

PART

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Why Worry About  
Poverty?: The Long-  
Term Effects on  
Children and Families

# How Poverty Gets Under the Skin: A Life Course Perspective

Gary W. Evans, Edith Chen, Gregory Miller, and Teresa Seeman

## Abstract

There is a large epidemiological literature documenting inverse relations between socioeconomic status (SES) and morbidity as well as mortality. In this chapter we focus on biological mechanisms to explain how disadvantage gets under the skin. We adopt a life course perspective on this topic because it illuminates several issues: whether the timing and duration of exposure to disadvantage over the life course matter, and factors that may cause biological mechanisms, changed by deprivation in early life, to persist throughout the life course. This chapter is organized into 5 major sections. Sections 1 through 3 review evidence linking SES or one of its primary constituents to disease-relevant biological mechanisms during childhood, during adulthood, and prospectively from childhood to adulthood, respectively, and section 4 examines the durability of early life deprivation and altered trajectories in biological mechanisms over the life course. We conclude with section 5, which presents a research agenda and discusses intervention consequences of a life course perspective on the biology of disadvantage.

**Key Words:** poverty, SES, life course perspective, biological mechanisms

There is a large epidemiological literature documenting inverse relations between socioeconomic status (SES) and morbidity as well as mortality (Adler & Rehkopf, 2008; Adler & Stewart, 2010; Braveman, Cubbin, Egerter, Williams, & Pamuk, 2010; Braveman & Egerter, 2008; U.S. Department of Health and Human Services, 2010). In this chapter we focus on biological mechanisms to explain how disadvantage gets under the skin. We adopt a life course perspective on this topic because it illuminates several issues: Conceptually, does the timing and duration of exposure to disadvantage over the life course matter (Chen, Matthews, & Boyce, 2002)? Furthermore, if biological mechanisms are changed by deprivation early in life, what causes these changes to persist throughout the life course? Emerging evidence, in addition to showing SES-morbidity/mortality correlates, indicates that early deprivation predicts adult health, independently

of adult SES (Cohen, Janicki-Deverts, Chen, & Matthews, 2010; Galobardes, Lynch, & Davey Smith, 2004, 2008). Moreover, early childhood deprivation as well as cumulative deprivation experiences in early childhood matter much more to subsequent health than social mobility, regardless of the direction of changes in SES (Chen, Martin, & Matthews, 2007). Something special about deprivation early in life fundamentally shapes life-long physical health trajectories. In this chapter we describe how biological processes could account for the impacts of early experiences of disadvantage on health trajectories over the life course.

As we review below, SES-related differences in a wide array of biological processes, first evident in childhood, persist and, if anything, grow larger through adulthood. Like childhood, these SES differentials in adulthood are seen for multiple, if not all, major regulatory systems. The breadth of these

SES-physiology links is not surprising if one thinks about how SES-associated experiences and exposures "get under the skin." It is likely that perceptions of disadvantage result in brain-mediated patterns of physiological response, starting with activation of the primary neuroendocrine systems (the hypothalamic-pituitary-adrenal [HPA] and both the sympathetic and parasympathetic arms of the autonomic nervous system) along with coordinated activity in the immune system as well as patterns of glucose and lipid metabolism among others. Thus, we should not be surprised that SES, with its associated physical/material, financial, educational, and social environmental features should result in brain-mediated differences in patterns of physiological arousal. Consistent with the concept of allostatic load and its focus on likely patterns of "wear and tear" in physiological regulatory systems as a function of the demands placed on these systems over time, SES-related differences in these physiological parameters—first seen in childhood—not only persist into adulthood but frequently grow larger, and, in many cases, reach levels of dysregulation commensurate with clinically significant pathology (e.g., elevations in blood pressure reach levels associated with diagnosed hypertension, poorer glucose regulation reaches levels associated with diagnosed diabetes). The fact that we see such a myriad of physiological processes differentially related to SES is consistent with, and indeed helps to explain, the well-known SES gradients for nearly every form of morbidity, disability, and mortality. In the following sections, we provide an overview of evidence for SES gradients across all major regulatory systems (see Figure 1.1).

The remainder of this chapter is organized into five major sections. Sections one through three review evidence linking SES or one of its primary constituents (i.e., income, education, occupation) to disease-relevant biological mechanisms during childhood, during adulthood, and prospectively from childhood to adulthood, respectively. The biological mechanisms reviewed in sections one

through three, as shown in Figure 1.1, include: the hypothalamic-pituitary-adrenal (HPA) axis, sympathetic nervous system (SNS), metabolic processes, inflammation and immune responses, and allostatic load. Section four examines the durability of early life deprivation and altered trajectories in biological mechanisms over the life course. This section calls attention to two dominant models of durable biological changes: embedding and accumulation. Embedding refers to the idea that early experiences of low SES may produce biological changes that program the organism for trajectories of physiological activity and eventually pathogenic processes. Accumulation argues that although these early shifts in biological processes are important, it is the continued shocks to the system from reoccurring risk exposures related to low SES that matter more. Finally, section five presents a research agenda and discusses intervention consequences of a life course perspective on the biology of disadvantage. The life course perspective emphasizes that the timing and duration of SES exposure is important as well as its overlap with critical transition points in maturation, such as birth, or movement from primary to middle school, or from early to late adulthood.

## SES and Biological Mechanisms During Childhood

### Sympathetic Nervous System

Up until puberty, lower SES is associated with higher resting blood pressure, but during adolescence there is no SES–blood pressure association (Chen et al., 2002). One puzzling life course aspect of SES and blood pressure is that significant SES correlates of blood pressure reemerge in adulthood. One possible explanation for this life course pattern of SES and blood pressure might be the increased amount of time adolescents spend with peers outside of their home. Interestingly, one study has documented that adolescent ambulatory blood pressure is inversely related to neighborhood SES but not household SES (McGrath, Matthews, & Brady, 2006).

In addition to the SES and resting blood pressure, we have examined cardiovascular reactivity to acute stressor exposures. Children with lower SES show elevated reactivity to acute stressors (Raphaelson, & Matthysen, 1997; Treiber, Tur-Kapuku, Treiber, & Dwyer, 1997). The opposite pattern of cardiovascular reactivity has been found in adolescents (Evans & Kim, 2007).

Walter and Hofritz (1997) found that children with lower SES show faster recovery following acute stressors. In fourth graders living in a New York City suburb or city, White but not Black children had less efficient recovery from acute stressors. White and Shanis (2007) also found that children from families with lower SES show faster recovery to an acute stressor such as poverty assessment, however, findings from studies of cardiovascular reactivity (Evans et al., 1999).

In terms of hormones, lower SES is associated with higher night epinephrine levels in adolescents (~13 years) and adolescents from low income families (Evans & Kim, 2007). Asthma prevalence is also higher in low income households also show higher levels of genes regulated by cortisol (Evans et al., 2009).

### Hypothalamic-Pituitary-Adrenal Axis

A number of cross-sectional studies have found elevated cortisol levels in children from low income families (Blair et al., 2002; Kalin, 2002; Evans & England, 1997; Gustafsson, 2006; Lupien, King, & McEwen, 2001). Two studies have found that over time throughout adolescence, higher cortisol levels (Chen, Cohen, & Garmann, 2007; Fernald and Gunnar, 2008) and conditional cash programs that provide money in exchange for school attendance at school lowered cortisol levels in 6-year-olds.

One study has examined the relationship between acute stressor exposure and cortisol levels in children from low income families (Evans et al., 1999).

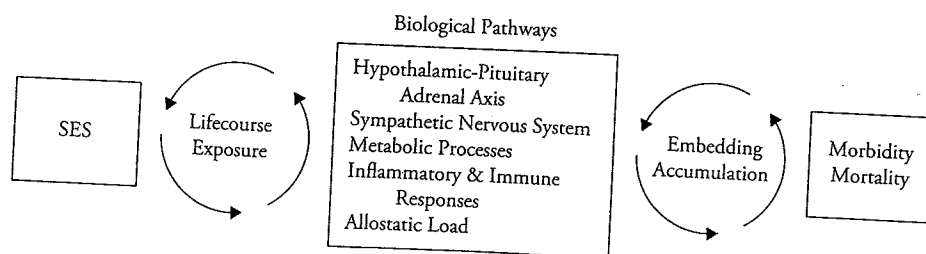


Fig. 1.1 Conceptual model for chapter.

Figure 1.1, include: the HPA axis, sympathetic processes, and allostatic durability of early-jectories in biological course. This section contains models of durable and accumulation. That early experiences biological changes that trajectories of physiopathogenic processes. Although these early are important, it is the from reoccurring SES that matter more. research agenda and ences of a life course disadvantage. The life that the timing and portant as well as its points in maturation, m primary to middle lthhood.

