caregivers [142, 143]. Relatedly, mothers of children with CF report higher levels of stress associated with decision-making and responsibility for parenting [144, 145].

4.3.2 Stress.—Socioeconomic position is associated with differential exposure to chronic stressors, such as financial strain, job insecurity, residential crowding, noise exposure, and social isolation [146–151]. Disproportionate exposure to continuous and repeated stressors, which results in physiologic ‘wear and tear’, is a known mechanism of health disparities [152–155]. Onerous and costly daily care, frequent interactions with the healthcare system, uncertainty about the future, and limited employment opportunities take a toll on the physical and mental health of people with CF and their caregivers [156–160]. A third of CF parents are clinically depressed [161], with low socioeconomic status being associated with a higher prevalence of depressive symptoms [162]. Depression is linked to worse health outcomes, including lower lung function [163, 164]. In a study by Quittner et al. [52], socioeconomic disadvantage was associated with worse quality of life for both CF children and their parents when adjusted for disease severity. A recent longitudinal study showed that 5-year mortality of people with CF screening positive for depression was twice that of those who did not, and nearly triple for those who screened in the severe range [165].

4.3.3 Social support.—The harmful effects of stress on health can be buffered by sense of control and other stress-mitigating resources, including social support. Although social support has been linked to a variety of health outcomes in people with and without chronic illness, relatively few studies focus on the importance of social support in CF [166, 167]. A study of 250 adults with CF showed that greater social support was associated with fewer

self-reported mental and physical health symptoms, lower treatment burden, better body image, and higher emotional, social, and role functioning [168]. Social support is protective against lung function decline[169] and hospitalizations[170] after transfer from pediatric to adult care.

4.4 Health system factors

Access to health care is an important social determinant of health. To determine whether socioeconomic disparities in CF outcomes in the US can be explained by differences in medical treatment, Schechter et al.[171] performed a cross-sectional analysis of data on pediatric patients in the Epidemiologic Study of Cystic Fibrosis. Disease severity showed a similar inverse correlation with all measures of socioeconomic status, but the number of clinic visits was unrelated to socioeconomic status, and disadvantaged patients were prescribed more – rather than less – chronic therapies. These results demonstrate that the socioeconomic disparities in CF health are not due to differential therapy prescription or use of health services. Another similar study found that pediatric patients of lower socioeconomic status are prescribed more – rather than less – antibiotic treatments for pulmonary exacerbations [172]. Among adults with CF, public insurance also was associated with equal or greater use of CF care compared to private insurance [173].

Although generally there are no socioeconomic differences in prescribed therapies or treatment of pulmonary exacerbations in CF [171, 172, 174], significant disparities have been observed in lung transplantation. Low socioeconomic status as measured by zip-code income, education level, and Medicaid insurance has been independently associated with not being referred to evaluation for lung transplantation [175] or accepted for lung transplantation [176] despite meeting all the criteria. A case-control study of in the linked CFFPR/Scientific Registry of Transplant Recipients found that accrual of socioeconomic barriers (race, marital status, education, health insurance, zip-code income, and distance to transplant program) limits access to lung transplant irrespective of disease severity [177]. Individuals with greater socioeconomic barriers accessed transplant about half as often as those with less barriers at the same level of medical severity [177]. Consequently, CF patients with Medicaid insurance have higher risk of death while awaiting lung transplantation compared to those with Medicare or private insurance [178]. They also have 22% worse survival after lung transplantation than those with private insurance [179].

The advent of cystic fibrosis transmembrane conductance regulator (CFTR) modulators, genomic-specific medications that target the malfunctioning protein made by the *CFTR* gene, is revolutionizing the treatment of CF due to their effectiveness in mitigating the downstream adverse effects of CFTR dysfunction in patients with responsive mutations. While the overall positive impact of this new treatment modality is clearly welcome, it may also serve to increase disparities. First, these drugs are not effective for “nonsense mutations” that are associated with premature stop codons, and this mutation class is more common is people with CF who are of non-European ancestry. Second, as noted earlier, there is some suggestion that tobacco smoke exposure, which is more common in lower socioeconomic groups, may have an inhibitory effect on CFTR modulators. Finally, an increased inventory of CFTR modulators and mutation-eligible patients may

trigger cost concerns among public and private payors alike[180]. This could result in restricted coverage or increased cost-sharing and out-of-pocket expenses [181], both of which will limit patient access to highly effective modulator therapies. It is imperative that the pharmaceutical industry, insurers, health-care providers, and CF stakeholders engage in a deliberate process to make sure that CF precision medicine is available to all.

