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Maternal and pediatric health and disease: integrating biopsychosocial models and epigenetics

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The concepts of allostasis (stability through adaptation) and accumulated life stress (McEwen's allostatic load) aim to understand childhood and adult outcomes. Chronic malnutrition, changes in social condition, and adverse early-life experiences may program phenotypes and contribute to long-lasting disease risk. However, integration of life course approaches, social and economic contexts, and comparison among different biopsychosocial models has not generally been explored. This review critically examines the literature and evaluates recent insights into how environmental stress can alter lifelong hypothalamic–pituitary–adrenal axis and immune system responsiveness and induce metabolic and neurodevelopmental maladaptation. Models of biopsychosocial stress overlap but may consider different conditions. Concepts include allostasis, which incorporates hormonal responses to predictable environmental changes, and Geronimus's "weathering," which aims to explain how socially structured, repeated stress can accumulate and increase disease vulnerability. Weathering emphasizes roles of internalized/interpersonal racism in outcomes disparities. For Mexican immigrants and Mexican Americans, the "acculturation" framework has proven especially useful to explore disparities, including preterm birth and neuropsychiatric risks in childhood. Complexities of stress assessments and recent research into epigenetic mechanisms mediating effects of physical, nutritional, psychological, and social stress are reviewed.

Adverse social and psychosocial circumstances, including exposure to social, economic, and psychological stressors, are associated with a variety of poor health outcomes in different parts of the world and in a range of ethnic and age groups (1,2). During the past two decades, epidemiological evidence that early-life stressors increase susceptibility to disease later in life has become supported by a wealth of prospective clinical data, experimental animal models, and an emerging appreciation of the underlying molecular and developmental mechanisms in humans. This emerging paradigm is known as the Developmental Origins of Health and Disease (3). Early-life psychosocial stress has an indirect lasting impact on physiological wear-and-tear via health behaviors, adiposity, and socioeconomic factors in adulthood (4,5). Psychosocial stress may also lead to preterm birth by altering immune system function either independently or in interaction with the neuroendocrine dysfunction (6).

The association between birth weight and the development of traditionally adult-onset diseases, such as type 2 diabetes mellitus and cardiovascular disease, was first demonstrated 25 y ago by Hales *et al.* (7). In subsequent decades, the hypothesis that environmental factors act on the genome to create differences in vulnerability or resilience has become a central concept in health research, especially maternal child health (8,9). One underlying biological mechanism for effects of fetal deprivation and stress is environmentally inducible epigenetic change (10).

Correspondingly, research on biological mechanisms of health and disease increasingly emphasizes the environmental developmental context. A "critical period" refers to a time window when developmental changes in the organism towards increasing complexity, greater plasticity, and more efficient functioning occur rapidly and may be most easily modified either in favorable or unfavorable directions. Also known as "biological programming," these critical, environmentally sensitive periods underlie the developmental origins of later childhood and adult disease. The critical developmental period model also embraces the possibility that effects of a developmental exposure may be dramatically changed by later physiological or psychological stressors. This expansion of critical period (fetal) effects with later-life effect modifiers provides a plausible framework to approach the interactions between early- and later-life risk factors (11).

A related concept, the "thrifty phenotype," implies that the "thrifty" aspects of adaptation to an early-life nutrient-limited environment can induce later unhealthy permanent changes. A key tenet of the developmental/fetal origins paradigm is fetal undernutrition in mid- to late gestation, which impairs fetal growth, can program later-life poor health including impaired growth, metabolic stress, aberrant glucose tolerance, type 2 diabetes mellitus (7), and cardiovascular disease (12). Experimental evidence stems from the 1960s, when Widdowson and McCance (13) demonstrated that brief periods of undernutrition during critical developmental times are not necessarily followed by "catch-up growth."

