CHAPTER 12

Early Environments, Developmental Plasticity and Chronic Degenerative Disease

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12.1 INTRODUCTION

In recent generations, populations around the globe have experienced dramatic shifts in the burden of disease, with infections increasingly replaced by chronic degenerative diseases as the major causes of morbidity and mortality. Explaining these trends has been a central problem for demographers, epidemiologists and biological anthropologists for some time.[1] Four decades ago, Omran[2] proposed a demographic explanation for these trends in the concept of the "epidemiologic transition". He noted that when a population succeeds in controlling infant mortality related to early life infections and malnutrition, life expectancy increases, and as a result a greater percentage of the population survives long enough to be affected by chronic degenerative diseases that only emerge at older ages.

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In addition to this role of population aging, modifiable lifestyle or environmental factors such as diet, physical activity, excess weight gain, smoking and stress also influence the development of many chronic degenerative diseases. Although some of these factors may be viewed as lifestyle "choices", in many societies, one's exposure to both good and bad environmental and lifestyle influences is often powerfully shaped and constrained by societal factors, such as poverty, inequality, class and various forms of discrimination.[3] Taken together, the aging of the global population, combined with these lifestyle and social—structural influences, have traditionally been viewed as explaining the rising global burden of chronic diseases and their differential impacts among different groups within societies.

This chapter will survey a new literature that is bringing a fresh perspective to our understanding of chronic disease epidemiology. Research in recent decades has shown that prenatal nutrition, stress and other early life factors can influence risk for developing conditions such as hypertension, diabetes, heart attack and stroke in adulthood. These relationships reflect the sensitivity of developmental biology to environmental experiences, which can have lingering effects that influence biology and health later in the life cycle. This research suggests that an individual's risk of developing many adult chronic conditions may be established, in part, by experiences much earlier in the life cycle, often beginning before birth. By extension, some of the burden of disease in the current generation of adults may be traced to the social and environmental experiences of their mothers and other recent ancestors.

This chapter will first review evidence from human populations that developmental responses to early life environments can influence adult risk for many common adult chronic degenerative conditions, with a primary focus on the cardiovascular diseases of hypertension, diabetes, heart attack and stroke. It will continue by briefly reviewing some of the developmental and epigenetic mechanisms known to contribute to these relationships, and then briefly explore the hypothesis that these sensitivities in developmental biology may have evolved to allow individuals to cope with changing environmental conditions. The chapter concludes by considering the insights that this literature sheds on two central problems in public health: the rise of chronic disease in populations experiencing rapid nutritional or lifestyle transition, and the patterns of health disparity that map onto social gradients of inequality related to class, ethnicity or socially defined race.

12.2 DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE: EVIDENCE AND MECHANISMS

12.2.1 Early Environments, Developmental Biology and Adult Health

Several decades ago, researchers in the UK observed that the risk of dying from cardiovascular disease (CVD), or of suffering from conditions that precede CVD, such as

hypertension or diabetes, is highest among individuals who were light as newborns.[4–6] Now, hundreds of human studies have replicated similar findings relating lower birth weight to later CVD in populations across the globe, many using longitudinal designs that follow cohorts of individuals over decades as they age.[7–13] It is now well supported that individuals who were born small are more likely to have hypertension,[14] insulin resistance and diabetes,[15,16] abnormal cholesterol profiles,[17] a high-risk visceral pattern of fat deposition[18] and elevated risk of CVD mortality.[19,20]

Infancy and childhood nutrition and growth also predict adult biological and health outcomes. Not unlike birth size, small size in infancy is associated with higher CVD risk in adulthood, while breast-fed infants have lower rates of hypertension, obesity and diabetes as adults.[21,22] There is also evidence that prenatal and postnatal exposures have interactive effects on adult health. For instance, being born small but gaining weight rapidly during childhood predicts the same cluster of adult chronic diseases.[23,24] Thus, it appears that the combination of small birth size and rapid weight gain during postnatal life may be an especially high-risk scenario with respect to developing adult CVD (Figure 12.1).

