CHAPTER 1

Childhood Adversity and Adult Physical Health

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A consensus in the developmental psychopathology literature is that the experience of early adversity—particularly the experience of chronic, uncontrollable stress—is a risk factor for a diverse set of poor outcomes across development (e.g., Appleyard, Egeland, van Dulmen, & Sroufe, 2005; Poulton et al., 2002; Shonkoff et al., 2012). In the last three decades, a growing number of studies have provided convincing evidence to conclude that adversity in childhood has a lasting influence on adult physical health, particularly chronic diseases associated with aging, like cardiovascular disease, diabetes, arthritis, and some cancers (Gluckman & Hanson, 2006; Miller, Chen, & Parker, 2011; Repetti, Taylor, & Seeman, 2002). This susceptibility to the chronic diseases of aging resulting from early adversity has been identified in diverse samples with a range of adverse risk factors, including socioeconomic disadvantage, maltreatment, and chaotic family environments. These findings suggest that these early stressful experiences leave a "biological residue," manifesting in physical health problems in adulthood.

This chapter provides a review of the current knowledge linking childhood adversity to adult physical health. We first provide a discussion of childhood adversity and the varied ways that children encounter stressful experiences in their daily lives. Then we review evidence for links between childhood adversity and chronic diseases of aging, with a focus on cardiovascular disease and metabolic disorders, where most of the research to date has occurred. We then describe conceptual models that help guide empirical investigation of the processes through which early adversity influences later health. We also review biological mechanisms that might play an intermediary role in translating psychosocial stress into health problems, which can help explain how early adversity "gets under the skin" and influences the onset of disease in adulthood. Our goal is to highlight the advantages and limitations in the conclusions

we can draw from research on these biological processes. Finally, we end this chapter with a series of important research questions that should be a focus in the next generation of empirical investigation on early adversity and adult physical health.

DEFINING CHILDHOOD ADVERSITY

There are a number of ways that children could experience significant adversity. In this chapter, we focus on adversity that is both chronic and severe in nature. We define *chronic* adversity as one that remains present in the child's life over a significant period of time (e.g., lack of material resources due to poverty). Adversity can also be chronic when children experience lingering threat over the possibility of a repeated stressful experience (e.g., stress resulting from a traumatic experience, such as abuse, that could reoccur) or aftereffects of adversities that create severe disruptions to daily life (e.g., long-term displacement resulting from a natural disaster). Adversity is considered *severe* when it results in a profound unsettling of normative childhood experiences and threatens the well-being of the child (e.g., exposure to gang violence while living in poverty).

Studies that have attempted to estimate the prevalence of adverse life experiences in childhood have found that these stressors actually are fairly common. Kessler and colleagues (Kessler, Davis, & Kendler, 1997) categorized early-life adversities into four domains, including (a) interpersonal traumas (e.g., rape, physical attacks); (b) loss events (e.g., death of a parent); (c) parental psychopathology (e.g., parental depression, antisocial personality disorder); and (d) a miscellaneous category of stressful life events (e.g., life-threatening accidents, man-made disasters). Using the National Comorbidity Survey, a nationally representative sample of families in the United States, Kessler et al. found that by the age of 16, nearly 75% of children have experienced at least one significant adversity and approximately 50% of children have experienced multiple adversities. In this sample, the most frequent adversities that children faced were maternal depression, paternal verbal abuse, paternal substance abuse, and parental separation or divorce.

Further, a startling number of children currently face adversity in impoverished or economically stressed conditions. According to the Children's Defense Fund (2012), 22% of children in the United States were living in poverty in 2010, meaning that a family of four earns less than $22,350 a year (U.S. Department of Health and Human Services, 2011). An additional 22% of children live in low-income families, defined as less than 200% of the federal poverty level (or less than $44,700 for a family of four). Children in low-income families may be exposed to many of the same stressors that children living below the poverty line face, including dangerous neighborhoods, material deprivation, parental underemployment, and familial mental health problems, all contributing to strained family relationships.

Overwhelmingly, research on the links between early adversity and later physical health has focused on two types of adversity: child maltreatment and socioeconomic disadvantage. Although these experiences of early adversity fall under the definition of adversity proposed above, they differ from each other in some critical aspects, including the *nature* and *source* of threatening experiences; the duration, frequency, and severity of those experiences; and the opportunities for coping. Yet maltreatment and socioeconomic disadvantage share several overlapping qualities, which may include cold, insensitive parenting; harsh discipline; exposure to conflict and violence; limited access to resources; and uncertainty of future environmental stability (Repetti et al., 2002). Next we take a closer look at several forms of adversity that are thought to be particularly detrimental for later physical health.

Child Maltreatment

A fundamental component of attachment theory is the notion that individuals develop representations (or internal working models) that reflect the extent to which a caregiver serves as a *secure base* for exploration and as a *safe haven* when needed for comfort and support (Bowlby, 1969/1982, 1973). These representations are experience-based, and they are developed over the first year of life in response to repeated interactions with a caregiver. When these caregiving experiences include neglect or abuse, children learn that their caregiver is not an available secure base or safe haven. Further, these children may develop unusual behaviors, characterized by odd, fearful, and disorganized patterns of interactions with a caregiver—characteristics that emerge when the caregiver becomes their primary source of fear *and* support (Lyons-Ruth & Jacobvitz, 2008). These behavioral responses reflect the child's inability to cope with a chaotic environment. Importantly, children who are maltreated by caregivers grow up without the experience of knowing that a reliable caregiver is available when needed—an aspect of the family emotional climate that plays a fundamental role in children's abilities to regulate distress and cope with negative emotions (Bowlby, 1988).

Child maltreatment is a serious public health concern that poses significant mental and physical health burdens on its victims (Cicchetti & Toth, 2005) as well as substantial economic burdens on society as a whole (Fang, Brown, Florence, & Mercy, 2012). Estimates suggest that almost 700,000 children were victimized in the United States in 2011, almost half of whom were under 6 years old at the time of the abuse (U.S. Dept. of Health and Human Services, 2011). Of course, because a large number of cases are unreported and a third of reported cases are not investigated (Cicchetti & Toth, 2005), the actual rate of child maltreatment may in fact be higher. The vast majority of cases (78%) included children suffering from neglect, but each year, hundreds of thousands of children are also victims of physical, sexual, or psychological abuse. Alarmingly, childhood maltreatment is perpetrated most often by primary caregivers, with over 80% of cases involving abuse by one or more parents.

Explanations for the causes of child maltreatment widely recognize that the phenomenon is multiply determined. Attempts to characterize the contexts of maltreatment have cited parental factors (e.g., mental illness, substance abuse), child factors (e.g., difficult temperament, disruptive behavior), interactional factors—that is, the dynamic transactions that take place between parents and children that might incite abuse (e.g., a child's aggressive behavior elicits physical punishment from parents that subsequently escalates to abuse), and environmental factors (e.g., cultural attitudes, poverty; Belsky, 1993; Cicchetti & Toth, 2005).

Socioeconomic Disadvantage

Children growing up with socioeconomic disadvantage have a higher probability of being exposed to stressful conditions across virtually every domain of daily life. Many of these stressful conditions center on the lack of security for basic resources, such as food and housing. For example, over 10% of children live in "food-insecure" families who struggle to provide enough food to meet children's daily nutritional needs, and over 20 million children receive free or reduced-cost lunches at school—meals they are eligible to receive because of their family's scarce financial resources (Children's Defense Fund, 2012). Children in poverty often do not have adequate access to medical care, resulting in infrequent visits to the doctor and risk for serious complications from untreated illnesses. Children growing up in poverty are at risk for low educational attainment, meager job success, and incarceration (Duncan, Kalil, & Ziol-Guest, 2008). Notably, children in poverty also face neighborhood stressors, and they are at increased risk for becoming victims of violence, theft, and other crimes (Ross & Mirowsky, 2001). Further, their caregivers are burdened by numerous demands, such as multiple part-time jobs, unaccommodating schedules, and psychosocial stress brought on by their lack of resources, making it more difficult for them to serve as sensitive sources of support for their children. The accumulation of deficits in resources—both material and psychological—cluster to create an environment that is ill-equipped to foster children's healthy development. Children living in disadvantaged families can face daily threats to their basic needs and be exposed to additional stressors that can jeopardize their mental and physical well-being.

Presumably, other adverse experiences in childhood (including many of the factors that Kessler et al. [1997] identified) have repercussions for adult health. To date, however, these links between exposure to other early adversities besides poverty and maltreatment and adult health have not been a primary focus in the literature. For example, with the exception of a handful of studies, we know very little about how the loss of a parent, the experience of severe interparental conflict, or exposure to neighborhood stress plays a role in shaping chronic disease outcomes in adulthood. Children are exposed to a wide array of adverse experiences, and it will be important to understand the extent to which each of these adversities is associated with long-term physical health outcomes.

Summary

Chronic adversity is a problem for many children in the United States. So far, the literature on health consequences has focused mainly on maltreatment and disadvantage. But an important question for future studies to consider is the impact of other significant adversities (e.g., interparental conflict, long-term separations from parents, natural disasters) on adult physical health. One challenge to this line of research, however, is that many forms of adversity—and socioeconomic disadvantage and maltreatment in particular—co-occur more often than would be expected by chance alone (Crouch, Hanson, Saunders, Kilpatrick, & Resnick, 2000), thus creating a unique challenge to parsing out the effects of different forms of adversity on later physical health outcomes. The use of a variety of statistical techniques (e.g., variable-centered and person-centered approaches to data analysis) as well as comprehensive models (described in more detail later in this chapter) offer opportunities to circumvent the

challenges associated with identifying the complex connections between early adversity and adult physical health.

DEFINING HEALTH OUTCOMES

Studies documenting the link between early adversity and adult physical health have assessed everything from the frequency of minor physical symptoms like headaches and constipation to rates of disorders and death from various conditions. As much as possible we focus on disease morbidity (the diagnosis of a disease or a clinical manifestation of it) and mortality rather than symptom reports. The advantages of focusing on disease endpoints and death are that they can be ascertained objectively and are viewed as reflecting differences in an underlying disease process. Further, these outcomes are much simpler to interpret than symptoms reported by patients, which tend to be heavily shaped by individual differences in symptom perception, labeling, and reporting (Feldman, Cohen, Doyle, Skoner, & Gwaltney, 1999).

Our focus in this chapter rests on the major chronic diseases associated with aging, including studies of risk for cardiovascular disease, stroke, cancer, diabetes, and metabolic syndrome, which is a precursor of cardiovascular disease and diabetes (Grundy et al., 2005). These diseases account for the vast majority of suffering and disability in the United States (and well over 1 million deaths in the United States each year; Murphy, Xu, & Kochanek, 2012). Further, the economic burden associated with health care costs for treating these chronic diseases—which amounts to more than three-quarters of the nation's health care spending—accounts for approximately $300 billion annually (DeVol & Bedroussian, 2007).

CHILDHOOD ADVERSITY AND LATER DISEASE: EPIDEMIOLOGICAL EVIDENCE

Mounting evidence suggests that early childhood adversity is associated with a number of chronic health problems later in life, including cardiovascular disease, diabetes, cerebrovascular disease, and even some cancers (Adler & Rehkopf, 2008; Gluckman & Hanson, 2006; Shonkoff et al., 2012). This quickly growing body of research has implicated psychosocial stress as a primary mediator of adversity's association with morbidity and mortality from chronic diseases of aging (Matthews & Gallo, 2011; Shonkoff, Boyce, & McEwen, 2009). In the sections that follow, we review epidemiological evidence for the role of early adversity in contributing to later disease. We focus mainly on the role of maltreatment and socioeconomic disadvantage, two forms of adversity that have been studied extensively in relation to later health problems. Where applicable, we review available literature documenting other forms of early adversity that have been linked to chronic diseases of aging. When possible, we selected studies that used nationally representative studies with large sample sizes, assessment of possible confounds, prospective study designs, and objective measures of health outcomes in adulthood. In some domains, these criteria could not be met within any single study, so we review available evidence and note the methodological concerns. Further, our discussion is restricted to studies that link childhood adversity to *adult* physical health. Although a growing body of research has documented links between exposure to stress in childhood and childhood disease outcomes, these studies are beyond the scope of this chapter.

Maltreatment and Later Disease

Studies of the long-lasting sequelae resulting from maltreatment in childhood have identified robust links between childhood abuse and chronic diseases of aging, including cardiovascular disease and diabetes. Evidence for these links comes from studies that focus on different forms of maltreatment, including physical abuse, sexual abuse, and neglect (e.g., Anda et al., 2006; Goodwin & Stein, 2004). The vast majority of these studies used retrospective reports about maltreatment, which presents some methodological concerns about the accuracy of the reports. Next we review a selection of studies that have examined links between maltreatment and specific disease outcomes.

Maltreatment and Cardiovascular Disease

Links between early maltreatment and cardiovascular disease are well documented (e.g., Batten, Aslan, Maciejewski, & Mazure, 2004; Dong et al., 2004; Draper et al., 2008; for meta-analytic findings, see Irish, Kobayashi, & Delahanty, 2010; Wegman & Stetler, 2009). For example, using data from the National Comorbidity Survey, Goodwin and Stein (2004) found that recalled sexual abuse in childhood was associated with increased risk for cardiovascular disease, including heart attacks. Similarly, findings from the Nurses' Health Study revealed links between women's recollections of childhood physical and sexual abuse and cardiovascular disease (Rich-Edwards et al., 2012). In this study, severe physical abuse was associated with a 46% greater risk of having a cardiovascular

event (e.g., heart attack, stroke). Similarly, sexual abuse was associated with 56% increased odds of having a cardiovascular event.

Links between maltreatment and cardiovascular disease have been found even in complex analyses that include possible alternative explanations, including adult health risk behaviors (e.g., smoking), stressors in adulthood (e.g., daily stress, low educational attainment), depression, and childhood stressors other than maltreatment (e.g., parental divorce). Even after accounting for these potential confounding variables, Fuller-Thomson, Brennenstuhl, and Frank (2010) found that recalled childhood physical abuse was associated with 45% greater likelihood of being diagnosed with heart disease. Felitti and colleagues (1998) have suggested that some of these confounding variables may serve as mediating mechanisms in the progression of heart disease (e.g., the experience of maltreatment may lead individuals to engage in unhealthy lifestyles), but the findings from many of these studies indicate that maltreatment still accounts for some of the risk for cardiovascular disease even after accounting for health behaviors, which may point to other mechanisms linking early maltreatment to cardiovascular disease.

Several investigations have identified gender-specific links between maltreatment and cardiovascular disease (e.g., Batten et al., 2004; Draper et al., 2008; Fuller-Thomson, Bejan, Hunter, Grundland, & Brennenstuhl, 2012; Goodwin & Stein, 2004). For example, Fuller-Thomson et al. (2012) found that childhood sexual abuse was associated with a greater risk for heart attacks for men but not for women. In contrast, in the National Comorbidity Survey, Goodwin and Stein (2004) and Batten et al. (2004) found connections between maltreatment and cardiovascular disease for women but not for men. Unfortunately, insufficient evidence exists currently to make broad conclusions about gender-specific risk for cardiovascular disease resulting from early maltreatment. Nevertheless, it will be important for future research to examine whether the link between maltreatment and cardiovascular disease differs for men and women. It may be that certain forms of maltreatment (e.g., sexual abuse or neglect) are associated with unique risk outcomes for men versus women.

These findings suggest that exposure to early maltreatment is linked to adult cardiovascular disease, but the studies' methodological limitations make it difficult to conclude that maltreatment *causally* contributes to heart disease. For example, these studies rely exclusively on retrospective self-reports of maltreatment (often with a single question about whether participants were ever abused or neglected), which calls into question the accuracy of the assessment due to possible memory errors or informant biases. In addition, most of these studies use participant reports about their medical diagnoses, which are less trustworthy than medical records. These study weaknesses are not easily discounted, and they limit our ability to make strong conclusions about the role of maltreatment in contributing to disease outcomes. To address these concerns, future studies will need to identify and control for factors that could give rise to spurious associations between maltreatment and subsequent cardiovascular disease (e.g., neuroticism). The use of strong methodological designs, including studies from administrative databases that can utilize objectively verified records of maltreatment and cardiovascular disease, would help assuage skepticism about the link between child maltreatment and adult cardiovascular disease.

Maltreatment and Metabolic Risk

Childhood maltreatment has been found to be predictive of diabetes and other metabolic abnormalities in adulthood (e.g., Danese et al., 2009; Felitti et al., 1998; Goodwin & Stein, 2004; Rich-Edwards et al., 2010; Thomas, Hyppönen, & Power, 2008). In recent investigations, researchers have examined a cluster of metabolic abnormalities known as the metabolic syndrome (Cornier et al., 2008; Grundy et al., 2005; previously known as Syndrome X). Metabolic syndrome is increasingly viewed as a precursor to cardiovascular disease and diabetes and reflects sedentary lifestyles and overnutrition. Its connection to potentially fatal cardiac events (e.g., heart attacks, strokes) and high prevalence in modern society (estimates suggest that around 30% of adults in the United States meet criteria for metabolic syndrome; Cornier et al., 2008) make it a promising predisease marker for individuals who have not yet developed chronic diseases.

