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Developmental responses to early-life adversity: Evolutionary and mechanistic perspectives

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Abstract

Adverse ecological and social conditions during early life are known to influence development, with rippling effects that may explain variation in adult health and fitness. The adaptive function of such developmental plasticity, however, remains relatively untested in long-lived animals, resulting in much debate over which evolutionary models are most applicable. Furthermore, despite the promise of clinical interventions that might alleviate the health consequences of early-life adversity, research on the proximate mechanisms governing phenotypic responses to adversity have been largely limited to studies on glucocorticoids. Here, we synthesize the current state of research on developmental plasticity, discussing both ultimate and proximate mechanisms. First, we evaluate the utility of adaptive models proposed to explain developmental responses to early-life adversity, particularly for long-lived mammals such as humans. In doing so, we highlight how parent-offspring conflict complicates our understanding of whether mothers or offspring benefit from these responses. Second, we discuss the role of glucocorticoids and a second physiological system—the gut microbiome—that has emerged as an additional, clinically relevant mechanism by which early-life adversity can influence development. Finally, we suggest ways in which nonhuman primates can serve as models to study the effects of early-life adversity, both from evolutionary and clinical perspectives.

KEYWORDS
developmental constraints, developmental plasticity, glucocorticoids, maternal capital, microbiome, predictive adaptive responses

1 | INTRODUCTION

Human biologists, epidemiologists, and primatologists have long been aware that adversity during early life can profoundly impact development and the resulting adult phenotype. Famine during prenatal life has been repeatedly linked to diseases such as hypertension, diabetes, and depression,[1] and exposure to nutritional (e.g., drought)[2,3] and social stressors (e.g., isolation, abusive parenting)[4] during early life have been associated with altered social development, dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis,[5] and reduced longevity and birth rate.[6]

Although such phenotypic outcomes have been traditionally viewed as maladaptive consequences of early-life stress, recent studies have increasingly interpreted them through the lens of *adaptive developmental plasticity*—the ability of genetically similar individuals to develop potentially adaptive phenotypic differences in response to different early-life experiences (see Box 1 for glossary of terms). Such models posit that offspring undergo adaptive developmental changes in

BOX 1 Glossary of terms

Adrenal cortex: the outer layer of the adrenal glands where glucocorticoids are produced.
Commensal: an organism (e.g., bacteria) that may benefit from another organism but not at a cost to that other organism (e.g., host).
Developmental programming: process through which conditions or events during critical developmental periods result in potentially lifelong physiological consequences.[77]
Germ-free model: a model in which the subjects (commonly mice) are bred to be devoid of all microorganisms and housed in isolation to avoid contamination, which allows studies to isolate the causal and mechanistic role of microorganisms in a wide variety of outcomes.
Hormetic: concept describing how mild exposure to environmental stressors can prepare physiology for improved function and outcomes later in life.[160]
Hypothalamus: a brain structure located in the diencephalon (forebrain) that is heavily involved in coordinating sensory input and generating both autonomic and endocrine responses; where corticotropin releasing hormone (CRH) is produced.
Lymphocyte: a type of white blood cell (leukocyte) that includes T-cells and natural killer cells.
Pathobiont: an organism that is pathogenic and disease-inducing to its host.
Receptor: a cell molecule to which chemical messengers (such as hormones) bind, thereby causing alterations to target cells through signaling pathways and/or gene expression.
Symbiont: an organism (e.g., bacteria) that lives in close association with another organism (the host; often assumed to be a mutualistic relationship).
TH1-mediated immunity: the pro-inflammatory component of cell-mediated immunity involved in autoimmune responses and combating intracellular pathogens.
TH2-mediated immunity: the anti-inflammatory component of humoral immunity involved in the production of antibodies.
Transplant models: a model in which an individual's gut microbiome is cultured (usually through a fecal sample) and then transplanted into a recipient individual.

response to cues of environmental quality.[7] In mammals, the processes of gestation and lactation coupled with extended parental care assure that environmental information received by offspring is largely transferred through the mother during early life. A large body of literature has demonstrated the central role of glucocorticoids (GCs), steroid hormones that increase in response to stress,[8] as a proximate mechanism for this process.[9,10] GCs can influence offspring phenotype both directly, by reaching the offspring via the placenta[10] and through milk,[11] and indirectly, by altering maternal physiology and behavior.[9] In addition, increasing evidence suggests that vertically transmitted maternal microbiota—which can be perturbed in response to stress—can also influence a number of offspring characteristics.[12–15] Such mechanisms support the major role that mothers can have on offspring outcomes.

