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SOCIAL EPIDEMIOLOGY (JM OAKES, SECTION EDITOR)

Developmental Programming: Priming Disease Susceptibility for Subsequent Generations

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Abstract Racial and/or ethnic minorities carry the highest burden of many adverse health outcomes intergenerationally. We propose a paradigm in which developmental programming exacerbates the effects of racial patterning of adverse environmental conditions, thereby contributing to health disparity persistence. Evidence that developmental programming induces a heightened response to adverse exposures ("second hits") encountered later in life is considered. We evaluated the evidence for the second hit phenomenon reported in animal and human studies from three domains (air, stress, nutrition). Original research including a gestational exposure and a childhood or adulthood second hit exposure was reviewed. Evidence from animal studies suggest that prenatal exposure to *air pollutants* is associated with an exaggerated reaction to postnatal air pollution exposure, which results in worse health outcomes. It also indicates offspring exposed to prenatal *maternal stress* produce an exaggerated response to subsequent stressors, including anxiety and hyper-responsiveness of the hypothalamic–pituitary–adrenal axis. Similarly, prenatal and postnatal *Western-style diets* induce synergistic effects on weight gain, metabolic dysfunction, and atherosclerotic risk. *Cross-domain* second hits (e.g., gestational air pollution followed by childhood stressor) were also considered. Suboptimal gestational environments induce exaggerated offspring responses to subsequent environmental and social exposures. These developmental programming effects may result in enhanced sensitivity of ongoing, racially patterned, adverse exposures in race/ethnic minorities, thereby exacerbating health disparities from one generation to the next. Empirical assessment of the hypothesized role of priming processes in the propagation of health disparities is needed. Future social epidemiology research must explicitly consider synergistic relationships among social environmental conditions to which gestating females are exposed and offspring exposures when assessing causes for persistent health disparities.

Keywords Developmental programming · Health disparities · Social epidemiology · Priming · Air pollutants · Psychosocial stress · Diet

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Introduction

Not long ago, scientists conceived of infants as unadulterated by historic behaviors or environmental insults but now understand that babies are record keepers of maternal and paternal exposures to environmental conditions [1–3]. We propose that this record keeping at least partially occurs through a biological process known as developmental programming whereby racial disparities in health are not only propagated [4–7] but, when combined with persistent environmental exposures, are magnified from one generation to the next.

Developmental programming, or developmental origins of health and disease, refers to the changes in fetal structure and physiology that result from adverse early life exposures that increase susceptibility to poor health outcomes later in life [8]. Programmed characteristics are believed to be largely stable

after the postnatal period and have been associated with increased risk of obesity, cancer, and heart disease, among others [9]. The maternal stressors that serve as exposures associated with developmental programming include environmental pollutants [10, 11], social stress [12, 13], and dietary restriction or high-calorie malnutrition [14–17].

Conceptual Framework

Decades of social epidemiologic research demonstrate that race and ethnic minorities face greater exposure to adverse social and environmental health determinants, resulting in health disparities. These disparities are persistent across generations and have been studied in numerous domains (e.g., environmental injustice, neighborhood deprivation, lower quality educational opportunities), yet the mechanisms underlying their proliferation remain unknown. We propose that developmental programming is a critical, previously overlooked factor in the propagation of health disparities from one generation to the next.

Figure 1 illustrates a paradigm of developmental programming on health, according to ongoing environmental exposures, across three generations. Health status in the first (F_0) generation is determined by a woman's lifetime accumulation of adverse exposures; D_0 denotes the health status for women in generation F_0 who experience adverse exposures, and A_0 denotes the health status of a woman whose exposure profile is healthier. It is well known that adverse exposures are more common at greater levels of social and economic disadvantage. Therefore, we characterize trajectories stemming from exposure likelihood in the baseline generation as representing disadvantaged (D) and advantaged (A) trajectories.

If no further harmful exposures were incurred in subsequent generations, health trajectories could be expected to remain somewhat constant, traveling along the solid lines in the figure, resulting in positions A_{10}, A_{20}, D_{10}, and D_{20}. Because disadvantage accumulates over time, one would expect the health of disadvantaged women to decline over their lifetimes. Furthermore, the weathering hypothesis, originally conceived to explain the premature worsening of health by African-American women as a consequence of cumulative social disadvantage, can be applied here as the acceleration of disease progression within a woman's life course [18]. α_g denotes the difference in health between the advantaged and disadvantaged trajectories in generation g.

β represents the decrement in health caused by an ongoing adverse exposure; both advantaged and disadvantaged women move to a position of worse health when so exposed. The F_1 generation communicates this health status to any developing offspring in generation F_2, who are then born from the combined baseline maternal risk (A_{10} or D_{10}) supplemented by effects of any adverse exposures accumulating prior to or during pregnancy (β_1 or β_1*). The scenario in which adverse exposures persist from one generation to the next produces an increasing health gap over time (α_1, represented by the difference between A_{11} and D_{11}; and α_2, the difference between A_{21}, and D_{21}). Such persistent exposures observed in the social epidemiology literature include the intergenerational