Although much of this research has focused on nutritional stress, psychological stressors experienced by the mother during or even before pregnancy can lead to similar changes in disease risk in her adult offspring, and these effects can occur even in the

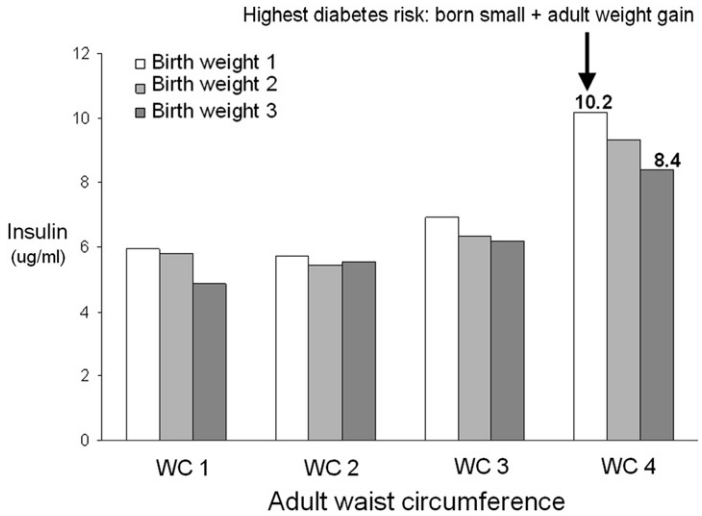

Figure 12.1 How adult fasting insulin relates to birth weight and adult waist circumference among young men living in Cebu City, the Philippines (unpublished data). Men with more abdominal body fat as adults have higher fasting insulin, indicating a higher risk of developing diabetes in the future. Note that the inverse relationship between birth weight and fasting insulin is strongest among the men who are heaviest as adults, and that the highest diabetes risk is found in men who were light at birth but then gained the most weight by adulthood.

absence of changes in birth weight. The fetus is normally shielded from exposure to the glucocorticoid hormone cortisol (a key stress hormone) produced by the mother's body by placental enzymes that inactivate the hormone. The placental capacity to buffer the fetus can be exceeded when the mother is severely stressed, leading to fetal exposure to maternal stress hormones. This, in turn, can contribute to reduced birth size by either directly reducing fetal growth rate or leading to early pregnancy termination.[25] When the fetus is exposed to high levels of cortisol, this can lead to similar changes in CVD risk as observed after fetal nutrient restriction, including high blood pressure, changes in stress reactivity, a tendency to deposit fat abdominally and resistance to the effects of insulin.[26] Collectively, this research is making clear that nutritional or psychosocial stress experienced by the fetus before birth can influence the risk of developing CVD and other chronic degenerative diseases in adulthood.

12.2.2 Mechanisms of Developmental Programming

What biological mechanisms might account for these relationships? Many of these studies relate adult health to birth weight, which is inherently challenging to interpret as a biological measure. Because birth weight partly reflects genetic factors, a relationship between birth weight and adult biology or disease risk could simply reflect the effects of any genes that influence both fetal growth rate and metabolic or physiological processes that contribute to chronic disease risk in adulthood. For instance, insulin not only is related to glucose metabolism and risk of diabetes, but also helps to regulate fetal growth rate. Thus, if individuals within a population vary in which insulin-influencing genes they carry, this could result in a correlation between fetal growth and adult risk of diabetes simply as a result of genetic correlations.[27,28] Although birth weight is a complex multifactorial phenotype,[29] there is now extensive evidence that the relationship between birth outcomes such as birth weight and adult chronic disease are not simply due to genetic influences of this sort.

First, heritabilities for birth weight tend to be quite low. Based upon twin registries, heritabilities for birth weight are typically reported in the range 0.2–0.4 (e.g. Refs 30–32), with national birth weight registry studies finding similar estimates (0.31 for birth weight and 0.27 for birth length in all Norwegian births from 1967 to 2004[33]). This implies that most of the variance in birth weight found within these populations traces to factors other than shared genetic ancestry. Other studies show that maternal influences such as nutritional status, exposure to stress or other factors influencing blood flow to the endometrial lining or placenta are important determinants of a baby's birth size.[34] Importantly, among monozygotic twins, who share identical genomes, the twin born lighter has elevated risk for adverse changes in body composition, risk for diabetes and hypertension later in life,[35,36] showing that differences in birth size predict adult CVD risk among genetically identical siblings.

