

THE BIOLOGICAL  
CONSEQUENCES OF  
SOCIOECONOMIC  
INEQUALITIES

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## Chapter 4 | Dissecting Pathways for Socioeconomic Gradients in Childhood Asthma

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The goal of this chapter is to describe a program of research on socioeconomic status (SES) and childhood asthma as a specific, in-depth illustration of an integrated biological and psychosocial approach to establishing the mechanisms underlying SES and health relationships. Beginning with an established clinical phenomenon—that is, the link between low SES and asthma morbidity—we focus on the importance of understanding the basic pathophysiology of a disease to determine which steps in the disease process are plausibly altered by social factors. Researchers will be able to develop a more accurate understanding of why health disparities are so pervasive in our society and what types of interventions may hold the most promise for reducing these disparities.

Socioeconomic status has profound effects on physical health outcomes throughout the lifespan (Adler et al. 1994; Braveman et al. 2010; Chen, Matthews, and Boyce 2002). For years, researchers have sought to understand why these relationships exist, but compelling explanations have proven elusive. For example, lack of insurance and access to health care is clearly one reason why low-SES individuals suffer worse health. And yet countries that have universal health-care systems show the same gradient relationship of SES with health as countries that do not, indicating that differential access to care is not the primary explanation for SES disparities (Adler et al. 1993). Similarly, low-SES individuals are known to engage in poorer health behaviors, and yet the impact of SES on health per-



sists after health behaviors are controlled for, suggesting that health behaviors also do not provide a complete explanation for the gradient (Lantz et al. 1998).

Hence a need exists for more sophisticated models that convincingly explain how SES has such pervasive effects on health. One approach is to simultaneously consider factors at multiple levels, spanning broad neighborhood and family influences to basic genomic processes within the individual, all in an effort to more thoroughly understand the contributors to health disparities. This type of approach is important because rarely have studies that conducted in-depth assessments of basic, biological processes also probed social contexts comprehensively. Similarly, research on neighborhood-level effects often does not incorporate individual-level factors into models, and vice versa. By considering factors across multiple levels of influence, researchers will be able to better answer the challenging question of why disparities by SES exist.

Thus the overall goal is to be able to explain how broad, distal social environment characteristics such as SES get manifest within an individual in a way that affects clinical disease outcomes. In this chapter, we focus on two primary research questions aimed at addressing this overall goal—using childhood asthma as our illustrative health outcome. First, what are the plausible biological mechanisms by which low SES can exert effects on physical health? To make convincing arguments about the social environment affecting disease, we need credible biological explanations for how social factors could plausibly influence disease processes. Second, what are the more proximal social factors that can explain the effects that distal variables such as SES have on individuals? To understand why SES has effects on individual health, we need models that articulate the neighborhood, family, and individual characteristics shaped by SES that have implications for biological processes linked to disease.

### AN APPROACH TO CONDUCTING MECHANISTIC RESEARCH

We have previously articulated an approach to conceptualizing a search for biological mechanisms to explain links between social factors and disease (Miller, Chen, and Cole 2009). First, a robust association needs to be documented between a social factor such as SES and a disease outcome; at that point, mechanisms can be investigated on both the biological and social fronts.

Biologically, it can be helpful to understand the basic processes that drive the progression of the specific disease linked to the social factor of

interest. This can allow researchers to draw on basic biomedical research regarding the pathophysiology of a disease and to systematically test which steps within the pathophysiological processes leading to disease are patterned by the social factor. In this way, researchers can begin to build a systematic and convincing argument about the causal chain of biological mechanisms that underlie the links between a social factor and a clinical outcome.

Complementing the biological approach, one also needs to understand the processes on the social end that operate to bring a social environment variable such as SES to the level of the individual. Thus one needs to move across different levels of social factors, such as neighborhood influences, family factors, individual characteristics, and test whether these are associated with biological disease processes. In this way, one can start broadly on the social end with a construct such as SES and broadly on the clinical end with an outcome like mortality and systematically establish the links in between that bring the social and the clinical health worlds closer together. The ultimate goal is to lay out a step-by-step mechanistic model of the linear progression from broader social environment to physical health outcome. In the remainder of this chapter, we illustrate this approach by describing research on childhood asthma disparities.

