

# Biological memories of past environments

## Epigenetic pathways to health disparities

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Human health tends to mirror gradients in social standing related to class, ethnicity and race. Past research in the social sciences suggests that environmental experiences related to social status contribute to these disparities, but the underlying biological mechanisms are only partially understood. Here, we review research related to three domains of environmental exposure that point to epigenetic contributions to health disparities: nutrition, psychosocial stress and environmental toxicant exposure. Each exposure has effects that may persist across the life course and in some instances may be transmitted to offspring via epigenetic inheritance. Since epigenetic markings provide a “memory” of past experiences, minimizing future disparities in health will be partially contingent upon our ability to address inequality in the current environment. We suggest that future research in environmental epigenetics focus on establishing the reversibility of stress-induced epigenetic modifications, and also on identifying positive epigenetic effects of environmental enrichment.

### Introduction

The brisk pace of research into the intricacies of gene regulation, which includes the study of epigenetic mechanisms, is rapidly expanding our understanding of the ways in which environmental influences can affect these processes. Research has revealed that environmental exposures influence biology and health among individuals by modifying epigenetic markings that are mitotically stable, thus linking early experience with future health.<sup>1</sup> In addition, a growing list of studies demonstrates meiotic stability in these markers, which allows epigenetic modifications to be passed on to offspring and even grandoffspring via germline epigenetic inheritance.<sup>2-4</sup> These findings are revolutionary, as they reveal in greater detail how the environments that individuals experience can shape their biology and health across the lifecycle and even within lineages through time.

One domain of inquiry that has received less attention in the epigenetics literature, but is of increasing interest, is the potential role of epigenetic processes as links between environmental influences and patterns of health and disease found within and

across societies.<sup>5,6</sup> Within epidemiology and related fields, it is well established that risk for many common diseases is elevated among individuals of lower social position.<sup>7-9</sup> This health gradient applies to both class and socially defined ethnicity or race, and is found in populations that are geographically, politically and economically diverse, spanning from India<sup>10</sup> to England.<sup>11,12</sup> Strikingly, similar patterns emerge whether comparing chronic conditions associated with old age, such as cardiovascular disease or cancer,<sup>13,14</sup> psychological disorders like depression<sup>15,16</sup> or developmental and health outcomes of infants and children.<sup>17-20</sup>

When the social gradient in health is analyzed in relation to wealth, the relationship is continuous, implying that there is no threshold above which health inequalities disappear.<sup>21</sup> Additionally, individuals with comparable incomes but who differ in occupational rank generally exhibit differences in health that mirror their respective social positions.<sup>12</sup> This has been interpreted as evidence that social status, independent of wealth, has important effects on physiology. In an intriguing analysis comparing Nobel Prize winners and nominees, who were assumed to have similar class standing, the winners of the prize were found to live an average of two years longer.<sup>22</sup> Research in non-human primates has similarly found that position within the social hierarchy influences health in ways that are not directly predicted by factors such as resource availability.<sup>23,24</sup> Together, this research suggests that an individual's social standing—and the psychosocial stress that accompanies lower status in particular—closely mirrors and contributes to gradients in health status.

Identifying the social and biological causes of these relationships has been a goal for public health researchers and individuals in related fields in the social sciences, including anthropology, sociology and economics.<sup>25-32</sup> Although genetic differences between groups could contribute to health disparities, there is little direct empirical evidence to support this hypothesis and many observations that undermine it. One line of evidence comes from immigrant studies, which reveal that health inequalities are more strongly influenced by contemporary environments than by common geographical origin.<sup>33-35</sup> Similarly, social models of racial group identity may be stronger predictors of health status than genetic ancestry.<sup>36</sup>

Perhaps the most compelling evidence that health disparities primarily trace their origin to social, rather than genetic, factors comes from an extensive literature documenting the deleterious health impacts of economic and status inequality, such as stress or discrimination. For instance, there is now much evidence that

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being of low social status, in terms of class or ethnicity, increases disease risk via a diverse array of biological pathways and outcomes.<sup>7,11,14,29,37-39</sup> Over the past decade, the pace of research in this area has been brisk, and now includes investigations that assess the influences of multiple levels of environmental experience, ranging from the interpersonal to the community, and that address a broader range of social, political and economic variables. All have been shown to predict environmental experience in ways that influence patterns of health and disease.