In the first study of links between early maltreatment and diabetes, Felitti et al. (1998) found that diabetes was more prevalent when individuals reported four or more indicators of childhood risk (including maltreatment and family dysfunction). Similarly, in a community sample of women in New Zealand, Romans, Belaise, Martin, Morris, and Raffi (2002) found that childhood abuse was associated with increased diabetes prevalence. Further evidence for a link between maltreatment and metabolic risk comes from the National Comorbidity Survey (Goodwin & Stein, 2004). In this sample, recalled childhood neglect (but not physical or sexual abuse) was associated with increased odds of having diabetes. Despite variations in definitions of maltreatment (e.g., neglect versus abuse), these studies suggest that the experience of poor caregiving conditions

in childhood is a risk factor for diabetes in adulthood. Interestingly, Goodwin and Stein's (2004) findings of the specific type of maltreatment experience that was associated with metabolic risk suggests that certain types of maltreatment may be particularly influential in shaping diabetes onset.

To date, only a handful of studies have examined whether maltreatment in childhood is a predictor of prediabetes metabolic risk in adulthood, but preliminary evidence provides some support for this link. Midei, Matthews, Chang, and Bromberger (2013) examined connections among emotional, physical, and sexual abuse and the onset of metabolic syndrome in a sample of women in middle adulthood. In this study, childhood physical abuse, but not sexual or emotional abuse, was associated with the onset of metabolic syndrome over a 7-year span.

In one of the only prospective studies of maltreatment and metabolic risk, Danese et al. (2009) examined the separate predictive roles of child maltreatment, social isolation, and socioeconomic status (SES) as well as the cumulative exposure to adversity across these domains. Using the Dunedin Multidisciplinary Health and Development Study, Danese et al. grouped participants into three categories according to their exposure to maltreatment in childhood: (a) no maltreatment; (b) probable maltreatment—meaning that children experienced one out of five indicators of maltreatment; and (c) definite maltreatment, wherein children experienced two or more indicators of maltreatment. Although low SES and social isolation were independently predictive of metabolic risk, child maltreatment was not reliably associated with higher rates of metabolic risk factors. Somewhat surprisingly, adults who were categorized as "probable maltreatment" had elevated risk for metabolic abnormalities, but adults who were categorized as "definite maltreatment" were not at increased risk. This finding is particularly noteworthy, as it is the only study to our knowledge that has multiple informant ratings of maltreatment assessed when participants were children and does not rely on retrospective reports. Given that participants were still relatively young (32 years old) and healthy at the time of assessment of metabolic indicators, it is not entirely surprising that maltreatment was not a reliable risk factor for metabolic disruptions. It may be the case that maltreatment takes longer to manifest itself in metabolic disruptions that will be seen when these participants are older. Yet it is also possible that other studies that have used retrospective self-reports of maltreatment have overstated the link between early maltreatment and adult metabolic risk. Thus, although it appears that early maltreatment is a risk factor for both diabetes and prediabetes metabolic risk, additional research with multiple informants and prospective study designs will be important for shedding light on the extent to which harsh caregiving experiences and maltreatment are predictive of later metabolic disruptions.

Maltreatment and Cancer

Compared to the well-established literature that examines early maltreatment and cardiovascular disease and diabetes, much less is known about the extent to which maltreatment in childhood confers additional risk for cancer. A handful of studies have studied this link using retrospective study designs, with mixed findings (e.g., Brown et al., 2010; Draper et al., 2008; Felitti et al., 1998; Fuller-Thomson & Brennenstuhl, 2009; Morton, Schafer, & Ferraro, 2012). In the first reported examination of this link, Felitti et al. (1998) found that individuals were at increased risk for cancer when they experienced four or more adverse childhood risk factors. Similarly, in the National Survey of Midlife Development in the United States (MIDUS), Morton and colleagues (2012) examined links between childhood abuse and cancer and found that emotional and physical abuse were associated with increased risk of cancer at midlife. These links remained significant even after controlling for potential confounding variables, including age, race, SES, and health-related behaviors (e.g., smoking). Additional evidence for a link between childhood maltreatment and cancer comes from a sample of over 13,000 Canadians who took part in the Canadian Community Health Survey (Fuller-Thomson & Brennenstuhl, 2009). In this sample, recalled physical abuse was associated with 47% higher odds of cancer, even when adjusting for risk factors, such as childhood stressors, adult health behaviors, and adult SES. Morton et al. and Fuller-Thomson and Brennenstuhl (2009) relied on studies that used self-reports of abuse and cancer, which raises interpretational ambiguities, as we noted earlier. However, self-reports about cancer diagnosis may be less subject to false reports than other disease outcomes or symptom reports. Prospective studies and studies utilizing administrative databases with objective measures of maltreatment and disease diagnoses will bolster support for the notion that child maltreatment is a risk factor for adult cancer diagnosis.

Other studies, however, have not found links between early maltreatment and later cancer risk. In a sample of over 21,000 older adults, Draper et al. (2008) examined links between childhood physical and sexual abuse and adult mental and physical health outcomes. In this study, although adults who had been abused reported worse

mental and physical health, abused participants were not at greater risk for experiencing cancer in adulthood. Similarly, Korpimäki, Sumanen, Silanmäki, and Mattila (2010) did not find a link between maltreatment and cancer in a large epidemiological study in Finland. A number of factors could account for these inconsistent findings. For one, researchers vary in their definitions of maltreatment: Some studies include a range of harsh parenting indices, whereas other studies take a more explicit approach by asking participants if they had been abused as children. Moreover, there is considerable variability across studies in sample characteristics and analytical approaches (e.g., the extent to which possible confounding variables are included in statistical models, whether maltreatment is considered as a continuous or binary variable). Another difficulty is that cancer prevalence rates are lower than the rates of heart disease and diabetes, thus making it a more difficult outcome to predict. Further, cancer is a much more heterogeneous disease compared to diabetes and cardiovascular disease; this heterogeneity may explain some of the inconsistent findings, particularly if studies vary in their focus on particular cancers versus all cancer diagnoses. Additional investigation into the connections between maltreatment and cancer risk will provide insight into whether the experience of maltreatment in childhood is a risk factor for later cancer diagnosis.

Summary of Research on Early Maltreatment and Later Disease

Consistent with the notion that early exposure to adversity is linked to many of the chronic diseases of aging, preliminary evidence suggests that maltreatment in childhood may be a risk factor for poor health outcomes in adulthood. In the vast majority of these studies, however, researchers have relied on retrospective reports of maltreatment, which are subject to significant reporting biases. Moreover, these reporting biases might not be random: It is possible that individuals with poor health remember their prior experiences in negatively biased ways. Further, many of these studies use self-reports of physician diagnoses of diseases. Although we prefer these markers of physical health over informants' own symptom reports, these assessments are nevertheless vulnerable to inaccurate reports.

Additional research will be useful for shedding light on the specific contexts in which maltreatment is likely to be a serious risk for later health problems. For example, it is possible that certain forms of maltreatment are more likely to contribute to health problems for women but not for men, or for people from particular racial or ethnic backgrounds. Another lingering question concerns the relative weight of various forms of maltreatment in the progression of long-term health problems: Do all forms of maltreatment pose risk for health problems, or are certain forms of abuse or neglect especially likely to have a negative effect on later physical health? Moreover, the experience of a particular type of maltreatment (e.g., physical abuse) and its impact on later health may depend, in part, on the cultural context in which it occurs. For example, in cultures that condone corporal punishment, links between childhood physical abuse and later health may be less identifiable. These research questions await empirical examination.

Socioeconomic Disadvantage and Later Disease

The literature on the role of childhood socioeconomic disadvantage in shaping risk for later disease and mortality risk is extensive and suggests that, like early maltreatment, it is a risk for poor health outcomes in adulthood. In particular, low SES in childhood is a risk factor for early mortality, cardiovascular disease, diabetes, and some cancers (Cohen, Janicki-Deverts, Chen, & Matthews, 2010; Galobardes, Lynch, & Smith, 2004, 2008; Kumari, Head, & Marmot, 2004).

When studying the long-term health outcomes associated with childhood socioeconomic disadvantage, an important factor to consider is that SES tends to be stable across the lifespan (Hertzman, 1999). Such stability makes attempts to disentangle the effects of early versus adult SES on health particularly difficult. Given that adult SES is a robust predictor of morbidity and mortality from chronic diseases of aging (Adler & Rehkopf, 2008; Lynch & Smith, 2005), many studies of early childhood SES statistically control for adult SES in analyses, thus allowing for better insight into the role that early-life experiences play in influencing the risk for later disease. In order to avoid multicollinearity issues associated with highly stable childhood and adult SES estimates, recently researchers have developed statistical modeling techniques to better account for early and adult SES (e.g., Nandi, Glymour, Kawachi, & VanderWeele, 2012).

Socioeconomic Disadvantage and Cardiovascular Disease

In their systematic review of the literature on SES and cardiovascular disease, Galobardes, Smith, and Lynch (2006) concluded that low SES in childhood is a significant risk for cardiovascular disease in adulthood. Even when adult SES was controlled in statistical analyses, the link between childhood SES and disease risk was still significant, accounting for 20% to 40% of the risk for cardiovascular

disease. In a large-scale investigation of socioeconomic disadvantage and cardiovascular disease, Claussen, Smith, and Thelle (2003) found that cardiovascular disease-related mortality was associated with childhood SES. Similarly, researchers found evidence for the role of early socioeconomic disadvantage in predicting cardiovascular disease in the British Whitehall II study (Singh-Manoux, Ferrie, Chandola, & Marmot, 2004). Another study tracked the onset of coronary heart disease over a period of 40 years in a sample of physicians who graduated from medical school at Johns Hopkins University (Kittleson et al., 2006). Even among these educated, affluent physicians, childhood adversity was associated with worse health in adulthood. The rates of cardiovascular disease by age 50 were 2.4 times higher in physicians who were raised in households that were low versus high in SES. These findings offer dramatic evidence in support of a link between socioeconomic disadvantage and cardiovascular disease.

Socioeconomic Disadvantage and Metabolic Risk

A number of studies have examined the role of early socioeconomic disadvantage and risk for metabolic abnormalities, including the metabolic syndrome and diabetes (e.g., Agardh et al., 2007; Brunner et al., 1997; Kumari et al., 2004; Parker et al., 2003). Support for this link has been somewhat mixed, although the majority of studies have found at least some evidence of a link between early low socioeconomic standing and greater risk for metabolic disruptions later in life. For example, in the British Whitehall II Study, Kumari and colleagues (2004) found that low SES predicted higher incidence of diabetes relative to individuals with higher social standing. Using the same sample, Brunner and colleagues (1997) identified a link between SES and the metabolic syndrome. Similarly, in the Panel Study of Income Dynamics, a nationally representative prospective longitudinal study in the United States, Johnson and Schoeni (2011) found that poverty in childhood was predictive of diabetes almost 40 years later.

In one of the few prospective studies of socioeconomic disadvantage and metabolic risk, Melchior, Moffitt, Milne, Poulton, and Caspi (2007) found that low SES in childhood was associated with a cluster of risk factors at age 32 (e.g., elevated blood pressure, adiposity, glycated hemoglobin). This finding remained significant, even when accounting for familial liability, childhood IQ, adolescent health behaviors, and adult SES.

Recently researchers have incorporated sophisticated analytical techniques to separate the effects of early versus adult SES in the prediction of metabolic disorders. Using prospective data from the Health and Retirement Study, Nandi et al. (2012) used marginal structural models, a statistical approach that allowed them to estimate (a) the direct effect of early SES, (b) the direct effect of adult SES, (c) effects of early SES that are mediated by risk factors (e.g., blood pressure, smoking, alcohol consumption), and (d) the effect of early SES that is mediated by adult SES (referred to as a social trajectories model). By separately estimating these effects, Nandi and colleagues were able to test the relative contributions of early and adult SES on adult diabetes. Using this modeling approach, Nandi et al. found that early-life SES was associated with adult diabetes—an effect that was not accounted for by adult SES. Interestingly, when Nandi et al. used traditional regression analyses to compare the role of early and adult SES on later diabetes, the effects of early status were largely attenuated by adult SES. In other words, comparison of the findings across the two statistical strategies suggests that studies that employ commonly used regression-based approaches for estimating effects (e.g., Agardh et al., 2007) may have significantly underestimated the effects of early-life SES. Future studies should take advantage of these advancements in analytic techniques in order to more accurately estimate the relative contributions of childhood and adult risk factors.

Although these studies offer convincing evidence for a link between low SES and metabolic abnormalities, recent evidence suggests that certain protective factors might play an important role in buffering children from the deleterious effects of early-life adversity. For example, low SES in childhood was associated with higher prevalence of metabolic syndrome at midlife in the MIDUS sample (Miller, Lachman, et al., 2011). However, for individuals who recalled high levels of maternal support, low SES was not associated with metabolic syndrome at midlife. Interestingly, this pattern was not explained by upward social mobility, suggesting that maternal nurturance, and not the addition of material resources, served as a buffer against low SES. These findings are encouraging, as they suggest that early adverse experiences might be offset by protective factors; continued examination of protective factors will be an important area for future research.

Socioeconomic Disadvantage and Cancer

A small but growing body of evidence suggests that early-life socioeconomic disadvantage may play a role in the development of cancer in adulthood (e.g., Lawlor, Sterne, Tynelius, Smith, & Rasmussen, 2006; Power, Hyppönen, & Smith, 2005; Pudrovska, Anishkin, & Shen, 2012). In the Wisconsin Longitudinal Study, which prospectively studied individuals over the course of 50 years, low early-life

SES was associated with breast cancer. Similarly, in a prospective study of women in Great Britain (Power et al., 2005), trend-level associations between childhood social class and lung and stomach cancers emerged, even after controlling for health behaviors and adult social class. Additional research will be important to add further insight into the extent to which low SES in childhood is a predictor of cancer diagnosis in adulthood.

Summary of Research on Early Socioeconomic Disadvantage and Later Disease

The studies of socioeconomic disadvantage on later health outcomes have notable strengths compared with the maltreatment literature. They make use of large and representative samples across countries, use prospective designs, often have objective indicators of SES, and measure outcomes through medical records and health care databases (rather than self-report measures). Many of these studies control for plausible alternative differences in lifestyle factors, such as smoking, diet and exercise, and adiposity. The consistency of findings across countries suggests some universalism in the phenomenon and makes it unlikely that culture-specific factors (e.g., class-related differences in access to health care) are driving the findings.

Despite these more rigorous study designs, the literature linking early SES with adult physical health has some weaknesses that complicate interpretation and conclusion. For instance, these studies largely make use of observational data, which is understandable, given that individuals cannot be randomly assigned into poor environmental conditions. Further, the possibility remains that the observed links are due to unmeasured confounds, such as a common genetic liability that predisposes offspring to low SES and poor health. An additional limitation is that most of the studies are not fully longitudinal in that they do not assess childhood health during exposure to low SES (Cohen et al., 2010). Given that many of these disease endpoints (e.g., cardiovascular disease, stroke) are not observed in young children, assessment of the same health measures would not add incremental value to the study designs. Nonetheless, assessment of general physical health would help address the possibility that poor children start out life sicker than more affluent children, affecting both their parents' earning potential and their own long-term health.

A handful of studies have capitalized on naturally occurring fluctuations in societal economic conditions to examine the impact of early-life resources on later physical health outcomes (e.g., van den Berg, Doblhammer, & Christensen, 2009; van den Berg, Doblhammer-Reiter, & Christensen, 2011). One advantage of these naturalistic experiments is that researchers can be fairly confident that a genetic liability is unlikely to be the cause of any observed connections between the adverse experience and physical health outcomes. Further, these studies still can be useful in documenting links between adverse experiences and later health problems, particularly when there are children from the same cohort who were not directly affected by the event (e.g., Heijmans et al., 2008). Moreover, given that the unusual event is due to random and external forces, these studies minimize the likelihood that unknown spurious factors (e.g., personality traits) explain the link between early exposure to adversity and later physical health problems.

For instance, children who were born under adverse economic conditions in Denmark between 1873 and 1906 had higher mortality rates from cardiovascular disease than their peers who were born during more prosperous economic cycles (van den Berg et al., 2011). Further, van den Berg and colleagues (2011) reported that individuals who were born during a recession (and survived until at least age 40) lived, on average, *11 months* less than other individuals born during an economically prosperous time, providing evidence that economic circumstances early in life may have a lasting effect on health outcomes.