## Mechanisms During

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In addition to the large literature on childhood SES and resting blood pressure, a few investigators have examined cardiovascular dynamics in relation to acute stressor exposure. Most of these studies reveal elevated reactivity to an acute stressor among children with lower SES backgrounds (Chen, Langer, Raphaelson, & Matthews, 2004; Gump et al., 2007; Jackson, Treiber, Turner, Davis, & Strong, 1999; Kapuku, Treiber, & Davis, 2002). Two studies, however, found the opposite pattern, showing muted cardiovascular reactivity among lower-SES adolescents (Evans & Kim, 2007; Musante et al., 2000).

Walter and Hofman (1987) contrasted heart rate recovery following a standard exercise protocol in fourth graders living either in an affluent New York City suburb or a low-SES borough of the city. White but not black, low-SES neighborhood children had less efficient recovery relative to their middle-SES counterparts. Evans, Kim, Ting, Tesser, and Shanis (2007) also found slower blood pressure recovery to an acute stressor among primary school age children from families with elevated cumulative risk such as poverty and lower education levels. Two studies, however, found no relations between SES and cardiovascular recovery (Evans & Kim, 2007; Jackson et al., 1999).

In terms of hormones reflecting the SNS, overnight epinephrine for 9-year-olds but not young adolescents (~13 years), was elevated among low-income children (Evans & English, 2002; Evans & Kim, 2007). Asthmatic children from low-SES households also showed decreased expression of genes regulated by catecholamines (Chen et al., 2009).

## Hypothalamic-Pituitary-Adrenal Axis

A number of cross-sectional studies have found elevated cortisol among children from lower-SES families (Blair et al., 2011; Essex, Klein, Cho, & Kalin, 2002; Evans & English, 2002; Flinn & England, 1997; Gustafsson, Gustafsson, & Nelson, 2006; Lupien, King, Meaney, & McEwen, 2000, 2001). Two studies reveal these relations persist over time throughout adolescence (Evans & Kim, 2007; Chen, Cohen, & Miller, 2010). In addition, Fernald and Gunnar (2009) demonstrated that a conditional cash program that provided poor mothers money in exchange for their child's participation in both recommended health care visits and attendance at school lowered cortisol levels among 2- to 6-year-olds.

One study has examined HPA reactivity to an acute stressor among children from varying SES

backgrounds. Gump, Reihman, Stewart, Lonky, and Matthews (2009) found elevated cortisol in response to an acute stressor among 9- to 10-year-olds who were from lower-SES backgrounds.

## Metabolic Processes

Mechanisms related to metabolic processes and SES include direct indices of metabolic dysregulation such as lipids and glucose tolerance as well as indices of adiposity, most typically body mass index (BMI). Reviews of studies published in English reveal inverse associations in most studies between SES and adiposity in children (Shrewsbury & Wardle, 2008; Sobal & Stunkard, 1989). Gender does not alter these SES patterns, but the trends are clearer for white children than other ethnic groups. There is also some suggestion that the SES-adiposity associations are larger in younger children, however, it is more difficult to accurately measure adiposity during puberty. In a recent study, Wells, Evans, Beavis, and Ong (2010) investigated BMI trajectories in 9- to 17-year-olds as a function of the proportion of the child's life from birth to age 9 spent in poverty. At age 9 poor children are heavier, and their increases in weight gain over the next 8-year period are faster than those of children from more affluent families.

Using data from NHANES, a large, nationally representative cross-sectional data set of Americans across a large age range, Seeman and colleagues (Seeman, Epel, Gruenewald, Karlamangla, & McEwen, 2010) showed that glucose metabolism (glycosylated hemoglobin) was elevated among children ages 1 to 19 in relation to household income. In a second study, parental occupational status was inversely related to total cholesterol, low-density lipoproteins (LDL), and the LDL/HDL ratio in a sample of Finnish 9- to 15-year-olds (Leino et al., 1996). High-density lipoproteins (HDL) and triglycerides were not related to parental occupational status. In Australia, neighborhood SES was inversely related to LDLs and triglycerides as well as body fat among 9- to 15-year-olds (Gliksman, Dwyer, & Wlodarczyk, 1990). Walter and Hofman (1987) compared several metabolic parameters among fourth-grade children living in an affluent suburb of New York City to those living in a low-SES borough. Children in the lower-SES area had higher total cholesterol. A sample of 5- to 14-year-old children from Bogalusa, Louisiana, revealed that ethnicity may be important in examining childhood markers of metabolic risk (Hunter, Frerichs, Webber, & Berenson, 1979). For white but not black children, total cholesterol and

triglycerides were associated with parental education, with those from the least and most educated families having the highest levels. On the other hand, parental occupation mattered only for African Americans, with children from blue-collar households having higher total cholesterol levels. These same children also had lower triglycerides, lower  $\beta$  lipoproteins, and higher  $\alpha$  lipoproteins than their white-collar counterparts.

### ***Inflammation and Immune Responses***

One of the reasons low-SES children suffer from higher rates of morbidity across a wide range of diseases may be because of disturbed immune function that results in exaggerated inflammatory responses to irritants, allergens, and pathogens. In two different samples of children with asthma, Chen and colleagues (Chen et al., 2006; Chen, Fisher, Bacharier, & Strunk, 2003) examined inflammatory mechanisms underlying host resistance to asthma, a major childhood disease with strong SES gradients. In the first study, 13- to 18-year-old children from lower-SES neighborhoods showed increased cytokine responses when their peripheral blood mononuclear cells (PBMCs) were stimulated in vitro with allergens relative to their counterparts from middle-SES neighborhoods. Eosinophil counts, however, did not differ between the two groups. Asthma severity was homogeneous and did not differ as a function of SES. In the second study, 9- to 18-year-old asthmatics were compared to similar age healthy children. Asthma severity, as in the first study, did not differ between the low- and high-SES groups of children. PBMC cytokine responses to mitogen challenge were larger in children from lower-SES families; eosinophil counts were also higher in these children. Statistical controls for exposure to allergens in the home (e.g., smoking, pets) and for asthma severity did not alter these results. Among the healthy children, inflammatory responses were unrelated to family SES.

Chen and colleagues then took their analyses further by examining gene transcription profiles hypothesized to account for the significant SES-related inflammatory responses uncovered in the above two studies (Chen et al., 2009). Their findings are important as they provide clear evidence that T-cell gene expression in children can be related to SES. Using the same sample of asthmatic children in study 2 above, they found that children from low-SES families exhibited relative overexpression of genes involved in functional activities like chemokine activity and wound responses. Further

bioinformatic analyses revealed transcription control pathways might underlie the differential patterns of gene expression and cytokine responsiveness in low-SES children with asthma. These analyses point to low-SES children's T-cells having decreased activity of the transcription factors cyclic AMP binding protein (CREB), AP1, and nuclear factor  $\kappa$ B (NF $\kappa$ B). In parallel the low-SES children displayed increased activity of genes regulated by the chief proinflammatory transcription factor, nuclear factor kappa-B (NF $\kappa$ B). These findings suggest that social gradients are apparent at the level of transcription pathways that regulate inflammatory gene expressions.

### ***Allostatic Load***

Recent interest in the concept of allostatic load (AL) dovetails with a growing appreciation of the multiplicity of "inputs" to the overall health of the human organism from the body's multiple physiological regulatory systems. A growing body of evidence now illustrates the extent to which healthy physiological functioning requires ongoing communication among these regulatory systems and, importantly, the extent to which dysregulations in one system can "ripple outward" to impact the functional integrity of multiple other systems. Dysregulations can arise from the body's attempts to continuously adjust its normal operating range or set points in response to multiple physical and social demands. Allostatic load is a marker of chronic wear and tear on the body caused by the mobilization of resources to meet changing environmental demands (McEwen, 1998; Seeman et al., 2010). Efforts to capture the range of such dysregulations initially reflected straightforward additive indices of allostatic load based on the summation of values at the high end of each physiological risk distribution for the sample of data in hand (e.g., blood pressure in the upper quartile = 1, all other blood pressure levels = 0). More complex algorithms have also been used to calculate such cumulative risk scores (Seeman et al., 2010).

Very little work has ensued on allostatic load and SES in children. Parental education is inversely associated with allostatic load in high school students ( $M = 16.2$  years), independent of age, gender, and ethnicity (Goodman, McEwen, Huang, Dolan, & Adler, 2005). Worthman and Panter-Brick (2008) assessed allostatic load in boys in Nepal from varying SES backgrounds between the ages of 10 and 14. A unique aspect of this study to appreciate in our analyses of SES and biological mechanisms is the much greater range of SES afforded by a sample from an economically

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undeveloped country. Children from rural villages and homeless urban children had the highest levels of allostatic load. Children residing with intact families in urban slums looked slightly better than the former two groups, and middle-class boys from a private school had the lowest levels of allostatic load. In cross-sectional and prospective longitudinal analyses, Evans and colleagues (Evans, 2003; Evans et al., 2007) demonstrated that an index of cumulative risk that includes poverty and other factors closely associated with it (e.g., poor housing quality, family turmoil) is positively associated with allostatic load among 9- and 13-year-olds, respectively. More recently, Evans and Schamberg (2009) demonstrated that the proportion of life spent in poverty from birth to age 13 is significantly correlated with higher allostatic load at age 13.