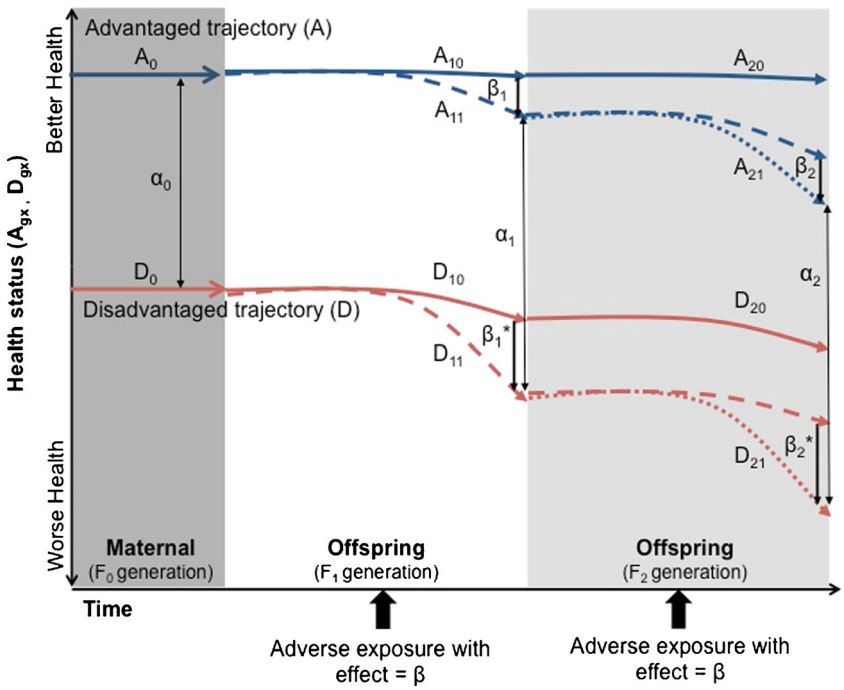

Fig. 1 Theoretical role of developmental programming in propagation and magnification of health disparities over three generations. A_{gx} and D_{gx} denote health status Y_{gx} for generation g and exposure status x. β_g and β_{g*} denote the difference in health on Y_{gx} between advantaged and disadvantaged trajectories. α_g denotes the magnitude of disparity in any in generation g

transmission of poverty, low educational expectations, and unhealthy coping behaviors.

One important element of Fig. 1 is that the effect β is not constant but instead varies according to exposure status in the previous generation. This effect difference, by advantaged or disadvantaged trajectories (A_{g1} minus A_{g0} or D_{g1} minus D_{g0}), is illustrated by comparing the exposure effects β_1 versus β_1* and β_2 versus β_2*. The magnitude of effect, β, may be influenced by the biological processes underlying developmental programming. That is, maternal prenatal exposures may alter the physiology of the gestating offspring such that the offspring is more sensitive to the effects of postnatal exposures such as environmental pollutants, stress, or high-fat diet.

Postnatal exposures, referred to above as ongoing adverse exposures, comprise second hits to biological predispositions determined during gestation. *We propose that this heightened sensitivity is a mechanism through which developmental programming exacerbates health disparities across generations*. The increasing magnitude of disparity that results from differential exposure effects can be seen by comparing α_1 with α_2. Not only are women in disadvantaged trajectories at increased risk of poor health in the absence of ongoing exposures, they, and by extension their offspring, may experience a greater health "penalty" to ongoing postnatal insults. By contrast, advantaged offspring will be less likely to experience detrimental exposures later in life but, more importantly, will be more resilient than their less advantaged counterparts. In this review, we focus on evidence that effects of key postnatal exposures differ according to maternal exposure status (β versus β*). One enduring question in the social epidemiologic literature is why health disparities persist in light of targeted health promotion endeavors. One part of the health disparities' intransigence may be that disadvantaged populations produce a larger than expected response to ongoing social-environmental insults in part, because they have been biologically primed to do so.

Objectives

We first review evidence that maternal exposure to air pollution, psychosocial stress, and overnutrition induces exaggerated offspring responses to subsequent social environmental exposures. We then discuss the social patterning of social environmental stressors and how each type of gestational exposure may contribute to the construction and transmission of health disparities. While existing reviews describe how gestational exposures impact offspring health (e.g., [16, 17, 19]), this paper focuses on how developmental programming can exacerbate the effects of socially patterned adverse environmental conditions, like those studied by social epidemiologists.

Methods

We performed an electronic search of publications on Google Scholar, PubMED, and EBSCO Host databases. The following search terms were used: "fetal priming," "fetal exposures," "fetal programming," "early life exposures," "developmental origins," and "intergenerational," in combination with a second group of key words such as, "adult health outcomes," "adult health," "offspring," "influences on health," "disease in later life," "second hit," and "child development." To search for relevant papers in domains of interest, we included additional terms including "air pollution" and "stress"; For maternal overnutrition exposures, we searched for (obesity or "high-fat" or "fat") and (maternal or gestation or pregnancy) and (offspring or fetal). In addition to using key word combinations, we employed the "related articles" electronic prompts provided with the search results and examined references from relevant papers. We retained original human and animal studies that included a gestational exposure and a childhood or adulthood second hit exposure. While the papers presented in the following tables do not represent the universe of possible manuscripts, they are representative of the second hit literature as of August 2014. This review does not discuss fetal outcomes resulting from gestational exposures, even though this work is relevant to future adult health.

Results

Environmental Pollutants

Poor environmental quality, like other social epidemiologic phenomena, has its greatest impact on those whose health status is already at risk [20], such as individuals living on the disadvantaged trajectory in our conceptual model. Exposure to environmental pollutants, inadequate buffering of environmental exposures, and increased susceptibility to environment-induced poor health owing to existing comorbidities are differentially distributed [21–24]. We propose developmental programming as an additional explanation for the disparate effects of environmental exposures by considering the evidence that gestational exposures to air pollution predispose offspring to worse physiological responses to subsequent air pollution experiences.

