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Deep Integration: Letting the Epigenome out of the Bottle without Losing Sight of the Structural Origins of Population Health and Disease

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Abstract

Investigators are applying advances in stress physiology and molecular dynamics to illuminate US population health inequalities. As examples, the "weathering" hypothesis posits that socially structured, repeated stress process activation across the life course increases disease vulnerability and accelerates aging in marginalized groups. The developmental origins of health and disease (DOHaD) hypothesis posits that a limiting uterine environment programs the fetus for later life disease via responsive, durable epigenetic modifications. Weathering and DOHaD are biopsychosocial models with overlapping features; yet, their emphases and implications vary, placing public health at a crossroads regarding where science and policy might best proceed to eliminate health inequality. We argue that the evidence for the primacy of early life experiences over those in young through middle adulthood for explaining population health inequality is weak. By considering weathering and DOHaD together, we call for molecular and biomedical researchers to be more cautious in their claims when applying their science to the social world and for a broader range of theoretically and methodologically sophisticated social researchers – including qualitative ones – to collaborate with them.

Recent progress in theorizing and researching stress physiology's role in chronic disease onset, epigenetics, oxidative stress and telomere dynamics, promises new understanding of the mechanistic pathways through which the social experience of race affects the health of individuals and populations. Studies find differences in epigenetic modifications among monozygotic twins that enlarge with age and lifestyle or residential differences, illustrating the continuing role of environment in translating a common genotype into different phenotypes.[1] Telomere length differences between twins become more pronounced with age, and are associated with adult social class and stress, suggesting that life experiences in adulthood have molecular impacts that affect aging.[2,3] Ultimately, such findings offer new hope of identifying means to short-circuit the processes – both social and biological – whereby membership in a racialized, gendered, and economically stratified society may lead to health inequalities.

Population Health Inequality and the Epigenetic Revolution

Within countries, population inequalities are apparent in health, growth and development, and aging across the life course. The scientific literature has documented that US populations facing social disadvantage almost always experience health disadvantage as

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well.[4] This vulnerability is shaped by social circumstances and environmental exposures structured by a society's response to the observable characteristics that define a group -- skin-color phenotype, secondary sex characteristics, accent, national origin of last name, or neighborhood of residence, to name a few – as well as by the group's response to the social contingencies that follow.[5] Eliminating social inequality in health has been a high priority, yet elusive, national public health objective.

Epigenetic modifications in gene expression spurred by environmental exposures signal the capacity for biological adaptation to environmental contingencies that is much more rapid than natural selection allows. Epigenetic modifications have received well-deserved attention in our otherwise DNA-centric era of biology,[6] and have been documented in many scientific articles, text books, and even popular books.[7, 8, 9, 10, 11, 12] Epigenetic findings provide correctives to one-dimensional views of genetic determinism or even of the role gene-environment interactions play in disease processes in individuals. They point to complex mechanistic answers to "how" race becomes biology beginning in fetal life, with health effects that may endure or accumulate over the life course. They leave open the fundamental social question of "why?"

Infant and Later Life Health

Many studies document associations between indicators of fetal development and disease onset in later life. For example, researchers have found a robust association between low birth weight and later cardiovascular disease in US blacks and whites (see[13] for examples). Two prominent biosocial interpretations of this association – the weathering hypothesis[14, 15] and the Developmental Origins of Health and Disease hypothesis (DOHaD)[13] – forward overlapping conceptual models that differ in their theoretical emphasis, with distinct research and policy implications. Neither is yet fully elaborated or dispositive. Both are concerned with the role of stressors, but emphasize different "critical periods" and biological processes through which stressors exert their most fateful biological impacts.

The weathering hypothesis is grounded in social research, and only recently is being examined in relationship to molecular dynamics, as biological and molecular concepts such as allostatic load,[15, 16] epigenetics,[9] and the impacts of social conditions and life stressors on telomere shortening,[17] enrich understanding of the nexus of cumulative stress hypotheses and population health and aging. DOHaD begins with epigenetic science, and extrapolates it to the social and population realms. By considering weathering and DOHaD together, we call for molecular and biomedical researchers to be more cautious in their claims when applying their science to the social world and for a broader range of theoretically and methodologically sophisticated social researchers – including qualitative ones – to collaborate with them.