A discussion of the therapeutic pipeline that led to the development of CFTR modulators must also touch on disparities in participation in clinical trials. In 2006, Goss et al. reported that, compared to the overall CF population in the US, clinical trial participants were more likely to have private insurance and to be White [182]. They further pointed out that clinical trial participants tended to have a lower average rate of decline in lung function than non-participants, an effect that seemed to be linked to closer clinical follow-up. In 2016, McGarry et al. further documented the absolute underrepresentation of minorities in CF clinical trials [183]. Inadequate inclusion of all population subgroups in clinical research may bias trial results and inhibit our understanding of factors that influence drug response.

In summary, multiple studies report an association between socioeconomic disadvantage and worse CF outcomes, which begins in early childhood and persists throughout the life course. The mechanisms of this association are varied and complex. Improved understanding of all various pathways will require in-depth studies that integrate clinical, socioeconomic, and environmental data. Such studies can provide critical evidence for policy, social, and healthcare initiatives to reduce disparities as well as for clinical interventions to optimize treatments.

5. IMPLICATIONS FOR TREATMENT

Abundant evidence supports the relationship between structural and intermediate social determinants and CF respiratory outcomes, with incremental improvements of CF health at every step of the socioeconomic ladder. The importance of economic and government-level policies for improving the social and environmental context is indisputable. The conceptual framework of the WHO Commission on the Social Determinants of Health illustrates that interventions must not be limited to addressing the intermediary determinants, but must include policies that tackle the social mechanisms that systematically generate an inequitable distribution of health-related resources among population groups. To tackle structural, as well as intermediary, determinants of health requires inter-sectoral and multilevel approaches [14].

5.1 Social policies

Population-level policy, system, and environmental interventions may be more difficult for clinicians to take on, but are more impactful than individual, patient-level interventions to improve CF health [184, 185]. Multi-level strategies that address both structural and intermediary determinants are particularly needed. Table 1 provides examples of such strategies for the general population and specifically for people with CF, organized according to the framework for action of the WHO Commission on the Social Determinants of Health.

5.2 Community-level interventions

Community interventions on social determinants that can affect the respiratory health of people with CF include urban planning policies that promote physical separation from pollution sources, complete streets policies that promote active transportation, and urban planning efforts that increase walkability and access to parks and recreational facilities. Several interventions developed specifically for the CF community have been particularly successful, as described further.

5.2.1 The CF Foundation patient assistance program (CF Compass).—

Compass is a CF Foundation-sponsored personalized service to help with insurance, financial, legal, and other issues faced by people with CF, their families, or their care teams [186]. Compass's team of case managers provide free expert advice and connect individuals to resources offered by community organizations, local and state governments, foundations, or other groups.

5.2.2 Patient and Family Advisory Councils.—

These groups advise CF care centers on the needs of people with CF and on implementing the types of support most needed by CF families.

5.2.3 CF Chapter and care center partnerships.—

CF Foundation chapters are uniquely positioned to create close relationships with local community organizations and CF care centers. In recent years, the role of chapters has expanded to include outreach and support programs for people with CF and their families.

5.3 Clinical interventions

5.3.1 Screening for unmet social needs.—

Under the umbrella of the social determinants of health, unmet social needs are defined as the social risks factors that an individual both recognizes and prioritizes [15]. For instance, a screening tool may uncover multiple social risks, such as inadequate food, housing, utilities, and transportation, but the individual may consider that her most pressing need is to find a safe place away from an abusive partner. Identifying unmet social needs can inform providers that a patient needs more support to manage their condition or could benefit from referrals to social services [187]. Screening for social needs can also make patients feel supported and understood even if their needs cannot be directly addressed by the clinic [188]. Although the feasibility of screening for unmet social needs in CF care has not been formally established, CF clinics may offer a natural setting for social needs evaluation because of routine visits and established relationships between patients and providers. However, there are both feasibility and ethical issues associated with social needs screening in clinical settings. Perceived lack of time is among the most significant barriers [189, 190]. Furthermore, while clinicians are aware of the importance of social determinants of health, most of them have inadequate training in extracting information related to sensitive social needs, such as housing and food insecurity, in a respectful and culturally appropriate way. Finally, screening for social needs can detect adverse social circumstances that require resources beyond the scope of clinical care. Referring families to nonmedical organizations to resolve social needs requires specialized training and dedicated staff that few clinicians have at their disposal [189, 191,

192]. Garg et al. warned about the unintended consequences of screening for SDOH in clinical care, especially when referral resources are unavailable for addressing identified needs [193].