Evidence from animal studies suggests that exposure to air pollutants by neonates (e.g., mouse pups) during gestation is associated with an exaggerated reaction to air pollution exposure during child- or adulthood (Table 1). In studies by Auten and colleagues [25••, 26], pups born to moms who were exposed to diesel exhaust while gestating, who were then exposed to ozone during their childhood, developed persistent airway hyper-reactivity. Effects of childhood ozone exposure were stronger in pups born to dams exposed to diesel exhaust

while gestating, than in pups born to dams that were instead exposed to filtered air [25••]. This paper follows earlier work, which reported that maternal diesel exposure induced inflammatory cytokine responses in the offspring that presumably contribute enhanced airway hyper-responsiveness to postnatal ozone exposure [26].

A handful of observational epidemiologic studies examining gestational and later-life exposures investigated if fetal priming of later response is generalizable to humans. Perera [27] and colleagues collected polycyclic aromatic hydrocarbon (PAH) data using a personal air monitor during the third trimester of pregnancy. Postnatal interviews were administered at 6 months postdelivery and annually thereafter to determine changes in PAH exposure. Youth exposed to high amounts of PAH in utero exhibited lower intelligence quotient scores, but postnatal exposure did not exacerbate this effect. A second epidemiologic effort to tease apart effects of gestational and adult exposures comes from Montgomery and Ekbom [28]. They considered maternal smoking, a form of gestational air pollution, and the offspring's own smoking at age 16 as the second air pollution hit related to diabetes development. After adjustment for maternal smoking, cigarette smoking during adolescence was independently associated with increased risk of diabetes. No evidence of hyper-sensitization was observed, but the authors went on to suggest mechanisms by which this observed effect is biologically plausible.

While the number of studies considering gestational air pollution exposures followed by subsequent air pollution is relatively small, the results suggest that gestational exposure primes the child or adult body for a more severe reaction to subsequent exposures. This finding is likely to be highly relevant for human health given the ubiquity of air pollution. Further, because social stratification results in non-randomly distributed adverse air quality, those most vulnerable to the effects of poor air quality are most likely ensured of ongoing adverse exposures.

Psychosocial Stress

Lack of autonomy within a social hierarchy, inadequate income, discrimination, and inadequacy of time and resources are sources of chronic psychosocial stress in disadvantaged populations and are linked with adverse health outcomes. Maternal stress induces elevations in the glucocorticoid hormone, cortisol [29]. Excessive maternal cortisol can overwhelm placental capacity to block its passage; fetal exposure to cortisol induces widespread developmental alterations that increase susceptibility to disease [12]. Notably, glucocorticoids are a common pathway through which a wide range of adverse maternal exposures induces developmental programming [30]. We reviewed evidence that maternal stress during pregnancy induces exaggerated response to stress experienced by the offspring.

In animal studies, offspring born to dams exposed to restraint stress, who then experienced stress during adolescence, have altered immune, neuroendocrine, or glucocorticoid systems, compared to those animals not exposed to prenatal maternal restraint (Table 2). Pascuan and colleagues [31] found that prenatal stress altered the intrinsic regulation response to acute stress in adult mice, while Xu and colleagues [32] found that prenatal restraint of pregnant rats led to a hyper-responsiveness of the HPA axis, and increased anxiety-like behavior in rats. Van den Hove and colleagues found that, compared with control rats, chronic variable mild stress in adolescent rats that had been exposed to maternal restraint stress during gestation partially offset the effects of prenatal stress, suggesting that responses to developmental stress may depend on later life exposures [33••]. In contrast, Schopper and colleagues [34] showed that intermittent light stress induced elevated glucocorticoid levels in maternal guinea pigs but that their offspring had an attenuated cortisol response over adult development and subsequent stress exposures.

Human evidence for the effect of second hit stress exposures following prenatal stress is scant. One study collected the peripheral blood mononuclear cells from 34 young women whose mothers reported negative life events during their pregnancy (and from a comparison group whose mothers did not experience negative life events). The cytokine response to a potent T cell stimulator, or a phytohemagglutinin (PHA) second hit, was significantly altered in women born to mothers who were stressed while gestating [35], suggesting that prenatal stress exposure may induce an exaggerated immune response in adult women. Regardless of the exact source of social stress, maternal stress while gestating likely induces physiologic changes in the developing fetus, such that subsequent postnatal (lifetime) stress elicits perturbations in the offspring's stress response.

Nutrition

"Western-style" diets, characterized by high fat and high refined sugar content, are ubiquitous in Western populations and even more pronounced in racial minority and low-income populations [36, 37]. The racial and neighborhood-level patterning of poor-quality food environments is a significant area of social epidemiologic research. We reviewed evidence for the hypothesis that prenatal Western-style diet (high fat, high sugar, or high-total energy) induces exaggerated offspring responses to Western-style diet in postnatal life (Table 3). A growing body of animal research supports this hypothesis. For example, Bruce and colleagues examined the combined effects of maternal high-fat diet during preconception, gestation, and lactation in mice and high-fat diet consumed by the offspring upon weaning [38]. Postweaning high-fat diet induced accelerated weight gain, higher adiposity, cholesterol

Table 1 Studies illustrating gestational air pollution priming followed by air pollution second hit