### Summary

From birth through age 18, children from lower-SES families are more likely to die prematurely and get sicker relative to their more affluent counterparts. SES-related variability in multiple, underlying physiological systems reveal parallel social gradients that may help us better understand these health inequalities. Note in terms of Figure 1.1, these studies are within childhood and thus do not reflect a true life course perspective, rather they show that childhood SES and childhood biological mechanisms with known morbidity outcomes, usually later in development, are related. Children up until puberty consistently show elevated resting levels of blood pressure. It is unclear why these basal cardiovascular social gradients cease in adolescence and then reappear later in life. A smaller number of studies reveal elevated catecholamines (e.g., epinephrine) among lower-SES children. The HPA axis is also more active among lower-SES children. Another reason low-SES children suffer greater morbidity is because of disturbances in immune function that result in exaggerated inflammatory responses to irritants, allergens, and pathogens. Emerging work suggests these exaggerated inflammatory responses to challenge are caused by overexpression of genes involved in immune responses. Moreover this SES-related differential gene expression may be caused by alterations in gene transcription pathways that regulate inflammatory gene expression. This latter epigenetic process illustrates the importance of framing questions about environment, genes, and health in a much more dynamic and complex manner than the typical Environment X Gene interaction formulation.

The obesity epidemic is not randomly distributed in the population—there are more overweight and obese children among the poor. Lower-SES children also suffer from early markers of the metabolic syndrome including elevated cholesterol and higher LDL and LDL/HDL ratios, as well as more triglycerides. Finally, children from lower-SES households may exhibit elevated allostatic load vis-à-vis their more advantaged counterparts. Allostatic load reflects chronic wear and tear on the body indexed by systematic physiological dysregulation across multiple biological systems centrally involved in helping the body adjust to chronic physical and social demands. All of the above biological pathways as indicated in Figure 1.1 provide potentially fruitful explanations for how poverty gets under the skin early in life.

## SES and Biological Mechanisms During Adulthood

### *Sympathetic Nervous System*

As with research on SES and SNS activity in childhood, the vast majority of available evidence linking adult SES to differences in SNS activity reflects data on SES differences in blood pressure. Dating back to the 1960s, these data largely document consistently inverse relationships with higher average levels of blood pressure evident among those of lower SES, particularly in more developed countries such as the United States, the UK, and Canada (see Kaplan & Keil, 1993, and Colhoun et al., 1998, for reviews). Exceptions to these trends tend to come from less developed countries, where there is no difference or where even positive associations are occasionally found (Fernald & Adler, 2008; see also Colhoun et al., 1998, for review). In addition to links between individual-level SES and blood pressure, evidence also suggests that neighborhood-level SES is also independently and inversely related to blood pressure—those living in more disadvantaged areas exhibiting higher blood pressure (Chaix et al., 2010; Chaix et al., 2008; Cubbin et al., 2001; Cozier et al., 2007; Diez-Roux et al., 2000; Harburg et al., 1973; McGrath et al., 2006).

Lower SES has also been related to patterns of greater blood pressure reactivity, monitored under both controlled laboratory challenge and naturalistic, ambulatory conditions in most (Steptoe, Kunz-Ebrecht, Owen, Feldman, Willemssen, Kirschbaum et al., 2003; Steptoe, Feldman, et al., 2002) but not all studies (Carroll et al., 1997; Matthews et al., 2000; Light et al., 1995; Gallo et al., 2004). One

study also found that reported reductions in financial strain over time were associated with parallel reductions in systolic blood pressure (SBP) reactivity in men and women aged 47–59 (Steptoe, Brydon, & Kunz-Ebrecht, 2005). More detailed assessments of relative sympathetic and parasympathetic activity based on tracking of heart rate variability (HRV) have also yielded evidence for poorer autonomic system regulation and associated with increased risk for cardiac problems (Dekker et al., 2000; Liao et al., 1995; Tsuji et al., 1996). Failure to exhibit nocturnal dipping of blood pressure—another index of poorer autonomic down-regulation that has been associated with increased cardiovascular risk (Ingelsson et al., 2006; Spruill et al., 2009; Ben-Dov et al., 2007) has also been found to be more common among those of lower SES (Spruill et al., 2009; Stepnowsky et al., 2004).

Direct assessments of neuroendocrine components of the SNS such as norepinephrine and epinephrine via urinary and, most recently, saliva assays for catecholamines provide further evidence linking adult SES to differences in SNS activity. Several studies of U.S. adults have reported inverse associations, with those of lower SES excreting greater amounts of urinary free norepinephrine and epinephrine over 12- and 24-hour periods (Janicki-Deverts et al., 2007; Cohen, Doyle, et al., 2006; Seeman et al., 2004). How these disparities in hormone concentrations reach the genome of relevant cells to affect tissue function remains unclear (Miller, Chen, & Cole, 2009). Gene expression profiling studies of the type done with children are needed to address this question.

### *Hypothalamic-Pituitary-Adrenal Axis*

Collection of 12-hour, overnight urines in several studies has provided integrated measures of urinary free cortisol during a period of the diurnal cortisol cycle when optimal HPA axis regulation calls for lower levels of activity. Studies in the United States have shown the expected inverse gradient, with higher levels of urinary cortisol among lower-SES groups (Gruenewald et al., in press; ). By contrast, studies of older Taiwanese (Dowd & Goldman, 2006) and older Costa Ricans (Rosero-Bixby & Dow, 2009) have yielded evidence for greater HPA activity among those of higher SES. Reasons for these unexpectedly positive gradients remain unclear, though some have speculated that they reflect the heightened stresses that may be

experienced initially among those of higher SES as a country moves through periods of rapid development and social change, where social status may be subject to greater flux. If so, such processes would mimic those documented in studies of shifts in cardiovascular risk profiles among male primates in the face of social status disruptions, where the greatest increases in risks were seen not among the lower status males but among the higher status males, whose status was threatened by the disruptions in group membership (Kaplan & Manuck, 1999).

A larger and growing body of evidence based on salivary protocols that yield data on diurnal rhythms of cortisol provides evidence largely consistent with the idea that lower SES is associated with less-defined diurnal rhythms (i.e., smaller morning rise and less decline) and with greater overall daily cortisol exposure. Brandtstadter and colleagues provided one of the first reports on SES gradients in salivary cortisol activity from a population-based study of adults aged 35–65 (Brandtstadter et al., 1991), finding higher morning cortisol (at 8 a.m.) among those of higher SES. Though initially seen as somewhat unexpected, as the general anticipation had been that SES would be associated with generally lower HPA axis activity, the research community has come to recognize that it is probably the diurnal rhythm of the axis that is critical to health and well-being, and that a more defined rhythm with a strong morning awakening response, followed by an equally defined decline to low levels by early evening and into the night may well be more salutary (Adam & Kumari, 2009). Consistent with this hypothesis, a recent multiethnic study in U.S. adults, aged 45–85, reported significantly lower cortisol levels on waking along with slower declines across the day for those with less wealth (Hajat et al., 2010). Similar findings of slower, flatter declines in cortisol among lower-SES groups have been reported for adults from the United States (Ranjit et al., 2005; Cohen, Schwartz, et al., 2006), UK (Kumari et al., 2010), and Sweden (Rosmond & Bjorntorp, 2000). Elevated cortisol levels during the working day have also been reported for men from lower-grade jobs in the Whitehall study (Steptoe, Kunz-Ebrecht, Owen, Feldman, Willemsen, Kirschbaum et al., 2003). This pattern of differences in morning waking responses and afternoon declines have been shown to result in significantly greater overall cortisol activity (i.e., greater total estimated area under the curve [AUC] for cortisol) among those of lower SES (Cohen, Schwartz, et al., 2006; Cohen, Doyle, & Baum, 2006; Li et al., 2007).