Although the power of social and economic inequality to influence health and disease is now well established, the biological mechanisms that contribute to these findings remain only partially understood. As emphasized recently by us and others,<sup>5,27,40,41</sup> the environmental sensitivity of epigenetic processes holds great promise to illuminate how these non-biological factors “get under the skin” to create social gradients in health.

In this brief article we review research linking three domains of environmentally-based epigenetic change that are helping clarify the social gradient in health: nutrition and nutritional stress, psychosocial stress and environmental toxins. After reviewing the acute, life course and transgenerational impacts of these exposures, we argue that understanding the roots of today’s health disparities may be enriched by considering not only the experiences of the present generation, but also the social, physical and nutritional experiences of ancestors in the recent past. From a policy standpoint, this research implies that addressing the health impacts of social disparities today will be essential in efforts to optimize future health in the next generation of adults. It also underscores the urgency of clarifying the potential to reverse any deleterious effects of stressors already experienced by present generations. We close by considering the research priorities in this promising new convergence of molecular biology, social science and public health practice.

### Nutritional Stress

Nutrition across the life course is now recognized as an important influence on adult health and chronic disease risk.<sup>42,43</sup> These relationships partly trace to the effects of early environments on plasticity in developmental biology,<sup>44,45</sup> which is increasingly being linked to epigenetic effects on gene regulation.<sup>46,47</sup> Nutritional status can influence epigenetic profiles by inhibiting enzymes that catalyze DNA methylation or histone modifications or by influencing dietary availability of substrates necessary for these enzymatic processes.<sup>48</sup>

Evidence from several studies suggests that nutritional exposures during critical periods of offspring development have epigenetic and physiological effects that persist throughout the life course.<sup>49-53</sup> As one example, changes in maternal folate availability during pregnancy has been shown to influence methylation at several loci in offspring, with long-term effects on offspring hair color, adiposity and behavioral patterns.<sup>54,55</sup> As another example, a recent study in rats found that a low-protein maternal diet during early pregnancy predicted epigenetic silencing of the gene encoding the hepatocyte nuclear factor 4- $\alpha$  (*Hnf4a*) transcription factor in offspring, which has elsewhere been associated with development of

type 2 diabetes.<sup>56</sup> The offspring exhibited premature age-related silencing of gene expression at this locus, suggesting that the effects of maternal diet persisted across the life course.

Although comparable studies of humans are not available, Dutch adults who were in utero when their mothers experienced a Nazi-imposed famine during World War II had differences in methylation at the insulin-like growth factor 2 (*IGF2*) locus when compared to same-sex siblings who were not exposed in utero.<sup>57</sup> This raises the possibility that some of the biological and behavioral differences that have been traced to prenatal famine exposure in this cohort reflect epigenetic programming.<sup>58,59</sup> A study in The Gambia found that individuals conceived during the nutritionally-stressful rainy season had significantly higher methylation at five loci than individuals conceived during the dry season.<sup>60</sup> Lastly a recent study in a British birth cohort found that lower maternal carbohydrate intake during early pregnancy was associated with increased umbilical cord methylation of the retinoid X receptor alpha (*RXR $\alpha$* ) gene, which was independently associated with increased adiposity in offspring at nine years of age.<sup>61</sup> This research suggests that nutritional experiences in utero have metabolic effects that persist into childhood and that metabolic programming is reflected in epigenetic modifications present at birth.