Reference	Sample pop	Prenatal exposure	Postnatal exposure	Childhood or adult outcome
Animal evidence				
Auten et al. [25••]	Mice	Diesel exhaust (DE) for 4 h/day during gestational days (9–17) or two times/week aspiration of diesel exhaust particles (DEP)	Filtered air (FA) or 1 ppm ozone (O3) day after birth; 3 h/day, 3 days/week for 4 weeks	Pups born to the DE-exposed dams had worse ozone-induced airway hyperreactivity (AHR), which persisted even after 4-week recovery. Gest DE+ postnatal O3 resulted in increased AHR, which persisted. Gest DE+ postnatal O3 resulted in worse secondary alveolar crest. Conclusion: Maternal inhalation of DE in pregnancy provokes fetal inflammatory response that, combined with postnatal ozone exposure, impairs alveolar development and cause more severe and long-lasting AHR to ozone exposure.
Auten et al. [26]	Mice	Particulate matter (PM) or no treatment by tracheal insufflation two times/week for 3 weeks	Dams and pups air or ozone (O3) 1 ppm 3 h/day, every other day, three times/week for 4 weeks	O3 Increased airway hyperreactivity (AHR), increase greatest in PM-exposed pups. O3 increased whole-lung TNF-a, IL-1b, KC, IL-6, and MCP-1; greatest in PM-exposed pups. O3 increased airway epithelial mucous metaplasia; greatest in PM-exposed pups. Conclusion: Maternal pulmonary exposure to PM during pregnancy augments placental cytokine expression and postnatal ozone-induced pulmonary inflammatory cytokine responses and ozone-induced airway hyperresponsiveness without altering airway structure. Note: TNF-a=tumor necrosis factor alpha, cytokines that can cause cell death); IL-1b=interleukin-1 beta (cytokine mediator of the inflammatory response); IL-6=interleukin-6, a pro-inflammatory cytokine; MCP=membrane cofactor protein
Human evidence				
Montgomery and Ekbom [28]	Human	Maternal smoking	Own smoking at age 16 years	After adjustment for maternal smoking, smoking at age 16 was associated with an increased odds of diabetes. Conclusion: In utero exposures to maternal smoking during pregnancy may increase the risk of both diabetes and obesity through programming, resulting in lifelong metabolic dysregulation, possibly due to fetal malnutrition or toxicity.

Table 2 Studies illustrating gestational stress priming followed by stress second hit

Reference	Sample pop	Prenatal exposure	Postnatal exposure	Childhood or adult outcome
Animal evidence				
Pascuan et al. [31]	Mice	PRS (during final trimester, placed in cylindrical restraint tube)	Acute stress (placed in well-ventilated polypropylene tube; animals were not physically compressed)	Prenatally exposed PRS mice had decreased antibody production after acute stress situation, altered lymphocyte response to hormones and inhibitory effect of corticosterone was higher on lymphocytes. Non-gestational PRS mice that were subsequently acutely stressed showed increase in antibody production after antigen stimulation Conclusion: Prenatal stress alters the immune intrinsic regulatory mechanism response following acute stress in adult life.
Van den Hove et al. [33]••	Rats	Prenatal stress (PS) (restraint stress three times a day for 45 min in last week of pregnancy, while exposed to bright light)	At postnatal day 77, subjected to chronic variable mild stress (CMS) (housing in mice cage, cage tilt, housing in an empty cage, wet bedding in cage, flashing light during the dark phase	Rats with PS exposure induced more anxiety-like behavior in the postnatal elevated zero maze test in both sexes, an effect that was normalized by subsequent exposure to CMS. PS was associated with increased depression-like behavior in the postnatal forced swim test in males only. Postnatally, sucrose intake was increased in PS males, but decreased in females when consecutively exposed to postnatal CMS Conclusion: PS induced anxiety- and depression-related behavioral and neuroendocrine changes, as well as alterations in central serotonin (5-HT) and TPH2) function, predominantly in male offspring. CMS exposure partially normalized the effects of previous PS experience, suggesting responses to developmental stress exposure largely depends on the environmental conditions later in life Note: 5-HT=5-hydroxytryptamine; TPH2=tryptophan hydroxylase 2
Xu et al. [32]	Rats	Randomly assigned pregnant dams to normal control group or restraint stress (RS; under bright light) group; 30 min/day gestational days 8–21	Postnatal day 38, additional RS for 30 or 60 min/day	Adolescent rats exposed to prenatal RS had a lower percentage of (deoxyribonucleic acid (DNA) demethylation of the corticotrophin releasing hormones (CRH) promotor following acute RS during adolescence, and more anxiety-like behaviors; they also showed hypothalamic-pituitary-adrenal (HPA) axis hyper-responsiveness. Conclusion: The data confirms that prenatal RS used as a model of early stress could lead to hyper-responsiveness of the HPA axis, and increased anxiety-like behavior in rat offspring. They also indicate that prenatal RS-related hyper-responsiveness of the HPA axis is associated with demethylation in the CRH promoter.
Schopper et al. [34]	Guinea Pig	Maternal stress (stressed with strobe light during early to mid-pregnancy)	Day 26 and day 100 stress (strobe light) (F1 generation)	Overall glucocorticoid levels following postnatal stress were lower in prenatally stressed F_1 animals. Fecal cortisol metabolites were initially lower in prenatally stressed F_1 animals, relative to controls, but shifted to higher levels around day 68, particularly among males. Effects persisted into the F_2 generation; male offspring of prenatally stressed F_1 animals have significantly higher fecal cortisol metabolites during weaning. Conclusion: Findings indicate that stress exposure of F_0 dams resulted in lower basal glucocorticoid levels in F_1 offspring

Table 2 (continued)

Reference	Sample pop	Prenatal exposure	Postnatal exposure	Childhood or adult outcome
				during the pre-pubertal phase and during stress exposure, but higher glucocorticoid levels in postadolescent F_1 animals. Also in males of F_2 generation, effects of stress exposure of F_0 dams were detected
Human evidence				
Entringer et al. [35]	Human	Maternal psychosocial (PS) stress measured using (negative life events)	In vitro phytohemagglutinin (PHA) stimulation	PS-stressed subjects showed significantly higher levels of interleukin (IL)-4, IL-10, and IL-6. IFN-g/IL-4 ratio was significantly lower in the PS group. Conclusion: Results suggest an association between maternal psychosocial stress during pregnancy and changes in cytokine production in response to antigen stimulation in the adult (female) offspring in humans.

and insulin resistance, and development of non-alcoholic fatty liver disease characteristics. Notably, these effects were exacerbated by maternal high-fat diet. Fan and colleagues conducted a similar experiment in non-human primates and evaluated prenatal and postnatal diet impacts on metabolic and cardiovascular outcomes [39••]. Compared to controls, insulin resistance was observed only among monkey offspring who consumed high-fat diets during both prenatal and postnatal life. Several markers of atherosclerotic risk such as intima-media thickness were more responsive to postnatal high-fat diet among offspring of high-fat diet-fed mothers, compared to offspring of control mothers.