### *Inflammatory*

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### *Metabolic*

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### ***Inflammation and Immune Responses***

Multiple parameters of immune function, especially markers of inflammation, have been found to vary by SES—those of lower SES exhibiting poorer immune function and higher levels of inflammation. Elevations in markers of inflammation such as C-reactive protein (CRP), interleukin-6 (IL-6) and fibrinogen among those of lower SES have been most extensively documented in the United States and UK (Alley et al., 2006; E. Brunner et al., 1996; E. J. Brunner et al., 1997; De Boever et al., 1995; Gruenewald, Cohen, Matthews, Tracy, & Seeman, 2009; Hemingway et al., 2003; Ishizaki, Martikainen, Nakagawa, & Marmot, 2000; Jousilahti, Salomaa, Rasi, Vahtera, & Palosuo, 2003; Kivimaki et al., 2005; Koster et al., 2006; Loucks et al., 2006; Lubbock, Goh, Ali, Ritchie, & Whooley, 2005; Markowe et al., 1985; McDade et al., 2006; McDade, Lindau, & Wroblewski, 2011; Nazmi & Victora, 2007; Owen, Poulton, Hay, Mohamed-Ali, & Steptoe, 2003; Panagiotakos et al., 2004; Petersen et al., 2008; Pollitt et al., 2007, 2008; Rathmann et al., 2006; Steptoe, Kunz-Ebrecht, Owen, Feldman, Rumely, Lowe, et al., 2003; Steptoe, Owen, Kunz-Ebrecht, & Mohamed-Ali, 2002; Wamala, Murray, et al., 1999; T. W. Wilson et al., 1993), but parallel SES gradients have also been documented in Greece (Panagiotakos et al., 2004) and India (Yudkin et al., 1999). At least one study has also reported greater and more prolonged IL-6, proinflammatory up-regulation in response to a laboratory stressor among lower-SES men (Brydon et al., 2004). Additional proinflammatory cytokines such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-1 receptor antagonist (IL-1Ra), and hemostatic factors such as factor VII (FVII), von Willebrand factor (vWF), and plasminogen activator inhibitor-1 (PAI-1) have also been reported to increase with decreasing SES (Wamala, Murray, et al., 1999; Steptoe, Owen, et al., 2002).

### ***Metabolic Processes***

SES has also shown consistent inverse associations with multiple parameters of metabolic function. As two comprehensive reviews document (McLaren, 2007; Sobal & Stunkard, 1989), a large evidence base links lower SES to greater prevalence of obesity and other indices of excess relative weight. Similar gradients of increasingly poor profiles of metabolic function among those of lower SES have been reported, with higher fasting and postload glucose (E. J. Brunner et al., 1997; Matthews et al., 1989), higher fasting triglycerides (E. J. Brunner et al., 1997; Matthews et al., 1989), higher low-density

lipoproteins and lower high-density lipoproteins (Matthews et al., 1989; Wamala et al., 1997). Not surprisingly, additional consequences of these patterns include increased levels of diagnosed diabetes among lower-SES groups (Everson, Maty, Lynch, & Kaplan, 2002; Guize et al., 2008; Lidfeldt, Li, Hu, Manson, & Kawachi, 2007; Maty, Everson-Rose, Haan, Raghunathan, & Kaplan, 2005; Maty, Lynch, Raghunathan, & Kaplan, 2008) as well as an increased prevalence of the metabolic syndrome (i.e., the combination of hypertension, obesity, dyslipidemia, and hyperglycemia) (Loucks et al., 2007; Wamala, Lynch, et al., 1999; Chichlowska et al., 2009; Brunner et al., 1997).

### ***Allostatic Load***

Consistent with the pervasive SES gradients in risks seen in the various major regulatory systems reviewed above, these cumulative risk indices all show consistent SES gradients, with significantly higher cumulative risk scores seen among those of lower SES across the adult life span (Crimmins et al., 2009; Geronimus et al., 2006; Karlamangla et al., 2005; Seeman et al., 2008; Singer & Ryff, 1999). Recent evidence also suggests that both childhood and adult SES contribute to levels of adult allostatic load (Gruenewald et al., in press). More macrolevel neighborhood SES also appears to contribute to levels of adult allostatic load, with residents of lower-SES neighborhoods exhibiting higher allostatic load, independent of their individual SES (Merkin et al., 2009; Bird et al., 2010).

### ***Summary***

As is the case with children, many critical health-related biological parameters track social standing among adults. Numerous studies reveal an inverse association between adult SES and resting blood pressure. A smaller number of studies suggest a mixed pattern of findings with respect to cardiovascular dynamics. Some studies show muted cardiovascular reactivity to an acute stressor (e.g., giving a public speech), whereas others find the opposite SES-reactivity relation. Parasympathetic mechanisms that downwardly regulate cardiovascular mobilization to external demands appear to be less efficient among lower-SES adults. Several studies reveal elevated catecholamine stress hormones among lower-SES adults, which, similar to elevated basal blood pressure, indicates heightened SNS activation. Lower-SES adults manifest less-defined diurnal rhythms (i.e., smaller morning rise and less decline) and in most studies show a greater overall



expenditure of daily cortisol. Multiple parameters of immune function, especially markers of inflammation, have been found to vary by SES—those of lower SES exhibiting poorer immune function and higher levels of inflammation. A large evidence base links lower SES to weight gain. The metabolic syndrome and its specific constituents including total cholesterol, glucose, triglycerides, LDLs, and HDLs, are associated with SES as well. A few studies also indicate higher levels of allostatic load among lower- relative to higher-SES adults.

### Childhood SES and Adult Biological Mechanisms

Life course exposure to SES (see Figure 1.1) implies that the timing as well as the duration of exposure is important to health. Linkages between SES and ill health in adulthood appear to begin in early childhood (Cohen et al., 2010). If biological mechanisms underlie these life course pathways, then we would expect to see that childhood SES can affect adult biological mechanisms. Studies that have examined this topic are reviewed in this section. Note that most but not all of these studies examine childhood SES and adult biological mechanisms, statistically controlling for adult SES. This is important in order to demonstrate that early childhood is a particularly important developmental period during which SES affects health over the life course.

### Sympathetic Nervous System

Independent of adult SES, childhood SES predicts adult blood pressure (Blane et al., 1996; Hardy, Kuh, Langenberg, & Wadsworth, 2003; Lehman et al., 2009). Furthermore, the degree of elevation over time is more rapid, particularly for SBP, among adults from a low-SES childhood (Hardy et al., 2003; Lehman et al., 2009). The patterning of change in biological mechanisms over time is relevant to the unfolding of disease processes. If the accumulation of multiple hits to the system are leading to pathogenetic outcomes, then one would expect to see an acceleration of shifts in biological processes over time, as found by Hardy and Lehman, respectively (see Figure 1.1).

We uncovered three investigations of cardiovascular dynamics in adults as a function of childhood SES. Williams and colleagues (2008) showed elevated blood pressure reactivity to an acute stressor among adults whose father had lower education. This effect was independent of current adult educational attainment. Wilson et al. (2000) found

that elevated reactivity to a competitive video game among adolescent African Americans in low- versus high-SES neighborhoods only occurred for the subset of youth from families with low parental educational attainment. Finally, Taylor and colleagues (Taylor, Lerner, Sage, Lehman, & Seeman, 2004) reported elevated blood pressure activity in males but not females to an acute stressor as a function of childhood SES.

### Hypothalamic-Pituitary-Adrenal Axis

For both men and women, lifetime SES (birth–42 years of age) was inversely related to cortisol levels at age 45 (Li, Power, Kelly, Kirschbaum, & Hertzman, 2007). Only men, however, revealed an effect of childhood SES after controlling for adult SES. For women neither childhood or adulthood SES by itself was related to cortisol levels at age 45. Total lifetime SES from birth to age 42, however, was inversely related to 45-year-old women's cortisol levels. The above gender differences in life course exposures hints at the relative salience of early embedding or programming compared to accumulation of risk exposures to characterize how early deprivation gets under the skin and stays there. For men it appears that early SES experience sets the organism on an HPA trajectory that is somewhat independent of subsequent experiences, whereas for women both early and subsequent experiences tied to SES appear salient, suggesting support for an accumulation model (see Figure 1.1). Gustafsson, Janlert, Theorell, and Hammarstrom (2010) examined a cohort of Swedish men and women at age 43 with cortisol measures taken previously during childhood. The awakening cortisol response at age 43 was most pronounced among adults from lower-SES homes at age 16, and this held independently of subsequent occupational status measures during adulthood. Taylor and colleagues (Taylor et al., 2004) found that both basal cortisol and elevations in response to an acute stressor were elevated in college students who reported lower SES in childhood. Interestingly, these effects were mediated by earlier experiences of harsh, unsupportive parenting.

Miller and Chen (2007) explored whether the primary receptor for white blood cell expression of cortisol might have been altered by early experiences of deprivation. In a sample of 13- to 19-year-olds, adolescents whose family had not owned a home when they were 2 years of age had reduced levels of glucocorticoid receptor messenger RNA compared to youth from more affluent backgrounds. Lack of

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### *Inflammation and Immune Responses*

Two large-scale epidemiological studies in the UK and the United States, respectively have examined childhood SES and multiple indices of inflammation in adults. Fibrinogen, C-reactive protein, von Willebrand factor antigen, and a tissue plasminogen activator antigen were assessed in a British birth cohort. SES at birth significantly predicted all four of these indices, controlling for concurrent, adult SES (Tabassum et al., 2008). In a U.S. sample of middle-aged adults, retrospective reports of childhood SES were associated with C-reactive protein, fibrinogen, white blood cell count, and von Willebrand factor (Pollitt et al., 2007). As in the UK study, these relations held independently of concurrent adult SES. Analysis of Whitehall data revealed that parental occupation predicted offspring's adult fibrinogen levels, independently of current occupational grade among British civil servants (Brunner, Davey Smith, et al., 1996). In another sample of middle-aged adults, parental educational attainment was significantly related to C-reactive protein (Taylor, Lehman, Kiefe, & Seeman, 2006).