That epigenetic effects potentially transcend multiple generations of offspring is gaining increasing attention, including evidence for direct transmission through both matrilineal and patrilineal germ lines (egg and sperm).<sup>62</sup> In one study, nutritional restriction in pregnant rats led to significantly lower methylation in hepatic peroxisome proliferator-activated receptor gamma (*PPAR- $\gamma$* ) and glucocorticoid receptor (*GR*) gene promoter regions in the next two generations.<sup>63</sup> While comparable epigenetic analyses have not been conducted in humans, one study found that paternal grandfather’s experience of food availability during childhood was associated with grandchild’s mortality risk ratio from cardiovascular disease and diabetes related deaths.<sup>64,65</sup>

Evidence for intergenerational effects of nutrition on epigenetic markings gains particular salience for public health in light of the fact that patterns of nutritional stress within human societies tends to mirror social stratification.<sup>66</sup> Not surprisingly, food insecurity is more common in economically disadvantaged groups across diverse geographical, social and political contexts,<sup>67-69</sup> but importantly, it is not only limited to low-income countries. A meta-analysis of 78 studies of food security in high-income countries found that food insecurity is relatively common, particularly among households with limited financial resources.<sup>70</sup> For example, a study in New Zealand found that 39% of Pacific Islander women with newborn infants reported having limited dietary variety and that they sometimes ran out of food.<sup>71</sup> Such food insecurity, to which pregnant women and growing children are especially vulnerable,<sup>72</sup> could have implications for epigenetic programming and a range of disease and functional outcomes in offspring.

### Psychosocial Stress

There is extensive evidence that psychosocial stress contributes to the social gradient in health. While traditional social science approaches have highlighted the impacts of stressors on traits such

as blood pressure, stress hormone metabolism or immune function,<sup>73-76</sup> current work is foregrounding the potential for psychosocial stress to induce durable, epigenetically-based changes in gene regulation that are linked with changes in physiology and behavior. As one example, chronic stress exposure in adult mice leads to hypothalamic demethylation of the gene that encodes the corticotrophin releasing factor, which in turn predicts stress-induced social avoidance.<sup>77</sup> A recent study of adult factory workers in Italy found that job seniority predicted patterns of methylation in an *Alu* sequence in peripheral blood DNA, which the researchers interpreted as a surrogate of global methylation patterns.<sup>78</sup> Methylation profiles were also changed in peripheral blood among shift workers, presumably due to the stresses associated with a changed circadian rhythm. Research thus suggests that stress experienced by adults can impact epigenetic profiles, with potential implications for health.

Akin to the work on nutrition reviewed above, there is evidence for stress-induced epigenetic changes that linger across lifecycles and that can potentially be transmitted to offspring. In rats, differences in maternal care provided to newborn pups have been shown to have durable effects on epigenetic profiles in offspring hippocampal neurons, which help regulate adult stress reactivity and behavior. In these experiments, individuals that were less nurtured as newborns were more reactive and anxiety-prone as adults.<sup>79,80</sup> Recent research provides preliminary evidence that similar epigenetic pathways may be operative in humans. For example, a study of teenage suicide victims found that a history of childhood abuse was associated with methylation differences at the *GR* locus in the hippocampus,<sup>81</sup> while another study found a significant effect of child abuse on methylation at the serotonin transporter protein (*SLC6A4*) locus.<sup>82</sup> An additional study focusing on prenatal influences found that maternal depression during pregnancy predicted stress reactivity and methylation of the *GR* locus in buccal cells of infants measured three months after birth.<sup>83</sup> Together these studies suggest that both prenatal and early postnatal environmental exposures can shape the epigenome of offspring with durable effects on stress physiology and related behavioral outcomes.

As with nutritional influences, there is evidence that psychosocial stress can have transgenerational effects on epigenetic profiles and related physiologic and health outcomes. For example, one study found that maternal separation in early life induced methylation changes in the sperm of males at CpG islands near promoters for several genes that influence affect and behavior.<sup>2</sup> Female offspring of the exposed males had similar changes in methylation and associated changes in mRNA production measured in neurons. These findings suggest that parental experience of psychosocial stress can be transmitted across generations through epigenetic modifications that affect the germline, and are therefore not limited to direct maternal-offspring transfer.