Perhaps the most important evidence that gestational experiences shape future adult health comes from animal model research, which has used experimentally induced stressors to replicate many of the disease outcomes found in relation to lower birth weight in human populations.[37] For instance, restricting the nutritional intake of pregnant rats, mice or sheep, or directly restricting blood flow to the fetus, increases postnatal blood pressure, cholesterol, abdominal fat deposition and diabetes risk in offspring.[38,39]

Several types of biological adjustment are made by the developing fetus in response to prenatal stressors that contribute to these long-term changes in disease risk. All are examples of *developmental plasticity,* which may be defined as the capacity of the developing body to modify its structure and function in response to environmental or behavioral experiences. The most straightforward mechanism of plasticity involves changes in growth of a tissue or an organ as reflected in size or cell number. For instance, the kidneys of prenatally undernourished individuals tend to be smaller and have fewer nephrons, which increases the risk of hypertension and renal failure in adulthood.[40,41] Similarly, changing the number or type of muscle cells can modify the body's ability to clear glucose from the bloodstream, leading to changes in insulin sensitivity and diabetes risk.[42]

One increasingly well-studied set of mechanisms linking early environments with adult health involves *epigenetic* changes, which are defined as chemical modifications that change the pattern of gene expression in a specific tissue or organ without changing the nucleotide sequences of the DNA.[43,44] Several epigenetic mechanisms have received considerable attention for their likely role as links between early environments and adult health. Chemical modification of histone proteins that the DNA strands are wound around in the cell nucleus can lead to tighter or looser DNA packing in the region of specific genes, reducing or enhancing gene expression, respectively. Methyl groups can also be attached in regions adjacent to specific gene promoters ("methylation"), which can impede binding by transcription factors and thereby silence gene expression in that cell.[45]

Experimental studies using animal models show that modification of nutritional or other characteristics of prenatal or early postnatal rearing environments can lead to durable epigenetic changes that persist into later life to influence biology and underlying processes that contribute to disease risk.[44,46,47] For instance (Figure 12.2A), restricting the protein intake of pregnant rats reduces methylation of the promoter region of the gene that encodes an important stress hormone receptor [glucocorticoid receptor (GR)] in the liver of adult offspring.[48] By reducing methylation, which silences gene expression, this intervention *increases* expression of this receptor, enhancing the liver's metabolic response to stress.[49] In a similar rat model, maternal protein restriction was found to reduce methylation of the angiotensinogen receptor gene in the adrenal gland. The resulting *enhanced* capacity for expression of this gene could contribute to the high blood pressure observed in these animals.[50]