This review is an effort to synthesize these evolutionary and proximate approaches toward understanding developmental plasticity and early-life adversity. We integrate recent work from anthropology, biology, psychology, and behavioral ecology, highlighting studies on humans and nonhuman primates when available. Our goals are threefold: First, we review the utility of major adaptive hypotheses proposed to explain developmental plasticity. In doing so, we also consider one of the primary criticisms of several existing models—specifically, that they ignore the potential role of maternal agency and manipulation in shaping offspring developmental trajectories. Second, we discuss two key proximate mechanisms—GCs and the gut microbiome—that regulate developmental responses to pre- and postnatal adversity and can easily be measured in both captive and field settings. Note that we only briefly touch on another important proximate mechanism, environmentally-induced epigenetic change, which has been discussed elsewhere in detail in recent reviews.[16–18] Finally, we propose ways in which studying nonhuman primates can substantially contribute to this research from both evolutionary and clinical perspectives.

Within our discussion, we limit our definition of adversity to include any energetically or socially challenging condition or event that is likely to alter an individual's physiology and life history, either because it limits energy available for development or because it signals that the social or nutritional environment is risky. Within this definition, adversity can include anything from seasonal shortfalls in energy, to social stressors such as maternal neglect, to extreme and unpredictable conditions such as famine, predation, or infanticide that are likely to induce the most profound developmental responses (Figure 1).

2 | ADAPTIVE MODELS OF DEVELOPMENTAL PLASTICITY

Although a number of adaptive frameworks have been proposed to explain developmental responses to early-life adversity (Box 2), we focus on three models commonly cited within anthropology and evolutionary biology: the predictive adaptive response (PAR),[19,20] developmental constraints,[21] and maternal capital[22–24] models. All three models seek to explain how phenotypic changes initiated in response to adversity might be adaptive, and propose links between