Not all studies of fluctuating economic conditions and long-term physical health have found support for this hypothesis, however. Cutler, Miller, and Norton (2007) did not find evidence of a link between economic fluctuations and physical health outcomes later in life in a sample of Americans who were born during the Great Depression. The detailed analysis of the Danish sample might shed light on why links between early-life economic circumstances and long-term health were not found in the U.S. study. In Denmark, the negative impact of economic adversity varied as a function of the community size: It was substantially less dramatic in major cities, such as Copenhagen, relative to smaller towns, where fewer resources were available. Similarly, individuals who lived in rural areas—with smaller communities of individuals who might take a more proactive approach to caring for each other—were similarly less affected than individuals who lived in midsize towns. It may be that a lack of early-life economic resources can be offset by community-level support systems, just as early-life socioeconomic adversity within the family appears to be mitigated by maternal support (e.g., Miller, Lachman, et al., 2011). Cutler et al. (2007) did not examine whether the link between early economic adversity and adult health varied based on the degree of urbanization in U.S.

communities, which may have obscured these possible community effects.

Other Forms of Adversity and Later Disease

To date, the epidemiological literature has provided some evidence that maltreatment and socioeconomic disadvantage may set the stage for a range of health problems in adulthood. Much less is known, however, about the extent to which other forms of adversity in childhood are risk factors for chronic diseases in adulthood. Of course, maltreatment and socioeconomic disadvantage are not the only forms of adversity that many children face that may shape the course of their long-term health trajectories. Next we briefly review evidence from several studies that have identified connections between other childhood adversities and later health outcomes. We note that these findings should be viewed as preliminary and will require further investigation in large, representative samples.

Parental Death and Later Disease

The death of a parent—resulting in the loss of an attachment figure—is widely regarded to be a profound stressor for children (e.g., Bowlby, 1980; Luecken & Roubinov, 2012). Studies have documented the risk for immediate and long-term mental health problems following parental death (e.g., Kivelä, Luukinen, Koski, Viramo, & Kimmo, 1998), but only recently have investigations studied the physical health consequences associated with parental loss in childhood. In an epidemiological study of women, Jacobs and Bovasso (2000) found that women who experienced the death of their mother in childhood were at increased risk for breast cancer. In another study, Krause (1998) examined early parental loss as well as recent life stressors in a national study of older adults. Although early parental loss alone was not associated with later disease, the interaction between parental loss and *current* stress levels predicted self-reported health and reports of acute conditions, including cancer, diabetes, and cardiovascular disease. In this case, the loss of a parent served as a vulnerability factor, and the addition of a current stressor increased the likelihood that individuals would have poor health outcomes. As we discuss in the next section, diathesis–stress models can add insight into links between early adversity and physical health, and they can shed light on specific contexts (e.g., stressful periods of life) and specific individuals (e.g., those who lost a parent in childhood) who might be especially prone to early onset of disease. Other studies, however, have not found links between early parental loss and later physical health (e.g., Maier & Lachman, 2000). When main effects do not emerge, it may be informative to examine whether there might be moderating factors that specify which individuals are most at risk, as Krause (1998) found.

Interparental Violence and Later Disease

To date, most studies examining the aftereffects of interparental violence on children's long-term outcomes have focused on emotional and behavioral problems (e.g., Hammen, Henry, & Daley, 2000), and little is known about how these early experiences might be associated with long-term physical health problems. The large-scale Adverse Childhood Experiences study (Felitti et al., 1998) included interparental violence in the cumulative risk assessment for adverse childhood experiences, but they did not examine the unique role that interparental violence played in contributing to long-term physical health problems. Several studies have reported links between individuals' exposure to interparental violence as children and self-rated health problems in adulthood. In a large-scale European sample of adults (Roustit et al., 2011), the odds of having poor self-reported physical health were 2.3 times greater if participants reported exposure to interparental violence in childhood. This preliminary evidence suggests that exposure to interparental violence in childhood may be a risk factor for the early onset of disease in adulthood, but additional research is needed to better understand the role of interparental violence in contributing to later disease. Further, studies that incorporate disease diagnosis rather than self-reports of health will be helpful for establishing support for a link between intimate partner violence and chronic disease.

Evidence from the study of children's short-term health outcomes associated with exposure to severe interparental conflict adds support to the idea that interparental violence may also be a risk factor for chronic health problems in adulthood (see Troxel & Matthews, 2004, for a review). Like much of the research on links between maltreatment and later physical health, this literature relies heavily on cross-sectional study designs and self-reports of physical health. Nevertheless, the evidence is compelling enough to warrant further examination of the role of interparental conflict in violence in contributing to long-term physical health problems later in life.

Extended Parental Absence and Later Disease

Some children encounter periods when their parents are absent for an extended period of time (e.g., military families where parents are deployed, families where a parent is imprisoned). Such long-term separations from

parents in childhood have been associated with long-term mental health problems, such as depression (Pesonen et al., 2007). Less is known about how these extended separations might be linked to later disease outcomes. Some naturalistic evidence from World War II suggests that long-term parental separation may be associated with physiological stress activity in late adulthood (Pesonen et al., 2010). During World War II, approximately 70,000 children were separated from their parents and sent to live in foster care to escape the dangers of war. Many of these children were separated from their parents for several years. Pesonen and colleagues (2010) found that adults who had been separated from both parents as children had higher average salivary cortisol and greater salivary cortisol reactivity during a laboratory stress task relative to adults who had not experienced long-term parental separation in childhood. Given the large numbers of children who experience lengthy parental separations due to ongoing military deployments and divorce, there is a need to examine what impact, if any, such disruptions in the parent-child relationship will have on long-term health outcomes.

Natural Disasters and Later Disease

Natural disasters, including hurricanes, tsunamis, tornadoes, earthquakes, and drought, result in dramatic disruptions to daily life. These disruptions range in severity from temporary setbacks to major transformations, including displacement and loss of one's home, inadequate access to food and other basic necessities, and uncertainty about the future. In some ways, natural disasters differ from exposure to some of the other adversities that have been a focus of this chapter, in that the cause of the distress is often not traceable back to poor parental care or disparities in resources. At the same time, however, the aftereffects that could result from living through a natural disaster may resemble the consequences of stressors that co-occur with poverty and maltreatment.

Several studies have documented the ways in which physical health can be affected in the short term by exposure to natural disasters. For example, in 1995, Japan experienced a 6.8-magnitude earthquake near Kobe, resulting in the loss of over 6,000 lives and leaving over 300,000 homeless. Following this disaster, there was a threefold increase in heart attacks and twofold increase in strokes, particularly for individuals who lived close to the epicenter (Kario, McEwen, & Pickering, 2003). These findings offer compelling evidence suggesting that natural disasters create enormous stress for individuals that might have serious health implications. To date, however, evidence for the long-term health impacts for individuals who endured natural disasters as children has been lacking. Further, although evidence suggests that children experience physical health problems in the months following a natural disaster (Datar, Liu, Linnemayr, & Stecher, 2013), the long-term effects of these stressful experiences still are largely unknown.

War and Later Disease

The immediate effects of war cause significant stress on children and their families. Children may face daily threats of violence, loss of loved ones, and fears about the future. In some cases, the effects of war have long-ranging influences on daily life, including reduced access to resources and basic necessities. For example, during World War II, a German blockade cut off the food supply to a large area of the Netherlands during the winter of 1944–1945. This tragic event provided the rare opportunity to examine the connection between starvation during pregnancy and long-term health outcomes of offspring affected by the war-induced famine (de Rooij, Wouters, Yonker, Painter, & Roseboom, 2010). Exposure to famine and malnutrition prenatally has been linked to Type 2 diabetes, cardiovascular disease risk, other metabolic abnormalities, and even breast cancer in adulthood (Barker & Clark, 1997; de Rooij et al., 2010; Painter et al., 2006; Painter, Roseboom, & Bleker, 2005; Rich-Edwards et al., 1999).

Findings from survivors of World War II suggest that exposure to wartime stressors may be associated with elevated rates of cancer. In one study, cancer rates were elevated in European-born immigrants who immigrated to Israel before or during the war (Keinan-Boker, Vin-Raviv, Liphshitz, Linn, & Barchana, 2009). The largest effects emerged for people born between 1940 and 1945, who would have been exposed to horrific conditions before age 5. Their cancer risk was elevated 3.5-fold relative to same-aged immigrants who arrived in Israel before the war.

Like the experience of socioeconomic disadvantage and maltreatment, these adversities described are likely to expose children to chronic, stressful circumstances, with lingering threats of repeated exposure to the stressor (e.g., lasting concerns of repeated interparental violence) and aftereffects resulting from the stressor (e.g., loss of all resources as a result of a natural disaster). To date, these adversities have not been examined extensively in relation to long-term health outcomes. As we develop a better understanding of the ways in which early adversity predicts later health outcomes, it will be important to understand the characteristics and contexts of early adversity that are most likely to contribute to poor health. Increased

specificity about the types of adversities that influence health will help researchers and policymakers focus efforts on mitigating the risks that are most likely to contribute to chronic disease.

Limitations and Alternative Explanations

Although the evidence linking early adversity to physical health is provocative, there are a number of weaknesses to this research that preclude a definitive interpretation. For example, many of the studies rely on one-time assessments, during which early stress and later health are measured via retrospective self-report. Understandably, this methodology raises concerns about the reliability of reporting, which would be particularly problematic if reporters are systematically biased in their assessments of early adversity and adult health. Some evidence suggests, however, that adults underreport negative experiences from childhood (Dill, Chu, Grob, & Eisen, 1991). Another concern is that these studies may reflect differences in the *reporting* of health problems as a function of early adversity, rather than real differences in the manifestation of disease. Notably, however, many studies—particularly studies linking socioeconomic disadvantage to later health outcomes—utilize medical records and physician diagnoses, thereby eliminating informant bias in symptom reports (e.g., Felitti et al., 1998; Rich-Edwards et al., 2012).

Yet another possibility is that genetic confounds might play a large role in creating the observed connections between early adversity and physical health. For example, there could be a familial genetic liability that contributes to abusive parenting and disease vulnerability. Or it could be the case that the direction of effects is wrong. For instance, a sick child can accumulate enormous medical bills, not to mention chronic stress on caregivers and other family members. The net effects of expensive medical care and lost earnings due to time spent caring for sick children might result in low SES in adulthood. A handful of studies have controlled for child sickness (e.g., Caspi et al., 2002), but this practice needs to be adopted more widely before we can definitively rule out this alternative explanation.

Using Animal Studies to Supplement Epidemiological Evidence

In light of the fact that it would be unethical and impractical to experimentally manipulate early human experiences or exposure to pathogens in adulthood, it is difficult and perhaps impossible to evaluate whether early adversity causally influences adult disease in humans. However, studies of this nature can be done with animals, and it is useful to consider how these studies have informed our understanding of connections between early adversity and adult physical health. In this section, we describe some of the findings that have emerged from experimental studies with animals that bolster support for the findings from epidemiological studies with humans.

Evidence from studies using experimental manipulations with animals suggests a causal link between early adversity and health outcomes. Animal models often provide good mechanistic evidence relating psychosocial risk factors to physical health. Unlike humans, animals can be randomly assigned to psychologically difficult circumstances and monitored over time to determine whether these stressful experiences influence disease outcomes. Further, questions about the effects of the relative timing of adverse experiences (e.g., early infancy versus later childhood) can be addressed by manipulating the onset of the stressor and examining differences in later health consequences associated with these timing differences. Often findings from animal studies converge with correlational evidence from human epidemiologic research.

Hofer's (2002) observations that rat pups responded with significant distress when separated from their mothers—similar to distress signals in humans—raised questions about the mechanisms of separation distress in nonhuman mammals. To explore this question, Hofer conducted a series of experiments to identify what physiological subsystems become disrupted when mothers were removed from their pups (for a review, see Hofer, 2002). These studies revealed a number of hidden regulators that no longer functioned properly if rat pups were separated from their mothers. Hofer found that when rat pups were removed from their mothers, they showed a dramatic decline in multiple physiological and behavioral systems, such as those controlling heart rate, body temperature, food intake, movement, and exploratory behavior. Hofer argued that maternal separation resulted in the removal of the important regulatory functions that the mother serves for her offspring, and the absence of these regulatory components resulted in rat pups' visible behavioral distress. These studies led Hofer to conclude that mother-infant interactions have embedded within them a number of vital physiological regulatory functions that are negatively affected by separation from maternal care.

In this regard, animal studies have some parallels to the experiences of children in poverty or unsupportive caregiving environments. On the whole, children exposed to these stressors receive less sensory, cognitive, and emotional stimulation and are more likely to be deprived of basic necessities, such as food and heat, than children growing up

without extreme adversity (e.g., Evans, 2004). That said, it is difficult to know how closely these deprivation studies in animals actually resemble human experience. Permanent maternal separation and extreme sensory deprivation are relatively uncommon in humans, even in families where maltreatment and disadvantage are present. At best, what these animal studies model is extreme and unusual human stress. Species differences in developmental growth are another major challenge in translating conclusions from animal studies to meaningful information for human development. At the time of birth, rodents are much less mature than humans. As a result, their physiology may need external regulation by caregivers in a manner that is not comparable to full-term human newborns.

These caveats aside, a number of studies indicate that premature separation can have long-term effects on animals' susceptibility to disease. In one study, mice pups were separated from their mothers for 6 hours a day over the first 2 weeks of life (Avitsur, Hunzeker, & Sheridan, 2006). As adults, the mice were challenged with intranasal exposure to an influenza virus. Compared to controls that remained with their mothers until weaning, the separated mice had greater viral replication and worse symptoms of infection, which was a result of an overly aggressive inflammatory response to the virus. Moreover, the proinflammatory response was present 9 days after the infection, a time when viral particles had declined to the point of being almost undetectable. These findings suggest that early stress calibrated the immune system to mount overly aggressive and extended inflammatory responses to the virus.

In another study, rats endured a stressful situation at 100 days of life (corresponding to early adulthood in humans). In order to obtain food and drink over a 4-day period, rats incurred electric shocks (Ader, Tatum, & Beels, 1960). Nearly all of the rats developed gastric ulcers following this stressful experience. However, the density of these ulcers was fivefold greater in rats that had been prematurely separated from their mothers at 15 days of life. In a follow-up study, a third group was added to evaluate whether nutritional disparities accounted for the health effects of the maternal separation manipulation. To test this hypothesis, rat mothers were removed from her offspring at 15 days, had their nipples cauterized to prevent nursing, and then were returned until 21 days. The median number of ulcers in this group was similar to the control condition. Because both groups in which the mother remained present had significantly fewer ulcers than the prematurely separated and weaned rats, these findings suggest that the effects were due to the absence of maternal nurturance rather than nutritional deficiencies per se (Ader, 1962).

There also has been mounting interest in early-life influences on asthma in animal models. In one study, mice were randomized into one of three conditions: In one condition, they received regular footshocks for 1hr on 3 days during the fourth week of life; in another condition, mice watched and heard other mice undergo this experience but were not shocked themselves; and in the third condition, the mice were undisturbed in their home cages (Chida, Sudo, Sonoda, Hiramoto, & Kubo, 2007). When the mice reached young adulthood (at 8–10 weeks of life), they were sensitized to ovalbumin, a protein in eggs that causes allergic reactions. At 11 weeks, all mice were given airway challenges with ovalbumin. Relative to controls, those mice that received or observed footshocks showed greater airway inflammation and more bronchial reactivity to the challenge. Similar patterns were observed in another study of rats that, over the first month of life, were either separated from their mothers daily for 2 hours and then reunited or remained undisturbed in their home cages (Kruschinski et al., 2008). When the rats were adults, asthma was induced by sensitizing subjects to ovalbumin, and airway tissue was collected. Analyses revealed striking differences. Adult rats that had been repeatedly separated from their mothers early in life showed more severe airway pathology than adult controls, with increased numbers of eosinophils, T-cells, and other proinflammatory mediators found in their lungs upon dissection.

Summary

Collectively, these studies provide evidence to support the notion that early adversity has long-term effects on physical health. To be sure, more work needs to be done to definitively rule out alternative explanations and clarify what the associations reflect in terms of underlying pathophysiology. But the weight of the evidence, from observational data and natural experiments in humans and randomized studies in animal models, leads us to conclude that there is evidence indicative of a causal effect. With that said, increased precision in the definition and assessment of early adversity and adult health will aid in our understanding of how and under what conditions early adversity leads to later health problems. This increased specificity in measurement will provide insight into what characteristics and contexts of early adversity prove to be most detrimental for physical health outcomes. Further, increased attention to whether there are protective factors that can mitigate the risk associated with early adversity and what mechanisms put people on a trajectory from

early adversity to poor health across development will be an important direction for future research.