## ASTHMA

Asthma is the most common chronic illness in childhood. Approximately 9 million children (12.5 percent) in the United States have had asthma during their lifetime (Dey and Bloom 2005). Asthma is the third-ranking cause of hospitalizations among children (Kozak, Owings, and Hall 2004), resulting in close to 200,000 hospitalizations a year (Akinbami 2006). The economic impact of asthma, in terms of the annual estimated cost of asthma care for children, lies around \$3.2 billion (Weiss, Sullivan, and Lytle 2000). Asthma is also one of the leading causes of school absenteeism, resulting in 12.8 million missed school days a year (Akinbami 2006).

## SES Disparities in Childhood Asthma

Importantly, asthma morbidity is not equally distributed across the population. Children with lower-SES backgrounds are twice as likely to be hospitalized for asthma, and to suffer activity limitations due to asthma, than their counterparts (Miller 2000; Simon et al. 2003). More specifically, poor children with asthma are significantly more likely to have greater asthma symptoms, to have more severe asthma episodes, and to be hospi-



talized for asthma than more affluent children with asthma (Miller 2000; Simon et al. 2003; Wood et al. 2002). Fewer years of parent education also are associated with greater risk of asthma hospitalizations and emergency department visits in children with asthma (Dales et al. 2002; Maziak et al. 2004). At the neighborhood level, similar relationships exist. Neighborhoods with lower income levels and higher unemployment rates have been found to have higher rates of pediatric asthma hospitalizations (Castro et al. 2001; Claudio, Stingone, and Godbold 2006; Goodman, Stukel, and Chang 1998). These relationships are stronger for predicting outcomes among those already diagnosed with disease (morbidity) than for predicting risk of getting the disease among those who are initially healthy (prevalence; Chen, Matthews, and Boyce 2002). Overall, however, there is a pressing public health need to better understand the reasons why disparities by SES in asthma exist: to identify promising targets for interventions aimed at alleviating asthma disparities in our society.

### Why Is Low SES Associated with Greater Asthma Morbidity?

Increasing health disparities research is being conducted on general biological markers that can be linked to low SES. This work has implicated hormonal pathways such as cortisol, markers of systemic inflammation such as C-reactive protein, and the accumulation of long-term pathogenic mechanisms such as allostatic load (Cohen, Doyle, and Baum 2006; Cohen, Schwartz, et al. 2006; Evans et al. 2007; Evans 2003; McDade, Hawkey, and Cacioppo 2006; Seeman et al. 2004, 2008). However, these studies have largely been conducted in healthy individuals. Hence, though this work is able to shed some light on general biological mechanisms, it may not be as useful for explaining specific disease outcomes, given that different diseases will have different underlying mechanisms. Hence to understand associations of SES with asthma morbidity, we turn to models of the biology of asthma.

*Biological Models of Asthma* Asthma is a disease involving inflammation of the airways. Certain cytokines (chemical messengers of the immune system) are important for orchestrating cellular events related to airway inflammation (Busse and Lemanske 2001; Chung and Barnes 1999). These cytokines are produced by T helper (Th) cells, often in response to an external stimulus such as allergen exposure. Th cells are now recognized to have multiple phenotypes, but the best characterized are Th-1 and Th-2 cells. Th-1 cells generally coordinate cellular immune responses by de-

ploying cytokines such as IL-2 and IFN- $\gamma$ . In contrast, Th-2 cells coordinate what are called humoral responses—that is, those that involve the production of antibodies. These cells do this by inducing B cells to proliferate, and it is the B cells that then secrete antibodies.

Th-2 cells release specific cytokines such as IL-4, IL-5, and IL-13, and these Th-2 cytokines have been implicated in asthma. For example, secretion of IL-4 and IL-13 induces B cells to produce IgE antibodies, which initiates an inflammatory cascade leading to airway constriction and mucus production (Bacharier and Geha 2000). IL-5 also recruits eosinophils to the airways and activates them, leading to a late-phase asthma response including airway inflammation and obstruction (Kamfar, Koshak, and Milaat 1999; Ying et al. 1997).

*What Biological Pathways Relevant to Asthma Are Patterned by SES?* To establish the biological mechanisms linking SES and asthma, we tested whether SES could be linked to the various types of inflammatory processes implicated in asthma. As we alluded to earlier, the literature does link SES to systemic inflammatory markers (Hemingway et al. 2003; McDade, Hawkey, and Cacioppo 2006; Owen et al. 2003; Panagiotakos et al. 2005; Phillips et al. 2009). However, these studies typically use healthy populations and measure risk markers, such as C-reactive protein. As far as we are aware, our studies are among the first to establish associations of SES with disease-specific biological markers in patient populations.