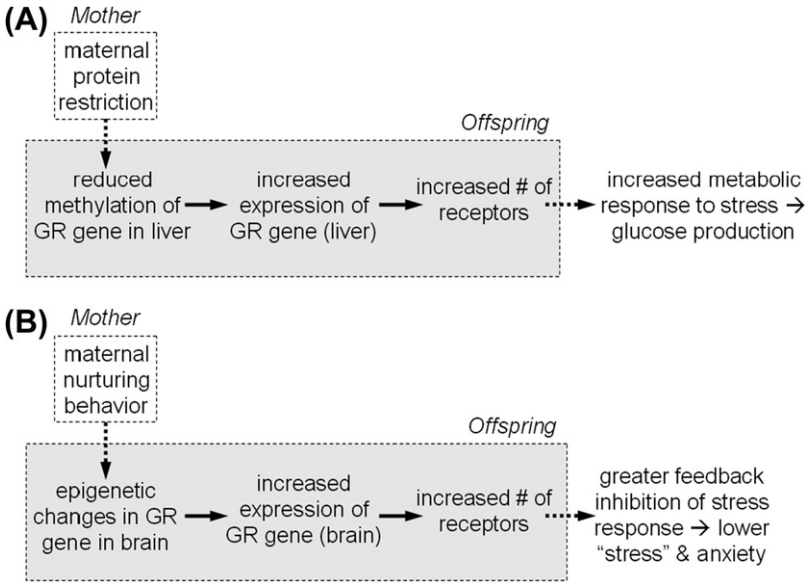

Figure 12.2 Two examples of how early maternal experience or behavior can shape offspring biology via epigenetic changes in gene regulation. (A) When pregnant rats are fed a protein-restricted diet, this can reduce methylation of the receptor that binds to and senses stress hormones (glucocorticoids) in the liver of offspring.[48] Because methylation generally suppresses gene expression, reducing methylation increases expression at the GR gene and thus increases the number of glucocorticoid receptors expressed in the liver. When glucocorticoids increase as a result of stress, these animals have an accentuated capacity to produce glucose for use as energy. This can help them cope with the stressor, but can also heighten risk of diabetes. (B) When rats are raised by nurturing females, they exhibit complex epigenetic changes that increase expression of glucocorticoid receptors, this time in hippocampal (brain) neurons.[51] When these animals experience stress later in life, the increased number of receptors allows the brain to quickly sense rising hormone levels and to shut down further stress hormone production. This contributes to a blunted stress response that reduces anxiety.

The postnatal environment also has important influences on the epigenome. Well-described rat studies have shown that a nurturing maternal rearing style can lead to epigenetic changes in the brain of offspring (Figure 12.2B), lowering their reactivity to stress and reducing anxiety as adults.[51,52] In humans, untreated maternal depression or famine exposure during pregnancy has been shown to predict similar epigenetic changes in offspring, suggesting that comparable epigenetic processes may link early experiences with adult health in humans.[53,54]

In summary, we now have good confidence that the widely documented relationships between early life measures such as birth weight and later CVD partially reflect the effects of the gestational and infancy environments on the development of biological systems, including effects on how the body manages glucose and lipids, deposits fat, regulates blood pressure and responds to stress (for further review see Gluckman et al.[55]) (Figure 12.3). These effects typically reflect changes in the growth and development of

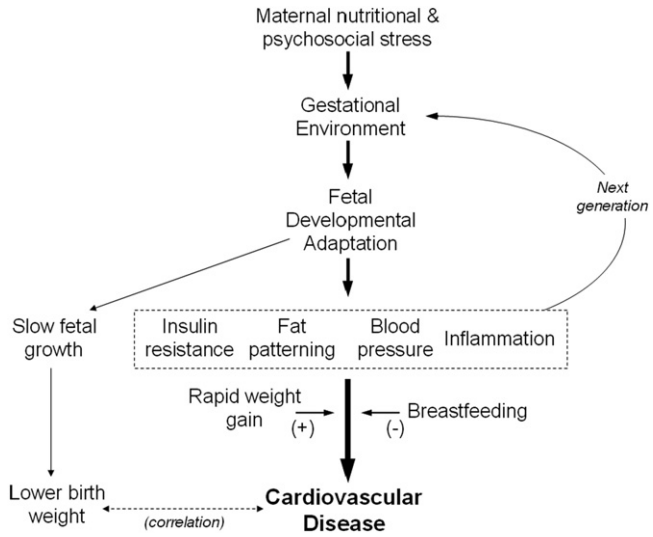

Figure 12.3 Developmental origins of adult chronic disease. Maternal nutritional or psychosocial stressors influence the nutrient and hormonal characteristics of the gestational environment experienced by the developing fetus, which can durably modify multiple biological functions and elevate adult risk for cardiovascular disease (CVD). The arrow relating lower birth weight with CVD risk is dashed to indicate that the relationship is only correlational rather than causal. CVD risk is also elevated by rapid postnatal weight gain, and may be reduced by being breast fed. Some of the adverse adult biological effects of compromised early environments may in turn influence the maternal/gestational environment experienced by the next generation before birth, potentially perpetuating patterns of adverse health across generations.

specific organs and tissues or modifications in the regulation of hormones, metabolism or physiology. They are increasingly being traced to durable, environmentally induced epigenetic changes in the chromosomes that modify gene expression in specific tissues or organs without modifying the DNA itself.