In other studies using mice, rats, sheep, and non-human primates, adverse measures of adiposity, liver triglyceride content, fatty acid content, leptin, glucose, and insulin were more pronounced in offspring exposed to both prenatal and postnatal high-fat or high-sugar diet compared to offspring having only prenatal dietary exposures [40–47]. Such augmented sensitivity could be due to changes in insulin production [48], perturbation to central appetite control [43, 47, 49, 50], altered circadian regulation of liver metabolism [51], or changes in the microbiome [52]. The effects of postnatal diet among offspring exposed to prenatal Western-style diet, compared to offspring of control-fed dams, varied within study by gender [42, 45, 46]. In other studies, the effects of postnatal overnutrition were similar across prenatal diet groups [53, 54] or, for body weight outcomes, even weaker [55, 56]. In many studies, it was difficult to distinguish between cumulative versus synergistic effects of prenatal and postnatal diets, as investigation of "priming" or "hyper-responsivity" to postnatal exposures was not the primary aim of the research. We were not able to identify relevant human studies. Nevertheless, animal data send the clear message that determining how prenatal high calorie malnutrition exaggerates the detrimental effects of a poor postnatal diet in at-risk human populations is urgent.

Cross-Domain Exposure Effects

Humans live in environments characterized by simultaneous exposures from multiple domains, each of which are socially structured and would likely exacerbate existing health disparities. The animal literature has begun to replicate this exposure complexity by conducting cross-exposure experiments (Table 4). Recent research by Wei and colleagues exemplifies this work. Wei [57] found that prenatal exposure to bisphenol A, a synthetic compound with hormone-like properties commonly employed in plastics production, resulted in defective insulin signaling among offspring exposed to standard diets. However, compared to unexposed controls, the prenatally exposed BPA pups developed more extensive liver impairment (e.g., increased inflammation and mild fibrosis) following exposure to high-fat diets. The authors concluded that

Table 3 Selected studies illustrating gestational diet priming (overnutrition) followed by dietary second hit

Reference	Study population	Prenatal (maternal) exposure	Postnatal exposure	Childhood or adult outcome
Bruce et al. [38]	Mice	HFD vs. chow; preconception (4 weeks), pregnancy, lactation	HFD vs. chow; from weaning	Female data presented; similar patterns by sex; follow-up through 15 or 30 weeks; Postnatal HFD effects on higher weight gain, adiposity, cholesterol, insulin resistance, development of non-alcoholic fatty liver disease-like outcome via inflammatory and lipogenic pathways were stronger in prenatal HFD group
King et al. [53]	Mice	HFD vs. chow; preconception (12 weeks), pregnancy, lactation	HFD vs. control diet; from weaning	Males and females; follow-up through 3–6 months. At 6 months, postnatal HFD had strong effect on higher lipids and insulin resistance; these effects were similar for both prenatal diet groups
Zhang et al. [40]	Rats	Chow supplemented with chocolate and fructose beverage, with (ON) or without protein (MN) vs. chow only; pregnancy, lactation	HFD vs. chow; from weaning	Males only; follow-up through 1, 3, 7, and 14 weeks; postnatal HFD effects on higher-fat mass and liver triglycerides were stronger in prenatal MN (vs. chow) group. Postnatal HFD did not affect blood glucose within prenatal diet groups. No differences in serum lipids across groups.
White et al. [54]	Rats	HFD, pair fed; (HFD with matched caloric intake of chow control group), low-fat diet; preconception (4 weeks), pregnancy, lactation	HFD vs. low fat diet; from 5 weeks postweaning	Males only; follow-up through 20 weeks; postnatal HFD effects on greater body weight, adiposity were additive with prenatal HFD; postnatal HFD did not affect insulin sensitivity, regardless of prenatal diet
Khanal et al. [44]	Sheep	Diet with high, low, or normal energy and protein; pregnancy (last 6 weeks)	High-carbohydrate, high-fat diet vs. conventional diet; 3 days to 6 months	Males and females combined; follow-up through 6 months (puberty); postnatal diet effect on hyperglycemia and hyperlactataemia was strongest in prenatal high-energy/protein diet (in comparison to normal). Postnatal diet effects on lipids were similar for high versus low prenatal diet.
Fan et al. [39••]	Non-human primates (Japanese macaques)	HFD vs. control diet; preconception (up to 5 years), pregnancy, lactation	HFD vs. control diet; from weaning	Males and females combined; follow-up through 13 months (juveniles); postnatal HFD effects on intima thickness (a marker of atherosclerotic risk) and endothelial function were stronger in prenatal HFD group

Studies selected for inclusion in the table to provide examples for a range of disease outcomes, prenatal "Western-type" diet exposures and animal models. Findings summarized for last time point reported. Weaning: 21 days in rats