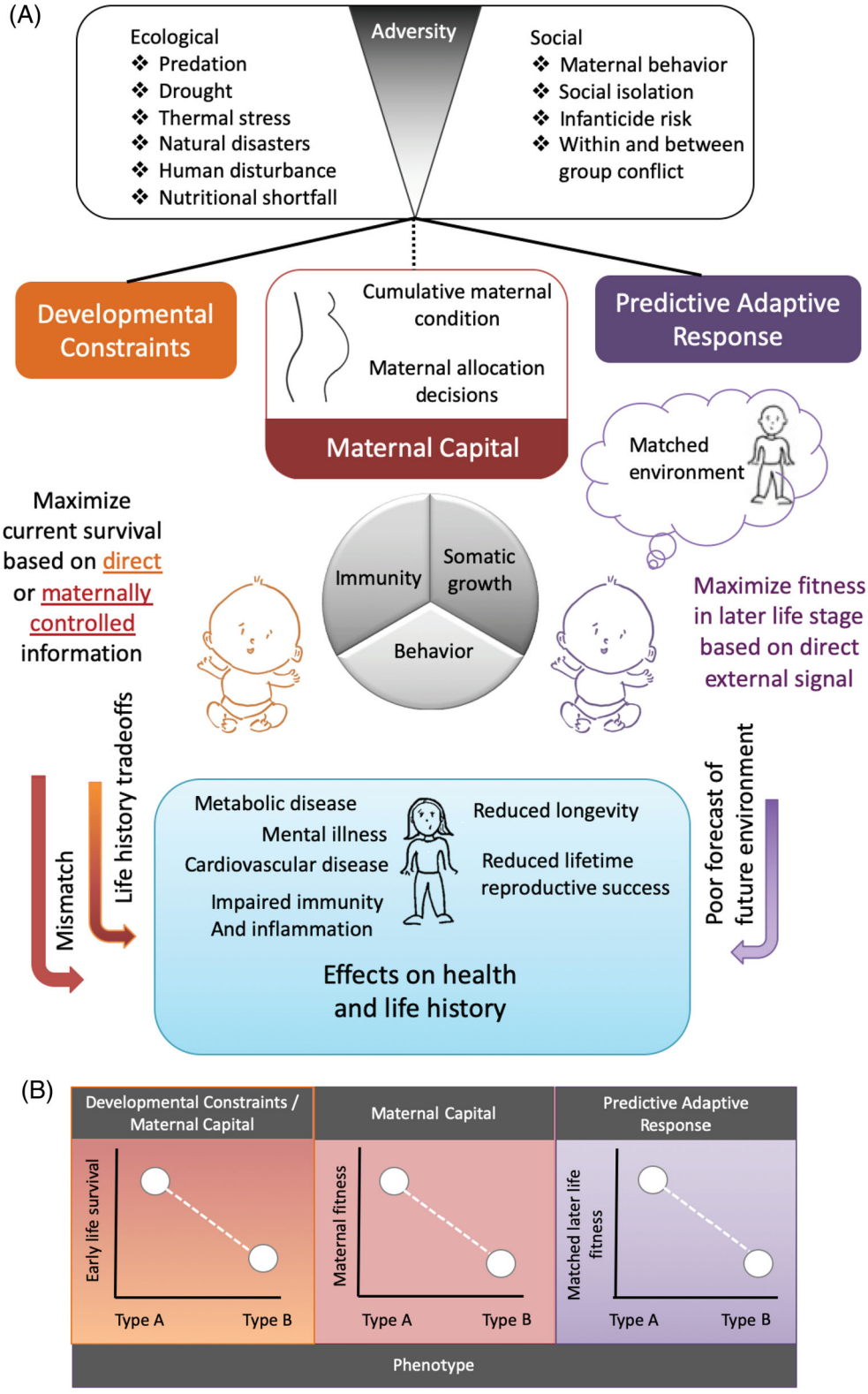


FIGURE 1 Major adaptive models for developmental plasticity. (a) The models. The developmental constraints (orange, left) and predictive adaptive response (PAR; purple, right) models hypothesize that organisms initiate adaptive developmental responses to direct environmental cues of adversity, which are beneficial to offspring either immediately (developmental constraints) or during matched later-life conditions (PAR). By contrast, the maternal capital model (middle, dark red) hypothesizes that maternal condition and maternal resource allocation decisions in response to the environment are the primary drivers of developmental plasticity. Although offspring may subsequently respond to maternally imposed constraints to improve immediate survival, such allocation decisions are considered ancillary to initial maternal decisions. Under the developmental constraints and maternal capital models, later-life disease is hypothesized to result from strategic life history tradeoffs made during early life or a mismatch of maternal signals (maternal capital only); under PAR, disease is expected when the early environment provides an inaccurate forecast of the future environment. (b) Testing the models. The developmental constraints model predicts that developmental changes (Phenotype Type A) in response to adversity (compared to the alternative - Type B) improve the immediate fitness (e.g., survival) of the offspring given a poor external environment. The maternal capital model predicts that developmental changes primarily benefit lifetime fitness for the mother, although benefits to offspring may be possible when maternal and offspring interests are aligned. Finally, the PAR model hypothesizes that phenotypic adjustments to a poor early environment are adaptive in a later-life phase only if the early- and later-life environments are matched [Color figure can be viewed at wileyonlinelibrary.com]

developmental responses and later-life health issues (Figure 1). However, these models diverge in several substantive ways. First, these models differentially emphasize the importance of environmental versus maternal input as drivers of development responses, and vary in whether they hold the offspring or mother to be the primary beneficiary of such responses. Second, they differ in the prediction of immediate versus long-term adaptive benefits and their relationships to disease in later life.