12.3 DEVELOPMENTAL PLASTICITY AS A MEANS OF ADAPTATION

12.3.1 Early Life Developmental Plasticity and Adaptation to Ecological Change

Why might the body modify its developmental biology in response to early life stressors? Some of the lingering effects of early experience on adult health simply reflect unintended side-effects of adaptations made by the fetus to improve its chances of surviving a nutritionally stressful prenatal environment. For instance, a smaller fetus has lower nutritional needs, and the reduced ability of their smaller muscle mass to clear glucose from the blood stream could spare energy for the glucose-hungry brain, which is fragile and large relative to the body during early life.[56,57] Another possibility, which in some ways may be the most straightforward, is incomplete buffering of the fetus against

maternal stressors.[58] A failure of the mother's body, or the placenta, to fully buffer the developing body from nutritional or other forms of stress can lead to impairments with long-term unintended side-effects on biological function and health.

Although these non-functional explanations for plasticity clearly are important, it has also been speculated that developmental plasticity could, in some instances, allow the fetus to prepare for conditions likely to be experienced *after* birth[59–62] (Figure 12.4). Some of the adjustments made by the nutritionally stressed fetus in utero, such as a tendency to deposit more abdominal body fat, and the reduced response of muscle to insulin that spares glucose for use elsewhere in the body, could provide advantages after birth if the postnatal environment is also nutritionally stressful.[61,64] In addition, other systems that change biological settings in response to early environments, such as stress physiology,[51] immunity[65] and reproductive biology,[66] might also be "fine-tuned" in response to early experience.

One challenge to this idea comes from the fact that humans have a long lifespan. Because we typically live for many decades, any conditions that we experience during a few months of early development, such as gestation or early infancy, may not be reliable cues of environments likely to be experienced decades in the future.[60,67] One intriguing possibility is that it is precisely the brief and early timing of many of the body's periods of heightened developmental sensitivity that paradoxically *helps* the developing organism overcome the challenge of reliably predicting conditions well into the future.[58,68] Here, the idea is that the mother's physiology could buffer the fetus against the day-to-day, month-to-month or seasonal fluctuations in the environment, while passing along information about local conditions that is more stable and reliable. Because the mother's biology and behavior have been modified by her lifetime of experiences, the nutrients, hormones and other resources that she transfers to the fetus in utero, or to her infant via breast milk, could correlate with her average experiences more than what she is experiencing during any week or month of gestation itself.[60,67]

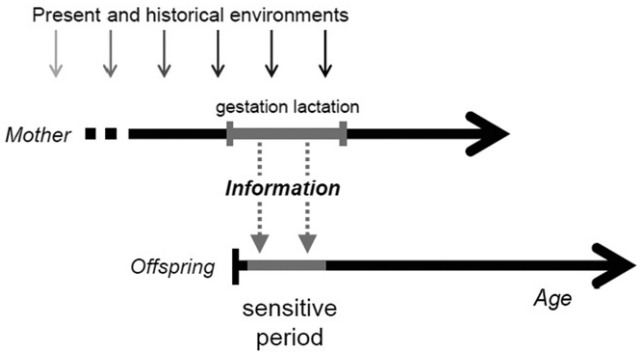

Figure 12.4 Maternal–offspring ecological information transfer and adaptation. The mother's biology and behavior embody a record of her cumulative environmental and social experiences, which can be conveyed to offspring as developmental information via nutrients, hormones, rearing behavior and other cues. *(*Source: *From Kuzawa and Quinn,[63] with permission.)*

Perhaps the best evidence for such a capacity to convey average, rather than transient, ecological information, comes from studies of the effects of a mother's nutrition on the birth weight of her baby.[60] Studies generally find that birth weights tend to be lighter in populations in which nutrition has been marginal for multiple generations. Despite this evidence for environmental influence on fetal growth rate and birth size, supplementing pregnant women generally has minimal effects on the birth weight of offspring. Thus, it appears that long-term history in an environment may be an important influence on the resources transferred in support of offspring growth, but that fluctuations in intake during pregnancy itself, reflected for instance in dietary supplementation, have comparably modest effects.