Much of the immunologic research on SES has focused on inflammatory mediators as a potential

explanatory mechanism because of their presumptive role in the pathogenesis of cardiovascular disease and other chronic conditions. However, some intriguing data suggest that childhood SES may also play a role in shaping the immune system's capacity to resist what are typically more acute challenges from infectious pathogens. In one study, healthy adults were quarantined and after 24 hours given viruses that cause the common cold (Cohen, Doyle, Turner, Alper, & Skoner, 2004). Independent of adult SES, adults whose parents did not own a home were more likely to develop a cold, assessed both by symptoms and by serological analysis while remaining quarantined for five more days. Moreover, subjects whose parents did not own a home in years 1–9 were especially sensitive to viral exposure. In an interesting supplemental analysis, the magnitude of the association between parental home ownership and developing a cold was linearly related to the age of parental home ownership. The earlier in the adults' life the parent rented, the stronger the association suggesting the potential for early experiences of deprivation to become embedded into the biology of the body (Figure 1.1).

In addition to their analysis of glucocorticoid mRNA, Miller and Chen (2007) also examined whether childhood SES was related to mRNA for TLR4, a toll-like receptor centrally involved in inflammatory response regulation. TLR4 instigates leukocyte inflammatory responses to endotoxins. Adolescents (13–19 years) from low-SES families had higher quantities of TLR4, mRNA. The higher levels of this molecule could explain why those from low-SES childhood backgrounds have more systematic inflammation and greater susceptibility to the common cold. Cold symptoms largely stem from local production of inflammatory cytokines.

In another study with adults from low-SES backgrounds, Miller and colleagues (Miller, Chen, Fok, et al., 2009) found up-regulation of CREB and NF $\kappa$ B responsive genes, suggesting that early deprivation has a lingering influence on catecholamine signaling to cells of the immune system, as well as activation of the transcriptional pathways that orchestrate inflammation. Given the extensive cross talk between the HPA axis, the SNS, and immune cells, all of these patterns could stem from the diminished cortisol-mediating signaling the authors reported in this sample, as highlighted in the previous section. Finally, to evaluate the functional significance of these patterns, Miller and colleagues challenged respondents' immune cells in vitro with various microbial stimuli. Respondents

from low-SES backgrounds had relatively elevated cytokine responses to both viral and bacterial stimuli *in vitro*.

Collectively these studies indicate that low childhood SES predisposes individuals to proinflammatory tendencies in adulthood. Their innate immune cells show increased resting activity of transcription control pathways that orchestrate inflammation, and decreased resting activity of pathways that counter-regulate inflammation. At the same time these cells have greater cytokine reactivity to selected pathogens *in vitro*. These tendencies may explain the relative increase in systemic inflammatory markers seen in most studies of low childhood SES, as well as the greater vulnerability of colds in the Cohen et al. (2004) study.

### *Metabolic Processes*

A number of studies have uncovered evidence that childhood SES predicts BMI later in life (Laaksonen, Sarlio-Lahteenkorva, & Lahelma, 2004; Langenberg, Hardy, Kuh, Brunner, & Wadsworth, 2003; Moore, Stunkard, & Srole, 1962; Poulton et al., 2002; Power, Graham, et al., 2005; Power, Manor, & Matthews, 2003). All of these studies but Moore et al. (1962) also control for adult SES. Lee, Harris, and Gordon-Larsen (2008) showed that SES in 15-year-olds was related subsequently to obesity in female but not male adolescents at ages 16 and 21. Of additional interest in examining transitions from 16 to 21 years of age, lower SES at age 15 was positively associated with becoming obese and staying obese.

Turning to other individual metabolic risk parameters and SES, several studies have uncovered evidence of childhood SES influences on adult risk factors. Two studies have uncovered positive associations between father's occupational status during childhood and current HDL levels in adults, independent of concurrent SES (E. Brunner, Shipley, Blane, Davey Smith, & Marmot, 1999; Wanamethee, Whincup, Shaper, & Walker, 1996). Findings on total cholesterol are more mixed, however (Blane et al., 1996; E. Brunner et al., 1999; Wanamethee et al., 1996). In a particularly interesting study because of participants' ages, Lawlor, Ebrahim, and Davey Smith (2002) examined a sample of healthy British women 60 years of age and above. Father's occupational status during childhood, independent of respondent's level of highest occupational attainment in adulthood, was significantly related to insulin resistance, HDL, and triglycerides. The investigators then took their analyses

a step further, classifying women into four groups based on combination of childhood and adulthood occupation: childhood father manual/nonmanual occupation by adult household manual/nonmanual occupation. The trends reveal two interesting facts. First, childhood occupational status had greater influence than adulthood occupational status on insulin resistance, dyslipidemia, and obesity. Second, there were cumulative effects such that the combination of childhood and adulthood lower SES was particularly problematic. For example, compared to women who were never in a low-SES household, those persistently in lower-SES circumstances were 58% more likely to be insulin resistant, 99% more likely to have low HDLs, 59% more likely to have high triglycerides, and 238% more likely to be obese. These results suggest the operation of embedding with early experiences being critical but also cumulative exposure, since early deprivation plus subsequent deprivation exacerbated the apparent low-HDL trajectory created by deprivation early in life. Thus, when examining the second link in the chain between SES and health over the life course (see Figure 1.1), there is evidence that both embedding and accumulation occur.

Childhood SES at age 4 was significantly related to the metabolic syndrome of adult women, but not men, in a longitudinal birth cohort study in the UK (Langenberg, Kuh, Wadsworth, Brunner, & Hardy, 2006). This prospective association was independent of adult SES. The UK investigators also reported data on individual components of the metabolic syndrome and found the same prospective effects of childhood SES on adult women's HDL and body fat.

### *Allostatic Load*

Singer and Ryff (1999) found an inverse association between income over the life course and adult allostatic load at age 60. Adults from low-income childhood families were significantly more likely to have high allostatic load scores at age 60 than their counterparts from relatively affluent childhood backgrounds. Parallel results existed when comparing allostatic load at age 60 with middle-age income status. The authors then took their analyses a step further, examining SES pathways over the life course (childhood income low/not low; middle-age income low/not low) in relation to allostatic load at age 60. Individuals from low-income childhood background who remained poor during middle adulthood had the highest levels of allostatic load at 60 (50%). Interestingly, the next highest elderly

group with high income in adulthood was not from middle adulthood but from middle childhood. The remaining individuals in the more affluent income, high education, high equivalent variation proclivity group (Gustafsson, Theorell, & Westerlund, 2003) were examining all results indicating exposure at age 4 to a developmental load at age 4 or any other time to a developmental load. Evidence for this is discussed above, the accumulation of more consequences than a critical load, thus favoring a dynamic

### *Summary*

A life course approach entails close scientific attention to the SES-biological link. In this section we have reviewed life exposure to SES and its parameters. Subsequent studies suggest that early life exposure to SES is difficult to alter subsequently. The effect of adult SES, however, is more malleable. A study that early childhood adult HPA axis activity is caused by diminished glucocorticoid exposure in adulthood, and of inflammation in conjunction with the inflammatory response. The innate immune system has greater cytokine activity *in vitro*. Low childhood income and increases in the metabolic syndrome. Metabolic dysregulation accumulates with age. Early in life def

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group with high allostatic load scores (43%) were individuals with low-income during middle age but from more affluent childhood backgrounds. The remaining two groups (low childhood income/more affluent middle-age income; high childhood income, high middle-age income) had lower but equivalent proportions of high allostatic load scores. Gustafsson and colleagues (Gustafsson, Janlert, Theorell, Westerlund, & Hammarstrom, 2011) examining allostatic load at age 43 found similar results indicating that the accumulation of low-SES exposure at ages 16, 21, 30, and 43 predicted allostatic load at age 43 better than SES during adolescence or any other age period. Note that in contrast to a developmental pattern that we have seen some evidence for in other physiological mechanisms discussed above, both of these data sets suggest that the accumulation of exposure to disadvantage rather than a critical period of early in life poverty was more consequential for allostatic load later in life, thus favoring an accumulation rather than embedding dynamic effects over the life course.

### Summary

A life course perspective on poverty and health entails close scrutiny of the timing and duration of SES-biological pathways (see Figure 1.1). In this section we have reviewed the evidence that early-life exposure to disadvantage can affect biological parameters subsequently in adulthood. Most of these studies suggest that exposure to disadvantage during infancy sets individuals on a health trajectory that is difficult to alter even when upward social mobility subsequently occurs. For example, independent of adult SES, childhood SES predicts adult blood pressure. A small number of studies also suggest that early childhood SES is related prospectively to adult HPA activity. This HPA dysregulation may be caused by diminished cortisol-mediated signaling in glucocorticoid receptors. Low childhood SES predisposes individuals to proinflammatory tendencies in adulthood, reflected by increased resting activity of inflammation transcription control pathways in conjunction with decreased resting activity of counterinflammatory control circuits. At the same time the innate immune cells of lower-SES adults have greater cytokine reactivity to selected pathogens *in vitro*. Low childhood SES also predicts adult weight and increases the chances one will suffer from metabolic syndrome. The effects of SES exposure on metabolic dysregulation start early and appear to accumulate with longer exposure to disadvantage. Early in life deprivation may also lead to subsequent

elevated allostatic load, but more work is needed to replicate the initial suggestive findings described above. Some biological pathways may be more susceptible to embedding from early experiences (e.g., SNS, HPA) whereas others (e.g., metabolic) may function jointly in response to early experiences of deprivation and subsequent shocks to the system as one matures.