Allostasis, which incorporates hormonal responses to predictable environmental changes, can provide an

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integrative framework for understanding biopsychosocial stress. Additionally, Geronimus's concept of "weathering" (14) aims to explain how socially structured, repeated stress can accumulate and increase disease vulnerability. Weathering emphasizes the importance of internalized/interpersonal racism as a driver of racial outcomes disparities for African Americans. Similarly, for Mexican immigrants and Mexican Americans, "acculturation" can be an informative and predictive framework to explore disparities, including preterm birth and neuropsychiatric risk in childhood. Although traditional disciplinary investigations have focused separately on how social and physical environmental factors affect children's health, evolving research underscores the importance of integrating approaches (14). Socioeconomic and physical/chemical environmental dimensions interact, stress being a permissive factor for susceptibility to certain immunologic and toxic insults (15). In addition, unhealthy residential environments and psychosocial stress can co-vary (16), potentiating adverse effects on health and development.

SOCIOECONOMIC STRESSORS AND INFANT AND CHILD HEALTH

The American psychologist James Garbarino coined the term "socially toxic environments" to describe conditions of poverty and violence (17). Despite improvements in maternal healthcare, socioeconomic differences in birth outcomes remain pervasive, show substantial variation by racial or ethnic subgroup, and are associated with adverse health behaviors that are themselves socially patterned (18). Overall, there is a stepwise gradient in health according to socioeconomic status (SES); that is, people in each class commonly have poorer health outcomes than those just above them and have better outcomes than those below (19,20). The shape of this relationship between SES and health actually may be curvilinear, decreasing health outcomes becoming more common at even higher SES levels (21).

Relative deprivation may be a core mechanism for how income impacts health in societies, i.e., many problems associated with relative deprivation are more prevalent in more unequal societies (22,23). Specific deleterious health outcomes include preterm birth, low birth weight (LBW) (24,25), and child mortality (26). For international disparities in economics, social science, and policy, a commonly utilized measure of statistical dispersion representing the income distribution of a country's population is the Gini Index (27), developed by the statistician and sociologist Corrado Gini in 1912. Modifications of the Gini Index (25) are beginning to be utilized as an indicator of income/wealth inequality in health research. For a century, socioeconomic deprivation in Europe (28,29) and South Asia (30) has been linked to fetal growth. Conversely, improved socioeconomic conditions and nutrition have been associated with increasing birth weight, as occurred in post-World War II Japan. Observations of extreme deprivation during World War II and longitudinal analysis of these historical cohorts have profoundly informed the development of developmental origins theory in the later 20th century. During the Dutch Hunger Winter of 1943–44, the average birth weight declined 200 g (31) and during the Nazi siege of Leningrad by 500 g (32).

A second, not mutually exclusive, explanation for effects of scarcity and poverty on health outcomes is psychosocial (or neurobiological) stress. The economic tie is deep-seated social problems, associated with poverty, relative deprivation, or low social status, appear to be more common in more stratified societies (22). Income inequality theory emphasizes that *relative deprivation* and social stratification, more than direct effects of deprivation of physical living conditions, are a causal link with poor health outcomes (33). In a test of this principle, associations between longitudinal neighborhood poverty trajectories and preterm birth were compared among neighborhoods with long-term low poverty, those with long-term high poverty, and those that experienced increasing poverty early in the study period (34); the latter two neighborhood types had 41 and 37% increased odds of preterm birth (34). The finding that high (compared with low) cross-sectional neighborhood poverty was not associated with preterm birth (35) supports a relative deprivation thesis.

ALLOSTASIS AND ALLOSTATIC LOAD

Adaptation to stress comes at a price. The benefits of adaptation (allostasis) and the costs of adaptation (allostatic load (AL)) lead to different trade-offs in health and disease, reinforcing a Darwinian concept of stress. Developmental plasticity has evolved to match an organism to its early environment. But a mismatch between phenotypic outcomes of adaptive plasticity and environmental conditions later in life increases the risk of metabolic and cardiovascular disease.