This *phenotypic inertia* — reflecting the lingering biological but non-genetic effects of the mother's average experiences in the past — could allow the fetus to track those dynamic features of environments that are relatively stable on the timescale of decades or several generations (see Refs 60 and 68). This could allow adjustment to environmental changes that are too rapid to result in modifications in gene frequencies via natural selection, which requires many generations, but that are too chronic to be buffered efficiently by reversible homeostatic processes. In this way, the mother's body could pass biological "memories", reflecting her own lifetime of experiences in the local environment, to her developing offspring, allowing developmental adjustments to be made in anticipation of conditions likely to be experienced locally.

12.4 IMPLICATIONS OF DEVELOPMENTAL PROGRAMMING FOR HUMAN HEALTH DISPARITIES

The preceding sections have surveyed some of the evidence that early life stressors can have health effects that linger into adulthood and in some instances may even transcend the present generation to be passed on to offspring. These findings hold promise to help explain why health and disease tend to relate strongly to environmental, social and economic conditions both within and between populations. There is growing evidence that early environment-triggered developmental plasticity can help to clarify two broad problems in public health: disease transitions in populations experiencing rapid cultural, nutritional or lifestyle change, and health disparities within populations marked by chronic inequality and social stratification related to class, ethnicity or social "race". The discussion ends with a brief review of the evidence that developmental processes contribute to each of these public health issues.

12.4.1 High-Risk Scenario 1: When Early Life Undernutrition is Followed by Adult Weight Gain

The above text discussed the hypothesis that the fetus has a capacity to "anchor" its nutritional expectations to a gestational signal (e.g. hormones, nutrients) of average

recent nutrition as experienced by the mother. This might allow the developing organism to modify its own nutritional expenditure, as reflected in its growth rate, body size and other traits, as locally experienced nutritional conditions change. It is easy to see how metabolic changes that could be favorable to a nutritionally stressed fetus or infant — such as sparing glucose or depositing more fat in the abdomen — might also plant the seeds for heightened risk of developing metabolic diseases if that individual ends up gaining weight rapidly during childhood or as an adult. Thus, any context in which individuals routinely face nutritional stress before birth or during infancy but then gain excess weight during later childhood or as an adult should be associated with a high susceptibility of developing metabolic disease.

The now common finding that CVD risk is highest among individuals who were born small but later put on weight is consistent with this idea.[18,69] Under what societal conditions might this pattern of early dearth followed by later excess be especially prominent or influential within a population? One way is as a result of rapid cultural, political or economic transition.[70] In many societies, industrialization of farming is increasing affordability of cheap calories,[71] while populations are also increasingly relying upon automobiles and other forms of transportation to move from place to place.[72] As individuals take in more calories while expending fewer during the day, weight gain is inevitable. When the transition to relative caloric excess takes place within a single generation, individuals raised under austere nutritional conditions during early life may go on to gain excess weight as older children or adults and have heightened CVD risk as a result. Consistent with this model, stunting — a measure of early life undernutrition — has been shown to be a risk factor for metabolic syndrome and obesity in populations experiencing rapid nutritional transition.[73–75]

Poor early life nutrition may also coexist with adult overnutrition simply because nutritional stressors are often concentrated during periods of heightened nutritional vulnerability early in the life cycle. In contrast to trends towards positive adult energy balance and weight gain in many global populations, the nutritional experiences of infants and young children are often more strongly influenced by common communicable diseases and their underlying social determinants, such as sanitation, crowding and the availability of clean water. That nutritional stress around the age of weaning is often severe is revealed by the mammalian strategy of depositing extra body fat after birth in preparation for weaning. Among mammals, humans give birth to the fattest babies on record, which may help us to prepare for this weaning stress, which is accentuated in our species owing to the need to provide a constant supply of energy for our unusually large and energetically fragile brains.[76]