DOHaD and Weathering in Brief

The DOHaD hypothesis has generated great enthusiasm as an explanation for the early onset of chronic disease in individuals (e.g[18]) and, recently, racial disparities in such diseases. [13] While acknowledging environmental influences across the life-course that impact the epigenetic layer, and thus the phenotype, DOHaD proposes biological developmental windows as critical periods for such impacts, and has focused on fetal development, in particular. As described by Gluckman et al.,[6, 7, 8] the DOHaD hypothesis draws on the concepts of developmental plasticity and maternal constraint, proposing that "altered long-term risk of disease is initially induced through adaptive responses that the fetus or infant makes to cues from the mother about her health or physical state."[7 (p62)]

The environmental cues to fetal epigenetic modifications are believed to be signaled by maternal nutrition, behavior, and stress, and to target the promoter regions of specific genes, encapsulating signals from the mother, and, perhaps, also from information passed to the mother from the grandmother during her own fetal development.[8, 9] To the extent that the maternal or (grandmaternal) uterine environments lead to epigenetic adaptations whose predictive components are "mismatched" to post-fetal environments, the offspring are at increased risk of disease in later life.[6] In this model, the association between infant birth weight and the probability of developing chronic disease in adulthood reflects a "coordinated fetal response to a limiting intrauterine environment, resulting in changes in tissue and organ development that are not necessarily evident at birth but that result in perturbed responses later in life."[7(p62)] This formulation implies a *direct causal* link between fetal epigenetic modifications and later life disease.

Weathering is a cumulative stress perspective grounded in social research and drawing on stress physiology[16, 19] to posit that prolonged psychosocial or physical challenges to metabolic homeostasis in socially marginalized groups increase the risk of disease and early onset of chronic conditions,[5, 14, 15, 20, 21, 22] and, ultimately, accelerate aging .[17] This view emphasizes that population differences in the early onset of chronic disease result from the qualitatively different life experiences, exposure to stressors, and access to coping resources associated with socially constructed categories such as race, from conception onward.[14, 17, 20] Poor maternal health is the first socially patterned vulnerability to which black women's offspring are more likely to be exposed – though unfortunately, far from the last. Through socially structured material, psychosocial, and environmental influences on health affecting both the maternal environment and that of population members of all ages, the risk of low birth weight is greater in the same populations with excess prevalence of adult chronic disease. These links predict the often-found association between low birth weight and adult chronic disease prevalence across populations *without requiring any direct causal connection* between them in an individual's life.

When applied to population health inequality the conceptual foundations of DOHaD and the weathering (or other cumulative stress) hypotheses overlap in important ways. Both conceptualize race as a social construction with biological consequences when experienced in an unequal society. Both view molecular dynamics as potentially important mechanisms through which phenotypic racial identification becomes translated into racial disparities in health. Both agree that poor maternal health and stressors during pregnancy may start children on a path where their chances for a long or healthy life expectancy are diminished. Indeed, DOHaD could be viewed as one of many contributors to weathering. However, the two are also different in important ways that place those working to eliminate health disparities at a crossroads with respect to where science and policy might most productively proceed.

Questions of Emphasis

Some scientists have called for pressing ahead with the study of DOHaD full throttle, even prioritizing it ahead of other health related research.[18] Yet, at the heart of the hope for the epigenetic revolution to undo social disparities in health are three basic questions that also speak to the evaluation of how much emphasis on DOHaD research is merited in population health research: (1) Are the documented associations between indicators of fetal development and the onset of complex diseases in adult life *causal*? (2) If they are causal, how important are intrauterine relative to post-uterine life experiences, including ones that occur outside of "developmental windows"?; and (3) In light of the answers to questions 1 and 2, what are the best ways to intervene toward the goal of eliminating racial disparities in health?