HFD, high-fat diet

Table 4 Cross-exposure papers: studies illustrating gestational contaminant priming followed by nutrition second hit

Reference	Sample pop	Prenatal exposure	Postnatal exposure	Childhood or adult outcome
Animal evidence				
Wei et al. [57]	Rats	50 mg/kg per day bisphenol A (BPA) or corn oil during gestation and lactation by oral gavage	Standard chow diet (SD) or high-fat diet (HFD)	Offspring of BPA-exposed rats on SD exhibited moderate hepatic steatosis, altered insulin signaling in the liver, but with normal liver function. BPA-exposed offspring on HFD showed a non-alcoholic steatohepatitis-like phenotype (extensive accumulation of lipids, large lipid droplets, profound ballooning degeneration, impaired liver function, increased inflammation, mild fibrosis in the liver) Conclusion: Prenatal BPA exposure worsened hepatic damage caused by HFD in rat offspring
Bolton et al. [58••]	Mice	Vehicle (VEH) or diesel exhaust particles (DEP) during gestation	High-fat diet (HFD) or low-fat diet (LFD), each for 9 weeks	DEP+HFD resulted in exaggerated with gain, insulin resistance, anxiety-like behavior among males. HFD macrophage infiltration of both adipose tissue and brain in both males and females, but more in DEP+HFD males Conclusion: Prenatal air pollution exposure programs offspring for increased susceptibility to diet-induced metabolic, behavioral, neuroinflammatory changes in adulthood in sexually dimorphic manner
Bolton et al. [59]	Mice	Filtered air (FA) versus diesel exhaust (DE) during gestational days 9–17	Low-fat diet (LFD) or high-fat diet (HFD) for 6 weeks	DE-exposed male offspring weighed 12 % more, 35 % less active than FA-exposed male. No differences among female; DE+HFD resulted in same weight gain as FA+HFD males. DE+HFD females gained 340 % more weight than FA-exposed females. DE+HFD males 450 % higher insulin than FA-HFD males. All HFD males showed increased activity, anxiety. All HFD females showed no differences in activity, anxiety Conclusion: Prenatal air pollution can "program" offspring for increased susceptibility to diet-induced weight gain and neuroinflammation in adulthood in a sex-specific manner
Tamashiro et al. [60•]	Rats	High fat (HF) vs. control diet during gestation, and lactation; variable stress (restraint, swim, cold exposure) in gestational week 3	HF vs. control diet, starting at weaning	Postnatal HF diet resulted in greater body weight, body fat, glucose intolerance and elevated insulin to a greater extent in offspring of dams exposed to HF or stress during gestation. Conclusion: The data suggest that maternal prenatal stress or high-fat diet alters susceptibility of offspring to diet-induced obesity and its metabolic consequences.

prenatal BPA exposure predisposed offspring who later consumed high-fat diets to develop metabolic syndrome manifestations.

In 2014, Bolton and colleagues [58••] reported that prenatal diesel exhaust exposure, followed by a postnatal high fat (compared to a low fat) dietary second hit, programmed offspring for diet-induced metabolic, behavioral, and neuroinflammatory changes in adulthood and that these changes were greatest among males. This work followed their prior report [59] that prenatal exposure to diesel exhaust followed postnatally by high-fat diet programmed offspring for weight gain and neuro-inflammation in adulthood. These findings, too, differed by sex: postnatal high-fat diet induced 340 % more weight gain in females with prenatal diesel exposure than females with prenatal filtered air exposure, while postnatal high-fat diet induced 450 % higher insulin in prenatal diesel-exposed males, compared to prenatal filtered air-exposed males.

Another example illustrates the potential cumulative effects of multiple, cross-domain prenatal insults. Tamashiro and colleagues conducted a unique experiment in rats, in which dams were exposed to high-fat diet, an 8-day variable stress protocol, a combination of the two, or control conditions during pregnancy [60•]. Offspring were fed either a control or high-fat diet upon weaning. The postweaning high-fat diet induced greater weight gain and, among male offspring, lower glucose tolerance than in controls.

Humans living on the disadvantaged trajectory are most likely simultaneously exposed to poor air quality, high stress, and nutrition-poor food environments. Social epidemiologic research suggests that barring substantial intervention, residents in disadvantaged areas are likely to remain there. Therefore, these cross-domain exposure effects have profound implications for social epidemiologic research and the construction of persistent health disparities.

Discussion

The mechanisms by which health disparities propagate through generations are not well understood. In this article, we considered developmental programming as a possible contributor to persistent health disparities. We reviewed published research in three prenatal and postnatal exposure domains: air pollution, psychosocial stress, and overnutrition. A growing body of evidence supports the hypothesis that prenatal exposures to environmental stressors prime offspring for exaggerated response to childhood or adulthood exposures. While early in its development, these findings are similar across species, including a small number of observational human studies, as well as across domains. Taken together, this research justifies further consideration of how developmental programming may contribute to constructing and exacerbating health disparities across generations.

Effect Modification of Established Social Processes by Developmental Priming Status

Health is propagated across generations through multiple pathways, including genetics, behavioral modeling and literacy, and environmental continuity. We propose developmental programming not as a competing or alternate theory of intergenerational transmission but rather as *a previously unappreciated process that can magnify the effects of social epidemiologic intergenerational processes*. While genetic susceptibility puts some individuals at higher risk of specific health conditions, it rarely varies by race [61, 62] and is not modifiable, so will not be discussed further in this review.