2.1 | Offspring-centric models: Developmental constraints and PAR

The developmental constraints and PAR models can both be considered "offspring-centric" models. Both assume that offspring receive accurate cues of the external environment from mothers, and that such cues initiate adaptive developmental adjustments that are beneficial to offspring. However, they differ in the timeframe—whether immediate or at some later point in life—when adaptive benefits are likely to accrue.

The developmental constraints model (i.e., "silver spoon" effect) hypothesizes that cues of ecological adversity pressure organisms to adaptively allocate energy toward processes that promote *immediate* survival.[21] Thus, it describes "best of a bad job" strategies that maximize fitness given a poor developmental environment. Importantly however, such cost-cutting strategies are not expected to completely make up for the fitness costs associated with experiencing adversity to begin with.[21] Developing organisms must allocate energy toward many costly processes, including somatic growth, immune development, and brain and cognitive development.[25–27] In response to adversity, individuals might adaptively decrease their energetic expenditure across all processes—for example, to avoid starvation during famine. Alternatively, adaptive preferential resource allocation decisions may be made, such as accelerating growth at a cost to locomotor and immune development[28]; prioritizing brain development at a cost to other somatic tissues[29]; or investing in innate immunity, which may be more immediately beneficial and less costly to develop, at the expense of acquired immunity, which may be more distantly relevant but more energetically expensive upfront.[27]

The developmental constraints model also invokes life history tradeoffs to explain the link between early-life adversity and noncommunicable disease in humans.[21] Within this framework, later-life cardiovascular, metabolic, and inflammatory disease, as well as reduced longevity, are considered tradeoffs of adaptive early-life cost-cutting strategies in somatic maintenance, immunity, and neurodevelopment.

By contrast, the PAR model—originally developed by Gluckman and Hanson[19,30]—argues that mothers transmit signals of environmental adversity (e.g., drought, predation) to offspring during early life, which then initiate anticipatory developmental changes aimed at benefiting the offspring during later life. Thus, early-life cues are assumed to be accurate forecasts of later-life conditions, and developmental responses to those cues are adaptively calibrated to enhance fitness in later-life environments that "match" early-life environments. However, should the predictive value of early-life cues break down—for instance, in modern humans who encounter food abundance despite prenatal nutritional constraints—reduced fitness and disease are expected to ensue. Under this model, the high prevalence of noncommunicable disease in low birth weight individuals[20] is not viewed as a life history tradeoff, but rather a consequence of modern human diets creating a mismatch between the prenatal and adult environments. Importantly, Gluckman and Hanson recently pointed out that, contrary to what has been assumed in the literature, the PAR model does not assume that individuals raised in adverse environments experience no constraints—only that those constraints are at least alleviated if not erased by adaptive developmental calibrations.[31]

Of late, both developmental constraints and PAR models have garnered much interest, and a large body of work has been dedicated toward teasing apart the predictions of each model.[17,21,32] However, empirical tests of evolutionary models require fitness data on reproduction and survival. Such data are not only rare, but particularly difficult to interpret in modern humans, for which rapid improvements in medicine and birth control may cloud the interpretation of existing data. Furthermore, in the few cases where empirical data on nonhuman species have been brought forth, debate remains over whether these studies have accurately tested the fundamental hypotheses of each model.[31,33]

A common approach in recent years is to use a 2-by-2 factorial framework to tease apart whether early-life adversity primarily leads to fitness constraints (i.e., developmental constraints) or adaptive advantages when later-life environments are matched (i.e., PAR).[17,21] While the developmental constraints model predicts that early-life adjustments lead to reduced fitness, which might be exacerbated but not improved if later-life conditions are equally poor, the PAR model predicts that phenotypes arising from poor early-life environments can have *improved* fitness if later-life environments are equally poor. The PAR model also predicts the inverse: phenotypes developing in good environments perform better if later-life environments are equally good. Thus, comparisons of individual fitness in matched versus unmatched later-life environments *given the same early life environment* are necessary to disentangle the models (Figure 2).