Research documenting epigenetic impacts of psychosocial stress is important in light of evidence from social science research that stress experience is inequitably distributed within and across societies. For instance, research demonstrates that socially disadvantaged individuals tend to live in less safe neighborhoods,<sup>84</sup> report more chronic stress<sup>85</sup> and more perceived discrimination<sup>28</sup> and suffer from higher rates of depression.<sup>15</sup> As an example, ethnic immigrants to countries such as the United States,<sup>86</sup> England<sup>87</sup>

and Norway<sup>88</sup> report greater experience of perceived discrimination, as do individuals of lower socioeconomic status.<sup>89</sup> When combined with the evidence reviewed above that psychosocial stress can influence epigenetic profiles and health, it is clear that socially disadvantaged individuals are at increased risk of exposure to these stressors and are thus more likely to develop adverse disease outcomes.<sup>27</sup> Evidence for impacts on the next generation, and even on grandoffspring, suggest that the full health costs of such experiences may not be realized for several generations.

## Environmental Toxicants

In many communities, individuals are exposed to high levels of toxicants, despite the fact that these compounds have well-known health impacts.<sup>6,90</sup> A growing list of studies illustrates the role of epigenetic mechanisms as links between these exposures and biological function and health.<sup>91-97</sup> For example, studies have found that higher concentrations of several persistent organic pollutants (POPs) are associated with a decrease in global methylation in humans,<sup>98,99</sup> while exposure to urban pollution has been shown to modify epigenetic markers and related regulatory enzymes in mice.<sup>4,100</sup> Exposure to heavy metals, such as arsenic, also alters methylation patterns, possibly due to competition for methyl donors since these metals become methylated during the metabolic process of detoxification.<sup>101</sup> As one example, a study in India reported a dose-response relationship between exposure to arsenic in drinking water and methylation at the promoter regions for the tumor suppressing p53 gene (*p53*) and the cyclin-dependent kinase inhibitor 2A (*p16*) gene.<sup>102</sup> Similarly, studies have linked cigarette smoking to changes in methylation at genes involved in serotonin regulation<sup>103</sup> and in platelet aggregation,<sup>93</sup> which can have numerous behavioral and physiological effects.

Exposure to such pollutants during pregnancy has been shown to influence offspring epigenetic profiles and health risk,<sup>104</sup> illustrating that the health impacts of these exposures can in some cases be transmitted to offspring. For example, smoking during pregnancy modifies histone proteins that influence gene expression at pro-inflammatory genes in offspring.<sup>105</sup> Additionally, studies of prenatal exposure to air pollution find that high exposure to traffic exhaust particles modifies methylation at the acyl-coA synthetase long-chain family member 3 (*ACSL3*) gene, which is involved in lipid biosynthesis and is associated with the development of asthma in offspring.<sup>106</sup> Together, these studies suggest that exposure to airborne pollutants during pregnancy can modify epigenetic markings in offspring, thereby modifying risk for various diseases prior to birth.

There is some evidence that exposure to environmental toxicants can also have transgenerational effects across several generations. One study evaluated changes in DNA methylation in the sperm of mice exposed to air pollution in an industrial area in Canada.<sup>4</sup> The researchers found that exposure for ten or more weeks led to significantly elevated global methylation in the sperm of exposed males, which remained after removal from exposure to the pollution. Another study found that exposure to the endocrine disruptor vinclozolin during gestation led to the development of abnormal methylation patterns in sperm

with adverse effects on reproductive function persisting across at least three generations of male progeny.<sup>97</sup> Together, these studies demonstrate that exposure to toxicants can lead to epigenetic modifications in the germline, which can potentially link current exposures with adverse health outcomes in future generations.