The concept of allostasis (stability through adaptation) and accumulated life stress, McEwen's AL (36), offers a versatile paradigm to understand childhood and adult health outcomes. The AL essentially is a composite indicator of accumulated stress-induced biological risk whereby chronic or recurrent stress leads to cascading, potentially irreversible changes in biological stress-regulatory systems. Over time, effects of early-life stressors may lead to individual differences in cumulative effects of stress and in stress-related physical and psychological disorders. AL informs several overlapping conceptual biopsychosocial frameworks including weathering (14), acculturation, cumulative physiological dysregulation, and the biological risk profile (37).

Chronic stress exposure can lead to increased AL (36) and premature aging. For example, early-life stress alters brain structure and neuronal connectivity (38). McEwen and Seeman (36) have argued that the AL can be quantified by cataloging specific biomarkers including physiological signs across major biological regulatory systems. This quantification of AL has proved its explanatory power in understanding the relationship between specific stressors and physical health, initially using data from the MacArthur Studies of Successful Aging (39) and National Health and Nutrition Examination Survey (NHANES) data for adults (14). More recently, AL has been employed to predict risk of adverse reproductive (40) and pediatric health outcomes (5), although empiric evidence on

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its utility in pregnancy is conflicting (35,41). Incorporation of a profile of biomarkers for stress, aging, and immune response may permit a more comprehensive and predictive AL assessment.

WEATHERING

In the United States, epidemiologic research in the 1990s began to devote attention to the relationships obtaining among racism, social class, and health (42,43). Especially in terms of the American black experience of race, Geronimus's concept of "weathering" was devised to explain how socially structured, repeated stress can accumulate and increase disease vulnerability. Weathering is founded in cumulative disadvantage theory as a framework to explain physical consequences of social inequality. Indeed, chronic stressors are recognized to be particularly salient for poor and minority women, who also experience the highest rates of adverse birth outcomes (44). In the United States, although infant mortality has steadily decreased over several decades, significant racial disparities persist, which suggests that factors that drive rates down may be different from the factors that drive them apart (45).

An important emphasis of weathering is internalized/interpersonal racism and cumulative socioeconomic disadvantage to explain racial health disparities, especially the dramatic black/white differences in birth outcomes. This framework facilitates a reorientation of perinatal psychosocial research from measurement of acute stress, e.g., counts of life events occurring during pregnancy, to measures of chronic stressors. Increased "wear and tear" on an individual who is subjected to repeated challenge or stress chronically taxes the hypothalamic–pituitary–adrenal (HPA) axis leading ultimately to physical and psychological disease vulnerability.

Although race is very much a social construct (46), several linkages might explain associations between race and subsequent health: latent variable institutionalized racism, which may explain racial differences across SES; periconceptional maternal health and support; interpersonal racism (47); potential correlations between phenotypic race and genotype; and epigenetic gene regulation (48), i.e., genetic predisposition or gene–environment/epigenetic modifying risk. In a series of studies in Chicago, between-neighborhood variation (49) in concentrated poverty and low social support predicted the relationship between LBW and maternal age (50). Racial residential racial and socioeconomic segregation disproportionately places African Americans and the poor in more impoverished neighborhoods where access to supermarkets is more limited (51), called food deserts.

A weathering pattern of age-related birth outcomes is particularly observed for African-American women. Maternal age is an important determinant of birth outcomes, in part, presumably representing the mother's level of biological and psychosocial preparation for childbearing. However, in contrast to the J- or U-shaped relationships that exist between maternal age and LBW rates among non-Hispanic white, Mexican-American, and non-US-born black women (52), LBW rates among US-born African-American women are lowest in the teens and rise with increasing age (53,54). A population-based test of the weathering hypothesis conducted in first births in Michigan showed African-American women, on average, and those who reside in low-income areas, in particular, experience worsening health profiles between their teens and young adulthood (53). That profile contributes to an increased threefold and fourfold risk for LBW and very LBW, respectively, with advancing maternal age as well as to the black–white prematurity gap (48,53). Further evidence of weathering is the persistence of a black disadvantage in infant mortality for higher SES individuals, a finding attributable entirely to the much higher incidence of LBW (primarily very LBW) among black infants (54,55). The tenacity of this increased risk for African-American infants, even among wealthier and educated mothers, highlights the current imperfect understanding of the biopsychosocial determinants of preterm birth and current policy barriers on preventing prematurity.