As with many questions in social research, it is not possible to generate human experimental data to test the question of how much experiences during developmental periods in early life impact later life health, relative to ongoing social experiences in adulthood. Humanevidence for the DOHaD hypothesis comes from (a) observational studies that estimate the association between infant characteristics and later life health after controlling for some potential demographic, behavioral, or socioeconomic confounders; and (b) natural experiments that establish a connection between exogenous events or "shocks" that occur while human infants are in utero (e.g., the Dutch Hunger Winter or the 1918 Influenza Pandemic) and later health outcomes in the affected cohort.

Studying Humans: Unobserved heterogeneity and causal inferences in quantitative studies

To make a balanced evaluation of the extent to which associations between infant and adult health outcomes are causally connected requires deep familiarity with methods of making credible causal inferences within the context of nonexperimental data and a knowledge of possible sources of unobserved heterogeneity -- consequential differences among populations that confound the association between race and health.

Underlying the threat of unobserved heterogeneity is the fact that many of the indicators and outcomes used in DOHaD research, while indicative of biological vulnerabilities, are also indicators of social context. A prime example is birth weight itself, which while an anthropometric measure reflecting fetal growth and development, is also highly predictive of maternal socioeconomic position and, at the population level, of general socioeconomic well-being. [23] Associations between racial population distributions of birth weight and of cardiovascular diseases such as hypertension cannot be interpreted as causal or reflecting biological origins of adult disease in fetal life without accounting for the unobserved heterogeneity in resources and life experiences between black and white mothers.

As a consequence, observational studies that have been interpreted as strong evidence for DOHaD may have been misevaluated. For example, a study[24] using data from the Bogalusa Heart Study was described as providing strong (human-based) support for the DOHaD hypothesis because it found that "the hypertension disparity between US whites and African Americans…was no longer significant after models adjusted for the effects of birth weight."[13(p10)] Interpreting this statistical eradication of the race disparity as evidence for the fetal origins of black-white differences in blood pressure is premature. From the perspective of social population research, two design features weaken this interpretation. First, the highly selective Bogalusa Heart Study (BHS) sample used in the study included 185 children (out of the 16,000 participants in the BHS), born in the 1970s in Bogalusa, Louisiana, a semi-rural population. The study included no socioeconomic controls in the regression models.[24] Because birth weight distributions are reflective of the social and economic well-being of populations, the lack of socioeconomic covariates would result in residual confounding. It is likely that the effects of unmeasured social variables that impact blood pressure were, in effect, measured by the birth weight variable, exaggerating any biological effects of birth weight, per se. In this case the fact that the racial disparity in hypertension was no longer significant after controlling for birth weight would be neither surprising nor informative. Yet, scientific and policy implications for eliminating racial disparities in hypertension differ dramatically depending on whether these disparities are interpreted to result more from the effects of the intrauterine environment on fetal vascular development than from the effects of socioeconomic, environmental, or psychosocial experiences on blood pressure thereafter.

Virtually every aspect of reproduction and parenting is culturally mediated, socially patterned, and structurally informed and constrained, while simultaneously having potential biological impacts on growth, development, and health. At the population level, historians, anthropologists, and family demographers have documented that family structure, parenting behavior, and norms and expectations of mothers and children vary across societies and time. These differences reflect varying cultural traditions, material constraints, and other social/structural factors that influence the sequence and rhythm of life course demands and are generally responsive to context.[25, 26] In addition to birth weight, other key variables interpreted in the DOHaD literature as biologically causal of later life health are also understood by social researchers to be markers of unobserved heterogeneity in the life experience of different populations of mothers and infants. These include maternal and paternal age at conception, maternal nutrition and behaviors during pregnancy, and breastfeeding. For example, compared to other mothers, US mothers who breastfeed are more highly educated, economically better off, disproportionately white, have sufficient job flexibility to breastfeed, have a cultural commitment to and social support for breastfeeding, and have sufficient nutrition and low stress levels to produce the necessary milk supply. Accordingly, scientists should not be surprised to find that breastfed babies have lower adult rates of obesity, diabetes, and hypertension. But they should be cautious in the extent to which they attribute this association to the direct impact of breastfeeding, per se, because populations with low breastfeeding rates differ from those with high rates in ways that, themselves, contribute to adult CVD risk.