CONCEPTUAL MODELS LINKING CHILDHOOD ADVERSITY TO ADULT PHYSICAL HEALTH

Researchers have long recognized that no single risk factor can account for all chronic diseases of aging, and research on the early origins of adult physical health outcomes has supported the notion that there are multiple pathways linking early experience to adult disease (e.g., Felitti et al., 1998; Miller et al., 2011; Taylor, Repetti, & Seeman, 1997). Yet to date, much research on the experience of early adversity and adult health has explored risk factors in isolation without consideration of the broader context in which the risk factors occur. Moreover, despite an interest in the impact of early adverse experiences on later health, existing studies have not thoroughly examined the relative timing of adverse experiences. Evidence from other areas of developmental research suggests that meaningful critical and sensitive periods constrain the impact of early experience on later outcomes (e.g., Knudsen, 2004), and it stands to reason that similar sensitive periods may constrain the impact of early adversity on long-term physical health outcomes as well.

Given that chronic disease is a multiply determined phenomenon, it is useful to clarify the complex pathways from childhood adversity to adult physical health by testing larger conceptual models that integrate multiple risks across multiple time points. In this section, we review several theoretical models that can be used to guide the investigations of connections between early-life adversity and adult physical health. Many of these models take into account the notion that multiple factors contribute to physical health outcomes; further, these models describe processes through which intervening factors (e.g., buffers, vulnerability factors) can alter individuals' health trajectories over time, leading to endpoints that may not have been expected, given individuals' starting points. These models provide a foundation for clear, testable hypotheses about the processes through which early adversity contributes to disease risk.

Cumulative Models

In contrast to models that examine a single risk factor in isolation, cumulative risk models provide a testable framework for studying how risk factors operate in the context of other risk factors to influence later health outcomes. Cumulative models of risk focus on the accumulation of risk factors and on how an increase in the number of risk factors an individual is exposed to might translate into an increase in risk for poor functioning (Sameroff, 2000). In other words, cumulative models predict that as the number of risk factors increases, there is an increase in the likelihood of poor outcomes. Two types of cumulative risk models, described next, offer variations in the hypotheses about how the presence of additional risk factors might be associated with poor physical health outcomes in adulthood.

Linear Risk Models

One type of cumulative risk model is a *linear* model, which emphasizes that each increase in early risk is associated with significantly greater risk for later disease. Two key assumptions go along with this model. First, one must assume that each adverse experience conveys more or less equal risk in shaping health. Linear models do not place any weight on the *relative severity* of risk factors. Instead of focusing on the characteristics of the risks, linear models focus on the *quantity* of risk factors. The second assumption of this model is that the various adverse experiences are nonredundant in their ability to predict later health. In other words, each risk factor creates additional strain or burden on individuals in a way that leads to worse health in adulthood. Although some early adverse experiences, such as neglect and poverty, may lead to the same specific deficit in access to resources (e.g., poor or neglected children may struggle to receive adequate food and health care), according to a linear risk model, an individual who is poor *and* neglected would have worse health outcomes than an individual who is poor but *not* neglected.

Support for a linear risk model comes from a recent study by Evans and Kim (2012), who examined the role of cumulative risk exposure as a predictor of markers of physiological wear and tear (i.e., allostatic load, a biological marker described in more detail in the next section). In this study, researchers created an index of cumulative risk exposure score by summing across items about physical risk (e.g., noise, housing problems) and psychosocial risk (e.g., violence in the home). Evans and Kim found that cumulative risk exposure at age 13 was a predictor of allostatic load at age 17. These findings are particularly notable because the markers of wear and tear (including measures of endocrine, cardiovascular, and metabolic functioning) were measured while participants were still young (i.e., during adolescence), so it will be important to examine whether cumulative risk exposure predicts individuals' accelerated aging and chronic disease later in life.

Threshold Risk Models

Threshold risk models, like linear risk models, focus on the number of risk factors present. Unlike linear risk models, however, threshold models predict that only after people experience a certain number of adverse experiences will their risk for poor health increase. Once people pass this threshold, they are likely to experience health problems. In this way, threshold models allow for the experience of some adversity without necessitating that each exposure to stress must lead to later health problems, as is the case in linear models. In other words, for every health outcome, there is some tipping point at which early adversity poses a serious risk for poor health. Moreover, at this tipping point, risk factors may have synergistic properties, such that the combined effect of the risk factors is much worse than the sum of each risk factor in isolation.

Some of the best evidence for threshold risk models comes from the Adverse Childhood Experiences study, which examined over 9,000 individuals who were enrolled in a large insurance health maintenance organization (Felitti et al., 1998). Participants completed self-report assessments about 17 adverse experiences that may have occurred in childhood, including abuse, violence, and parental mental illness. These experiences were categorized into seven domains of adversity, and participants received a total score indicating the total number of domains in which they were exposed to risk. This cumulative risk score was then used to predict physician-diagnosed diseases. As predicted, early adversity was associated with heart disease, cancer, and strokes. Interestingly, however, individuals were at increased risk for these diseases only when they reported four or more adverse experiences. When participants reported three or fewer adverse experiences, they were not at increased risk for these diseases.

Notably, in many studies, adverse experiences cluster together more than one would expect by chance (Crouch et al., 2000). This pattern of clustered risks may explain some of the observed threshold findings. For example, one risk in isolation might reflect circumstances that are beyond the control of caregivers (e.g., single parents in poverty may have limited abilities to raise their social status). Children who experience poverty but not maltreatment, parental psychopathology, or other serious risks may grow up in an environment that is lacking in material resources but otherwise stable and conducive to healthy development. These children may in fact be shielded from some of the most toxic aspects of poverty. Despite their economically stressed conditions, they would have access to a supportive caregiver who is reliable and responsive to their needs. In contrast, children who are exposed to many adverse experiences might endure chaotic, unsupportive family contexts that are ill-equipped to meet the needs of growing children. For these children, who face a multitude of risks, it is quite possible that their total exposure to stress is well beyond the sum of each stress alone; such multiplicative effects can be identified with threshold models.

In summary, both linear and threshold cumulative models offer a heuristic for explaining the role of early adversity in shaping later health. These models suggest that risk is best captured at the level of total exposure to risk, with the general framework that greater exposure to adversity will translate to more physical health problems in adulthood. These models do not differentiate between different *domains* of risk exposure (e.g., abuse from primary caregivers, neighborhood violence, access to resources); instead, these models posit that adverse experiences across domains will exert a negative influence on long-term health outcomes. In addition, these models typically do not take into account the timing of exposure to adversity, which limits researchers' ability to examine whether there are sensitive periods in which the experience of early adversity is most likely to translate into health problems in adulthood. Further, cumulative models explicitly ignore the relative severity of risk factors; as such, these models can be viewed as relatively crude approaches to defining risk. Yet despite this somewhat unsophisticated approach to quantifying adversity, many researchers have found strong evidence for cumulative risk models in the prediction of chronic disease outcomes in adulthood.

Diathesis–Stress Models

One question of great interest to developmental psychopathologists focuses on why some individuals seem to be at greater risk than others for poor functioning (Shonkoff & Phillips, 2000). One popular approach to answering this question is through testing of diathesis–stress models (e.g., Ingram & Luxton, 2005). In these models, a particular risk factor (e.g., poverty) is associated with poor outcomes only for individuals who have some sort of vulnerability, which might include a genetic risk factor, temperamental quality, or other personality characteristic. These vulnerability factors increase individuals' susceptibility to the negative effects of adversity. This model can be useful in examining connections between early exposure to adversity and adult health by focusing on whether there are specific individuals for whom stressors might be most likely to lead to poor health outcomes as a result of their early experiences.

To date, most diathesis–stress studies of vulnerability to early adversity have focused on adult mental health outcomes (e.g., Moffitt, Caspi, & Rutter, 2006). Recent evidence suggests that diathesis–stress models will be useful in future examinations of the links between early adversity and physical health. Brody and colleagues (2013) examined the family emotional climate in early adolescence and two gene polymorphisms (the short allele of the 5-HTTLPR gene and 7+ repeat of DRD4) as predictors of allostatic load in early adulthood. These two genetic polymorphisms were of particular interest because they have been suggested to confer sensitivity to family environments (e.g., Bakermans-Kranenberg & van IJzendoorn, 2011; Belsky, Bakermans-Kranenberg, & van IJzendoorn, 2007). Brody et al. found that individuals who had the short allele for 5-HTTLPR and 7R allele for DRD4 and who were exposed to less supportive family environments had greater allostatic load (a composite measure that included body mass index (BMI), blood pressure, and neuroendocrine functioning) relative to individuals without both "sensitivity" alleles. Individuals with these same alleles but living in supportive family environments did not have elevated allostatic load. Further, the quality of the family environment was not directly associated with allostatic load. These findings are provocative in suggesting more nuanced ways that family experiences might confer risk for allostatic load for certain individuals with particular genetic vulnerabilities. This line of research is still in its infancy; additional work is needed to better understand what vulnerability factors (e.g., genetic liabilities, temperament) best identify individuals for whom early adversity is most likely to be associated with poor health in adulthood.

Differential Susceptibility

In contrast to diathesis–stress models, models of differential susceptibility posit that vulnerability sources actually are better viewed as *plasticity* factors that magnify the risk for poor outcomes in adverse conditions and amplify the likelihood of positive outcomes in more supportive environments (Belsky, 1997; Belsky et al., 2007; Ellis, Boyce, Belsky, Bakermans-Kranenberg, & van IJzendoorn, 2011). Theories of differential susceptibility, including Belsky's (2005) differential susceptibility theory and Boyce and Ellis's (2005) biological sensitivity to context theory, are similar to diathesis–stress models in that they predict that certain individuals with particular characteristics (e.g., genetic predispositions, temperaments) will be more negatively affected by unsupportive environments relative to other individuals who have different genetic or temperamental characteristics. At the same time, however, differential susceptibility models assert that the traits that put some individuals at risk for exponentially worse outcomes also predispose the same individuals to better-than-expected outcomes given supportive contexts, leading researchers to argue that these individuals are both "for better and for worse," depending on their environment (Belsky et al., 2007, p. 300). Like diathesis–stress models, differential susceptibility models may be useful as a way of documenting why some individuals are more adversely affected than others by exposure to harsh conditions in early life. Differential susceptibility models take this idea a step further, however, by suggesting that the same individuals who flounder in adverse conditions may be ones who would thrive in more supportive contexts.

Evidence for differential susceptibility has been found for the prediction of a variety of outcomes, including mental health and behavior (for a review, see Belsky & Pluess, 2009), but to our knowledge, no evidence has been documented for differential susceptibility in studies of early adversity and adult physical health. Notably, however, it was Boyce et al.'s (1995) observations of children's illness rates that motivated the theory of biological sensitivity to context. In this study, highly reactive children had the *lowest* rates of illness in supportive environments and the *highest* rates of illness in unsupportive environments. Thus, it seems reasonable to predict that similar models of differential susceptibility will be evident in the study of early adversity and adult physical health.

Buffering Models

Similar to diathesis–stress models, buffering models help clarify the specific contexts in which risk factors are associated with poor outcomes. The main difference, however, is that buffering models uncover *protective* factors that can help mitigate the negative effects associated with early risk (e.g., Chen Miller, Kobor, & Cole, 2011; Miller, Lachman, et al., 2011). These models offer great starting points for the development of interventions; once a protective factor has been identified, interventions can target this domain with the goal of minimizing the negative outcomes associated with risk.

For example, as mentioned earlier in this chapter, Miller and colleagues (2011) examined the connection between early SES and metabolic syndrome at midlife and found that maternal care served as a buffer, such that individuals from poor backgrounds who experienced high levels of maternal nurturance were not at risk for metabolic syndrome. Given that many of the early

adversities that children face are difficult to resolve quickly (e.g., poverty is a chronic and pervasive form of adversity), efforts to uncover buffers that can lessen the negative impact of adverse experiences may prove to be particularly instrumental from a public health perspective.

Developmental Trajectory Models

One of the core themes of development is the notion that individual differences exist across development (Shonkoff & Phillips, 2000). Waddington (1957) argued that early in development, organisms have a range of possible developmental pathways (what Waddington called the epigenetic landscape). Over time, these pathways become more constrained and deterministic as a function of increasing constraints and limitations on the developing system. Further, the developing behaviors and systems become more canalized and resistant to change over time. According to Waddington, changes in the developmental trajectory are most likely to occur at decision points—transition periods with multiple options for the subsequent course of development. This theory proposes that major deviations from normative development early in life (e.g., child neglect) would lead to major changes in expected outcome (in this case, physical health) relative to minor deviations that take place at later points in development. Waddington's ideas about developmental pathways became the foundation for many theories that sought to explain variation in developmental trajectories.

Developmental trajectory models posit that there is a progressive pruning of possible pathways across development, an idea that is consistent with other developmental theories that emphasize the importance of early critical or sensitive periods in development (e.g., Bowlby, 1973; Shonkoff & Phillips, 2000). The issue of sensitive periods has been relatively unexplored in relation to early adversity and adult physical health. There is an assumption that early childhood represents a sensitive period in which adverse experiences have a disproportionately large influence on health trajectories, but empirical tests of this idea have been lacking. Is early childhood a unique time for the development of long-term health problems? Might there be other periods of development—such as adolescence—in which exposure to adversity is likely to confer greater risk for health problems?

Some evidence suggests that each exposure to adversity at different developmental periods confers risk for poor health outcomes (e.g., Singh-Manoux et al., 2004). Other evidence, however, suggests that experiences in infancy and early childhood are particularly potent for the long-term risk for infectious disease (e.g., Cohen, Doyle, Turner, Alper, & Skoner, 2004). For example, Cohen et al. (2004) examined adult participants' reactions to virus exposure as a function of early-life socioeconomic conditions. Following intranasal exposure to rhinovirus, participants were monitored for cold symptoms. As hypothesized, childhood SES was associated with cold systems. Notably, the strongest effects were found for SES at the earliest ages of measurement (12–24 months), with a progressive decline in the strength of the connection between SES and susceptibility to colds when examining later-childhood and adolescent family SES.

Evidence from some animal studies suggests that there may be windows of development in which stressful experiences lead to biological tendencies (e.g., Meaney & Aitken, 1985) and health outcomes (e.g., Ackerman, Hofer, & Weiner, 1975). These kinds of developmental timing studies are difficult to conduct in humans; intervention studies and the use of naturalistic experiments can help identify whether there are particular periods in development during which individuals are especially sensitive to exposure to adverse conditions.

Waddington's epigenetic landscape can be used to explain the processes involved in two developmental trajectory models (described in the next two subsections). These models document the processes through which development unfolds over time in a nonlinear pattern and can help explain how (a) individuals with different backgrounds and risk exposure experience the same physical health problems later in life and (b) how individuals with the same risk exposure ultimately experience dramatically different outcomes in adulthood. These models can serve as useful guides for understanding the complex ways in which early childhood adversity can contribute to adult physical health.

Equifinality

As we have already discussed, there is evidence linking early adversity to cardiovascular disease, diabetes, and a number of other chronic diseases of aging. One question that arises when looking at the links between adversity and health is: How do different adverse experiences—many of which are nonoverlapping experiences—lead to the same poor health outcomes? What happens across development that leads individuals with different backgrounds ultimately to share the same chronic diseases? Models of *equifinality* document the process through which different starting points in development may lead to the same outcome (Cicchetti & Rogosch, 1996). As Waddington (1957) theorized, individuals will vary in their developmental

trajectories, in part because of variations in choices and conditions at key decision points that shape subsequent experiences. As such, it is possible that a complex series of decisions made across the early years of life will set into motion a series of developmental trajectories that share a common endpoint (e.g., diabetes, cardiovascular disease). It may be that even though individuals from impoverished or abusive backgrounds experience different day-to-day stressors in childhood, the consequences of such stressful experiences may have the same effect on physiological regulatory systems, coping and regulation of emotional distress, and health behaviors that shape the course of disease.

For example, early adversity—whether such adversity includes maltreatment or poverty—may cause individuals to be vigilant toward threatening information in the environment and mistrusting of others. These characteristics shape the manner in which people engage their social worlds, making them more likely to elicit conflict and rejection and less likely to garner warmth and support. The experience of early adversity may shape success in forming and keeping long-term, high-quality relationships. Early adversity also is associated with poor self-regulation and coping skills, wherein the future is highly discounted in favor of immediate gratification, including engagement in risky or unhealthy lifestyle behaviors (e.g., high-fat diets, excessive alcohol consumption, drug use). Over time, these proclivities and experiences exert wear and tear on the body, with potential repercussions for disease outcomes. Thus, even though two individuals may have had unique starting points and sources of adversity (e.g., poverty versus abuse), they may come to share the same chronic health problems in adulthood because of a series of events across the life span that constrained their development and shaped their progression toward disease (Cicchetti & Rogosch, 1996; Miller et al., 2011).