ACCULTURATION AND THE HISPANIC PARADOX

Consideration of health outcomes in ethnic immigrants presents unique challenges. Immigrant health research has emphasized cultural explanations but, until recently, a "social determinants of health" framework, which emphasizes social and structural explanations, has been less commonly used (56). Moreover, ethnicity is a broad category that may incorporate race, cultural tradition, common population history, religion, language, and, often, a shared genetic heritage (46,57).

A striking observation is that health outcomes for Hispanics/Latinos in the United States, despite frequent socioeconomic disadvantage, are generally more favorable than other ethnic/racial groups such as African and Native Americans. The epidemiologic paradox in longevity was originally proposed more than 30 y ago by Markides and Eschbach (58) and has since been extended to reproductive health and outcomes as a Hispanic Paradox or healthy immigrant paradox. A "Latina epidemiologic paradox" points to the finding that Hispanic mothers in the United States have a similar or lower risk for delivering an LBW infant than non-Hispanic white mothers. However, longer residence for Mexicans in the United States appears to erase any immigrant advantage. An acculturation context becomes valuable to examine this generally observed intergenerational decline in health. A caveat is more granular health outcomes data for US Hispanics shows substantial heterogeneity among countries of origin and number of generations living in the United States.

The US Hispanic paradox in infant and child outcomes is a relatively new epidemiologic phenomenon. Infant mortality rates for the largely Mexican Southwest US Spanish-surname population were not always similar to, or lower than, those for non-Hispanic whites. In fact, throughout the first half of the 20th century, they were much higher than those of whites, due primarily to shifts in postneonatal mortality (59,60). A change apparently occurred by 1980, when demographic data sets showed parity or near-parity between infant mortality rates of Hispanic and non-Hispanic white populations in Texas (59) and California (61).

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Acculturation is a transitional process that occurs as immigrant groups are exposed to beliefs, traits, and lifestyles of the mainstream culture (62–64). In the mid-20th century, Warner and Strole (65) described a unidirectional acculturation process as ethnic groups shed presumably inferior culturally based health behaviors. Since then, the nativity composition of the United States has changed substantially, largely as a result of immigration from Latin America and Asia following adoption of the Immigration Act of 1965. At present, foreign-born African, Cuban, Mexican, and Chinese women appear to have significantly *lower* risks of infant mortality, LBW, and preterm birth (66). Recent immigrants generally have better mental health than natives ("immigration advantage") and Mexican immigrants have lower reported rates of psychopathology than the overall US population. Nevertheless, acculturation is different among Hispanic immigrant groups. For example, this mental health observation for Mexican immigrants is less true for Cubans and not true for Puerto Ricans (67).

In some instances, acculturation to the "core culture" may subject individuals to unfavorable social conditions including societal and financial stressors, i.e., AL (68), and attendant poor outcomes (69–71). Mexican acculturation may also be accompanied by loss of social supports, strong family ties, and group identity. Accordingly, health outcomes for immigrants might be bimodal, that is, a combination of the "healthy immigrant" effect (i.e., newer immigrants are healthier) and the effects of acculturation: the longer Mexican immigrants reside in the United States, the greater their likelihood of losing culture-related health protective features (37). Empiric data are inconsistent whether latent sociocultural advantages conferred on Mexican Americans who live in high-density Mexican-American neighborhoods outweigh the disadvantages conferred by high poverty in many of those neighborhoods (72,73).

Acculturation is particularly applicable for understanding health status and intergenerational effects for Mexican women who have emigrated to the United States or live on the US/Mexico border and their offspring. Indeed, the few studies comparing the effect of acculturation across Hispanic subgroups suggest that the experience of acculturation and its effects on health may be different for Mexicans compared with different Caribbean, Central, or South American Latino groups (63,74,75). For Mexican Americans, a graded effect of residence in the United States is seen particularly in pregnancy complications such as excessive gestational weight gain and pediatric morbidities. More generally, Mexican-American women seem to have different health profiles stratified by generation in the United States, which serves as a surrogate measure for acculturation. In particular, LBW increases from first- to third-generation residence (66,76–79).