Research demonstrating the epigenetic response to toxicant exposure takes on increased relevance in light of the fact that socially disadvantaged individuals are at increased risk for exposure to many of these toxicants.<sup>107-114</sup> For example, male Inuit in Greenland have been found to have significantly higher serum POP levels than Europeans in adulthood.<sup>115</sup> Additionally, socially disadvantaged individuals are more likely to smoke,<sup>116</sup> thereby increasing their own and their family's exposure to this source of epigenetic modification. Since socially disadvantaged individuals are more likely to be exposed to environmental pollutants, the finding of links between these exposures and epigenetic change suggests that this is another important group of exposures that contribute to health disparities by inducing durable epigenetic memories of environmental experience.

### Future Directions

Human populations face disparities in health across groups defined by class, race and ethnicity.<sup>9,117</sup> These relationships are highly predictable both within and across populations that vary widely in genetic relatedness, suggesting that they are governed by regularities within the environment rather than tracing to genetic ancestry.<sup>26,27,36,118</sup> The epigenetic research that we review above underscores that the roots of these health gradients likely trace, in part, to conditions experienced in the past, whether by the present generation or by recent ancestors.<sup>40,119</sup> Although this does imply that some current health problems were already established in the past, this by no means undermines the need for current interventions or public health action. Instead, bringing an understanding of epigenetic processes together with the study of human health disparities underscores the need for new public health strategies, and for new epigenetic research designed to promote beneficial impacts on population health rather than simply avoiding the adverse effects of stress.<sup>40,120</sup>

Although the research that we review highlights the lingering, often adverse impacts of early life stress, many of these studies are designed to merely identify such long-term effects, rather than reverse them. The finding that epigenetic changes are durable does not imply that, under changed conditions, the impacts could not be fully or partially reversed. For example, HPA-axis programming in response to maternal care in mice is reversed if offspring are fed a diet supplemented with methyl donors as adults.<sup>121</sup> Similarly,

some of the negative metabolic effects of prenatal undernutrition in mice can be reversed by exposure to the fat-derived hormone leptin immediately after birth.<sup>122</sup> Because this hormone is found in breast milk,<sup>123</sup> and has long-term effects on offspring metabolism,<sup>124</sup> promotion of breastfeeding may be one means of reversing the negative impacts of some stressors experienced prior to birth. The applied impact of epigenetic research will be enhanced as future studies move beyond simply documenting long-term effects of early life exposures, and take the next step to establish which of these effects might be reversed.

On a related note, in addition to the current focus on strategies to avoid the negative health effects of environmental stress, we need to know more about whether environmental enrichment might have positive effects on biology and health via epigenetic modification. In mice, recent studies report environmental enrichment is associated with changes in methylation patterns.<sup>125-127</sup> Other studies suggest that increased exercise in mice modifies methylation at genes that regulate metabolism.<sup>128</sup> Thus studies in humans that evaluate the potential positive effects of behavioral interventions in early life or even adulthood would be useful for determining whether administering such interventions could modify epigenetic profiles and health risk. Based upon past work on the epigenetic effects of environmental stressors, one exciting possibility is that the health benefits of environmental enrichment might also carry across multiple generations through epigenetic inheritance.

As a final note, we feel that the emerging understanding of the environmental sensitivity of gene regulation holds great promise to enrich public awareness of the determinants of health and disease. Epigenetic modifications triggered by environmental experiences can change gene expression without changing one's genotype. The notion that genes are regulated by biological "memories" of experiences acquired earlier in our own lives, and even by recent predecessors, serves as a heuristically powerful alternative to the simple model of genetic determinism that is predominant among the lay public.<sup>129,130</sup> We feel that communicating the importance of environmentally-driven epigenetic change as an influence on health disparities has an essential role to play in helping the public, and policy makers, move beyond the nature-nurture debates of the past and toward a more realistic understanding of how genetic factors and the socially and economically-structured environments that we inhabit interact to influence patterns of health and disease.

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