When fitness data have been used to test the predictions of these models, they have mostly been interpreted as supporting developmental constraints over PAR (see recent reviews[17,32]), particularly in long-lived mammals.[2,34–36] In studies of wild baboons,[2] humans,[36] bighorn ewes,[34] and roe deer,[35] the fitness costs of being reared in poor environments were either persistent across time or exacerbated when later-life environments were also poor. These results supports the key prediction of the developmental constraints rather than the PAR model.

Despite these findings, some researchers have suggested a more cautious interpretation of the data.[31,33] A major weakness of previous studies is that fitness outcomes associated with matched and unmatched conditions were assumed to be fairly homogenous across individuals (i.e., individuals all develop the same developmental responses to environmental gradients). If this assumption is violated, however, the failure to identify later-life fitness benefits may be a methodological artifact of lumping individuals that initiated adaptive developmental responses with those that did not. More generally,

BOX 2 Alternative constraints and predictive models of adaptive plasticity

Numerous evolutionary models spanning the fields of psychology, anthropology, evolutionary biology, and evolutionary medicine have been proposed to explain developmental responses to early-life adversity. Within psychology, for example, it has long been recognized that some individuals exhibit resilience to stress-related disease, despite similar exposures to stress during adult life.[161,162] The stress inoculation model[162,163] was proposed to explain these differences, arguing that exposure to moderate amounts of stress during development adaptively "primes" the body to cope with similar conditions during later life, a hypothesis echoed by *hormetic*[160] arguments proposed in ecology to explain why mild exposure to chemicals or temperature extremes increases tolerance to those same conditions in adulthood.

Within evolutionary medicine, the thrifty phenotype hypothesis[164] was proposed early on to explain associations between poor fetal nutrition and later-life metabolic illness, specifically the occurrence of Type II diabetes. It argues that diabetes results from adaptive thrifty divestment of developmental resources away from pancreatic beta cells that produce insulin, the primary hormone responsible for energy storage. Like the developmental constraints model, the thrifty phenotype model argues that poor fetal nutrition pressures offspring to make cost-cutting strategies that lead to later-life health issues. However, the thrifty phenotype hypothesis later became aligned with predictive models because its authors proposed a mismatch argument to explain the likelihood of disease, arguing that deficits in pancreatic beta cells are adaptive in energy poor adult environments, but maladaptive in rich adult environments in which individuals face energy abundance, but have inadequate physiological mechanisms to cope with abundance.

More recently, two additional iterations of predictive models have been proposed within psychology. The internal PAR model (iPAR) provides an alternative to classic or "external" PAR (ePAR) by hypothesizing that early-life adversity serves as a cue that an organism's future internal somatic state will be poor, thus initiating developmental responses that maximize fitness given this future internal fate.[41] Like the developmental constraints model, iPAR argues that later-life health issues are the result of life history tradeoffs made during earlier life; however, unlike the constraints model, it posits that individuals accelerate their life history (e.g., maturing faster, reproducing at a higher rate) to maximize reproduction given greater somatic wear and tear, and likely, a shortened lifespan. Although some recent models have tested iPARs by examining whether early-life adversity accelerates the pace of life history,[28,165] strong correlations between life history traits make it difficult to determine whether characteristics such as accelerated maturation are really adaptively calibrated to an anticipated early senescence, or simple correlates of adjustments made to increase early-life survival. Nevertheless, extrinsic mortality risk is widely argued to be a major driver of "faster" life histories,[25] supporting the likelihood of such developmental calibrations.

The adaptive calibration model (ACM)[166] is another predictive model focusing specifically on how early-life adversity influences stress responsivity and the pace of life history. Like PAR, the ACM[166] argues that individuals adjust their developmental phenotype to maximize fitness in predictably adverse environments. In contrast to PAR, however, ACM argues that predictive "re-calibrations" can be made across the life course, with important phenotypic switchpoints possible during key developmental periods such as fetal life, infancy, and the transition to juvenility and puberty. Although the ACM has not been explicitly tested from an evolutionary perspective, there is some evidence that experimental manipulation via hormone replacement[167] or microbial transplants[126] can reverse developmental effects associated with early-life adversity. Thus far, however, successful reversals have primarily involved prenatal programming effects reversed by early postnatal intervention. Furthermore, some prenatal effects appear irreversible,[12] suggesting that plastic responses during the earliest periods of life are likely to be canalized.

examining fitness consequences without reference to variable phenotypic responses precludes adequate tests of whether developmental responses are truly "best of a bad job" strategies that can have immediate or later-life benefits. This issue is particularly problematic for the developmental constraints model, where pairing information on variable phenotypes and immediate survival outcomes during early life is exceedingly difficult. Without such data, researchers are only testing the existence of constraints, not the existence of adaptive responses to those constraints.