In a sample of thirty-seven children, age nine through eighteen, recruited from the community, with a physician-diagnosis of asthma, and a comparison sample of thirty-nine healthy children in the same age range with no chronic illnesses, blood samples were collected, and parents were interviewed about family SES in terms of family savings and home ownership. As mentioned, one of the last steps in the biology of asthma exacerbations is the recruitment and activation of cells called eosinophils, which bring about edema, smooth muscle constriction, and mucus production in the airways, resulting in clinical symptoms of asthma like wheezing, chest tightness, and shortness of breath. We found that children with asthma who had lower-SES backgrounds had significantly greater eosinophil counts than those with higher-SES backgrounds, even after controlling for a variety of medical and demographic characteristics (Chen et al. 2006). In contrast, no associations were found among healthy children.

We next investigated the immune processes that foster the production and activation of eosinophils—that is, Th-2 cytokines in this same sample. Because cytokines are released only when immune cells are activated, we set up a laboratory model for activating immune cells in vitro and tested



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whether low SES would be associated with the production of IL-5 (which specifically activates eosinophils) after participants' mononuclear cells were stimulated with a mitogen cocktail. This approach provides a laboratory approximation of what the immune cells might do if they encountered allergens in real life and also allows researchers greater control by equalizing the dose of exposure (to the mitogen cocktail) across all participants' cells. We found that lower SES was associated with significantly greater stimulated production of IL-5 in children with asthma (Chen et al. 2006), suggesting that even if the exposure is equivalent, children with asthma and lower-SES backgrounds will exhibit heightened inflammatory responses to a stimulus compared to children with asthma but higher-SES backgrounds.

*Can SES Effects Be Seen at the Level of the Genome?* Thus far, we have highlighted research that focuses on what cells do, such as produce cytokines, and whether this function can be potentially shaped by SES. Another question is what regulates the function of these immune cells and whether this process may also be patterned by SES. To better understand these mechanisms, we focused on the genomic processes that control the production of proteins secreted by immune cells. Proteins such as cytokines are made by immune cells when the genes coding them get switched on by transcription factors. Transcription factors are molecules that serve as conduits between a cell's environment and the genes that govern its behavior. For example, when a receptor on an immune cell registers the presence of external stimuli (such as bacteria), it initiates a signaling cascade that results in a specific transcription factor migrating to the cell's nucleus. There it binds to a specific segment of DNA and switches on a gene that codes for a certain protein, such as a cytokine. Dysregulation of a number of transcription factors has been implicated in asthma inflammation (Barnes and Adcock 1998; Busse and Lemanske 2001).

Bringing this biological understanding back to the social world, we asked the question of whether we could document associations between SES and the activity of transcription factors that regulate inflammation. Other aspects of social adversity have been linked in recent studies to gene expression profiles (Cole et al. 2007; Lutgendorf et al. 2009; Miller et al. 2008). However, never has this understanding of genomic pathways been used as a way to understand SES and health relationships.

We conducted genome-wide transcriptional profiling on the immune cells of a sample of thirty-one children ages nine through eighteen recruited from the community with a physician diagnosis of asthma and either a low-SES or a high-SES family (bottom or top 15 percent of the



distribution in terms of both family income and parent education). Bioinformatic analyses suggested that across overexpressed genes, low-SES children with asthma showed a pattern consistent with significantly increased activity of NF- $\kappa$ B and decreased activity of CREB transcriptional signaling compared to high-SES children with asthma (Chen et al. 2009). NF- $\kappa$ B is a transcription factor that mediates induction of pro-inflammatory cytokines, whereas CREB is a transcription factor that relays messages between catecholamines and immune cells via beta 2 adrenergic receptors. This was the first study to provide evidence that even molecular pathways involved in the regulation of inflammation can be shown to be patterned by SES in children with asthma.

Note that in all of these studies, we find more robust associations of SES with asthma-relevant biological markers when using resource-based SES measures, such as family income or savings. This suggests that material resources—more so than status or prestige (such as parental occupation)—may play an important role in affecting the physiological processes underlying diseases such as asthma.