Although many of these studies demonstrate that immigrant health advantage diminishes over time, rates of LBW in three large datasets instead show a curvilinear effect—first an initial improvement with US residence, then decline—as opposed to the prevailing model of monotonic decline in health measures (80). Over time and US residence/acculturation, prematurity rates (81–84), pregnancy-related hypertension, prenatal depressive symptoms and maternal depression in pregnancy (83), and increased neonatal mortality (68) worsen. From a physiological perspective, increased acculturation has been associated with blunted maternal cortisol rhythms during pregnancy and increased maternal measures of immunity and inflammation (85,86).

A research challenge is many acculturation measures such as language, generation, or self-reported ethnic identity, serve, at best, as proxies that do not fully capture the experience of acculturation (59,87). Acculturation instruments for children and adolescents need more sensitive items to discriminate linguistic differences or measure other factors. Along these lines, the Hispanic Community Health Study/Study of Latino Youth is a multisite epidemiologic study of obesity and cardiometabolic risk among US Hispanic/Latino children. The SOL Youth Study incorporates a parent/child socioecological framework, social cognitive theory, family systems theory, and acculturation research to refine a predictive conceptual model for Hispanic children and adolescent health outcomes (88). From a perspective of mechanism, the extent to which intergenerational differences in reproductive and childhood outcomes are attributable to the intrauterine environment and fetal programming remains poorly understood (89).

A LIFE COURSE APPROACH AND THE DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE

Longitudinal models of health disparities have developed (i) from the programming perspective, in which early-life (including fetal) exposures influence health over the lifespan, and (ii) emphasis on cumulative pathways that conceptualize health decline as a result of cumulative wear-and-tear to allostatic systems. Both perspectives build on a stress paradigm and both are synthesized in a "life course" perspective (87) or "life history theory." In reality, disparities in birth outcomes are consequences of differential developmental trajectories set forth by early-life experiences *and* cumulative AL over the life course (58). Life course epidemiology, therefore, is concerned with risk from biopsychosocial and physical exposures throughout the lifespan (11,90) that influence health and disease independently, cumulatively, and interactively.

The catalyst for a life course approach applied to health research stemmed from a revival of interest in the long-term role of early-life factors. These foundational ecological and historical cohort studies led to the "fetal origins hypothesis" refashioned as the Developmental Origins of Health and Disease (DOHaD) associated with David Barker (91,92), Peter Gluckman (3), and others. The original work examined fetal antecedents of cardiovascular disease in England (93) and has been followed by comprehensive cohort studies from other localities.

The DOHaD hypothesis, which has become a scientific paradigm, states that environmental exposures such as undernutrition during critical periods may have long-term effects on chronic disease risk by "programming" organs, tissues, or body system structure or function. The idea of "biological programming" emerged as an alternative, complementary concept to the adult lifestyle approach to adult chronic disease

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that focuses on how adult behaviors (notably smoking, diet, exercise, alcohol consumption) affect the onset and progression of diseases.

In addition, some long-term consequences of fetal programming show differences in response and susceptibility according to the sex of the individual (94,95). Sex hormones and sexually dimorphic effects of excess glucocorticoid exposure are potential mediators of sex-specific programming of cardiovascular disease (95,96) and depression (96). Proposed mechanisms include sexually dimorphic regulation of blood pressure, vascular remodeling, the fetal HPA and renin–angiotensin systems, and epigenetic marks.