In our conceptual model (Fig. 1), health disparities are exacerbated from one generation to the next as a result of (a) the effects of suboptimal gestational environments on exaggerated offspring response to subsequent environmental and social exposures (β_1 versus β_1* and β_2 versus β_2*) and (b) intergenerational continuity of adverse exposures (prevalence of A_{g0}, A_{g1}, D_{g0}, D_{g1} scenarios). Vast social epidemiologic evidence supports the continuity of adverse exposures, perhaps most thoroughly for residential conditions. Racial residential segregation results in the geographic clustering of nonwhite or non-wealthy individuals in the USA [63]. Environmental disamenities are also non-randomly distributed [64] and cluster geographically, particularly in low-wealth, nonwhite neighborhoods. This is true for sources of air pollution [65, 66], crime, environmental sources of psychosocial stress such as graffiti and social disorder [67–70], liquor stores [71, 72], unhealthy food environments [73–76], and inadequate physical activity resources [77–79]. Social epidemiologic research consistently indicates that residence in close proximity to negative environmental conditions is associated with increased risk of a variety of poor health outcomes [80–82].

Other mechanisms that contribute to the inequitable allocation of chronic, adverse exposures have been proposed; their effects could also be modified by an individual's developmental priming status. Contemporary social conditions deriving from historic injustices, including subjugation (slavery for African Americans and displacement of Native Americans) [83, 84] and ongoing racial/ethnic discrimination [85–87] contribute to chronic social stress and have been considered in the social epidemiologic literature. Intergenerational poverty [88, 89] and parental modeling of health-related behavior [90] have also been implicated in poor offspring health outcomes and are among the possible pathways through which health disparities are propagated.

The implications of the combined gestational priming *plus* differential distribution of adverse exposures is that residents of suboptimal environments will have both poorer health at

baseline *and* a propensity for an exaggerated negative health response to subsequent adverse exposures, which are differentially distributed throughout the next generation's life course. It suggests that developmental priming processes and social epidemiologic exposures interact to socially structure health states.

Social Epidemiologic Research Gaps

Our proposed theory of the contribution of developmental programming to intergenerational health disparities is based upon empirical evidence in our literature review and decades of social epidemiologic research. Yet, research on the intersection between developmental programming and health disparities is scant.

A handful of studies suggest differences in methylation patterns according to social factors [91, 92], but this area of study is in its infancy. Another critical component in testing our theory is investigation of the extent to which developmental programming biomarkers explain differences in health and responsivity to exposures in advantaged versus disadvantaged groups. Such differences likely vary according to disease outcome, specific social groups, and life stage.

Inclusion of developmental programming biomarkers would help to overcome limitations stemming from the vast number of factors that are entangled with social disadvantage. However, key barriers to this line of inquiry are the still growing knowledge about methylation sites and other biomarkers relevant to specific disease processes. Such knowledge is critical for linking intergenerational health disparities with mechanisms identified in biological developmental programming research.

Social Epidemiologic Research Challenges

Investigation of developmental programming as a contributor to health disparities requires observational research on socially patterned exposures and outcomes in human study populations. Such epidemiologic research poses several methodological challenges.

Resilience Not every person whose mother is exposed to poor air quality goes on to develop airway hyperreactivity; nor does every person whose mother was obese during pregnancy become obese him/herself. The presence of resilience, or the ability to properly adapt to stress and adversity, is either a robust homeostasis-supporting biologic phenomenon or it constitutes counter-evidence for developmental programming effects. Research that carefully assesses prenatal and postnatal exposure from a developmental priming perspective, with special attention to resilience and the factors that seem to support healthy coping, will help quantify what portion of health outcomes, if any, might be attributable to programming effects.

Long-Term, Intergenerational Follow-Up Our most robust understanding of developmental programming examines intergenerational effects of experimentally assigned maternal exposures. Adverse offspring later-life effects are often observed even when the gestationally exposed and non-exposed are similar (in their size, other biomarkers) at birth. Therefore, the indicators of adverse fetal development (e.g., birth weight) typically used in epidemiologic studies are inadequate as measures of adverse developmental programming. Rather, measurement of developmental programming requires data collection on both mothers and offspring, in study populations large enough to test prenatal and postnatal interactions. Research needs will include the use of data linkage, improved retrospective maternal health status assessment, and intergenerational follow-up. Studying priming effects or second hits in humans, even observationally, will require long-term cohort construction and funding programs that endure across generations.

Within-Person, Within-Family Variability Many of the exposures that we know contribute to fetal priming are ubiquitous (e.g., social stress) and have become part of our daily environment (e.g., diesel exposure). As a result, constructing unexposed groups for causal comparisons is challenging. In addition, it is difficult to disentangle maternal effects (e.g., maternal high-fat diet) from offspring effects (e.g., ongoing offspring high-fat diet). Existing human research studying prenatal/postnatal interactions typically rely on short-term experimental interventions such as a short period of overfeeding or inactivity [93] to attain variability in postnatal exposures. However, such effects are unlikely to be comparable with the chronic exposures humans experience. Social epidemiologic research of developmental priming may require large, cross-national studies to construct adequate exposure variability to observe intergenerational effects.

Complexity Our review suggests that multiple, interrelated and socially patterned prenatal and postnatal exposures contribute to intergenerational disparities. The inclusion of developmental programming into social epidemiologic models introduces additional complexity to etiologic pathways for understanding health disparities. For example, maternal overnutrition leads to neurological rewiring of appetite circuits and the propensity to gain weight among offspring; thus elevated appetite is a partial *mediator* in the pathway from developmental programming to obesity. The investigation of developmental programming as both a mediator and a moderator of typical social epidemiologic exposures requires innovative analytic approaches such as emerging decomposition methods [94]. Furthermore, these second hits may have lagged effects within the life cycle or across generations and may induce differential effects according to life stage. Examination of these types of complexities requires approaches such as structural equation modeling (SEM) [95] or complex systems modeling [96].