Controlling for socioeconomic indicators

While it is essential to be aware of the fundamental weakness of studies of molecular dynamics in human populations that do not account for *any* social variables when studying population differences, controlling for demographic or socioeconomic indicators does not fully address unobserved heterogeneity.[4, 27] The unobserved differences are so entrenched and the residual confounding so great that even including detailed socioeconomic controls is only a partial solution.[27, 28] To address residual confounding in studies of the association between maternal characteristics and infant, child, or later-life outcomes, social scientists have exploited natural experiments (e.g.[28, 29, 30, 31]). Thus, for example, in the case of breastfeeding and health, Baker and Milligan[**31**] found that the expansion of Canadian maternity leave mandates increased the extent and duration of breastfeeding, but found little evidence that the increased breastfeeding improved health outcomes thought to be influenced by breastfeeding, per se. This finding raises doubt about whether encouraging poor women to breastfeed – while possibly salutary for other compelling reasons -- will have the expected positive consequences for the adult health of their offspring predicted by the DOHaD hypothesis.

Economists have employed natural experiments specifically in the context of DOHaD.[32] These offer the strongest evidence to date of a causal link between intrauterine environment and later life health in humans. Still, the findings of these studies do not imply that early life exposures are more important than cumulative exposures over the life course for explaining the impact of environmental factors on later life health.

Social scientists bring knowledge of relevant social theory and substance to epigenetic interpretations of findings from quantitative observational studies. For example, investigators have noted that the birth weight distribution of first-generation black children whose mothers immigrated to the US closely approximates that of US whites and is far healthier than US blacks.[33, 34] However, subsequent US-born generations (second generation and higher) of these black immigrants have a lower birth weight distribution that

converges toward that of US blacks. Some have used this observation in support of DOHaD.[13]

This observation is potentially consistent with DOHaD or cumulative stress hypotheses, with different implications in the two formulations. There is no a priori reason to conclude that poorer maternal health among the second- or third-generation black adults was largely the result of fetal epigenetic modifications, if one assumes that their immigrant mothers and grandmothers were not subjected to similarly maladaptive maternal constraints when they were in utero. Furthermore, findings that the health advantage of recently arrived immigrants is eroded not only in subsequent generations, but also over time in the US for the immigrants themselves[35, 36] suggest that health deterioration of immigrants and their progeny depends on social realities in the US that have measureable effects on the health of those who developed in (or whose mothers developed in) less hostile uterine environments, and also on those who arrived as adults, already older than proposed developmental windows.

What aspects of life in the US might account for generational changes in birth weight distributions among immigrant populations and their progeny, or a deterioration in health associated with duration of US residence among new adult immigrants? One intriguing line of social research consistent with a cumulative stress perspective focuses on possible negative health impacts of coping with life in the marginalized realms of the social hierarchy. Viruell-Fuentes[37(p1531)] found qualitative evidence that “the long-term labor of constructing an ethnic identity under a stigmatizing racial structure and the accumulation of ‘othering’ experiences over the life course might take a toll on the health of the second and later generations.” As new immigrants reside in the US longer, or as the progeny of immigrants are raised in the US, they become aware of and attuned to US racial hierarchies and ideologies, and are vulnerable to the physiological impacts of racialized contingencies of social identity.[4, 37, 38, 39]

Generalizing from Animal Experiments

Lab science is central to DOHaD research, including experiments with animal models meant to provide human analogs of the impact of variations in maternal nutrition and stress on chemical mechanisms underlying epigenetic modifications, and their association with disease processes in offspring. For example, in rodent experiments, diet and stressors can be manipulated and their possible influences on obvious phenotypes (such as coat color, body size, insulin resistance, blood sugar) can be readily measured at different age points for first and later generation progeny. Such experiments are suggestive of the plausibility of fetal programming in humans, possibly including transgenerational inheritance of epigenetic modifications.[9]