Poor childhood health has been associated with more than threefold greater odds of having poor adult (self-rated) health and twice the risk of a work-limiting disability or a chronic health condition; these associations are independent of childhood and current socioeconomic position or health-related risk behaviors (97,98). Of particular importance in child health, unfavorable birth outcomes and psychosocial deprivation early in life have been associated with adverse health and developmental outcomes and changes in brain architecture (99,100). Moreover, maternal psychological stress or depression during pregnancy, which more often occurs in individuals with low SES, can have profound adverse effects across generations. Biological mechanisms include, "diurnal cortisol coupling," i.e., maternal cortisol dysregulation programs cortisol dysregulation in the offspring (101,102). The findings that fetal and maternal programming occur in parallel has important implications for understanding long-term child development and mother/child interactions (102).

RESILIENCE

The capacity of brain and body to withstand challenges to stability (homeostasis) is "resilience." Positive early social experience might have a mitigating effect on stress responses later in life via epigenetic mechanisms, which implies a protective role for positive early parental care (103,104). Recent follow-up from the Bucharest Early Intervention Project asked if randomized placement into a family caregiving environment alters development of the autonomic nervous system and HPA axis in children who were exposed to early-life deprivation and institutional rearing; the results show a causal link between an early caregiving environment and stress response system reactivity in these children (90,105). In this and other studies, although prenatal and early postnatal development is a period of enhanced sensitivity to environmentally inducible deprivation, plasticity beyond human infancy into adolescence and adulthood neurobiological resilience appears possible. Under the right circumstances, the brain can reenter plastic states, and negative outcomes may be mitigated, even later in life (106).

EPIGENETIC REGULATION OF EFFECTS OF PSYCHOSOCIAL STRESS

Epigenetics studies changes in gene expression that occur without changes in DNA sequence. The term "epigenetics" was first used by Conrad Waddington in 1940 to define the "interaction of genes with their environment which brings the phenotype into being" (107). In effect, the functional history of a gene in one generation can influence its expression in the next. Inherited epigenetic changes in the structure of chromatin can influence neo-Darwinian evolution as well as cause a type of "Lamarckian" inheritance (108).

Epigenetic change is developmental and environmental. Mechanisms underlying the developmental origins of disease and psychosocial models of disease risk involve *environmental* epigenetics. The developing HPA stress axis is exquisitely sensitive to regulation by social forces represented at the level of the epigenome (20). Specifically, DNA methylation marks have been postulated to be a mechanism for the enduring effects of the prenatal environment. In essence, a newborn's methylome contains a molecular memory of the *in utero* experience. Epigenetic modifications include DNA methylation (to date, the most extensively studied), covalent modifications of histone tails, and effects mediated by noncoding RNAs such as microRNAs (miRNAs) and long noncoding RNAs (lncRNAs). DNA methylation functions in regulating chromatin structure and remodeling, X-chromosome inactivation, genomic imprinting, chromosome stability, and gene transcription. Addition of a methyl group to cytosines in the DNA sequence as 5-methyl-cytosine (5MeC) represents 2–5% of all cytosines in mammalian genomes and is found primarily on CpG dinucleotides. 5MeC may be considered as a fifth (developmentally and environmentally regulated) ribonucleotide. One category of developmental epigenetics is "genomic imprinting," a genetic phenomenon by which certain genes are expressed in a parent-of-origin-specific manner via methylation of the unexpressed allele.

Epigenetic marks may be transmitted across generations, either directly by persisting through meiosis or indirectly through replication in the next generation of the conditions in which the epigenetic change occurred. In one commonly cited example of epigenetic inheritance, Hugh Morgan *et al.* (109) related inherited variations in coat color, diabetes, and other abnormalities in an inbred line of mice (agouti) to variations in the methylation patterns of an inserted retrotransposon. In this instance, the variations are transmitted through female meiosis. In other cases, epigenetic changes are environmentally induced. An example of how variation in maternal diet during early pregnancy can cause persistent changes in DNA methylation in offspring comes from The Gambia, where Dominguez-Salas *et al.* (110) examined DNA methylation in blood leukocyte and hair follicle samples collected from children born to mothers either during the rainy (hungry) or the dry (harvest) season. Children born in the rainy season, and hence exposed to higher maternal methyl-donor nutrient intake around the time of conception, showed increased methylation of six metastable alleles (110).