Translation for Public Health Policy

The reduction or elimination of health disparities is a national priority named by many health-related agencies, including the Centers for Disease Control and Prevention, Healthy People 2020 and Agency for Healthcare Research and Quality. Despite resources devoted to this endeavor, health disparities persist. The evidence reported here, which developmental programming primes subsequent generational responses to ubiquitous social-epidemiologic exposures, introduces important considerations for efforts aimed at reducing health disparities.

Targeted Exposure and Intervention Effects In this review, we provide evidence that postnatal exposures in three domains—air pollution, psychosocial stress, and overnutrition—result in stronger negative effects among prenatally exposed individuals (Fig. 1: β versus β*). Left unaddressed, poor health outcomes associated with these exposures are likely to exacerbate existing health disparities through developmental programming and social patterning mechanisms. Conversely, interventions targeting these exposures among the most vulnerable populations have the potential to exert powerful, positive effects (Fig. 2: α_1* versus α_2*).

Environmental Remediation and Enrichment The research reviewed here suggests that biological predispositions for adverse health effects may be established during gestation through developmental programming or priming. For priming to exert an adverse effect, however, it requires a second adverse environmental exposure for a predisposition to become actualized. Therefore, environmental enrichment represents a potent tool for improving health trajectories (Fig. 2: α_1* versus α_2*). While we cannot undo the priming that has already occurred, we can reduce its ultimate effects by restricting the number and nature of second insults a given primed individual receives. Public policy and industrial regulation can be used to improve air quality while economic and cultural reform could reduce social stressors by socially and financially supporting disadvantaged populations. Changing social environments is one of the most effective routes to affecting population prevalence of both risk factors and disease outcomes [97]. Likewise, long-term improvements in dietary practices will likely require policy changes targeting food availability, affordability, and culture [98]. Addressing these contextual exposures is undoubtedly challenging; yet evidence suggests that altering environmental exposures is one of the few interventions that can be used to improve health for the most vulnerable groups. For instance, environmental enrichment following lead exposure among children has been associated with cognitive improvements [99]. The research presented here also suggests that environmental remediation will not only reduce the magnitude and/or likelihood of the second hit, it will also reduce the priming effect for the next generation.

Expanded Time Frame While national public health objectives seek to eliminate health disparities by 2020, our conceptual model illustrates the long period of time that may be required to ameliorate them, even with dramatic and sustained reduction in exposure prevalence. The magnitude of risk transmission from one generation to the next is unknown. Quantification of the intergenerational transmission rate, as called for under *Resilience* above, would improve our ability to redefine the time frame in which elimination of health disparities is possible.

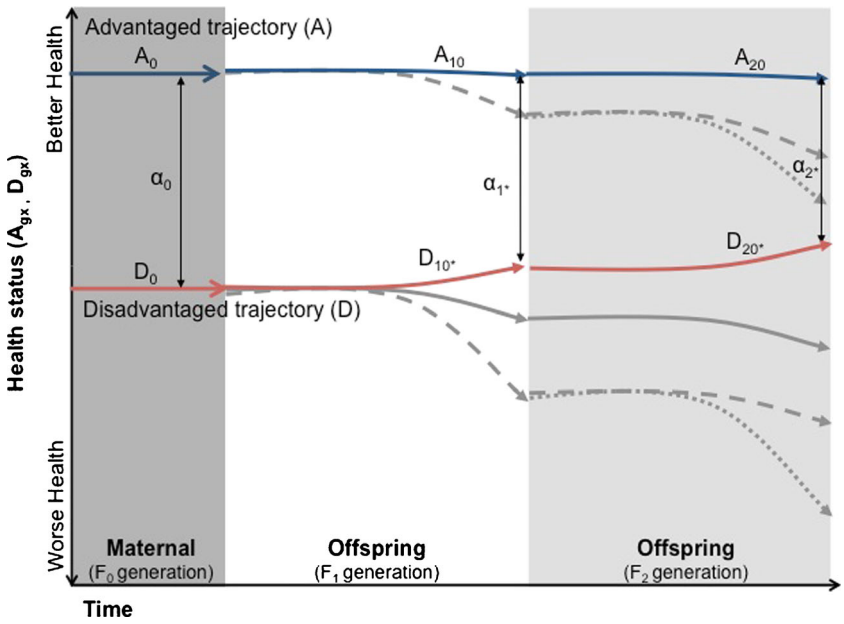

Fig. 2 Theoretical role of the relationship between environmental enrichment and developmental programming on reducing health disparities over three generations. A_{gx} and D_{gx} denote health status Y_{gx} for generation g and exposure status x. α_g denotes the magnitude of disparity in any in generation g

With multicomponent interventions that target both environmental and behavioral objectives thought to most potently reduce adverse developmental programming, we should seek to attain incremental improvements in health from one generation to the next (e.g., the health improvement from D_0 to D_{10}, and D_{10} to D_{20} in Fig. 2). Identification of such targets is needed and will require interdisciplinary research and programs of broad scope.

Conclusion

Public health scholars, practitioners, and policymakers have called for an explicit examination of drivers of disparities. Our conceptual framework suggests that this is even more important due effect magnification of social epidemiologic exposures by developmental programming. Awareness of key developmental programming processes provides an opportunity to identify high-leverage factors for reducing persistent disparities. It also affirms that environmental modification—providing healthy and safe environments in which to live, work, and play—is likely the single best intervention to ensure health for all.

Compliance with Ethics Guidelines

Conflict of Interest LC Messer, J Boone-Heinonen, L Mponwane, L Wallack, and KL Thornburg all declare no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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