It is an unfortunate fact that in many developing economies today, nutritional stressors at this early age tend to be common — tracing to factors such as diarrhea and respiratory tract infections — despite the fact that those same individuals may later experience excess weight gain as adults. Because infancy nutrition remains tightly linked

to social conditions related to poverty, while the availability of cheap calories is increasingly common and driving adult weight gain, many individuals may now experience early life nutrition stress followed by adult caloric excess even in the absence of rapid societal transition. This is reflected, for instance, in the common co-occurrence of obese and malnourished individuals in the same household within some low-income populations.[77] The body's developmental response to early nutritional stressors can help to explain why these populations often have high rates of cardiovascular and other metabolic diseases.[70]

12.4.2 High-Risk Scenario 2: The Social Origins of Health Disparities Related to Ethnicity, Class and Race

In addition to helping to explain heightened CVD risk in scenarios of early life undernutrition followed by later nutritional excess, the developmental origins framework can help to explain why CVD and related metabolic diseases tend to map onto social categories such as ethnicity, class and race. These "health disparities" are among the most pressing of contemporary public health issues.[3]

As one well-studied example, African-Americans on average have a higher burden of many CVDs, including hypertension and diabetes, when compared to other demographic subgroups in the USA. When studies find that self-identified race is still a significant predictor of these conditions after statistically adjusting for various lifestyle and socioeconomic characteristics, some researchers have been tempted to conclude that genetic factors might explain the black–white difference in health. The problem is that there is in fact very little evidence for a genetic contribution to these health differences,[78,79] which instead relate powerfully to social and environmental factors. Importantly, these factors often reflect influences beyond the control of individuals, such as unequal patterns of opportunity or stress. For instance, chronic stressors such as discrimination, or living in segregated low-income neighborhoods with high crime rates or few safe opportunities for exercise, are important influences on stress levels, the rate of weight gain and the prevalence of high blood pressure.[80]

These effects of unhealthy environments on adult health are not surprising, and in fact are well established. Where these traditional effects of stressful environments converge with the present story is in the realization that they also contribute to poor birth outcomes and compromised gestational environments, which have health effects that can linger into adulthood, and even transcend the present generation of adults. Indeed, African-Americans not only have higher rates of adult CVD, but are also disproportionately affected by the early life antecedents to these conditions, such as a lower mean birth weight, intrauterine growth retardation and premature delivery. Importantly, these early life health disparities have also been linked to experiences of stress and discrimination rather than to genes.[81,82]

Bringing these threads of evidence together suggests that the developmental and intergenerational processes discussed above are likely to be an important part of the story of US health disparities.[83] Imagine the following sequence of effects. First, a pregnant mother experiences chronic stress that elevates her production of stress hormones (e.g. cortisol) during pregnancy. As the level of this hormone rises, the ability of the placenta to shield the fetus from it is exceeded, and the fetus is exposed to high levels of this maternal hormone. This modifies various aspects of developmental biology, for instance by changing how the offspring's body regulates stress hormones, glucose homeostasis, blood pressure or fat deposition. Some of these changes involve epigenetic or developmental modifications in the regulation of organs, tissues or metabolism, which are relatively durable. Later in life, the offspring — now an adult — has higher glucose, insulin, blood pressure and stress hormones as a result of these early life effects. In this way, stressors experienced unequally by the adults of one generation (the mother during pregnancy) might contribute to adult health disparities in the next generation of offspring.

Unfortunately, the story does not stop here, however, because among these adult offspring are females who become pregnant and have offspring of their own. How might the