The appeal of studying epigenetic mechanisms in rodents is clear. One can study hundreds of genetically identical mammals; manipulate specific environmental exposures under well-controlled conditions; and, given rodents’ relatively short lifespans, readily observe and measure biological responses to manipulations across lifetimes and generations.[11] Animal models provide evidence that epigenetic modifications occur during fetal development and enable description of the chemical mechanisms through which they occur, such as DNA methylation.[9, 40, 41, 42]

However, in animal models, the post-uterine exposures are few, brief, contrived, and controlled. Outcomes are limited to specific measurable “adult” phenotypes or diseases rather than to more general vulnerability or wear and tear. These limitations have crucial implications when generalizing to human population health inequality. For example, animal studies have shown that “stress” in the first week of life – operationalized as rodent pups

experiencing less maternal licking and grooming or a greater time separated from their mother – results in later "adult" conditions indicative of high stress.[40, 41, 42] Mechanistic cellular processes that result in epigenetic modifications in the rodent experimental subjects have been described.[42] However, early maternal rat deprivation seems a poor analog to the scope and depth of stressors to which human populations are disproportionately subjected over decades-long-lives. These stressors are chronic and acute; objective and subjective; comprising social, material, environmental and structural disadvantages, and inhere to everyday encounters, micro-aggressions, and relationships.[39] Nor does it account for contextual variation or human agency, including the physiological effects of active effortful coping with stressors.[4, 15, 20] Elaborating the nature and impact of health-harmful stressors in the lives of human populations, and determining the relative contribution to later life health of the uterine environment verses long-term exposure to and coping with structurally unequal social, political, or environmental ecologies is well beyond the scope of animal models.

Ethnographic investigations can provide a window into the nature of the stressors that loom large in specific populations, but which are otherwise unfamiliar to many biomedical researchers. For example, consider the case of urban black residents of high-poverty neighborhoods. In their urban ethnographic study on welfare, children, and families, Burton and Whitfield[43] found that most of the primary caregivers in their study led "highly challenging" lives and "could never get a break." Mullings and Wali[44] documented in their ethnographic study of Harlem mothers the ubiquity of unsafe housing -- more than 70% reported roaches in their residences; more than 50% reported mice; and about 30% reported rats. More than 60% of the mothers lived in apartments in need of major repairs, exemplified by lack of heating and cooling, broken windows and doors, or holes in the walls through which rodents entered. These women's housing problems "affected many of the other aspects of their lives,"[44(p47)] including, for half of the women, having to engage protracted and stressful efforts to resolve these conditions.

Numerous studies document structural violence in poor and black neighborhoods.[45, 46, 47] Hyper-vigilance and its physiological impacts become pervasive. In her ethnography of a segregated Midwestern neighborhood, Hicks-Bartlett[45(p32)] observed: "Keeping children safe consumes parents…(during research interviews) mothers habitually peek out the window. …tirelessly scanning the environment." So too, Mullings and Wali[44(p31)] noted in their Harlem ethnography: "Many of the women in our study remained constantly alert about the possibility of violence and its impact on themselves and their children…." Balko[46] described frequent raids on people's homes by heavily armed paramilitary units pursuant to the War on Drugs resulting in "needless deaths and injuries…of police officers, children, bystanders, and innocent suspects."[46(p1)] A Harlem focus group member averred "the constant nighttime noise from shouts and gunshots kept him, his wife, and his children awake. He said they were reawakened so often throughout the night that they were chronically exhausted."[44(p31)] Meanwhile, exposure to environmental toxins that pose significant challenge to homeostatis, like exhaust fumes and lead, is also socially patterned.

In sum, animal research and some natural experiments provide strong evidence that early exposures, including intrauterine exposures, can influence later life health. However, estimated associations between early life health indicators and later life outcomes in observational studies exaggerate the causal effects of early life exposures because of residual confounding. When accounting for population health inequality, social research investigations from many disciplines provide reasons to take seriously the proposition that socially patterned material, psychosocial and environmental contingencies in young and middle adulthood are as or, possibly, more important than intrauterine, early life, or adolescent exposures.