### Durability of Childhood SES and Morbidity Over the Life Course

The evidence that low childhood SES is associated with excess morbidity and mortality late in life raises questions about underlying biological mechanisms that can explain how a social experience early in life comes to have persistent effects on health into adulthood. Researchers have posited two broad classes of models to explain in conceptual terms how this phenomenon might arise. As depicted in Figure 1.1, these are embedding and accumulation.

### Biological Embedding Models

Drawing on concepts that were developed in the fetal-origins literature (Barker, 1992), some theorists have proposed that the early years of childhood represent a critical period during which adversity can become "embedded" or "programmed" into biological systems in a manner that persists across the life span and thereby accentuates vulnerability to disease (Finch & Crimmins, 2004; Hertzman, 1999). The fetal-origins literature provides compelling evidence that such programming can occur, at least when animals are exposed to nutritional imbalance in utero through manipulation of maternal diet or administration of glucocorticoids (Gluckman & Hanson, 2006). There is also robust evidence from animal studies that early-life stressors that are more psychological in nature can have lasting effects on the activity of the HPA axis, the SNS, and some immune functions (Coe & Lubach, 2005; Levine, 2005; Newport et al., 2002). In some cases these programming effects have been shown to influence the development or expression of chronic diseases in animal models of ulcers, asthma, and some cancers (Ackerman et al., 1975; Ader et al., 1960; Chida et al., 2007; Kruschinski et al., 2008).

In recent years there has been a surge of interest in the mechanisms that might underlie this embedding process. Much of the attention has focused on epigenetic modifications, which are stable changes in a gene's activity that arise without alterations to its DNA sequence (Jirtle & Skinner, 2007). A primary function of epigenetic alterations is to allow

cells to develop and maintain specialized functions. Epigenetic alterations occur in two main ways: methylation of the DNA itself or remodeling of the chromatin structure (Whitelaw & Garrick, 2006). In methylation, enzymes cause methyl groups to bind to cytosine residues, often in promoter regions, which control whether a gene is switched on. The methyl groups can prevent regulatory molecules from binding to the promoter, the effect of which is to either suppress or enhance the rate of transcription. Chromatin remodeling involves various chemicals attaching to (or detaching from) the histone proteins around which DNA is wrapped in the cell's nucleus. These chemicals cause the DNA near the gene to become more or less tightly wrapped around the histones. This affects how easily regulatory molecules can access the promoter to initiate transcription. As is evident, both types of epigenetic alterations operate by changing the rate at which a particular gene is transcribed, and as a result the amount of its mRNA and protein that will be available to the cell. Perhaps most relevant to the programming hypothesis, some epigenetic modifications appear to be mitotically heritable, and thus remain stably embedded in tissues across the life span (Reik, 2007).

A landmark series of studies by Meaney and Szyf implicated epigenetic mechanisms in the programming of early social experience (Szyf et al., 2008). This group drew on a long line of studies showing that neonatal rodents who are handled daily exhibit diminished cortisol responses to stress when they reach adulthood (Levine, 2005). They found that this enhanced regulation of the hormonal stress response was attributable to epigenetic processes, including demethylation of DNA and acetylation of histone proteins, that facilitated expression of the glucocorticoid receptor gene in hippocampal tissue (Weaver et al., 2004). HPA axis activity is regulated by a negative feedback circuit, wherein cortisol binds to hippocampal glucocorticoid receptors, and in doing so inhibits release of corticotropin-releasing factor, which is the first step in a hormonal cascade that turns on the axis. These findings provide an elegant demonstration of how early experience can get epigenetically programmed into a biological system in a manner that persists across time.

That said, it remains unclear how well these findings translate into the human experience of low SES, and whether the phenotypic changes they create are sufficient to modify disease risks. The microarray studies described in earlier sections of this chapter provide some initial evidence relevant to these

questions, suggesting that early socioeconomic disadvantage leaves an imprint on the leukocyte transcriptome that persists into adulthood (Miller, Chen, Fok, et al., 2009). Whether these effects arise because of SES-induced epigenetic modifications remains unclear. Future research will have to address this issue as well as the clinical relevance of the identified transcriptional disparities.

A general weakness of the embedding hypothesis is that it fails to consider factors beyond early life, thereby treating people as somewhat passive victims of the biology their childhood social climate imbues. To us it seems quite likely that early life socioeconomic circumstances shape not only biology, but also the kinds of environments individuals seek out (and create) for themselves in adulthood, as well as the ways in which they respond to challenges that arise from those environments. Thus early-life conditions could shape ensuing environmental features like housing and neighborhood quality, in addition to later behaviors and social interactions, which themselves have implications for biological processes. From their early social context people develop likes and dislikes, patterns of interacting with others, strategies for regulating their desires and emotions, and ways of dealing with the slings and arrows that life throws at them (Bowlby, 1969; Cassidy & Shaver, 1999; Luecken & Lemery, 2004). From infancy through adulthood these tendencies, and the experiences that arise from them, modulate a variety of disease-relevant behavioral and biological processes (Chen et al., 2002; Repetti et al., 2002; Shonkoff et al., 2009). A complete model thus needs to articulate how early experience sets people on life trajectories that result in varying degrees of exposure to disease-relevant stimuli.

### *Accumulation and the Life Course Epidemiology Approach*

The other class of models that has been used to explain the health effects of childhood stress comes from life course epidemiology (Lynch & Smith, 2005). These models emphasize the pathways that childhood SES sets people on, as well as the cumulative effects that they are likely to have on risk for diseases in adulthood (Pollitt et al., 2005). The pathway models focus on the ability of early life experiences to set people on trajectories of advantage and opportunity, or lack thereof. These trajectories are referred to as "chains of risk" (Kuh & Ben-Shlomo, 2004) and "accumulating chains of advantage or disadvantage" (Blane, 1999). The notion inherent in these models is that adversity

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 e models is that adversity

begets adversity. A child raised in poverty is likely to attend a school with limited financial resources and receive a suboptimal education. This in turn makes it likely that s/he will be a low-income adult, have a job with routine exposure to pollutants and irritants, live in a neighborhood where fresh foods are hard to find, green spaces for exercise are not available, access to health care is limited, and so on (Evans, 2004). These exposures affect health in a cumulative fashion.

The other class of models arising from the life course approach emphasizes the health effects of cumulative adversity (Hertzman, 1999; Pollitt et al., 2005). These models posit that the more low SES a person experiences, the more likely he or she is to develop the target disease. Some versions of these models propose that periods of low SES have additive influences on health, whereas others emphasize more complex interactive and synergistic effects (Kuh & Ben-Shlomo, 2004). What unites the stricter versions of these models is the underlying assumption that timing is unimportant. What matters for health is the duration of disadvantage experienced, not when it occurs. Although the assumptions about timing have not yet been tested thoroughly, there is a good deal of evidence for the basic accumulation hypothesis. The more of their lives that individuals spend in low SES, the more likely they are to show risky profiles of the type we have outlined—for example, more cortisol output and systemic inflammation, worse glucose control and cholesterol profiles, high blood pressure and poor health behaviors, and greater rates of metabolic syndrome, higher allostatic load, and morbidity and mortality from cardiovascular disease (Chichlowska et al., 2009; Evans & Schamberg, 2009; Gustafsson, Janlert, Theorell, & Hammarstrom, 2010; Gustafsson, Janlert, Theorell, Westerlund, & Hammarstrom, 2011; Li et al., 2007; Pollitt et al., 2005; Pollitt et al., 2007).

The life course models are appealing in their emphasis on the trajectories initiated by early SES and on the health effects of exposures over the entire life course. That said, neither accords any special influence to exposures that occur during early childhood, which seems like an important oversight given the mounting evidence of biological programming in both studies of SES and human SNS dysregulation, elevated HPA axis, inflammation and immune responses, metabolic response systems, and allostatic load (see section above, "Childhood SES and Adult Biological Mechanisms," for more details) and stress more broadly in animals (Ackerman et al., 1975;

Ader et al., 1960; Cameron et al., 2005; Chida et al., 2007; Fenoglio et al., 2006; Kruschinski et al., 2008; Lyons et al., 2009).