5.3.2 Referrals to community organizations.—Screening in clinical settings has limited impact unless it is followed by an action to help alleviate the identified social needs. One common intervention is the referral of patients to community organizations that routinely provide such assistance. However, the availability of such community resources is often limited. A 2020 study analyzed the capacity of social service agencies to meet the needs of those who called 211, a toll-free number that connects callers with community services [194]. There was both a high prevalence of and high capacity to meet food needs. Needs with high prevalence but a low capacity of resources included public transportation and housing assistance. Similarly, in 2019 there were nearly 600 requests to CFF Compass program for assistance with food, housing, transportation, or utilities. In 19% of these cases, there was not an existing community resource to meet the caller's needs.

5.3.3 Screening for tobacco smoke exposure and delivery of tobacco treatment services.—Cessation of tobacco smoke exposure improves pediatric CF outcomes, so this is low-hanging fruit [109]. CF care teams can screen for exposure and deploy evidence-based smoking cessation services, such as behavioral counseling, nicotine replacement therapy, and pharmacotherapy [91, 195, 196]. Determining what cessation strategies are most effective for CF families will be critical. Identifying and intervening with smoke-exposed CF patients may also require changes to current CF clinical guidelines regarding screening and interventions. Barriers to such efforts include lack of trained staff to deliver smoking cessation interventions, inadequate reimbursement for cessation services, and a perception of low levels of success [197]. Still, smoke exposure is one of few modifiable risk factors in CF that can be targeted to optimize therapies and maximize the health potential of people with CF. Programs that can be initiated in the setting of pediatric practices have been shown to reduce second-hand smoke exposure, and surveys show that advice on smoking cessation from their child's physician would be welcomed by most parents [198].

5.3.4 Ensuring equitable access to treatment, including transplant.—Although previous studies have indicated that access to care and differential treatment of patients from lower socioeconomic status do not appear to be the problem typically seen in other disease populations, there may still be nuance and important unmeasured differences. For example, uptake of new medications seems slower in disadvantaged CF patients. In the 2009 study by Schechter et al., the only medication prescribed less often to patients with public insurance was azithromycin, which at the time was a relatively new therapy [199]. More recently, patients with public insurance received prescriptions for lumacaftor-ivacaftor more slowly after its approval than those with private insurances [200]; race but not insurance status was associated with slower uptake of ivacaftor following its approval [201]. Given the lack of differential prescribing of other medications, it is unlikely that slower prescribing of new medications is intentional. Rather, delays may be due to insurance barriers to approval of the new medications, but it is also possible that wealthier and/or better-educated patients

are more aware of new breakthroughs and more skilled at self-advocating, thus ensuring that their physicians promptly prescribe these newer medications. The relationship between health literacy and self-advocacy in families of lower socioeconomic status and its effect on treatment have been noted [202]. Therefore, quality improvement efforts by CF care teams to ensure consistently optimal treatment to all patients may have a differential impact on disadvantaged patients. The literature on this topic in the general population is mixed, but preliminary findings regarding a reduction in lung function disparities following successful institution of a quality improvement program that focused on increasing the consistency of antibiotic treatment for pulmonary exacerbations support the concept [203, 204].

It was noted previously that there is a differential referral for lung transplant, and acceptance into the program, by socioeconomic status [175–179], largely due to a perception that the resources and social support needed to successfully undergo organ transplantation are beyond the reach of people with limited finances and education. Although such concerns may be legitimate, the resulting disparities in transplantation access and outcomes are unacceptable. Transplant programs must focus additional resources to make the process more equitable.

5.3.5 Screening for and treatment of depression.—

International CF care guidelines recommend universal screening and treatment for anxiety and depression in people with CF [205], and those guidelines have generally been adopted in the US [206]. However, screening, as well as the diagnosis and treatment of mental health disorders, continues to vary across care centers [1]. Improvements in the rate of screening through QI efforts and ensuring access to mental health services to those in need would likely have a positive effect on people with CF from lower socioeconomic status.