Research Priorities

As expressed by one DOHaD scientific visioning workshop, their hope is to rally the public to make "DOHaD research a contemporary 'space race.'"[18(p14)] These scientists anticipate a cycle in which, "DOHaD research leads to discovery, which leads to effective dissemination of findings, which leads to change (behavioral change, social change, environmental change, attitude change), which informs policy, which then provides support for another cycle of discovery."[18(p13)]

Through the prism of weathering, molecular dynamics are viewed as mechanisms and not as the primary drivers of research and policy. The weathering or cumulative stress perspective prioritizes continued research on the lived experience of vulnerable populations at all ages, and how aspects of experience are translated, through physiological stress process activation and molecular dynamics, into excess morbidity and mortality in ways that are socially contingent, not universally applicable. In this context, epigenetic research will be more likely to make an important contribution to health disparities research if it is tied to an understanding of how gene expression is both shaped by the social processes that precede it and interacts with the social processes that follow.

Elaborating weathering requires identification of the dynamic and socially- situated objective and subjective stressors that impact population health, and are socially patterned by a history of race-consciousness.[22, 39] In contrast, a sampling of research questions proposed in one DOHaD agenda include, "To what degree can the placenta serve as a diary of pregnancy? Is this also true for amniotic fluid? Can additional amniotic fluid measures be considered, i.e., drug metabolites, nutritional byproducts, and the microbiome? Can placental biology be related to surrogate markers of maternal and child health, and robustness later in life?"[18(p10)] Moreover, because human experiments to affect fetal development are unethical, DOHaD researchers understandably hope to leverage natural experiments among unique populations. Examples include: women of childbearing age who have undergone bariatric surgery, surrogate mothers, offspring from HIV/AIDS antiretroviral therapy programs or of cesarean versus vaginal delivery, adoptees, and twins separated at birth.[18] These are highly select groups of mothers and offspring. The need for substantive knowledge to interpret the nature of the social selection, along with methodological prowess for addressing social selectivity, should not go unnoted by epigenetic researchers.

Prioritizing DOHaD necessarily points to studying developmental windows and their dynamic characterization chemically and clinically. While DOHaD emphasizes the prenatal environment, in theory it also encompasses how social environments drive later developmental processes during infancy, childhood, and adolescence. [6, 13] This perspective suggests important empirical questions including the degree to which experiences during these "critical developmental windows" contribute to health disparities, and the importance of such contributions compared to the impacts of experiences at other ages.

Cumulative stress hypotheses encompass a broader understanding of possible sensitive periods, noting the heterogeneity across populations regarding when engagement with stressors may be most intense. If we concentrate our efforts to understand the impact of socially structured stressors on those thought to be biologically distilled at discrete "critical" time points, we cannot evaluate the comparative effects of social environmental assaults that occur every step of the way. For example, in the US, black populations of highly segregated urban areas face a distinct set of social and structural constraints that may have health implications. Young black men in this context have seen a long secular decline in employment rates and rising incarceration rates, with all of the personal, family, and

community disruption that these trends imply.[47, 48, 49] Black women in these neighborhoods often bear central responsibility for the social and economic survival of their families and communities, and thus may suffer the disproportionate wear and tear on biological systems inherent in costly adaptation to related stressors.[15] A raft of studies find that poor black women in their 20s, 30s, and 40s are primary caregivers of children and also ailing or disabled peers and elders. [43, 50, 51, 52] Some estimates find that most poor households are characterized by "family comorbidity," wherein multiple family members suffer concurrent physical and mental health problems. [43]

These and other factors suggest that in urban black populations, the young adult through middle ages may be a particularly challenging period for women as they assume family leadership roles, and contend with competing obligations between work and family and to dependants across generations. Might these social pressures and competing demands be as or even more important determinants of ill-health than youthful epigenetic modifications? In their study comparing white mothers (mean age of 38) who were more or less stressed based on whether or not they were caring for an autistic child, Epel et al[2] found those facing the demands of caregiving for a special needs child had shorter telomeres than those who did not have those demands. If otherwise healthy and economically secure mothers could suffer such impacts from caregiving experiences in their 30s, it is reasonable to wonder how large the biological impact might be of engaging all of the caregiving and other stressors faced by young through middle aged adult women in poor or marginalized populations.