## Comparing the Models

Studies that have sought to compare the validity of the models have found support for both embedding and accumulative life course scenarios (Galobardes et al., 2008; Pollitt et al., 2005). When they are considered together, the comparative studies suggest two conclusions. First, cumulative disadvantage is a robust predictor of morbidity and mortality across many diseases, regardless of childhood SES (Lynch & Smith, 2005). Second, there is excess disease risk conferred by low childhood SES, which is not completely explained by cumulative disadvantage, or abrogated when people have upward social mobility (Chen et al., 2010; Hart et al., 2000; Kuh et al., 2002; Ljung & Hallqvist, 2006; Pensola & Martikainen, 2003; Power, Hypponen & Smith, 2005; Smith et al., 1998). These findings are viewed as evidence for a critical-period model, in which "it matters how and when" people are exposed to low SES (Ljung & Hallqvist, 2006, p. 1082). Note, however, such findings do not settle whether biological embedding itself is the causal mechanism for disease; childhood could be emerging as a critical period for other as yet unknown reasons.

Despite the efforts these comparative studies have made, it turns out to be exceedingly difficult to disentangle these models empirically (Hallqvist et al., 2004). The problem here is overlap. Within most populations, it is difficult to form mutually exclusive categories of individuals who had the relevant exposures necessary for comparisons to be made, that is, those who were low SES in childhood but had upward mobility in adulthood versus those who were poor across the life span. Without having the ability to randomize people to low SES at varying points in the life course, it will be difficult for researchers to definitively settle this issue in humans. Intervention studies that provide cash transfers to families with young children could theoretically help tease these effects apart (Fernald et al., 2009), particularly if they varied the development stage at which the transfer occurred. Animal models would also seem to be particularly helpful in resolving this issue as they can systemically manipulate the timing and duration of exposure to adversity in early life.

Indeed, animal studies using this approach suggest the existence of critical periods for a number of biological processes we have discussed as plausible mediators. For example, in rodents the first 8 days



of life represent a specific window during which the quality of maternal care has potent and lasting influences on responsivity of the HPA axis to stress and the density of hippocampal glucocorticoid receptors that regulate it (Hess et al., 1969; Meaney & Aitken, 1985; van Oers et al., 1997). Stress over the second week of life has less potent effects, and when given in the third week, has no influence whatsoever on hippocampal glucocorticoid receptor expression (Meaney & Aitken, 1985). Most relevant to the argument about the role of cumulative exposure, this work reveals that adult HPA responsivity is equivalent in animals exposed to stress during week 1 versus weeks 1–3 of life (Hess et al., 1969; Meaney & Aitken, 1985). Besides this work on HPA activity, studies of disease have pointed to specific developmental windows during which maternal separation enhances later vulnerability to peptic ulcers and implanted tumors (Ackerman et al., 1975; Ader et al., 1960). Collectively, this work provides evidence that early stress has direct and lasting influences on some disease-relevant biological processes, which are not simply a function of boosting total lifetime exposure to adversity.

### Future Directions and Intervention Implications

The research reviewed above provides evidence for robust links between SES and biological mechanisms relevant to disease across the life course. In this section, we discuss directions and next steps that this research should take.

If poverty and low SES affect adult morbidity and mortality because of alterations in biological mechanisms, then we should expect biological mechanisms to mediate the SES → Morbidity pathway. Furthermore biological mechanisms early in life should prove particularly promising in explaining the development of health disparities among adults from varying backgrounds. Unfortunately what little data are available tend to be cross-sectional and restricted to a limited set of biological mechanisms assessed during adulthood as they predict mortality. The preponderance of findings from such studies indicates little or no mediation of the SES → Mortality gradient by biological mechanisms (Davey Smith, Shipley, & Rose, 1990; Dennis et al., 1993; Rose & Marmot, 1981; Rutledge et al., 2003; Salonen, 1982; Pocock, Shafer, Cook, Phillips, & Walker, 1987). The lack of mediational findings that account for the SES → Mortality pathway may be because earlier studies examined a limited range of biological pathways. More recent studies with a

broader panel of mechanisms have been more successful in documenting mediational effects. For example, SES disparities in all cause and cardiovascular mortality in Finnish men were significantly attenuated by the inclusion of a large set of 15 biomarkers (Lynch et al., 1996). A more recent study compared allostatic load to specific constituents of biological risk to account for SES-related mortality (Seeman et al., 2004). This study has two additional features of interest. First, 7.5-year mortality was examined in a cohort of healthy elderly men and women between 70 and 80 years of age. As expected, adult SES was related to mortality. This effect was mediated by allostatic load (an additive index of 16 biological risk factors). Second, there was little or no evidence of mediation by any one of the 16 singular risk factors—only the allostatic load composite index appeared to explain the SES–mortality link among their elderly sample. Clearly, a priority area of future investigation is longitudinal work examining whether SES impacts on morbidity and mortality are explained by alterations across multiple physiological mechanisms.

In addition, a biological approach to SES and health research increasingly requires collaboration across disciplines spanning from epidemiology and sociology down to immunology and molecular biology. Collaborations with basic scientists allow for the most up-to-date technologies and knowledge about disease pathogenesis to be incorporated into studies investigating SES effects on biological mechanisms. At the same time, the smaller-scale studies typically utilized by researchers investigating biological mechanisms would benefit from a broader, population-based approach that would allow researchers to ascertain the generalizability of findings to the population as a whole.

In line with this idea, there are a number of nationally representative, population-based studies that were not initially designed to collect biomarker data, but which are now incorporating more in-depth mechanistic assessments into follow-up waves of data collection (e.g., National Longitudinal Study of Adolescent Health, Add Health; Midlife in the United States, MIDUS; Health and Retirement Study). This approach has provided the field with important population-level understandings of SES and candidate biological mechanisms (Dowd & Aiello, 2009; Friedman & Herd, 2010). To the extent these assessments can be incorporated into future waves, we will continue to learn more about the specific pathogenic processes that are shaped by SES.

In addition, a new wave of studies involve longitudinal designs that incorporate in-depth SES assessments across multiple generations (e.g., Dynamics, PSID; SAGE). These studies would be especially important to address life course mechanisms that truly address life course effects on the same participant over a lifetime affect in disease? How does biological markers over a lifetime affect biological perturbations for health disparities?

Another important area of research is population-based studies that adequately test for the role of individual differences in the consequences of low SES. Preliminary patterns of findings suggest the need for further studies. Early childhood course in cross-sectional studies is inconsistent vulnerability to disease. A critical missing piece is longitudinal data that can identify mechanisms including physiological responses, and metabolic and genomic processes seen in childhood. If transcriptional changes in early experiences of life are the case that heritability also alter vulnerability to disease. Kim-Cohen and colleagues (2002) and Caspi, & Taylor, 2005 show that this in childhood SES. Metabolic activity in adulthood may be moderated by more consistent involvement in obesity among white adults. Finally, several studies suggest protective effects of response and richer social support that buffer the SES and morbidity link, suggesting that socially supported SES → Biological Mechanisms.

In order to better understand the relationship between SES and biological mechanisms, research addressing the role of social support in helping bring broad social support to the level of the

have been more succedential effects. For all cause and cardiovascular mortality were significantly affected by a large set of 15 biological factors. A more recent study of specific constituents of the allostatic load or SES-related mortality risk in this study has two additional findings: first, 7.5-year mortality of healthy elderly men aged 65 to 80 years of age. As related to mortality. This is an additive factor (an additive factor). Second, there is no mediation by any one factor—only the allostatic load is needed to explain the SES–mortality link in the elderly sample. Clearly, the need for longitudinal studies to assess the impacts of SES on morbidity and mortality is underscored by alterations across mechanisms.

A new approach to SES and health requires collaboration from epidemiology and sociology and molecular biology and basic scientists allow the use of new technologies and knowledge to be incorporated into the study of SES effects on biological processes. In time, the smaller-scale studies by researchers investigating the mechanisms would benefit from a new approach that would maintain the generalizability of the findings as a whole.

Finally, there are a number of limitations to population-based studies that are now incorporating mechanistic assessments into the collection (e.g., National Longitudinal Adolescent Health, Add Health, United States, MIDUS; Health and Retirement Study). This approach has the important population-level and candidate biological mechanisms. (Miello, 2009; Friedman & Miello, 2009). These assessments can be used to identify specific pathogenic processes in SES.

In addition, a number of these national survey studies involve longitudinal collection of data from participants. Some of these that are considering incorporating biomarker assessments have in-depth SES assessments prospectively that span multiple generations (e.g., Panel Study of Income Dynamics, PSID; Sastry et al., 2009). These studies would be especially important to SES and biological mechanism research, as they would allow us to truly address life course questions. That is, within the same participants, how do fluctuations in SES over a lifetime affect biological processes involved in disease? How does SES affect trajectories of biological markers over time? And eventually, do these biological perturbations in relation to SES account for health disparities?