5.3.6 Improving enrollment in clinical trials.—

The downside to excluding socioeconomically disadvantaged and minority patients from clinical trials is the introduction of bias into study results and extrapolating findings to populations that may not necessarily respond to the treatments in the same way as those enrolled in the trials. This should be a concern to study sponsors and pharmaceutical companies. Furthermore, inclusion in clinical trials will benefit these populations, especially given the possibility that some drugs may behave differently in certain ethnic and racial subgroups with non-European ancestry (or, as noted for the CFTR modulators, in disadvantaged populations with higher tobacco smoke exposure). The sociodemographic characteristics of all study participants should be reported, with necessary steps taken to ensure adequate representation of vulnerable populations in clinical trials. This may require extra efforts aimed at building trust, particularly for individuals belonging to racial and ethnic communities that have experienced a history of insidious and pervasive mistreatment in research settings.

6. EXPERT OPINION

With advancements in early diagnosis and medical treatment, survival in CF has improved rapidly, yet variations in disease progression persist. People with CF from socioeconomically disadvantaged backgrounds have worse health and die younger than those in more advantaged positions. Multiple mechanisms are responsible for producing

disparities in CF health, and we outlined some of the ways by which social determinants translate into health advantages or disadvantages in people with CF.

As discussed, the health effect of socioeconomic and environmental factors is not dichotomous but exist at every step of the social ladder. Therefore, we need interventions that not only reduce disparities but optimize outcomes for people with CF across the entire socioeconomic spectrum. CF care programs in the U.S. need to adopt a systematic, protocolized screening for health-related social risk factors such as food insecurity, housing instability, lack of transportation needs, utilities insecurity, and harmful environmental exposures, and then connect patients to available resources to meet identified needs. Federal and state government benefits, such as food assistance programs, supplemental security insurance, and social security disability, as well as local resources and patient assistance programs can help ensure a level of material well-being that is a prerequisite for CF health. Screening for social risk factors in people with CF and their families should also include often-overlooked aspects of daily life with CF such as daycare needs, schooling options, living and working conditions, and opportunities for physical exercise and recreation. For example, subsidized day care and home-based nursing assistance programs can relieve major daily stressors for CF families. Health insurance plans or patient assistance programs that cover nutritional supplements, exercise equipment, gym memberships, medical equipment, and all medically indicated therapies, can minimize inequities in CF health. Finally, CF care programs and patient advocacy organizations such as the CF Foundation need to support changes in public policies on economic affairs and taxation, health insurance, environmental regulations, social welfare, and education – that can address the root causes of CF health inequities.

6.1. Five-year view:

In the era of highly effective CFTR modulator therapies, as the mean age of the CF patient population increases, socioeconomic disparities in CF will become more prominent. Consequently, we expect that care teams and patient advocacy organizations will show growing interest in identifying and intervening on the social determinants of CF outcomes, from unmet basic needs such as food, housing, and utilities, to preventable environmental exposures, to self-management factors. We anticipate increased focus on developing interventions that target modifiable aspects of the social environment and expanded use of social and behavioral science to support daily CF care. Finally, we foresee interest in research on race, ethnicity, socioeconomic status, sexual orientation, and other social vulnerabilities in CF, and efforts to ensure equitable treatment and care for all CF patient population subgroups.

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** of considerable interest

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Article highlights

- Factors termed social determinants of health have both direct and indirect implications for CF health and contribute to the observed variability in CF respiratory outcomes.
- Structural social determinants that indirectly impact CF respiratory outcomes include social policies, socioeconomic position (income, education, occupation, health insurance), and race/ethnicity.
- Intermediate social determinants that directly affect CF respiratory outcomes include food, housing and living conditions, environmental exposures (tobacco smoke, outdoor and indoor air quality, infectious agents), psychosocial factors (family structure, stress, social support), and health system factors.
- Multi-level strategies that address both structural and intermediary social determinants through policy, system, and environment changes are particularly needed.
- Interventions that can be adopted in clinical settings include screening for unmet social needs and referral to available resources, screening for smoke exposure and provision of tobacco treatment services, screening for and treatment of depression, and ensuring equitable access to care and representation in clinical trials.