Overall, these findings demonstrate that if one takes an approach of systematically investigating the steps in the pathophysiology of a disease, one can develop a working model of the specific biological processes that may be susceptible to alterations based on changes in the broader social environment. Here we document this specifically with respect to asthma and show that SES is linked to peripheral markers related to asthma inflammation such as eosinophil counts, cellular processes like the production of Th-2 cytokines that govern inflammation, and genomic pathways that coordinate these cellular responses such as the activation of transcription control pathways that regulate inflammation such as NF- $\kappa$ B. Importantly, all of these relationships are in a direction consistent with the clinical phenomenon of lower-SES children experiencing greater asthma morbidity.

### What Social Processes Govern SES Effects on Asthma Inflammation?

As mentioned, in developing plausible models linking the social environment and physical health outcomes, it is important to identify the intervening social processes that explain how distal variables such as SES register at the level of the individual. To do this, one needs to understand the various neighborhood, family, and individual levels of social factors linked to SES. We present several examples of such an approach in the context of asthma.

*What Individual Factors Link SES to Asthma Inflammatory Processes?* One of the most promising psychosocial explanations at the individual level for the SES and health relationship is the notion that lower-SES individuals experience greater stress in their daily lives, which in turn takes a physiological toll, affecting physical health outcomes (Adler et al. 1994). Low SES has been associated with more frequent exposure to stressful life events (Attar, Guerra, and Tolan 1994; Brady and Matthews 2002; Garbarino, Kostelny, and Dubrow 1991; Hatch and Dohrenwend 2007), and children who live in low-SES environments report greater subjective stress (Goodman et al. 2005). Moreover, stress has been found to form one pathway between SES and health (Cohen, Kaplan, and Salonen 1999; Khang and Kim 2005; Lantz et al. 2005).

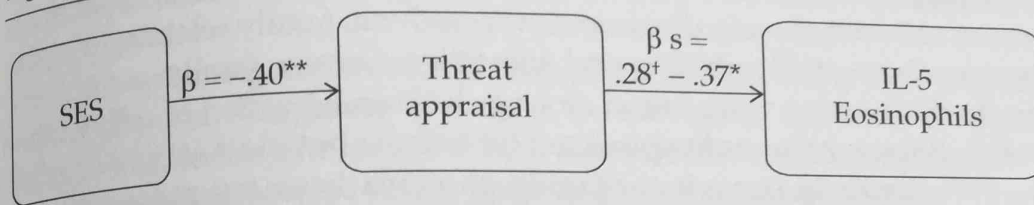
Asthma itself has been linked to psychological stress (for a review, see Chen and Miller 2007). Clinically, experiencing stressful life events is associated with an increased risk for a subsequent asthma attack in children with asthma (Sandberg et al. 2000). Daily diary studies have shown that daily stress is associated with poorer lung functioning as well as increased reports of asthma symptoms (Smyth et al. 1999). In young children, perceived stress in parents has been linked prospectively to children's risk of developing wheezing in the first two years of life (Wright et al. 2002).

In turn, research has linked experiences of stress to immune responses relevant to asthma. For example, college students with asthma showed a greater immune response to allergen challenge during high-stress periods (final exams) than in low-stress (no exam) periods (Liu et al. 2002). High school students with asthma showed greater IL-5 production after high stress (post-exam) than students who were healthy and experiencing stress (Kang et al. 1997). Similarly, atopic individuals show a decreased Th-1/Th-2 ratio in response to exam stress relative to healthy control participants (Hoglund et al. 2006).

However, missing from this earlier research is an integration of stress into the broader social environment. That is, it remains unclear whether stress can provide one explanation for why low SES comes to affect asthma inflammatory pathways. We tested this idea with respect to how children with different SES backgrounds perceive the events in their social world. In previous work, we hypothesized that children who grow up in low-SES environments develop a pattern of thinking about the world as a threatening place that requires constant vigilance based on previous negative life experiences (Chen and Matthews 2003). We hypothesized that these children would develop a tendency toward interpreting even ambiguous events as threatening. That is, when outcomes are ambiguous, such as a teacher asking to speak with you after class, low-SES children will be more



Figure 4.1 SES and Inflammatory Responses



Source: Authors' compilation based on Chen et al. (2006).

Note: Indirect pathway from SES to asthma inflammatory pathways significant at  $p < .05$ .