Another important advantage of larger scale, population-based studies is their ability to more adequately test for statistical interactions indicating individual differences in susceptibility to consequences of low SES. In our literature review above, preliminary patterns of data suggest several candidates for further in-depth analysis with larger samples. Early childhood and adult periods of the life course in cross-sectional studies show relatively consistent vulnerability to SES, whereas adolescents do not. A critical missing piece of evidence about this is longitudinal data. Work across several biological mechanisms including the HPA axis, inflammatory responses, and metabolic activity reveals evidence of genomic processes sensitive to SES in early childhood. If transcriptional dynamics are malleable by early experiences of deprivation, then it may also be the case that heritable genotypic differences can also alter vulnerability of biological systems to SES. Kim-Cohen and colleagues (Kim-Cohen, Moffitt, Caspi, & Taylor, 2004) have shown evidence for this in childhood SES with mental health outcomes. Metabolic activity in relation to childhood SES may be moderated by race, with some evidence of more consistent inverse relations between SES and obesity among white relative to black children and adults. Finally, several studies have uncovered protective effects of responsive parenting in childhood and richer social support networks among adults in the SES and morbidity and mortality links, suggesting that socially supportive relationships may alter SES → Biological Mechanism pathways.

In order to better understand relationships between SES and biological markers, we need more research addressing the psychosocial factors that can help bring broad social environment variables like SES to the level of the individual and serve as bridges

potentially linking SES to basic, biological processes at the individual level. Research in this area has been growing in recent years (Chen et al., 2002; Evans & Kim, 2010; Gallo & Matthews, 2003; Matthews et al., 2010; Miller, Chen, Fok, et al., 2009), and has identified a number of key psychosocial factors throughout the life course.

In childhood, the factors that contribute to SES-biology relationships include individual child characteristics such as threat appraisal tendencies and hostility, as well as family environment quality. Lower SES children are more hostile and also more likely to interpret ambiguous situations in a threatening manner, both of which explain greater cardiovascular responses to acute stressors (Chen et al., 2004; Gump et al., 1999). Threat appraisals also comprise one pathway between low SES and inflammatory responses in children with asthma (Chen et al., 2006). Low-income children are much more likely to contend with a confluence of multiple stressors or cumulative risk factors, which in turn have been linked to biological markers such as SNS and HPA activity as well as allostatic load (Evans & Kim, 2010). Early life adversities such as substandard housing or elevated instability in adult relationships are associated with greater elevations in cortisol from 7 to 48 months of age (Blair et al., 2011). In addition, chaos in the family contributes to increasing cortisol trajectories over time in low-SES youth (Chen et al., 2010). Early childhood adversity that is highly associated with SES has direct, adverse impacts on multiple biological markers (Repetti, Taylor, & Seeman, 2002). Moreover the adverse impacts of early adversity may be exacerbated by genetic vulnerabilities (e.g., short allele of serotonin transporter gene) (Taylor, Way, et al., 2006).

Life course models that investigate childhood SES links to adult biological profiles find that psychosocially, the childhood family environment also plays an important role in the persistence of SES effects. For example, more risky childhood environments (ones that are more conflictual, or neglectful and cold) are predictive of cardiovascular, cortisol, and inflammatory risk profiles in adulthood (Luecken et al., 2005; Luecken, 1998; Repetti et al., 2002; Taylor, Lehman, et al., 2006), and as well, explain associations of low childhood SES with these adult biological markers (Lehman et al., 2009; Taylor et al., 2004).

Among adults, psychosocial pathways that have received attention in explaining adult SES to adult biology associations include psychological stress



(in particular, job strain), negative emotions (e.g., depression, hostility), intrapersonal resources such as perceived control, as well as interpersonal resources such as social support (Cohen, Doyle, et al., 2006; Cohen, Schwartz, et al., 2006; Kubzansky et al., 1999; Kunz-Ebrecht et al., 2004; Marmot et al., 1997). The vast majority of studies that have investigated the psychosocial mechanisms of SES-biology relationships have focused on explaining concurrent associations of SES with biological markers. Hence future research needs to apply the knowledge gained from this research about plausible psychosocial mechanisms to a more in-depth understanding of life course processes in order to address questions such as: What specific psychosocial mechanisms explain how early childhood environments create persistent effects on biological profiles into adulthood? And what specific psychosocial mechanisms best explain how the accumulation of SES across a lifetime affects biological markers in adulthood?

Finally, the brain plays a central role in regulating stress responses to environmental demands (McEwen & Gianaros, 2010), and several scholars have postulated that early experiences with low SES might adversely affect brain development, with potential lifelong implications for health and well-being (Hackman & Farah, 2009; Hackman et al., 2010). One recent human neuroimaging study documented that young adult's subjective perceptions of their families' social standing during childhood predicted amygdala responses to angry faces in adulthood, such that the lower the perceived childhood status, the greater the amygdala reactivity in adulthood (Gianaros et al., 2008). These findings persisted after controlling for current SES, suggesting that early childhood experiences of relative deprivation attune the amygdala to be especially sensitive to anger or hostility in adulthood, irrespective of adult SES. These findings are particularly interesting in light of other research from this group, which shows that among middle-aged adults, amygdala reactivity covaries with preclinical atherosclerosis in the carotid arteries (Gianaros et al., 2009). Together, these findings suggest the potential role of the amygdala in transducing the broader social context into pathologic processes underlying CVD.

In a second study, this same research group showed that lower parental education levels of middle-aged adults' predicted reduced activation in portions of the prefrontal cortex during a positive monetary reward, independently of the participant's current educational attainment (Gianaros et al., 2011). There was also lower connectivity between these

prefrontal areas and other areas involved in reward processing (orbitofrontal and striatal cortex). Thus, executive control or top-down regulation mechanisms appear to be compromised among adults who came from low-childhood-SES backgrounds. This matches behavioral work in children revealing evidence of deficits in self-regulatory ability in relation to poverty (Blair, 2010; Evans & Rosenbaum, 2008). Additional future research is needed in this area that brings together neuroimaging experts with SES researchers in order to better understand the effects that low SES has on both brain function and structure, and in turn the implications for long-term physical health outcomes.

We close this chapter with a few thoughts about implications for interventions. The policy relevance of understanding life course SES effects is potentially large (Shonkoff et al., 2009). At the most fundamental level, health disparities research requires a reframing of evaluation criteria for economic policies. Material deprivation is not only tragic and costly for individuals, because it leads to accelerated morbidity, it dramatically affects health care costs for societies. Early remediation of pathogenic conditions would save societies large amounts of capital (Knudsen et al., 2006). For example, research identifying specific periods in the life course during which SES has the most pronounced effects on health are important for informing policy makers about when interventions might produce their biggest effects, and hence bring in the biggest long-term returns for one's investment. Research into the ways in which SES early in life may have effects on health that persist decades later provides an important basis for justifying interventions implemented in early childhood. And research into the ways in which SES may accumulate over a life course to affect health later in life would speak to the value of interventions implemented at any point in the life course, in terms of their potential for shifting individuals from negative health trajectories onto more positive ones.

More research is also needed to determine which types of interventions might have the biggest effects on both biological mechanisms and health. For example, interventions could directly target low-SES circumstances through efforts to reduce poverty rates by increasing employment opportunities with adequate wages (Rank, 2004), or to provide health insurance coverage to the uninsured. Or interventions could target some of the proposed mediators, for example, social environment factors such as individual psychological

characteristics or family interventions could target the physical environment of the physical environment of SES individuals—for quality, and so forth (determined which type would be most effective in changing the context of life, and in turn, and health profiles.

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With a few thoughts about ons. The policy relevance of SES effects is potent (2009). At the most fundamental, research requires 1 criteria for economic ion is not only tragic and use it leads to accelerated affects health care costs ation of pathogenic consequences large amounts of capital). For example, research ls in the life course durst pronounced effects on informing policy makers might produce their bigging in the biggest long-term. Research into the n life may have effects on s later provides an important interventions implemented research into the ways in late over a life course to would speak to the value ented at any point in the heir potential for shifting e health trajectories onto

so needed to determine tions might have the biological mechanisms and terventions could directly tances through efforts to y increasing employment uate wages (Rank, 2004), nsurance coverage to the ions could target some of , for example, social environmental individual psychological

characteristics or family environment quality. Or interventions could target mediators that are part of the physical environment that characterizes low SES individuals—for example, pollutants, housing quality, and so forth (Evans, 2004). It remains to be determined which types of intervention approach would be most efficacious and cost-effective for changing the contexts in which low-SES individuals live, and in turn, improving their physiological and health profiles.

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### Abstract

Economic hardship families. Informal hardship experience process was linked factors decreased 10-year period. Growth in extracurricular hardship also was and lower conscientious generation diminished next generation.

**Key Words:** economic

Economic hardship immediate as well as family functioning and Conger, 2011; Donnell Neppel, 2009; Duncan review of the literature economic hardship and parenting and family relationship development (e.g., Bolger & Kessler, 1995; Brackley & Conger, 2007; Duncan & Brooks-Gunn, 2010; McLoyd, 1990). Family has been linked to physical well-being, and cognitive development in children and adults (e.g., Bradley & Corwyn, 2002; McLoyd & Shanahan, 2004; Duncan & Brooks-Gunn, 2010).