A second epigenetic mechanism, posttranslational modifications of histone tails, includes acetylation, methylation, phosphorylation, and ubiquitination. These modifications variably alter chromatin structure and, thereby, DNA accessibility to

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transcription factors and RNA polymerases. Functional effects depend on the specific amino acid modified and on the specific covalently attached group, e.g., acetylation commonly results in the loosening of chromatin and increased gene transcription, whereas methylated histones tightly bind DNA, restrict access to various enzymes, and reduce transcription.

miRNAs are single-stranded RNAs of ~21–23 nucleotides transcribed from DNA but not translated into proteins (noncoding RNAs). Their functional role includes gene expression regulation mediated by control of messenger RNA (mRNA) stability or translation. miRNA changes may be sensitive indicators of the effects of acute and chronic environmental exposures (111), perhaps permitting identification of miRNA signatures for specific physical and psychosocial environmental exposures.

HEALTH VULNERABILITIES CAN BE HERITABLE

In the past decade, heritable environmentally induced epigenetic modifications have been revealed to underlie *reversible* transgenerational alterations in phenotype. In rats, *in utero* exposure to hydrocarbons, plastics, and dioxin leads to early-onset puberty and spermatogenic cell apoptosis in three subsequent generations. Examination of the sperm promoter epigenome identifies differentially methylated DNA regions in descendants of exposed animals (112). A provocative study linked maternal experience of trauma and consequent posttraumatic stress disorder symptoms to disrupted behavioral and physiological response (i.e., cortisol levels) in the infants (113).

A transgenerational dataset of African Americans indicates women with early-life impoverishment who achieved upward economic mobility showed a decreased incidence of preterm birth compared with women with lifelong impoverishment (114). However, this effect was not seen in women with upward economic mobility who themselves had been LBW. Although numerous interpretations of these findings are plausible, a possible transgenerational epigenetic effect that could not be overcome with a change in SES may be suggested (114). These lines of investigation advance understanding for transgenerational epigenetic effects of disparate environmental exposures as well as possible explanations for the increased risk of adverse health outcomes in minority individuals who otherwise would be considered low risk.

CONCLUSIONS

More sophisticated and integrative theoretical frameworks variously integrate critical developmental periods, evolutionary-developmental theory, epigenetics, family and community ecology, maternal AL, resilience resources, and local neighborhood and community level influences (115,116). These comprehensive approaches are also applicable to low- and middle-income countries (117). It is imperative that these theoretic frameworks (based on correlations) be tested empirically in order to help build resilience and "stress inoculation." Too little is yet known how the social buffering of the HPA axis that occurs in supportive environments despite mild everyday stressors promotes health (118–120). As knowledge of epigenetic processes grows, so should the capacity to develop early-life interventions to prevent or mitigate child health disparities. As noted by Darlene Francis (20), understanding how genes are differentially regulated by experience will play a profound role in how we conceptualize health inequalities. This understanding should inform our concepts of the somatization or embodiment of social inequalities. Rather than engaging in nature-vs.-nurture debates concerning race as a genetic or social construct, in this sense, race may be viewed as an epigenomic construct in which genotype and the socially experienced world are perpetually entwined (20).

By highlighting sociocultural and socioeconomic attendants to newborn and childhood risk, AL, weathering, and acculturation models suggest policies and interventions grounded in longitudinal and contextual change. An understanding of economic theory about inequalities similarly informs analysis of maternal and childhood health inequities. Priority areas identified for maternal child health research in order to close these knowledge gaps include: epigenetic mechanisms and their potential mutability, periconception as a critical and sensitive period for environmental exposures, maternal health prior to pregnancy, the role of the placenta as an important regulator of the intrauterine environment, and ways to strengthen early mother–child interactions (90). Identification of environmentally modifiable epigenetic marks, such as gene-specific and global DNA methylation, is proceeding at a fast pace. These endeavors will advance sorting out causal relationships between loci-specific programmed epigenetic alterations in response to adverse early environments and metabolic, cardiovascular, and neurodevelopmental disease phenotypes later in life.

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