SES = socioeconomic status.

$^+p < .10$ .  $*p < .05$ .  $**p < .01$

likely to perceive a threat, whereas high-SES children will be more likely to read the situation as benign. Hence we hypothesized that above and beyond their life events, SES also shapes how individuals perceive their social world and that this has implications for biological responses.

To test this hypothesis, we developed a set of videos that depict life events with different types of outcomes (Chen and Matthews 2003). In this paradigm, participants are asked to imagine the event and then interviewed about their reactions to it. In this way, we are able to keep the event, or exposure, constant across all individuals and assess individual differences in interpretations. Across multiple studies, we find that lower-SES children make greater threat interpretations during ambiguous videos than their counterparts (Chen et al. 2003, 2006). In the biological pathways section example, greater threat interpretations were associated with higher eosinophil counts and greater Th-2 cytokine production (Chen et al. 2006). Furthermore, as presented in figure 4.1, we documented that threat interpretations constituted a statistically significant pathway between SES and asthma-relevant cellular and genomic processes in the two samples of children with asthma described (Chen et al. 2006, 2009). These findings are an important step toward constructing more comprehensive models of SES-health pathways by suggesting that SES shapes the ways in which individuals come to perceive their social world, which in turn shapes biological responses relevant to disease.

*What Family Factors Are Relevant to Asthma Inflammatory Processes?* Stress occurs not only at the individual level but also at the family level. Family stress has shown robust associations with childhood asthma. For example, greater parenting difficulties prospectively predict a greater likelihood of a child being diagnosed with asthma years later (Klennert et al. 2001;

Mrazek et al. 1999), as does the combination of parenting difficulties plus high parental stress (Klennert, Mrazek, and Mrazek 1994). In addition, among children already diagnosed with asthma, family relationship quality contributes to morbidity and mortality. Greater family conflict and family dysfunction were found among children who died of asthma than among those who were hospitalized for asthma but did not die (Strunk et al. 1985). Similarly, stress in the family, particularly among caregivers, predicts a greater likelihood of wheezing, greater asthma symptoms, and a greater likelihood of asthma hospitalizations in children (Shalowitz et al. 2001; Weil et al. 1999; Wright et al. 2002).

Some evidence links family stress to biological processes implicated in asthma. For example, among young children at risk for atopy, greater parent perceived stress was associated greater stimulated production of pro-inflammatory cytokines (Wright, Finn et al. 2004). In children already diagnosed with asthma, low levels of parent support were associated with greater Th-2 cytokine production and higher levels of IgE and eosinophil counts (Chen et al. 2007). Our group has also worked to tease apart the critical ingredients of family stress. In a longitudinal study, we assessed seventy-one children ages nine through eighteen, recruited from the community, with a physician diagnosis of asthma and seventy-six healthy children also recruited from the community in the same age range, but without any chronic illnesses, every six months for two years. At each time point, we drew blood to assess Th-2 cytokine production and conducted in-depth stress interviews with the children. We found that children with asthma who had higher levels of chronic family stress showed increased production of IL-4 and IL-5 at times they had experienced an acute event over times they had not (Marin et al. 2009). These findings are specific to family stress, in that we do not find these patterns when we explore life stress in other domains, such as school or friendships. These patterns also did not occur in children with low chronic family stress or in healthy children. Moreover, the combination of acute and chronic stress was associated with increased asthma symptoms in this sample.

We tested whether these effects of acute and chronic stress could also be seen at the level of the cellular processes that regulate cytokine production—that is, gene expression. Hormones such as cortisol are known to provide anti-inflammatory signals to immune cells. Although stress activates hormonal systems acutely (Kirschbaum, Pirke, and Hellhammer 1993), we hypothesized that under chronic stress, persistent hormonal elevations would result in a compensatory downregulation of the receptors for these hormones—that is, the glucocorticoid receptor (GR) and the  $\beta$ 2adrenergic receptor ( $\beta$ 2AR). As a result, the immune system's ability to respond to anti-inflammatory signals would be reduced, and inflamma-



tory processes would flourish (Miller, Cohen, and Ritchey 2002). To test these hypotheses, we quantified gene expression for the two receptors in leukocytes.