Multifinality

Like models of equifinality, the focus of multifinality models is on the trajectories that explain developmental processes and how unique experiences can change the long-term path toward health or disease. Of course, not all individuals are affected in the same way by the experience of early adversity. Multifinality models help explain how individuals with similar starting points (e.g., growing up in poverty) develop varied outcomes over time (Cicchetti & Rogosch, 1996). These models can be particularly informative for understanding the different mechanisms that explain how individuals who share common adverse experiences in childhood face unique health problems decades later.

Individuals can take different trajectories for a number of reasons. For example, intervening factors can offset negative trajectories, as illustrated in tests of buffering models (e.g., Miller, Lachman, et al., 2011). In these cases, individuals who experience adversity do not go on to develop poor health outcomes because something in their development (e.g., a supportive parent, a new role model) changed the course of their trajectory. Similarly, as discussed in models of diathesis–stress and differential susceptibility, individuals might possess vulnerability or plasticity factors (e.g., genetic liabilities, temperamental traits) that explain why some individuals are more adversely affected by negative environments than others (e.g., Brody et al., 2013). Further, evidence for multifinality can emerge when individuals who are exposed to the same adversity go on to face different disease outcomes in adulthood (e.g., heart disease versus cancers versus autoimmune disease). In this case, the nature of the disease endpoint may differ across individuals for a variety of reasons (e.g., genetic predispositions), but disease morbidity can be traced back to the same initial stressor.

Developmental Cascades

Another model of development emphasizes the possibility that early experiences may influence the development of subsequent systems or domains (Masten & Cicchetti, 2010; Rutter & Sroufe, 2000). These developmental cascade models are particularly useful in depicting the connections between early experience and later adaptation (or maladaptation), particularly when the causal explanation for such a link is unclear. These models explain how problems in one domain of functioning (e.g., physical abuse in the parent-child relationship) can spill over into other areas of functioning (e.g., poor lifestyle behaviors) across development. Methodologically, researchers measure multiple domains of functioning across several time points (usually at least three of each; Masten, Burt, & Coatsworth, 2006). Analytically, cascade models control for the longitudinal stability of each domain while also including the cross-lagged paths across domains to test the extent to which one domain of functioning is influencing another. Developmental cascade models might provide insight into how it is possible that detrimental effects resulting from early experiences of childhood adversity might lie relatively dormant for decades, only to emerge as experiences of chronic disease in mid- and late adulthood. For example, the experience of adversity in childhood is unlikely to transform immediately into cardiovascular disease or other chronic diseases of aging. Nevertheless, as

described earlier in relation to individuals' developmental trajectories, exposure to early stressors might influence children's health behaviors, interactions with others, and outlook for the future. These subtle intervening steps along the path from early adversity to adult health would represent instances in which early exposure creates a cascade of aftereffects, which reverberate biologically across numerous systems and ultimately lead to chronic diseases in adulthood. In this way, cascade models can identify the steps along the progression from early adversity to later physical health problems.

Although these models have become quite popular in identifying spillover effects associated with mental health problems and social functioning (e.g., Bornstein, Hahn, & Haynes, 2010), cascade models have been underutilized in investigations of early adversity and adult physical health, in part because longitudinal studies are needed with multiple waves of assessments of adversity and health. Another difficulty with these study designs is that the same measure of health across ages might be impractical. For example, disease outcomes such as diabetes and cardiovascular disease are less likely to emerge before adulthood, so equivalent health measures across time points may not be available.

One study examined the cascading effects from family adversity and poverty in childhood to self-reports of health in adulthood (Herrenkohl et al., 2010). In this study, childhood family adversity was associated with adolescent internalizing symptoms, which in turn were associated with poor self-reported health in adulthood. These findings demonstrate that cascade models can be useful in identifying mechanisms that explain the progression from early adversity to later health. Research is needed using these types of models in samples with more objective measures of adult health.

BIOLOGICAL INTERMEDIARIES LINKING EARLY ADVERSITY TO ADULT PHYSICAL HEALTH

Now that links between early adversity and adult physical health have been clearly identified, the next step is to identify what biological processes translate the stressful experiences into the physical environment of disease pathogenesis (i.e., what biological mediators carry the effects of early adversity under the skin). In the last several decades, significant progress has been made in understanding the biological correlates of stress. This burgeoning area of research is due, in part, to Campbell and Fiske's (1959) long-standing calls to conduct multitrait-multimethod research, as well as directives to conduct research at multiple levels of analysis (e.g., cellular, molecular, individual, family, and societal levels; Cicchetti & Dawson, 2002). These data provide new insights and establish a conceptual approach for future studies mapping relations between early adversity and physical health. Yet at the same time, there are limits to what these biological mechanisms can tell us about why early adversity is an important determinant of physical health and disease.

In this section, we provide a nonexhaustive review of several of the most widely studied biological processes thought to translate early adverse experiences into chronic diseases of aging. These biological mediators have received considerable theoretical and empirical attention for their potential role in explaining how early adverse experiences contribute to disease and accelerated aging. We provide a critical review, highlighting the strengths and weaknesses of each mechanism and documenting the limits of conclusions that can be drawn when evidence is found for a link between biological processes and early adversity. We note that other biological mediators have been examined in relation to early adversity and later health outcomes (e.g., sympathetic and parasympathetic nervous system activity), but our focus is on mediators that have been, and continue to be, the major thrust of research in this area.

Hypothalamic-Pituitary-Adrenocortical Axis

One potential mechanism that has received widespread attention is the HPA axis. This hormonal response system is present in organisms ranging from birds to humans and can be activated by a broad range of mental and physical stressors (McEwen, 1998; McEwen & Stellar, 1993; Weiner, 1992). Next we provide a review of the HPA axis and common measures used to capture HPA axis activity. After that, we review evidence supporting the notion that HPA axis activity functions as a biological mechanism linking early adversity to adult health outcomes. We then discuss some important caveats that should be taken into consideration when evaluating the role of HPA axis functioning as a mechanism linking early adversity with health outcomes.

Cortisol: Background and Measurement

Activation of the HPA axis occurs when neurons in the paraventricular nucleus of the hypothalamus secrete corticotropin-releasing hormone (CRH). This molecule travels to the anterior pituitary gland, which responds by secreting a pulse of adrenocorticotropin hormone (ACTH). The ACTH signal is carried in the blood to the

adrenal glands, which synthesize and release cortisol into the bloodstream. Cortisol then travels throughout the body through the bloodstream and acts on a wide range of tissues. Of all the hormones released in this cascade, cortisol has gained the most notoriety, probably because of its widespread regulatory influences. Cortisol is a steroid hormone belonging to the glucocorticoid family, and it is thought to play a key role in the biological stress response system. In addition, cortisol plays an important role in the central nervous system, where it is involved in learning, memory, and emotion; in the metabolic system, where it regulates glucose storage and utilization; and in the immune system, where it regulates the magnitude and duration of inflammatory responses and the maturation of lymphocytes (Sapolsky, Romero, & Munck, 2000). Cortisol's role in regulating such a wide range of physiological systems has helped motivate research focused on its possible role in linking early adversity to adult physical health.

Cortisol levels in the body exhibit a diurnal rhythm, characterized by high levels upon waking, proceeded by a rapid increase in cortisol after approximately 30 minutes (a feature known as the cortisol awakening response [CAR]), followed by a progressive decline in cortisol levels across the day (Kirschbaum & Hellhammer, 1989). Thus, cortisol research tends to incorporate one or more of the following indices of cortisol: (a) the size of the CAR; (b) the slope of the cortisol diurnal rhythm; (c) reactivity to naturalistic or laboratory-based stressors; and (d) metrics reflecting total cortisol output over some unit of time, typically the day, as reflected by area under the diurnal curve or urinary cortisol output (Adam & Kumari, 2009; Miller, Chen, & Zhou, 2007). These measures of cortisol output are thought to provide distinct information about HPA axis functioning. For instance, the CAR, which is regulated in part by the suprachiasmatic nucleus (Clow, Thorn, Evans, & Hucklebridge, 2004), is thought to play a role in mobilizing energy stores for the demands of the day (Hucklebridge, Mellins, Evans, & Clow, 2002). Further, an increase in the CAR is thought to reflect an increase in life stress, whereas a reduced or blunted awakening response is indicative of a failure to recruit the resources needed to tackle the day's demands (Chida & Steptoe, 2009). Normatively, cortisol has a diurnal rhythm that is characterized by a pronounced decline from morning through evening, although there appears to be substantial intra- and interindividual variability in this pattern, even among healthy persons (e.g., Stone et al., 2001). Nonetheless, flat rhythms that lack the typical diurnal decline often are seen in persons exposed to chronic stress (Gunnar & Vazquez, 2001) or with chronic psychiatric disorders, such as posttraumatic stress disorder (e.g., Yehuda, Golier, & Kaufman, 2005). Indices of total cortisol output are thought to provide a cumulative estimate of how much of this hormone bodily tissues get exposed to over some defined period of time, such as a day. Levels that are either too high or too low are thought to be detrimental for health (though via different pathways; see Heim, Ehlert, & Hellhammer, 2000; Raison & Miller, 2003; Miller et al., 2007; Sternberg, Chrousos, Wilder, & Gold, 1992).

Evidence for the Role of Cortisol as a Biological Intermediary

Evidence from a number of studies on stress-related changes in the output of cortisol has helped shape the notion that the HPA axis may serve as a biological intermediary linking early adversity to adult physical health. Meta-analytic findings of studies linking chronic stress to cortisol activity suggest that there is considerable variability (Miller et al., 2007), however. For example, connections between chronic stressors and HPA activity varied dramatically as a function of the timing of the stressor, whether the stressor involved trauma, whether the stressor was controllable or physically threatening, as well as individual emotional responses to the chronic stress (e.g., feelings of shame, loss). For example, individuals who faced physical stressors, such as war, and traumatic, uncontrollable stressors had high volumes of cortisol output over the day. In contrast, individuals facing chronic or controllable stressors did not differ from controls in their total daily output of cortisol. These findings suggest that cortisol is perhaps not best viewed as a generic marker of stress; it may, however, be a marker of stress under certain contexts and conditions (e.g., when experiencing traumatic and uncontrollable stressors). This view reinforces the findings of an influential meta-analytic study of cortisol responses to acute stress, which showed that levels of the hormone rise only in experimental settings that evoke uncontrollable social-evaluative threats (Dickerson & Kemeny, 2004).

Notably, the best predictor of cortisol levels is the timing of a chronic stressor (Miller et al., 2007). Studies that focused on temporally distant stressors found lower-than-normal cortisol, whereas studies that focused on individuals' current experience of stress found elevations in cortisol levels. This finding suggests that stress might initially trigger a burst of cortisol, eventually leading to adaptations to the HPA axis that are meant to limit the damage that might result from sustained periods of heightened cortisol levels. In other words, it may be that the body mounts a counterregulatory response such

that cortisol output rebounds below normal levels. This rebound effect makes sense in light of the fact that the HPA axis is regulated by a potent negative feedback circuit, in which elevated levels of cortisol suppress the output of CRH and ACTH by acting on glucocorticoid receptors in the brain.

Consistent with these meta-analytic findings, a number of studies have found that exposure to a wide range of early adversities, including socioeconomic disadvantage, neglect, abuse, and the loss of caregivers, is associated with later hypo-activation of the HPA axis. For example, in a prospective sample of adopted children, those who experienced severe neglect and abuse prior to the adoption (as reported by the adoptive parents) had lower morning cortisol values and flatter diurnal slopes in adulthood compared to individuals who did not experience neglect or abuse prior to the adoption (van der Vegt, van der Ende, Kirschbaum, Verhulst, & Tiemeier, 2009). Similarly, in a sample of older adults, Gerritson et al. (2010) found that the experience of any early adversity (e.g., abuse, poverty, parental divorce, loss) was associated with reduced morning cortisol levels and flatter diurnal slopes.

Further, several studies have found evidence for a long-term effect of parental separation and loss on HPA axis functioning. In a small study of adult men, the loss of a parent in childhood was associated with greater cortisol levels throughout the day compared to men who did not lose a parent (Nicolson, 2004). Additional evidence suggests that prolonged separations from parents could be connected to adult HPA axis functioning (Kumari, Head, Bartley, Stansfeld, & Kivimaki, 2013). Using data from the British Whitehall II study, Kumari and colleagues (2013) found that the experience of prolonged maternal separation before the age of 16 was associated with flatter diurnal slopes compared to adults who did not experience prolonged maternal separation. Notably, these effects did not differ as a function of the reason for the separation (e.g., maternal death, wartime evacuation). Further, individuals who experienced parental separation exhibited larger cortisol awakening responses relative to individuals who did not experience parental separation.

Some evidence suggests that socioeconomic disadvantage is associated with adult HPA axis functioning (e.g., Li, Power, Kelly, Kirschbaum, & Hertzman, 2007). For example, using data from the 1958 British cohort study, Li et al. (2007) examined participants' SES at birth and ages 7, 11, and 16. For men (but not women), low SES in childhood was associated with greater cortisol output as indexed by area under the curve, even when controlling for adult SES.

Cortisol as a Biological Intermediary: Considerations and Caveats

Although cortisol has regulatory influences on many bodily systems, these dynamics are highly complex. The result is that it is often difficult to interpret the biological significance of adversity-related differences in cortisol. Here we discuss these complexities in some detail, with the goal of facilitating more probative research on cortisol's role as an intermediary linking early adversity and later disease.

We begin by noting that a number of steps must take place before the presence (or absence) of cortisol can begin to influence one of the body's tissues or organs. First, cortisol must bind to a specific receptor located inside a cell. Most cortisol that is released into the bloodstream, however, is attached to carrier proteins, such as cortisol binding globulin (CBG) or albumin. When cortisol is attached to these proteins—which is about 90% of cortisol that is produced—it is unable to traverse cell membranes. Consequently, it cannot get inside the cell to bind to receptors. The other 10% of cortisol making its way through the bloodstream—which is free, or unattached to carrier proteins—must go through several steps before it is capable of modifying tissue. First, the hormone must traverse cell membranes and avoid being excreted by a structure called the multidrug resistance (MDR) pump, which expels molecules that threaten homeostasis. Further, it must avoid being converted to its inactive form by an enzyme called 11-β-hydroxysteroid dehydrogenase. Then it must bind to either a glucocorticoid or mineralocorticoid receptor, once those receptors shed some accessory molecules known as heat-shock proteins (see Raison & Miller, 2003, for a review of the mechanisms behind glucocorticoid signaling). Once cortisol has progressed through these steps, the newly formed receptor-hormone complex must translocate to the nucleus, where it is then capable of modifying the cell's program of gene expression.

Clearly, several (often overlooked) steps must take place between the release of cortisol and the ultimate effect of cortisol on tissues of interest. An important implication of this multistep progression of cortisol activity is that even if a particular psychosocial factor of interest can be linked to the release of cortisol, the signal may not be heard downstream in the tissues of interest. One reason for this is that, as already discussed, most tissues are equipped with a host of counterregulatory mechanisms, such as carrier proteins (e.g., CBG) and the MDR pump that potentially can intervene in this process to ensure that acute changes in cortisol do not drastically disrupt homeostasis. This means that even if cortisol levels are increased markedly by a stressor, the tissues that are regulated by cortisol may

not be affected because counterregulatory mechanisms may alter how loudly cortisol's signals are heard. For example, cells may alter the characteristics of the receptors to which cortisol binds. In addition, cells can reduce the density and activity of their receptors. Receptors that are downregulated or desensitized will pass on fewer signals to the nucleus of the cell, where gene expression occurs (Cole et al., 2007). Even in the absence of connections between a given stressor and cortisol, however, it is quite possible that there is ongoing activity at the level of the receptor that has important implications for physical health. In other words, the sheer volume of unbound cortisol in the body (and the amount that cortisol levels change in response to stressors) does not provide enough information to explain how the HPA axis could be involved in shaping physical health outcomes.

One study nicely illustrates these complexities. In a sample of adult participants who varied in early-life SES (Miller et al., 2009), participants with low-status backgrounds had modestly elevated cortisol relative to high-status participants. Importantly, however, examination of gene expression profiles in leukocytes indicated that individuals from low-SES backgrounds had decreased glucocorticoid signaling relative to people with high early-life SES. In other words, the leukocytes of individuals from low-SES backgrounds were registering *less* cortisol signal. These findings are provocative because examination of cortisol levels alone would have suggested that low early-life SES confers risk for elevated circulating cortisol in adulthood, with the corresponding assumption that this extra cortisol could have a damaging effect on tissues and organs. Yet the gene expression findings suggested that individuals from low-SES backgrounds had cells that were hearing less signal from cortisol, not more—a finding that indicates that examination of circulating levels of cortisol alone is an insufficient assessment of HPA axis activity. Thus, the study of cortisol in isolation—without also considering glucocorticoid signaling—does not provide an accurate picture of the ways in which HPA axis activity might serve as a biological intermediary linking early adversity and later health outcomes.