Translation: In Due Time or in Real Time?

DoHAD-based prevention solutions focus on averting fetal epigenetic adaptations that increase risk of later life disease through clinical treatment or individual behavior change (before, during, or shortly following pregnancy). These solutions include improving diet and, more broadly, buffering mothers from stress. Proponents, therefore, are concerned with focusing clinical and policy attention on youth during critical developmental periods, and on women who may reproduce, or are pregnant or lactating.[13, 18] The theoretical prediction is that if the fetus develops in an auspicious uterine environment, the adverse epigenetic modifications that would have programmed him to be at risk of early onset of chronic disease will be averted.

DOHaD scientists risk promoting ineffective policy approaches from this prediction. As noted above, they rely on DOHaD discovery to lead to broad, automatic dissemination that reframes policy agendas and motivates individual pregnant women, mothers, and youth in high-risk populations to change behavior. This is naïve. How will dissemination effectively occur between epigenetic researchers who are trained to understand women as gestating mothers with interchangeable composites of placentas, amniotic fluid, chemical reactions and molecules; and local stake holders, who are embedded in unique social systems that merit understanding?

Promoting maternal behaviors that are inconsistent with women's social realities is likely to produce frustration on all sides, unless those social realities are appreciated and efforts are made to address them as well as maternal behavior. For example, as sociologists, family demographers, and ethnographers have observed, breastfeeding is at the very least impractical to expect of poor mothers without other social changes. The complex kin network systems that serve as lifelines for many poor women, function, in part, through their flexibility of having kin other than the biological mother take important caretaking or even fosterage roles for infants and young children.[43, 44, 45, 52, 54] If infants spend large portions of time being cared for or even raised by extended family members, or if their biological mother is not only separated from them for large portions of the day, but also works under

conditions where breast pumping is impossible – as most US working women do -- it is hard to imagine that breastfeeding is an option. To the extent that poor mothers are structurally impeded from adhering to maternal behavioral proscriptions that follow from DOHaD, maintaining or increasing political will toward expanded services and benefits to poor mothers will become more difficult. The efforts may prove harmful to the population, itself, if program failure reinforces the popular framing of the problems of the poor as self-inflicted.[20, 53]

Political will is necessary to institutionalize policies that are envisioned to promote fetal and infant health. Policy recommendations set forth by some DOHaD researchers include supporting pregnant and new mothers by funding "access to adequate prenatal care and nutrition and help ensure that they are relatively buffered from stress while pregnant and lactating. Promotion of breastfeeding, and longer and more secure maternity leave, are additional examples of policies that could have long-term health benefits for future generations, and ease race based health differentials operating through developmental pathways"[13(p10)]. Such intervention approaches also seem attractive as they are believed to be feasible. Kuzawa and Sweet [13(p10)] argue, "Some sources of social inequality, such as racism, cannot be eliminated by legislation. But societies can legislate changes in public spending that benefit pregnant mothers."

Social researchers and lab scientists can agree that supporting pregnant and new mothers, including through the policies listed above, would be beneficial. Yet, viewing the legislation of prenatal care or maternity leave policies as substantially more feasible than addressing racism skirts the fundamental political issue of persistent racism and other structural impediments that thwart elevating such programs to meaningful levels.[22, 53] If it were straightforward to legislate and also institutionalize changes in public spending that benefit pregnant mothers such practices would be established. Advocates for maternal and child health and for family welfare have sought to improve access to prenatal care, promote breastfeeding, and institutionalize maternity leave, with little evidence of broad, meaningful success. The current deficit, congressional gridlock, decimation of state and local budgets, fear of "socialized medicine," skepticism of science, and, more fundamentally, ideological disagreements regarding the proper roles of the free market and government, all create a staging ground where legislating public spending to benefit pregnant mothers is a daunting task. In this environment, any policy gains to benefit mothers and infants will be hard fought and risk being politically fragile.