In this gene expression study, using a sample of thirty-nine children with a physician diagnosis of asthma (mean age of thirteen), we found that, parallel to the cytokine findings, those children who simultaneously experienced high levels of both acute and chronic family stress exhibited a 5.5-fold reduction in GR gene expression and a 9.5-fold reduction in  $\beta$ 2AR gene expression relative to children with asthma without comparable stressor exposure (Miller and Chen 2006). This diminished expression of the GR and  $\beta$ 2AR genes suggests that children with asthma who are experiencing acute and chronic stress may be both more vulnerable to inflammation and less responsive to asthma medications (such as inhaled corticosteroids and beta-agonists, which act through these receptors).

Overall, these findings point to the importance of characterizing not only the background, chronic level of stress in the family but also experiences of acute, time-limited events in terms of understanding effects on both the production of Th-2 cytokines as well as the expression of genes for receptors that regulate asthma responses. The experience of acute and chronic stress simultaneously appears to create a particularly potent vulnerability to asthma inflammatory processes.

*How Should We Incorporate an Understanding of Neighborhood-Level Factors?* Models of the role of the social environment in asthma would be remiss not to acknowledge the contribution of neighborhood characteristics to asthma. For example, one of the most commonly proposed explanations for associations between SES and asthma is that living in a low-SES neighborhood results in greater exposure to both outdoor and indoor environmental triggers of asthma, such as smoking, allergens, and air pollution. Hence models that implicate social factors need to demonstrate that these social factors are not merely serving as a proxy for physical exposures. We first briefly review some of the literature on neighborhood exposures in asthma and then present two recent studies that have attempted to document the simultaneous roles of both the physical and social environments in asthma.

*Physical exposures and asthma* Lower-SES families are more likely to have smokers in the homes of children with asthma (Dales et al. 2002; Wamboldt et al. 2002). In turn, exposure to tobacco smoke can lead to wheezing and asthmatic symptoms in vulnerable individuals (Jaakkola, Nafstad, and Magnus 2001). Similarly, low SES is associated with both greater sensitivity and exposure to allergens such as cockroaches (Sarpong

et al. 1996; Togias et al. 1997). Furthermore, children who had high exposure and were allergic to cockroach allergen were significantly more likely to be hospitalized, to have unplanned medical visits for asthma, and to have more asthma symptoms during a one-year follow-up (Rosenstreich et al. 1997). As well, exposure to outdoor air pollutants such as nitrogen dioxide (NO<sub>2</sub>) and sulphur dioxide (SO<sub>2</sub>) can cause significant respiratory morbidity (Brunekreef and Holgate 2002; Dockery et al. 1993; Kunzli et al. 2000; Nicolai 2002). Children with asthma who live in multifamily houses (likely lower in SES) are exposed to greater amounts of NO<sub>2</sub> than those who live in single-family housing (Belanger et al. 2006).

*Neighborhood social exposures and asthma* Some researchers have argued that social pollutants at the neighborhood level, not unlike physical pollutants, can affect asthma (Wright and Subramanian 2007). For example, exposure to violence represents a community-level stressor that can take a toll on health (Wright 2006). Research has documented that greater exposure to violence is associated with a greater number of symptom days in children with asthma (Wright, Mitchell et al. 2004). Similarly, greater problems in one's neighborhood, such as problems with crime and gangs, have been associated with greater asthma symptoms in children (Chen et al. 2007). In addition, this study found that neighborhood and family social factors appeared to operate through different pathways to affect asthma symptoms, thus highlighting the importance of including assessments of factors at multiple levels in studying pathways to asthma.

*Combined effects* One question that naturally arises is whether physical exposures largely explain the relationship between SES and asthma outcomes and whether psychosocial variables such as stress or violence are in fact simply proxies for these physical exposures. Two recent studies have addressed this issue and also suggest promising approaches for future multilevel studies. In particular, many factors that contribute to asthma are often studied in isolation. To better understand why disparities by SES exist in asthma, it is important to simultaneously consider factors at multiple levels. Although acknowledgement in the research community of the need for such an approach is clear, it is not that common for researchers to consider multiple levels of influence like neighborhood and family, or to evaluate different types of influences, such as social versus physical exposures, within a study.