An additional concern centers on the extent to which cortisol values exhibit within-person stability over time. Some recent studies highlighting cortisol's lack of temporal stability (Ross, Murphy, Adam, Chen, & Miller, 2014; Shirtcliff et al., 2012) call into question its plausibility as a mediator of the lengthy underlying pathologic processes that give rise to most chronic diseases of aging. For example, one recent study showed that only 13% of the variability in cortisol values over a 6-year period was attributable to a stable, traitlike component (e.g., Shirtcliff et al., 2012). Instead, over half of the variability in cortisol values could be explained by situational, or statelike, factors at the time of the assessment. Thus, even over relatively short periods of time, cortisol activity shows very little stability. In other words, if individuals' cortisol levels are not stable over relatively short intervals and appear instead to reflect dynamic changes in situational experiences of close temporal proximity, then it is unlikely that chronically dysregulated HPA axis activity is a mechanism that causally contributes to diseases such as cardiovascular disease, which evolves over decades.

In summary, the HPA axis has been a popular target for mechanistic research on early adversity and adult disease over the last several decades. This explosion of research has led to a greater understanding of how responsive the system is to stressful experiences. Important features of cortisol, however, often have been overlooked in this research (e.g., glucocorticoid receptor availability and sensitivity, counterregulatory mechanisms that influence cortisol's actions in tissue, temporal stability and dynamics of cortisol). These features are important details that cannot be ignored, particularly if researchers want to develop a biologically plausible understanding of cortisol's role in explaining how early experiences influence chronic disease outcomes.

Allostatic Load

Allostatic Load: Background and Measurement

Some of our physiological systems, such as body temperature and blood pH, are tightly regulated, such that they operate within a narrowly specified range of functioning, with *homeostatic* set points around which the body attempts to achieve stability. Other systems, however, operate under much more flexible states, and they can change adaptively in response to the demands of the environment. In these circumstances, the systems operate under conditions of *allostasis* ("stability through change"). The main difference between allostatic systems and homeostatic systems is that allostatic systems have dynamic and adjustable mechanisms in place that are responsive to the environment, whereas homeostatic systems operate to achieve a specific set point *despite* the environmental demands. For example, during exercise, our bodies achieve thermoregulation through perspiration (thus achieving a fairly static temperature despite changes in behavior), but our heart rate adjusts to the increased physical demands by beating faster.

Another way of viewing allostasis is as a measure of plasticity. This ability to adapt to environmental demands enables temporary adjustments in physiological systems that allow for the ultimate goal of overcoming stressful or challenging situations. This plasticity in physiological systems, however, is thought to come at a cost: When these systems repeatedly are required to adapt to meet the demands of the environment—as in cases when individuals are exposed to chronic, repeated stressors—the systems may become inefficient or less flexible in their ability to adapt. The systems may not shut off completely, or there may be delays in the return to baseline functioning as a result of repeated environmental stressors. McEwen and colleagues (McEwen, 1998; McEwen & Seeman, 1999; McEwen & Stellar, 1993; Singer, Ryff, & Seeman, 2004) developed the concept of allostatic load, which refers to the wear and tear that results from repeated stressors that activate the body's regulatory controls in an attempt to achieve a new level of stability (and recovery from stress). Over time, this wear and tear manifests itself in the dysregulation of multiple physiological systems. Measures of allostatic load, therefore, sometimes are viewed as reflecting the number of physiological systems that are experiencing disruption in optimal functioning.

A number of physiological systems are thought to be regulated under allostatic control, including the neuroendocrine, metabolic, cardiovascular, immune, and autonomic and sympathetic nervous systems (Singer et al., 2004). Accordingly, frequently a variety of biomarkers are included in measures of allostatic load. Neuroendocrine measures of allostatic load often include cortisol and catecholamines, such as epinephrine, norepinephrine, and dopamine. Immune measures often include markers of inflammation, including the cytokines interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) as well as C-reactive protein (CRP), an acute phase protein that promotes inflammation by enhancing phagocytosis. Indicators of metabolic dysfunction include high-density lipoprotein cholesterol (this value is reverse-scored so that low values indicate risk), low-density lipoprotein cholesterol, triglycerides, glycosylated hemoglobin, and blood sugar. Cardiovascular components of allostatic load frequently include systolic and diastolic blood pressure and heart rate. Finally, waist-to-hip ratio or BMI usually are included in measures of allostatic load as indicators of adiposity. Researchers frequently create quartiles for each index, assigning individuals into dichotomous categories depending on whether their values are in the top high-risk quartile. These categories are then summed across indices to create a total composite score for allostatic load.

One question related to this method of creating a composite score is whether the indicators of physiological dysregulation reflect a single underlying construct or if they are better conceptualized as separate components of physiological dysregulation. To answer this question, McCaffery, Marsland, Strohacker, Muldoon, and Manuck (2012) tested the factor structure of allostatic load indices. In this study, researchers found support for a single factor underlying the allostatic load indices, including measures of metabolic, inflammatory, and cardiac vagal activity measures. These findings lend support to the practice of using one composite score for the wide range of physiological systems that are included in assessments of allostatic load.

With that said, McEwen and others (e.g., McEwen & Seeman, 1999) have sorted allostatic load markers into categories, including primary mediators, secondary outcomes, and tertiary outcomes, in a way that is conceptually and methodologically useful. Primary mediators include chemical messengers, such as cortisol, dehydroepiandrosterone (DHEA), and catecholamines, which are thought to relay messages from the brain to organs and tissues that mobilize resources for coping with stress. Secondary outcomes are hypothesized to reflect the impact that repeated signaling from primary mediators has on target organs and tissues. These outcomes include tissue- and organ-specific indicators of health, including waist-to-hip ratio, blood pressure, glycosylated hemoglobin, and cholesterol. Finally, tertiary outcomes (which currently are not included in most measures of allostatic load) include actual diseases hypothesized to result in part from allostatic load (e.g., cancer, dementia, heart disease). The basic premise of this model is that primary mediators influence the development of secondary and finally tertiary (disease) outcomes. This hierarchical organization of allostatic load indicators offers a conceptually grounded approach to understanding how a stressor could contribute to wear and tear on the body and ultimately lead to the accumulation of chronic diseases. As far as we are aware, however, longitudinal studies have not yet been done to confirm the theorized progression from primary mediators to secondary and finally tertiary outcomes. Prospective studies of this sort will be useful for improving our understanding of the role of allostatic load in translating early adversity into disease.

Evidence for the Role of Allostatic Load as a Biological Intermediary

Allostatic load has been proposed as a biological intermediary linking early adversity to adult health (e.g., Repetti,

Robles, & Reynolds, 2011; Taylor, Way, & Seeman, 2011). For example, in a prospective study of individuals in Sweden, Gustafsson, Janlert, Theorell, Westerlund, and Hammarstrom (2012) found that the experience of social stressors (e.g., loss of a parent, social isolation) and material adversity (e.g., parental unemployment, poor standard of living) in adolescence and early adulthood were uniquely predictive of allostatic load in midlife. Similarly, using data from the MIDUS study, Gruenewald et al. (2012) found that low SES in childhood and adulthood predicted allostatic load in adulthood. Notably, low SES at each developmental period was associated uniquely with later allostatic load. Further, Gruenewald and colleagues found evidence of a cumulative effect: Individuals who were persistently low in SES across childhood and adulthood had greater allostatic load relative to individuals who were consistently high in SES or who were upwardly mobile. Interestingly, these effects remained significant even after controlling for health behaviors and psychosocial variables in adulthood. Evidence from studies with children and adolescents suggests that these processes might start early in life (e.g., Evans & Kim, 2012).

Allostatic load, in turn, has been shown to be predictive of cardiovascular disease and mortality (Seeman, McEwen, Rowe, & Singer, 2001; Seeman, Singer, Rowe, Horwitz, & McEwen, 1997). These links are not particularly surprising, given that the index includes measures of blood pressure and central adiposity, two of the most established risk factors for cardiovascular disease and health. Reductions in allostatic load have been associated with lower 7-year mortality risk (Karlamangla, Singer, & Seeman, 2006). These findings have led researchers to suggest that allostatic load may be a pathway through which exposure to early adversities can lead to greater health problems in adulthood (e.g., Danese & McEwen, 2012; Gruenewald et al., 2012). Indeed, one strength of the allostatic load model is that the composite score reflects the extent to which multiple physiological systems are operating under strained conditions. If early adversity results in different biological cascades across individuals, leading to a wide variety of endpoints with possible dysregulation, then a single biological marker might not always be linked to adverse experiences. By creating a composite measure of allostatic load, researchers are better positioned to capture the connection to early adversity. Thus, in a way, the practice of creating a composite measure of allostatic load provides a simplified way of testing for multifinality in the links between early adversity and long-term health outcomes by creating a single outcome variable that reflects a diverse array of physiological systems.

Allostatic Load as a Biological Intermediary: Considerations and Caveats

One of the concerns about allostatic load, as it has typically been operationalized in this literature, is that its components vary in how proximal they are to actual disease. As McEwen and Seeman (1999) emphasize, primary mediators, such as cortisol, probably are quite distal causes of physical health problems, which act through more proximal secondary outcomes, such as insulin resistance, to cause disease. Yet most studies to date group all of these components into a single aggregate, making the implicit assumption that they are equally powerful and equally detrimental in terms of long-term health. We recognize that there is factor-analytic evidence to support a single composite score for allostatic load (McCaffery et al., 2012). However, it still seems likely that allostatic load components vary considerably in how proximal, necessary, and sufficient they are in the disease process. Indeed, allostatic load might foreshadow cardiovascular disease not because individuals are elevated on a diverse set of physiological measures but because they have high blood pressure and excess central adiposity, which are well-established risk factors for this condition. This lack of clarity in the utility of allostatic load indices makes it difficult to know whether this measure provides incremental value over already established stand-alone risk factors for poor health and whether some components may be more powerful contributors than others for poor health outcomes. Moreover, the practice of creating nonstandardized cut points for dichotomizing the indicators raises several methodological issues. For one, this practice often is done using sample-specific cutoffs, such as top quartiles, which makes it difficult to compare across studies and increases the odds of chance findings. Another problem with the cutoff approach is that it ignores the fact that functioning and risk within each domain may follow a more linear gradient. If domains have validated cutoffs with prognostic significance (e.g., blood pressure, cholesterol), then these established criteria may be more meaningful indices to use when sorting individuals into high- and low-risk categories.

One final concern relates to the choice of measures included in allostatic load composites. As described earlier, indices of allostatic load are categorized into primary mediators, secondary outcomes, and tertiary outcomes. Yet this level of categorization is not reflected in the single composite measure of allostatic load. Instead, these markers are aggregated across the different stages without consideration of the relative importance of each indicator or acknowledgment that primary mediators should prospectively predict secondary outcomes, which

should in turn shape the onset and progression of diseases. Given that the hierarchy is so fundamental to the theory behind allostatic load, it is unclear why these indicators are treated equally. In fact, some measures in and of themselves may pose no clear health risk, or do so in only a very distal manner, whereas other indices (e.g., blood pressure) are actually measures of damage already done to the system. For example, having higher-than-average levels of dopamine is not considered a risk factor on its own, but elevated blood pressure and cholesterol are risk factors for cardiovascular disease. Based on the theoretical model, early adversity should be related most closely to the primary mediators of allostatic load, and these changes should presage the onset of secondary outcomes. This kind of cascading model has not been tested to date, however.

In summary, allostatic load has been implicated as a potential biological mechanism linking early adversity to later disease and early mortality. We look forward to the next generation of research on this construct, which we hope will clarify some of the complex issues surrounding conceptualization and measurement of allostatic load. Future studies that can clarify the clinical significance of allostatic load and the processes through which allostatic load contributes to disease will be especially useful.

Telomeres

Telomeres: Background and Measurement

Recently there has been an active interest in the ways in which psychosocial stressors might accelerate cellular aging through changes in telomere structure (Aubert & Lansdorp, 2008; Aviv, 2008; Mather, Jorm, Parslow, & Christensen, 2011; Price, Kao, Burgers, Carpenter, & Tyrka, 2013). Telomeres are nucleoproteins located at the end of chromosomes. Telomeres act like caps that prevent DNA degradation when cells divide and in doing so ensure the stability of chromosomes and the cells themselves. Briefly, when cells divide, replication enzymes are unable to function at the very end of chromosomes (an issue known as the end replication problem; De Lange, 2009). Without telomeres, each cell division would result in segments of chromosomal DNA being lost to replication, meaning that as time went on, progressively more of genetic code (DNA) would disappear. The presence of telomeres slows the progressive erosion of genetic material. Telomeres serve as a kind of buffer for the chromosome, which can absorb successive losses of material with each replication. Because telomeres are comprised of noncoding DNA, or material that is not essential for building proteins, their degradation does not have significant consequences for cellular function in the short term. Moreover, as telomeres shorten with successive replication cycles, cells produce an enzyme, known as telomerase, which acts to restore their length. However, most cells do not contain enough telomerase to maintain telomere length indefinitely. So, with time, telomeres degrade. When this occurs, healthy cells enter a phase known as senescence, where they cease replication and can have limited functional capacity. Thus, cellular senescence is the endpoint of a lengthy process involving repeated cell replications and waning telomerase activity to counterbalance it.

Evidence for the Role of Telomere Degradation as a Biological Intermediary

Telomere length has been viewed by some as a biological marker of aging (Aubert & Lansdorp, 2008; Epel, 2009; Mather et al., 2011). Indeed, health-compromising behaviors, such as smoking, have been related to shorter leukocyte telomere lengths. And to the extent people have shorter leukocyte telomeres, their risks for morbidity and mortality from various conditions increase (e.g., Kimura et al., 2008; Valdes et al., 2005). Some researchers argue that shorter telomeres (relative to telomeres of other individuals of the same age) are an indication of accelerated aging, with the potential for long-term health consequences.

Emerging evidence suggests that early exposure to adversity may be associated with telomere degradation (Drury et al., 2012; Kananen et al., 2010; Tyrka et al., 2010). For example, Tyrka et al. (2010) found that recalled emotional and physical neglect in childhood were associated with shorter telomeres in white blood cells. Similarly, Kananen et al. (2010) reported a connection between early adversity (e.g., parental unemployment, parental mental health problems) and telomere length in white blood cells in a sample of anxious and nonanxious adults. Further, in a sample of Romanian children, Drury and colleagues (2012) found a link between buccal cell telomere length in middle childhood and time spent in early institutional care. Additional evidence for a link between early exposure to adversity and later telomere attrition comes from Kiecolt-Glaser and colleagues (2011), who found that older adults who had experienced multiple childhood adversities had shorter telomeres in white blood cells compared to adults who were not exposed to early adversities in childhood.

Some evidence suggests that supportive parenting experiences may play a role in buffering children from telomere degradation associated with early adversity. In a cross-sectional study, Asok, Bernard, Roth, Rosen, and

Dozier (2013) found that children from high-risk families who experienced responsive parenting had greater buccal cell telomere length than children from high-risk families whose parents were less responsive. These findings offer some insight into the ways in which telomere length may be influenced by both supportive and unsupportive environmental contexts, although longitudinal studies will be needed to lend support to the notion that these environmental inputs play a causal role in affecting telomere length.

Telomere Degradation as a Biological Intermediary: Considerations and Caveats

The studies just reviewed consistently find linkages between early adversity and telomere length, which suggests the provocative hypothesis that accelerated cell aging might be a mechanistic pathway to later disease. However, as is the case with the broader literature on telomeres, several features of these studies complicate interpretation. First, all of the studies were based on a single measurement of telomere length. There are significant individual differences in telomere length across the population (Aviv, Valdes, & Spector, 2006; Geronimus et al., 2010; Takubo et al., 2002). Thus, with a single time point measure, we cannot be certain whether the disparities in telomere length are a consequence of the earlier adversity or are simply a correlate. For example, it could be that the same children who are exposed to adversity are born with relatively short telomeres, for partly or fully unrelated reasons. To sort this complexity out, multiwave studies or natural experiments are needed.

Along these lines, some of the most convincing evidence that exposure to adverse conditions in childhood accelerates telomere degradation comes from the Environmental-Risk Longitudinal Twin Study, a nationally representative sample of children in Great Britain (Shalev et al., 2013). Researchers assessed children's exposure to violence in childhood, including domestic violence, bullying and victimization, and maltreatment from an adult. Telomere length in buccal cells was assessed at baseline (age 5) and 5 years later (age 10). Shalev and colleagues (2013) found that children who were exposed to two or more types of violence had accelerated telomere erosion across the 5 years compared to children who were exposed to one type of violence or who were not exposed to violence.