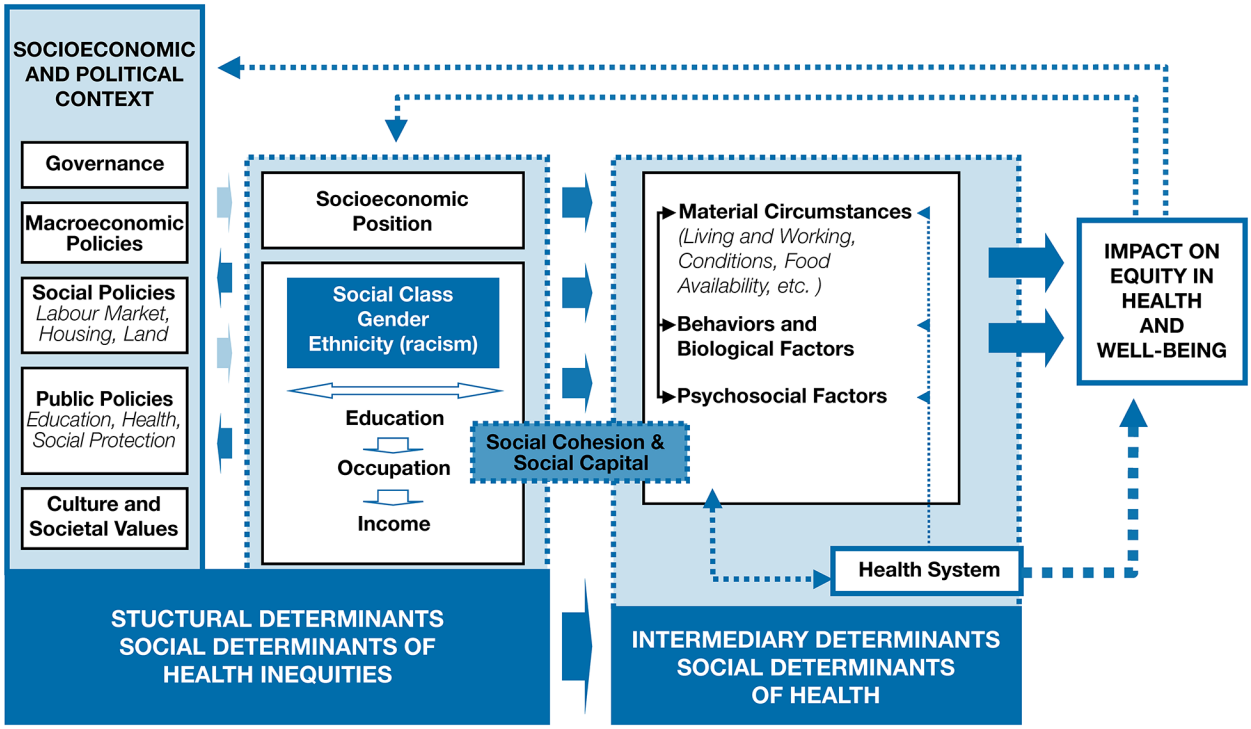

Figure 1.

The World Health Organization Commission on Social Determinants of Health conceptual framework. Reproduced from A conceptual framework for action on the social determinants of health. Social Determinants of Health Discussion Paper 2 (Policy and Practice), Solar O, Irwin A, Copyright (2010). [14]

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Table 1.

Examples of interventions on the social determinants of health

Level	Strategies	
	General Population	**People with CF**
Social stratification: Policies to reduce social inequalities and mitigate the effects of stratification	• Reduce income inequality through taxes and subsidizes public services • Policies for free and universal health, education, and public transportation • Labor policies to ensure adequate wages • Equal opportunity policies for gender, racial, and other minorities • Early childhood policies • Parental leave policies	• Social security schemes and supplemental income • Universal health coverage • Free nutritional supplements and enteral feeding
Environmental exposures: Policies to reduce exposures of disadvantaged people to health-damaging factors	• Safe neighborhoods • Guaranteed access to basic services (water, plumbing) • Healthy living conditions (lead, molds, pests) • Emission reduction and climate change policies • Tobacco control policies • Land use, urban planning policies	• Tobacco-free living and working conditions • Clean indoor air policies
Vulnerability: Policies to reduce vulnerability	• Employment protection and unemployment insurance • Social protection policies for single mothers • Free school lunches	• Training and workforce development policies • Additional resources for care and rehabilitation • Additional support for health-promoting activities