One study that has taken this approach investigated the effects of both neighborhood physical and social exposures on childhood asthma. In this study, 413 children who were part of a community-based pregnancy cohort were assessed on lifetime exposure to violence. At the same time,



geographic information system models were created to estimate residential exposures to traffic-related air pollution. This team found that there were interactive effects between physical and social exposures, such that children were at greater risk for being diagnosed with asthma if they had both high levels of exposure to traffic-related air pollution combined with high exposure to violence (Clougherty et al. 2007).

A subsequent study from our team, using a sample of seventy-three children already presenting with asthma (mean age of thirteen) who were followed longitudinally for six months, also found support for the notion of interactive effects between physical and social exposures. In this case, we tested factors across levels—that is, physical exposures at the neighborhood level together with social exposures at the family level. Children were interviewed about family stress, and we also obtained high-resolution spatio-temporal estimates of traffic-related air pollution exposures based on study participants' addresses. We found that neighborhood air pollution and stress interacted in predicting asthma inflammatory markers (Chen et al. 2008). The interactions were such that children under high levels of family stress but exposed to modest air pollution displayed high levels of eosinophil counts and IL-5 production similar to those children exposed to high levels of pollution. Longitudinally, associations of higher family stress with greater increases in asthma symptoms and decreases in lung function over the six-month follow-up period were evident only in that same subgroup of children.

Taken together, these findings highlight the importance of studying factors at multiple levels simultaneously to better understand pathways to health. Studying factors individually will not provide us with a full picture of how mechanisms operate to link the social and physical health worlds. Rather, recognizing that diverse factors at multiple levels are intertwined, and documenting the ways in which these factors can interact to create effects on health, is an important approach for researchers interested in building comprehensive models of how SES affects physical health outcomes.

## LIMITATIONS AND FUTURE DIRECTIONS

In this chapter, we have not been able to be comprehensive in describing the types of factors at the individual, family, and neighborhood levels that explain SES and health relationships. Numerous other factors at each of these levels were not discussed. Rather, our aim was to use the case of childhood asthma and to provide examples of a research strategy for uncovering mechanisms. However, developing models of the pathways underlying SES and health relationships will necessarily involve assessing a

more comprehensive set of factors at each of these levels and determining which factors hold the most promise as pathways linking SES to health. This type of research will require multidisciplinary teams—that is, bringing together epidemiologists, sociologists, economists, psychologists, biomedical scientists, and physicians who in turn each bring a different type of expertise to addressing the question of how it is that SES comes to have such profound effects on physical health outcomes.

Moreover, the research presented here is primarily small-scale research that involves intensive interviews and biological assessments on small groups of participants. Future research should strive to blend, where possible, the advantages gained by more thorough assessments with larger-scale survey and epidemiological studies in order to reach firmer conclusions about the validity and generalizability of the types of findings we described. This would mean, for example, incorporating more extensive biological assessments into large-scale survey studies that have not traditionally been able to answer questions about the biological mechanisms underlying SES and health relationships. And, as we alluded to previously, the best data will be generated when social scientists and basic scientists collaborate and tap the strengths of each when designing studies and interpreting data.