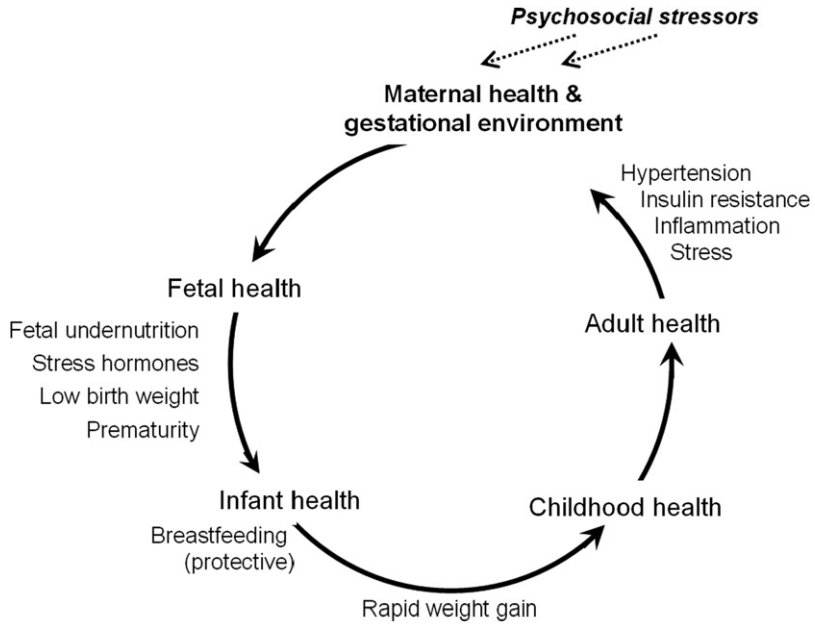

Figure 12.5 A life-course, intergenerational model of health disparities. A mother's experience of stressors influences biological settings and health of her offspring. In female offspring, some of these changes persist into adulthood to influence the gestational environment experienced by the grand-offspring. Thus, developmental responses to early environments can perpetuate patterns of health disparity not only across life cycles but potentially also across generations. *(*Source: *Modified after Kuzawa.*[68]*)*

original stress, experienced by the mother, affect the health of her grand-offspring? The simple answer is that we do not know because studies have yet to investigate this definitively in human populations. But, there are good reasons to suspect that the effects of the original stressor could be passed on, albeit more weakly, across several generations. This is because some of the long-term effects of an adverse gestational environment on adult health in offspring, such as insulin resistance, high blood pressure or inflammation, can negatively affect the gestational environments experienced by the next generation, and can also lead to low-birth-weight deliveries (Figure 12.5). In this way, life-course influences of early life stressors can be transformed into intergenerational pathways for the perpetuation of health disparities across generations.[84] This type of intergenerational transmission is believed to help explain why conditions such as gestational diabetes can influence health in multiple generations of offspring, potentially amplifying obesity or diabetes rates across generations.[83]

12.5 CONCLUSION

This chapter has discussed how fetal and infancy stressors can influence developmental biology to modify one's risk of developing many common degenerative diseases as one ages, including but not limited to hypertension, diabetes, heart attacks and stroke. This research shows how adult health in one generation may be linked with the environmental experiences of recent ancestors, especially the mother during and before pregnancy. This chapter also surveyed the biological mechanisms underlying these effects, and considered the insights that these findings bring to our understanding of two common contexts for socially driven disease in today's human populations. The first involves situations in which an individual experiences nutritional or infectious disease stressors early in life but subsequently gains weight rapidly during childhood or adulthood owing to caloric excess and positive energy balance. The second example is the tendency for health inequality to map onto social gradients of privilege, opportunity, discrimination and stress within societies, as exemplified by the stark differences in health that typically relate to class, ethnicity and socially defined race. The developmental origins framework shows one set of mechanisms by which social inequalities can become embodied physically as health inequalities in the next generation, operating through the effects of maternal biology on offspring development. Collectively, these findings point to the long-term benefits to society of ensuring adequate nutrition, health care and buffering of stress among pregnant women and their young offspring.

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SUGGESTED READING

Barker DJ, Osmond C, Golding J, Kuh D, Wadsworth ME. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. *BMJ* 1989;**298**:564–7.
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Reviews evidence that early developmental plasticity allows organisms to adapt to the environment.

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Reviews evidence for long-term effects of early environments on adult health in five cohort studies from lower and middle income nations.

Waterland RA, Michels KB. Epigenetic epidemiology of the developmental origins hypothesis. *Annu Rev Nutr* 2007;**27**:363–88.
Reviews evidence for epigenetic contributions to the developmental origins of adult disease.

INTERNET RESOURCES

Official webpage of the International Society for Developmental Origins of Health and Disease: http://www.mrc.soton.ac.uk/dohad/