These are provocative findings from a methodologically rigorous study. They represent an important starting point for mechanistic research on early adversity. Nevertheless, there is some uncertainty about the clinical relevance of telomeres in buccal cells for the kinds of chronic diseases of aging we are concerned with in this chapter. For those conditions, telomere length at the site of disease pathogenesis—for example, in the heart for cardiovascular disease, the pancreas for diabetes, the immune system for virally mediated cancers and infectious diseases—would be more germane. It is possible that buccal cells, or other easily accessed specimens, such as white blood cells, can serve as a proxy for telomeres in these tissues of interest. But given the degree of tissue specificity seen in most cellular processes, this seems like a dubious assumption to proceed on, at least until the field has accumulated sufficient evidence to justify it. Indeed, recent studies indicate that the correlations between telomere length in buccal and immune cells are modest at best (Gadalla, Cawthon, Giri, Alter, & Savage, 2010).

This problem is not limited to buccal cells. As an alternative, researchers often measure telomere length in leukocytes, based on the quite reasonable presumption that immune cell aging could have deleterious consequences for host resistance to infections and cancers. But even when leukocytes are collected, most studies assess telomere length in bulk populations with heterogeneous cellular content. Peripheral blood contains a number of different types of leukocytes, including granulocytes, lymphocytes, and monocytes. These cell types differ significantly in their telomere profiles (Aubert & Lansdorp, 2008). What makes this methodological decision even more problematic is that people vary in the relative proportion of these cell types in peripheral blood, and adversity is known to shift that balance (Segerstrom & Miller, 2004). Thus, any linkage between adversity and telomeres could reflect individual differences in the balance of cell types present in the assay rather than cellular aging per se. To rule out this possibility, researchers need to account for cellular heterogeneity through statistical controls, or, even better, physically sort cells into different phenotypic clusters prior to telomere analysis (e.g., see research on stress and telomeres by Cohen et al., 2013; Damjanovic et al., 2007).

Aside from the heterogeneity in cell types used for telomere assessment, it is important to consider the fact that not all cells in the body replicate. Of the major immune cells, only lymphocytes do so routinely. This fact raises the question of what telomere length means in samples that are mainly composed of nonreplicating cells. (This is the case with most whole blood analyses of telomeres, where roughly 50% to 80% of the cells are nondividing granulocytes or monocytes.) Some researchers have argued that in nondividing cells, such as granulocytes, telomere length might index senescence of the parent cell—the cell

that divided to form the granulocyte. If so, these measures would take on significant new meaning. But until this issue and others are settled, we remain cautious about the interpretation of the telomere data.

Epigenetics

Epigenetics: Background and Measurement

All cells within an individual carry an identical DNA sequence, which is established at conception and fixed for life. (Lymphocytes and cells that have acquired mutations are exceptions to this rule.) The DNA sequence serves as a blueprint for transcription, the process whereby cells synthesize ribonucleic acid (RNA) molecules—a process known as gene expression. RNA molecules are later translated into proteins, which cells use for structural and functional purposes. Epigenetics describes stable changes in gene expression activity that arise without changes to the gene's DNA sequence (Jaenisch & Bird, 2003; Jirtle & Skinner, 2007). A primary function of epigenetic alterations is to allow cells to develop and maintain specialized functions. For example, epigenetic alterations can modify a cell's ability to transcribe a particular gene into RNA. Because RNA serves as a template for translation of proteins, these epigenetic alterations have downstream influences on how much of the gene's protein ultimately is synthesized. When this process takes place across many different genes, it can give rise to significant phenotypic diversity in cells. This variability is thought to play a role in the long-term development of physical disease (e.g., Rakyan, Down, Balding, & Beck, 2011), although the nature of these pathways is still largely unknown.

Epigenetic modifications to DNA typically occur in one of two ways (Whitelaw & Garrick, 2006). The first modification is DNA methylation, which involves the attachment or removal of a methyl group to cytosine residues in a gene's promoter. The methyl groups prevent transcription factors from interacting with DNA to modulate gene expression, which makes the gene inactive. The second form of epigenetic modification involves changes to the chromatin structure that packages the DNA. This process occurs by attaching or removing chemicals from the histone proteins that hold DNA within the cell's nucleus. These proteins cause the DNA near the gene to become more or less tightly coiled, which makes it more or less difficult for RNA polymerase and transcription factors to access its promoter (Whitelaw & Garrick, 2006). These epigenetic modifications can be quite stable over the life span, and sometimes they are passed along to daughter cells during mitosis. As such, it is possible for early experiences—such as early exposure to adversity—to create lasting epigenetic modifications that persist over the life span, which may help explain how early experiences become embedded in the epigenome and contribute to chronic diseases many decades later. Measurement of epigenetic modifications typically relies on DNA microarray analysis. This process assesses the presence of methylation at multiple promoter sites in each of many thousands of different genes (e.g., these analyses can quantify the proportion of sites that are methylated).

Evidence for the Role of Epigenetic Modifications as a Biological Intermediary

Recent evidence suggests that epigenetic processes might serve as pathways through which early experiences can bring about long-term changes in the activity of genes, thereby contributing to the pathogenesis of disease (e.g., Roth, Lubin, Funk, & Sweatt, 2009). Much of the early work in this area centered on animal models, including the work by Meaney and colleagues (see Meaney, 2001, for a review). Meaney found that, in rats, certain caregiving experiences early in infancy were associated with long-term changes in rat pups' stress response physiology (Liu et al., 1997). Specifically, rat pups that received high levels of maternal licking and grooming and arched-back nursing showed attenuated cortisol responses to threat and increased exploratory behavior—effects that lasted into adulthood (Caldji et al., 1998; Liu et al., 1997). In a series of elegant mechanistic studies, Meaney and his colleagues discovered that these lasting differences in stress responsivity arose through epigenetic changes to glucocorticoid receptor genes in the hippocampus of the offspring (Weaver et al., 2004)—in other words, in the rat pups that received more licking and grooming. In essence, maternal nurturance in the early days of life led to epigenetic changes in the offspring's hippocampus including demethylation of DNA and acetylation of histone proteins, which facilitated expression of the glucocorticoid receptor gene across the life span (Weaver et al., 2004). Greater expression of this receptor, in turn, enabled tighter regulation of the HPA axis, the hormonal system that controls the release of cortisol in response to stress. Notably, Weaver et al.'s (2004) findings revealed that the epigenetic modifications that took place during the first week of the rat pups' lives persisted into adulthood, suggesting considerable stability in these early programming effects.

Recent work with humans suggests that early experiences—including adversity—also bring about epigenetic changes that affect gene expression (e.g., Bick et al.,

2012; McGowan et al., 2009; Oberlander et al., 2008). In one study, hippocampal tissue from suicide victims was assessed postmortem (McGowan et al., 2009). Epigenetic modifications varied as a function of whether participants had been abused as children: Individuals who had been abused had greater methylation at sites in the glucocorticoid receptor gene promoter. In a prospective study of maternal depression and infant cortisol reactivity, Oberlander and colleagues (2008) found that exposure to prenatal maternal depression led to epigenetic changes in infants' gene expression that were associated with elevated stress reactivity in the HPA axis. Specifically, prenatal exposure to depression during the third trimester was associated with increased methylation at sites in the glucocorticoid receptor gene promoter. Further, methylation at this location was related to heightened cortisol reactivity when the infants were 3 months old, suggesting that this epigenetic alteration may have functional implications for HPA axis regulation. Additional evidence for lasting epigenetic modifications as a result of early adversity comes from a sample of adults who were exposed to famine prenatally as a result of wartime food scarcity and their unexposed same-sex siblings (Heijmans et al., 2008). Compared to their unaffected siblings, prenatal exposure to famine was associated with reduced DNA methylation in the promoter of the insulin-like growth factor II gene, which plays a role in insulin- and growth-related activities.

Additional evidence from studies of early adversity and epigenetic modifications also supports the notion that adverse experiences are biologically embedded in the epigenome (Borghol et al., 2012; Essex et al., 2013; Tyrka, Price, Marsit, Walters, & Carpenter, 2012). For example, Essex and colleagues studied DNA methylation in the buccal cells of 109 adolescents from a larger longitudinal study. In this sample, the extent to which adolescents' buccal cells were methylated varied as a function of their parents' stressors years earlier. The timing of stress influences differed for mothers and fathers. Specifically, methylation during adolescence was related to maternal stress during infancy but paternal stress during preschool. These findings are consistent with those of Tyrka and colleagues (2012), who found connections between early-life familial adversity (e.g., parental death, maltreatment) and methylation of the glucocorticoid gene promoter in white blood cells. Adults who, as children, experienced early familial adversity had increased methylation of the promoter region relative to adults who experienced more stable and nurturing care in childhood. Borghol and colleagues (2012) similarly identified connections between early SES and methylation of white blood cells in 40 participants from the 1958 British cohort study. In this detailed microarray analysis of approximately 20,000 genes, over 1,200 gene promoters were differentially methylated as a function of early-life SES—over twice as many regions that were differentially methylated as a function of adult SES. Lam et al. (2012) posed similar questions about early SES in a sample of healthy adults aged 25 to 45 but found a more modest association with methylation patterns.

These findings suggest that early adversity may leave an epigenetic residue in the genome of some cells. Based on basic research in model systems, there is reason to suspect these residues may be durable and persist over lengthy periods of time. This stability could help explain how early experiences can develop into diseases decades after the exposure to adversity has subsided. With that said, we do not yet have the prospective, longitudinal evidence in humans to know whether the findings reflect this kind of lasting biological imprint versus some other process or methodological artifact.

Epigenetic Modifications as a Biological Intermediary: Considerations and Caveats

Like the other biological mechanisms we have discussed, the study of epigenetic modifications to DNA poses some important methodological challenges that will need to be addressed in future studies. For example, in trying to extend Meaney and colleagues' findings (Weaver et al., 2004) to humans, research has made use of cord blood cells, white blood cells, and buccal cells. These approaches make sense logistically. Hippocampal tissue cannot be noninvasively acquired in living humans, whereas cells from the blood, mouth, and umbilical cord can be extracted noninvasively. With that said, it is important to keep in mind that very little is known about how well these tissues can serve as a proxy for the extent of methylation in the hippocampus. Many researchers believe the epigenetic processes exist mainly to allow tissues to functionally specialize. If that is true, we need to be cautious about assuming cross-tissue consistency in epigenetic marks, at least until there is evidence to support doing so. Further, the use of heterogeneous pools of cells for measuring DNA methylation raises some concerns. As was the case with telomeres, people vary in the relative proportion of cell types that make up their immune systems and their cord blood, and stress can shift the balance of cell types. And as was the case with telomeres, the degree of methylation varies across cell types (Lam et al., 2012; Ohgane, Yagi, & Shiota, 2008). Together, these issues complicate interpretation of the existing epigenetic data in humans—any disparities linked to adversity

could reflect differences in the cellular composition of samples or the degree of methylation. Some studies have addressed the issue of cellular composition in their analyses. Lam and colleagues (2012), for example, found that white blood cell methylation was correlated with the relative amount of lymphocytes and monocytes present in individuals. Thus, assessments of DNA methylation may need to take into account the relative proportion of cell types in the sample.

Finally, it will be important for future studies to explore the functional implications of adversity-related changes in methylation. Much work in this area proceeds on the assumption that epigenetic changes will have consequences for gene expression, as they do in the animal studies. But this assumption is not always borne out in studies of humans, which rely on large heterogeneous pools of cells from the buccal cavity or the immune system. For example, in the study by Lam et al. (2012), associations between methylation and transcriptional profiles were very modest, and this has been the case in other studies too. These findings suggest that methylation is likely to be one process among many that are important in regulating gene expression patterns. Thus, future epigenetic research in this area would be most helpful if it supplemented methylation data with studies of the functional consequences of methylation for gene expression or other relevant outcomes (e.g., see Oberlander et al., 2008, study). Also important in future research will be consideration of other epigenetic mechanisms—such as histone modifications and microRNA expression—that can work in concert with methylation to influence patterns of gene expression.

Inflammation

Inflammation: Background and Measurement

Inflammation occurs when cells of the innate immune system, including neutrophils, dendritic cells, monocytes, and macrophages, gather at the site of an infection or injury. These cells attempt to eliminate the pathogen, rid the body of infected tissue, repair any damage the pathogen caused, and begin the process of healing. The inflammatory response is essential for survival. Without it, minor injuries or infections would be lethal. However, the inflammatory response must be regulated carefully; otherwise, inflammation can become persistent and contribute to the emergence of multiple diseases of aging.

Inflammation is orchestrated by signaling molecules known as cytokines, which are released by immune cells and the damaged tissue. The major cytokines involved with inflammation are interleukin (IL)-1, IL-6, and TNF-α. Researchers sometimes use concentrations of these molecules in circulation as a rough estimate of ongoing inflammatory activity. However, these cytokines are fairly unstable in blood, so a more common approach is to measure CRP, a molecule produced by the liver during inflammation. CRP provides a reliable index of low-grade chronic inflammation over the preceding month or so and is prognostic of morbidity and mortality from a number of chronic diseases of aging, such as diabetes, obesity-related problems, cardiovascular disease, autoimmune disease, and cancer (Danesh, Collins, Appleby, & Peto, 2000; Libby, Ridker, & Hansson, 2009; Ridker, 2007; Yeh & Willerson, 2003). CRP's role is particularly well established in the progression of cardiovascular disease, where in apparently healthy individuals, it presages disease risk in a roughly dose-response manner. The role of inflammation in such a broad array of diseases, along with the relative ease of assessment, has prompted researchers to consider it as a mechanism linking early adversity to later disease.

Evidence for the Role of Inflammation as a Biological Intermediary

Mounting evidence supports the idea that exposure to early adversities is linked to measures of chronic inflammation. For example, in a prospective study of 12,000 adults from diverse backgrounds, early-life SES measured in childhood was inversely associated with CRP, independent of current SES (Pollitt et al., 2007). Similarly, in the British Women's Heart Health Study, evidence for a cumulative effect of SES was found: Lower status across development was associated with increases in CRP (Lawlor, Smith, Rumley, Lowe, & Ebrahim, 2005). Further, links between childhood SES and inflammation were examined in a sample of adults who took part in the Coronary Artery Risk Development in Young Adults study (CARDIA; Taylor, Lehman, Kiefe, & Seeman, 2006). In this study, Taylor, Lehman, Kiefe, and Seeman (2006) found that childhood SES was associated prospectively with measures of psychosocial functioning (e.g., depression, social contacts), which in turn predicted CRP.

Additional evidence suggests that early-life socioeconomic disadvantage confers risk for immune system profiles characterized by proinflammatory responses (Miller et al., 2009). In this study, researchers examined healthy adults who were either low or high in childhood SES (as defined by the prestige of their parents' occupations). Participants' white blood cells were cultured in vitro with a series of microbial products, and the magnitude of the cell responses to these stimuli was indexed by subsequent production of IL-6. Participants who were exposed

to socioeconomic disadvantage as children showed more pronounced IL-6 production in response to bacterial challenges relative to participants from families of high SES. Notably, participant groups in this study were balanced on the prestige of their adult occupations, which removed the possibility that these findings were attributable to adult SES.

Similar evidence has been found for the role of the early family emotional climate on adult inflammation. In the Dunedin longitudinal study, for instance, multiple assessments of early maltreatment and harsh parenting were predictive of CRP at age 32 (Danese et al., 2009; Danese, Pariante, Caspi, Taylor, & Poulton, 2007). For example, Danese and colleagues (2007) reported that adults who had been maltreated as children had a threefold higher level of CRP at age 32 relative to individuals who had not been maltreated. Similarly, those who came from poor backgrounds and were socially isolated as children were also more likely to show high CRP; notably, these risk factors were independent of each other.

Several other studies have assessed inflammation in samples of adults who were asked to report retrospectively on experiences of childhood abuse. In one study, adults who had been abused as children had higher circulating IL-6 and TNF-α levels relative to adults who did not report being abused as children (Kiecolt-Glaser et al., 2011). In the Nurses' Health Study II, Bertone-Johnson and colleagues found a link between retrospectively reported sexual abuse in adolescence and CRP and IL-6 in adulthood (Bertone-Johnson, Whitcomb, Missmer, Karlson, & Rich-Edwards, 2012). Interestingly, however, this pattern did not emerge when examining the link between inflammation and reports of physical abuse.