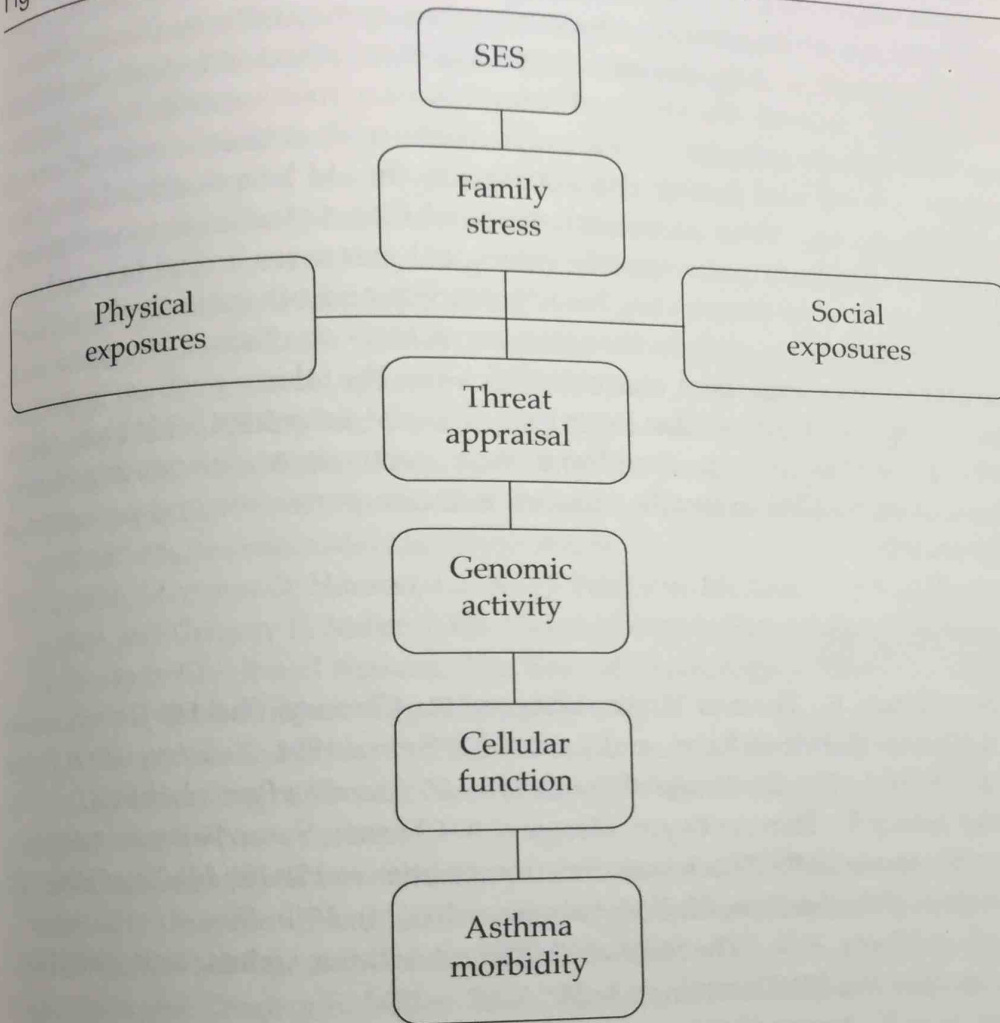
## CONCLUSIONS

We have presented a biological and psychosocial approach to investigating the mechanisms underlying SES and health relationships. Beginning with an established clinical phenomenon, such as the one linking SES to asthma morbidity, we then argue that it is necessary to understand the basic pathophysiology of that disease in order to determine which points in the pathophysiological process are potentially altered by SES. At the same time, it is important to construct comprehensive models on the social end of the factors that can explain how distal variables such as SES are registered at the level of the individual in a way that can plausibly alter biological processes. Factors should be investigated at the neighborhood, family, and individual levels, with the aim of developing a causal chain that connects the various components from the social environment end with the various steps on the biological end to create more comprehensive models of how SES comes to affect clinical health outcomes.

In this chapter, we create one such model using childhood asthma as one example (see figure 4.2). We illustrate how SES can be linked to inflammatory processes related to asthma at the level of peripheral blood cells such as eosinophil counts, cellular processes—such as the production of Th-2 cytokines that govern inflammation—and genomic pathways—



Figure 4.2 Model: SES Effects and Clinical Health Outcomes



Source: Authors' figure.

Note: SES = socioeconomic status.

such as the activation of transcription control pathways that regulate inflammation such as NF- $\kappa$ B—that coordinate these cellular responses. We provide examples of factors that explain how broad, distal variables such as SES can shape the psychological states of individuals, for example, affecting how they perceive their social world, and in turn their asthma-relevant inflammatory responses. We also provide examples of how family stress can interact with both social exposures (acute negative life events) as well as with neighborhood physical exposures (air pollution) to affect asthma inflammatory processes. This approach to uncovering mechanisms behind SES and health relationships is important for a num-

ber of reasons. First, the study of multiple levels of influence, including neighborhood and family factors, will help shape priorities for interventions by directing attention toward either community or family factors, based on which characteristics have the most direct influence on asthma morbidity. Second, the study of interactions across levels will help us determine which subgroups, or individuals with certain combinations of neighborhood and family characteristics, should be prioritized for interventions given their increased vulnerability to asthma exacerbations. Third, documenting the specific biological processes linked to social contexts is critical to convincing basic scientists and others in the biomedical community that social factors can contribute to disease progression in similar ways as medical characteristics do. By taking such an approach, and bringing together the expertise of social scientists with basic scientists, we will be able to develop a more accurate understanding of why disparities by SES in health outcomes are so pervasive and persistent in our society.

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