Solutions following from cumulative stress hypotheses target the social patterning of stressors across the life-span – importantly including young through middle-aged adults -- and flow from an understanding that health behaviors are embedded in larger social systems, with changes in behaviors difficult to achieve and potentially reverberating adversely through communities when achieved in isolation.[54] Even assuming the best scientific evidence and knowledge of social realities, forming policies that buffer black pregnant women and mothers from stress is no small task. No bubble exists for pregnant or lactating mothers to inhabit apart from the stressors they cope with throughout their lives. The stressors faced by members of marginalized populations are monumental and, to varying degrees, a reflection of entrenched US racial history. Massive incarceration, decaying housing structures, environmental inequity, the psychosocial stressors of being marginalized in integrated settings – all have roots in a racist past and are sustained by a racist present. None will be addressable through prenatal care or by the "Surgeon General Proclamation on Embryonic Sensitivity" suggested as a strategy by one DOHaD working group.[18(p13)] Arguably, the public spending needed to substantially benefit pregnant mothers and truly buffer them from stress would require major investments in infrastructure and housing, ends to the War on Drugs, racial profiling in the criminal justice system, and mass incarceration,

and, yes, confronting embedded racial biases. Doing so, while hard, should not be abandoned as hopeless: it is the larger and more essential social change.

DoHaD offers little in theory or research evidence to be applied to improving health in current generations of adults who developed (or whose mother's developed) in constrained uterine environments. If transgenerational inheritance of adverse epigenetic programming occurs, the only possibilities for supervention are therapies for undoing epigenetic modifications. It is certainly appealing to hope that any aspects of living systems that can be described through chemistry can, someday and somehow, be modified by chemistry.[55] However, such therapies would represent an ineffective way to address what are fundamental population-level social problems. Structurally, they are likely to be the subject of market-based approaches[56, 57] with all that implies in terms of the priority of the profit motive and the differential accessibility of new and expensive pharmaceuticals to members of more and less privileged populations.[58, 59,] Even simple dietary approaches that may counteract negative epigenetic effects are less likely to be available to members of disadvantaged groups who often live in food deserts and are targeted by advertisers marketing unhealthy and easily accessible consumption choices.[60] From a political standpoint, there is really no way to finesse or side-step the fundamental social causes of racial inequalities in health,[58] whichever conceptual perspective on their biological origins one takes.

In sum, social researchers of many stripes are needed to contribute theoretical, methodological, and substantive insights to the design and interpretation of studies bridging bench and social science that aspire to illuminate population health inequality. They also have a crucial role to play in translating study findings into policy and intervention approaches to eliminate them. Short of such inclusion, the interpretation and application of biomedical findings to population health may be charted by lay notions of how the social world works or interacts with the natural one that are, themselves, socially structured and often stereotypical in matters related to race;[16] and as well by market forces pressing scientists, clinicians, and pharmaceutical companies to reap the hoped for financial benefits of "personalized medicine."[56, 57] The promise of DOHaD for eliminating racial disparities in health offers hope primarily to generations yet to be born. This observation does not detract from the fact that new discoveries of the sources of epigenetic modifications in utero and, perhaps, during other developmental windows, are exciting in their own right. What is missing is as stringent an expectation that epigenetic scientists moving into the social realm deeply engage collaborators with social research bona fides, as we would all agree there is the requirement that social researchers considering molecular mechanisms use quality assured labs with a track record of generating accurate and reproducible measurements, and involve molecular scientists, knowledgeable in the latest findings in their field.

Because of its roots in biomedical science, DOHaD researchers have the more direct line to powerful players at NIH, scientific journals, and the media. This is a virtue if it commands resources toward eliminating population health inequalities. At the same time, that high priority public health objective will be harder to achieve if the specialized training of DOHaD researchers leads to misinterpretation of existing social science evidence, or worse, sidelines continued, necessary, socially-grounded research in health inequality. To constructively apply epigenetic science to understanding and eliminating population health inequality requires deeply integrating social science theory, research, and techniques with molecular science. It is important to recognize that whatever pieces of the puzzle basic epigenetics research may supply, the study of social inequalities in health is first and always a matter of robust social research.

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