In the MIDUS sample, Slopen and colleagues (2010) examined a range of adverse early-life experiences as predictors of inflammation. In particular, adversity in childhood and adolescence was measured across three domains, including stressful life events (e.g., parental alcohol or drug problems, school failure), parent-child relationship quality (including relationships with mothers and fathers), and the frequency of verbal and physical abuse. Scores across each of these domains were standardized and then summed to create a composite of early-life adversity. This composite measure was associated with five different biomarkers of inflammation for African-American participants but not for participants of European descent (Slopen et al., 2010).

In summary, emerging evidence suggests that to the extent that individuals are exposed to early adversity, as adults they display evidence of mild, chronic inflammation. Further, many of the chronic diseases of aging (e.g., cardiovascular disease, strokes, autoimmune diseases, some forms of cancer) are widely recognized to involve chronic inflammation. Thus, inflammation could play a mediating role in the links between early adversity and adult physical health.

Inflammation as a Biological Intermediary: Considerations and Caveats

Converging evidence suggests that early adversity may contribute to later disease through inflammatory processes. Despite these encouraging findings, we note that there are several limitations that will need to be addressed in future studies. Like the studies of other biological mechanisms, many of the studies linking early adversity to inflammation rely on a single assessment of inflammation, which limits our ability to conclude that exposure to adversity causally shapes inflammatory activity. Longitudinal studies, with multiple assessments of inflammation, will help clarify the extent to which early stressors lead to changes in inflammation over time. These types of studies also will help to clarify the chronicity of the inflammation. To be plausibly involved in accelerating disease, the inflammation would need to be long standing. Only via multiwave studies can we ascertain whether inflammation is transitory or chronic. Another issue to be addressed in future studies is the fact that most existing studies of inflammation capture ongoing inflammatory activity in peripheral blood rather than inflammation in tissues or organs. Thus, it is unclear whether these measures of inflammation reflect activity happening in the tissues that are directly relevant for chronic diseases (e.g., coronary arteries, pancreas). Finally, nearly all studies focus on proinflammatory processes, but anti-inflammatory signals play an important role in regulating the balance of inflammatory activity. Going forward, researchers should examine both pro- and anti-inflammatory signals to capture a more comprehensive picture of how the immune system responds to adversity.

CONCLUDING COMMENTS AND DIRECTIONS FOR FUTURE RESEARCH

Over the last 30 years, researchers have made considerable progress in identifying links between early adversity and adult physical health outcomes. Findings from epidemiological studies, animal studies, and naturalistic experiments converge on the idea that exposure to early adversity is a risk factor for cardiovascular disease, metabolic disruptions, some cancers, and even early mortality. Great strides

have been made in formulating hypothesis-driven, conceptually based models that set out to test the processes by which early stressful experiences become embedded in the body only to emerge as physical health problems, early aging, and chronic disease several decades later.

Yet despite this wave of exciting research progress, we are only beginning to understand the pathways linking early adversity and health. Many of the studies to date, including retrospective reports and cross-sectional study designs, have significant methodological limitations, which limit our ability to draw strong conclusions about causality. Similarly, our knowledge about the biological mechanisms that might explain the progression from early adversity to accelerated aging and disease in adulthood is considerably lacking. Next we identify several key research areas that will be important to explore in the next generation of studies linking early adversity to adult physical health. The list of research priorities is far from exhaustive; nevertheless, advancements in each of these areas will increase our understanding of how and under what contexts early adversity shapes long-term physical health outcomes.

Expanding Research to Other Periods of Development

The large majority of the research reviewed in this chapter focuses on the impact of adversity that occurs during the early childhood years. There is good reason for this emphasis: During these early years, many biological systems are especially sensitive to environmental effects, and many organ systems and tissues are undergoing a rapid period of development, expansion, and specialization. At the same time, however, these early years capture only a brief glimpse of development, and we believe that other developmental periods as well as transitions across developmental periods may be particularly sensitive to the effects of adversity in ways that can make individuals susceptible to physiological disruptions and progression toward disease. We describe several of these opportunities for future research next.

Prenatal Period

The *fetal-programming model* (Lucas, Fewtrell, & Cole, 1999) posits that in utero experiences shape infants' development by exposing them to maternal signals about environmental conditions to be expected at the time of birth. From an evolutionary perspective, the ability to send signals to the developing fetus has a number of advantages for survival: The fetus, in response, can alter its development in preparation for the demands of the environment. Cottrell and Seckl (2009) have suggested that prenatal overexposure to glucocorticoids might be one mechanism through which prenatal stress results in greater risk for health problems, such as cardiovascular disease and metabolic abnormalities. Evidence from animal studies lends support to this hypothesis, but whether such an effect is present in humans remains to be seen.

Findings from a number of studies suggest an important link between prenatal experiences and subsequent outcomes in infants (e.g., Field et al., 2004; Oberlander et al., 2008; Sandman, Davis, & Glynn, 2012; Sharp et al., 2012) and adults (Heijmans et al., 2008). Using a sample of mothers who varied in their levels of depression during and after pregnancy, Sandman and colleagues (2012) examined the hypothesis that infants are calibrated in utero for postnatal environmental conditions. As predicted, infants with the best performance on measures of mental development (e.g., sensory-perceptual acuity) and psychomotor development (e.g., body control) were ones who had similar pre- and postnatal environmental experiences—even when those experiences included maternal depression. In other words, infants who experienced maternal depression pre- *and* postnatally fared better than infants whose mothers were depressed at only one time point. These somewhat counterintuitive findings suggest that infants receive important programming signals in utero, and when these signals do not correspond with the external environment, infants show early delays in motor skills and mental development. Evidence about the long-term deficits related to the incongruence between prenatal and postnatal environments is lacking, however. It is possible that these effects disappear by childhood or have little long-term health relevance. Nevertheless, continued research in this area will be useful for determining the extent to which prenatal exposure to adversity confers risk for long-term physical health problems.

Adolescence

Adolescence is a developmental period of multiple transitions, characterized by fundamental changes in biological, cognitive, social, and psychological processes (Holmbeck, 1994; Lerner & Castellino, 2002). Researchers now widely consider adolescence to be the second critical period of development, and experiences during this period are thought to have an unusually strong influence on long-term health outcomes. This plasticity confers unique sensitivity to environmental and contextual experiences that can have a lasting impact on health. Indeed, from a health perspective, adolescence represents a critical time in which long-term health trajectories are set in motion, and the precursors of chronic disease often emerge during this period (Lule, Rosen, Singh, Knowles, & Behrman, 2006).

Further, recent estimates suggest that a growing number of adolescents show symptoms that are indicative of metabolic disruption (Cornier et al., 2008).

Compared to the extensive body of research on pediatric and adult health, adolescent health has received far less attention, which is surprising given that adolescents represent 25% of the world's population (Sawyer et al., 2012). The World Health Organization, UNICEF, and the *Lancet* (Sawyer et al., 2012; United Nations Children's Fund, 2012; World Health Organization, 2014) recently highlighted the importance of investing in adolescent health research in order to address significant gaps in knowledge about determinants of health across the life span. The growing prevalence of health problems in childhood and early adulthood, including obesity and diabetes, has both immediate and long-term social, economic, and medical consequences. Although adolescent mortality rates are quite low, the precursors of chronic disease often emerge during this period (Balagopal et al., 2011; Berenson & Srinivasan, 2005). For example, risk for heart disease, including the early formation of atherosclerotic plaques, becomes apparent in adolescence. Thus, attempts to identify the processes that set adolescents on trajectories that culminate in health problems across the life span are of significant public health and economic importance. Moreover, identification of early-onset predisease processes has the potential to identify individuals for whom targeted interventions may be most beneficial.

An additional question about the connection between stressors and health outcomes in adolescence relates to the fact that the onset of puberty corresponds with many of the transitions that take place during this developmental period. We know little about how puberty and the corresponding shifts in stress hormones interact with stressful experiences to shape physical health outcomes—both in adolescence and into adulthood. These questions will be important to address in future research.

The Study of Transitional Periods Across Development

Transitional periods in development, such as the transition from elementary school to middle school and the transition to adolescence, have the potential to be stressful periods for children (Graber & Brooks-Gunn, 1996). These periods often are marked by dramatic shifts in behavior, responsibility, rules, and opportunities. Given the sweeping changes across social, cognitive, affective, and biological domains and the onset of new stressors that take place around developmental transitions, researchers should examine how transitions may create stressors that put children at risk for health problems. Transitional periods that affect social and emotional functioning also may engender changes in physiology and risk for poor health. To study biological changes that co-occur with transitional periods, longitudinal studies will be necessary, an issue we discuss in more detail later.

Strengthening Study Designs

Throughout this chapter, we have noted some of the important methodological limitations that limit our ability to make definitive conclusions about the extent to which early exposure to adversity leads to chronic diseases of aging in adulthood. Next we review a few of the main study design limitations and offer some solutions for stronger research designs that can be used to test research questions about how early adversity becomes biologically embedded in the body and translates into physical disease in adulthood.

To date, cross-sectional and retrospective studies make up the bulk of studies on early adversity, biological intermediaries, and later health outcomes. Although there certainly is merit in identifying connections at the cross-sectional level, our ability to draw conclusions about the causal nature of these links is substantially limited with these study designs. For one thing, retrospective reports have significant weaknesses (as discussed earlier in the chapter), which call into question the validity of the reports. Further, cross-sectional study designs cannot shed light on whether exposure to adversity contributes to dysregulation and disease or is simply a correlate of these outcomes. Future research needs to incorporate longitudinal study designs with multiple assessments of biology to allow for stronger statements about the direction of effects. These study designs can be costly and time-intensive, but they are important for researchers who wish to take a developmental approach to understanding the processes through which early adversity influences health. Of course, it is not necessary for researchers to conduct decades-long research investigations focused on experiences from infancy through adulthood in order to add to our understanding of adversity and health. For researchers who wish to test mediational models and developmental cascades models, at least three time points are preferable, with sufficient time between assessments for measures of interest to change during that period. Longitudinal designs that are conducted over relatively short time frames still can add insight into the intermediary processes that take place on the road from early adversity to chronic disease.

Another concern focuses on the nature of various proposed biological mediators of the link between early adversity and adult health. Many of the biological

mechanisms that we have described in this chapter are thought to serve as intermediate phenotypes, and they should be assessed at multiple time points to examine change over time. Research that can map the trajectories of these biological markers across time would greatly add to our understanding of how these mechanisms eventually lead to disease. Moreover, researchers studying these biological mediators should be aware of the strengths and weaknesses of the mechanistic concepts and methods used to measure them. They also should be aware of the untested assumptions about the clinical relevance of a number of proposed biological mechanisms (e.g., telomeres in nonreplicating cells, circulating cortisol).

Another way to strengthen future study designs is to conduct experimental and quasi-experimental studies. Given that some environmental experiences cannot be assigned randomly for ethical reasons, intervention studies may be a useful way to evaluate changes that result when reducing environmental exposure to adversity. Some evidence suggests that interventions designed to address socioeconomic disadvantage may lead to improvements in physical health. In the 1990s, the United States Department of Housing and Urban Development undertook a large-scale randomized intervention study in five large U.S. cities to examine the health outcomes associated with moving out of poverty (Ludwig et al., 2011). Families were randomly assigned to one of three groups: One group received housing vouchers to move to a low-poverty area, another group received the vouchers without the low-poverty location restriction, and a third control group did not receive vouchers or counseling. Approximately 10 years later, Ludwig and colleagues measured a variety of metabolic outcomes, including glycosylated hemoglobin and BMI. Women who moved to low-poverty neighborhoods had decreased rates of extreme obesity and glycosylated hemoglobin relative to women in the control families. These findings suggest that reducing exposure to adverse neighborhood experiences may have long-term health implications. This study was focused on health outcomes of adult women, but it is possible that similar intervention programs will have beneficial effects for children living in poverty. In fact, these types of intervention programs may have a stronger influence on children compared to adults if such an experience can create a lasting change in children's developmental trajectories.

Buffers and Protective Factors

As described earlier in this chapter, epidemiological findings suggest that exposure to stressful adverse experiences is a significant risk factor for poor health outcomes. Nevertheless, not all individuals who experience adversity get sick (e.g., Chen et al., 2011; Miller, Lachman, et al., 2011). Research focused on buffers against the negative mental health outcomes associated with adversity has uncovered key variables that might help explain why some individuals thrive despite early experience with adversity. Researchers have identified intrapersonal characteristics (e.g., temperament, emotion regulation capacities), family characteristics (e.g., sensitive caregiving), and neighborhood factors (e.g., connections to adults in the community, access to support services) that serve as buffers and help protect children from some of the negative consequences associated with exposure to socioeconomic disadvantage and maltreatment.

To date, most of this research has focused on protective factors for mental health outcomes, and only recently have researchers studied whether there might be buffers that mitigate the negative physical health outcomes associated with exposure to early adversity (Chen, Lee, Cavey, & Ho, 2013; Miller et al., 2011). For example, in a sample of healthy adolescents, low SES was associated with higher circulating markers of inflammation, but only for adolescents who did not have a supportive role model (Chen et al., 2013). Similarly, in a sample of adults who experienced low SES in childhood, high levels of maternal warmth buffered adults against a phenotype characterized by proinflammatory signaling (Chen et al., 2011). These findings are notable because they offer insight into the reasons why not all individuals exposed to early adversity go on to experience poor health in adulthood.

Another related question concerns the timing of these buffers. Recent empirical evidence for the positive outcomes associated with protective factors has focused on buffers that are temporally connected to the experience of adversity (e.g., receiving supportive caregiving or having a role model while living in poverty). Research on the effects of these buffering factors also should examine the extent to which buffers at other important periods of development might play a role in mitigating risk. For example, adolescents who experience adversity in early childhood may benefit from supportive caregivers or role models in adolescence. It may be, however, that support systems need to be in place at the time of exposure to adversity to offset the negative experience. These questions will be particularly important to explore in order to shed light on what factors are most effective at ameliorating the negative health outcomes associated with exposure to adverse experiences.

Translational Implications

After identifying the protective factors that shield children from the negative health effects associated with early adversity, clinicians and researchers should use this information to develop testable interventions to examine whether the programs that foster behavioral changes also shape biological intermediaries in ways that have long-term implications for physical health. For example, programs designed to provide mentors and supportive role models to at-risk children may alter biological pathways that ultimately could improve long-term physical health outcomes. Similarly, parenting interventions that reduce children's exposure to harsh parental caregiving could shape biological processes in ways that minimize risk for accelerated aging and early mortality. For example, evidence from an intervention study suggests that children whose foster parents received a positive parenting intervention showed declines in basal cortisol levels relative to control children whose foster parents did not receive the intervention (Fisher, Gunnar, Chamberlain, & Reid, 2000). Although this study had a small sample size (just 10 children in each condition), the findings offer some indication that parenting interventions might affect predisease pathways in ways that are beneficial to health. Community programs that are designed to improve family socioeconomic conditions may provide opportunities for researchers to examine whether a modest change in the experience of early adversity shapes epigenetic modifications, HPA axis activity, and inflammation. These kinds of translational studies will require researchers and community advocates to work together to advance our understanding of how early adversity shapes physical health.

Linking Research on Developmental Psychopathology and Health Psychology

Throughout this chapter, we have noted a number of instances in which exposure to early adversity has been associated with long-term mental health but not physical health outcomes (e.g., effects of exposure to interparental violence, natural disasters). This trend is not entirely surprising, given that programs of research often are focused on a narrow set of outcomes (e.g., mental health *or* physical health). Yet this tradition of focusing on a restricted range of outcomes ignores the fact that researchers interested in developmental psychopathology and health psychology often are motivated by a similar set of research goals. Going forward, we believe that a more integrated and interdisciplinary approach to research on mental and physical health is warranted. To the extent that researchers in these fields can share theories, methods, and work together collaboratively, scientific progress on all fronts will be much more rapid. Indeed, there are some exciting questions at the intersection of these fields, which we hope researchers will soon answer. For example, researchers across these disciplines frequently seek to understand the long-term developmental effects of early exposure to adversity and whether there are intrinsic or extrinsic buffers that can offset the negative outcomes associated with stress. These questions—and many others—will be of central interest in the years to come.

Conclusions

We look forward to the next generation of studies on early adversity and adult physical health. In the coming years, more research on the biological intermediaries linking early adversity and adult physical health will help uncover the processes by which stressful life events translate into chronic disease and accelerated aging. This research should take a developmental approach, using prospective studies and incorporating multiple levels of analysis, from molecular studies to large-scale epidemiological studies. The use of comprehensive models (e.g., models of equifinality and multifinality, developmental cascades, differential susceptibility) will help shed light on questions about (a) the relative timing of events in development (e.g., sensitive periods, transitional periods), (b) the complex interconnections among risk and protective factors, and (c) the biological consequences associated with early adversity. Findings from these studies will offer new ideas that can help inform public policy and clinical practice.

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