To complicate the issue, recent experimental studies on small mammals and birds that *have* paired fitness data with developmental phenotypes have provided strong support for PAR.[37–39] In ground squirrels, pregnant females exposed to auditory cues of high population density produced offspring that grew faster. Faster growth allowed these offspring to establish reproductive territories ahead of those that grew slower, but only under matched later-life adult conditions.[38] In snowshoe hares, vigilant phenotypes induced by high predator density were adaptive only in matched predator-rich adult environments,[37] and in zebra finches, temperature-induced changes in growth resulted in greater reproductive success only when the adult temperature matched the early-life temperature.[39]

Recent mathematical models suggest one promising explanation for some of these differences: PARs may be more likely to evolve in species with shorter life histories because intragenerational predictability of early and later-life environments is more likely to be high. This predictability creates conditions under which calibrated

developmental responses are likely to yield positive fitness returns.[40,41] When predictability is poor, calibrated adjustments are likely to fail, creating weak selection for predictive plasticity. Thus, in large-bodied mammals with longer life histories such as humans, PARs may be less likely to evolve. Indeed, climatic data demonstrate that the ecological conditions (e.g., rainfall, temperature) faced by humans fluctuate rapidly within a lifetime, suggesting poor intragenerational environmental predictability.[22,42] More recent reports, however, suggest that the social environment may be more predictable, opening up the possibility that PARs are more likely to develop in response to some forms of adversity (e.g., low social status), but not others.[43]

Importantly, one misunderstanding of the PAR model is the notion that developmental decisions in response to adversity are necessarily calibrated for *adult* life.[44] Instead, developmental decisions during early life may exact fitness benefits prior to maturity[45,46] when the force of selection is likely to be greatest.[47] Furthermore, the temporal closeness of fetal life, infancy, and juvenility means that environmental conditions are more likely to be matched across these periods, even in long-lived mammals. These arguments suggest that earlier windows of development may be important for testing future fitness payoffs. Indeed, the only study in humans that has examined fitness payoffs of developmental plasticity prior to adulthood found that underweight infants were more likely to develop marasmus, a syndrome associated with childhood malnutrition characterized by higher lipid and protein turnover and increased survival.[48] By contrast, infants born at higher body weights were more likely to develop kwashiorkor in response to childhood famine, a syndrome characterized by lower lipid and protein turnover and lower survival rates. Such data suggest that fitness benefits might accrue to underweight infants during matched childhood rather than adult conditions. Thus, an expanded approach to predictive models that examines fitness payoffs during earlier windows of development may be warranted.

2.2 | Maternal-centric models: The maternal capital model

Despite frequent discussions of PAR and developmental constraints as contrasting models, they share remarkable similarities in their emphasis on how developmental plasticity benefits offspring, with little regard to maternal agency.[49,50] However, mammalian mothers contribute substantial behavioral, chemical, and nutritional input during fetal and early postnatal life, and thus can potentially act as a filter through which information about the early environment passes.[22,51,52]

The maternal capital model[23,24] — developed by Wells — is the only evolutionary model that emphasizes maternal agency in shaping offspring developmental trajectories.[23,24] This model argues that developmental responses are optimally designed to increase maternal fitness, which may or may not be aligned with offspring fitness. Such developmental decisions are based primarily on cumulative maternal condition ("maternal capital"), not the external environment. Wells argues that for capital breeders such as humans, reproductive decisions may have evolved to be more sensitive to maternal condition because it provides a better predictor of reproductive success than the current environment, which may be a less reliable cue.[53] Likewise, offspring may also benefit by "submitting" to this combined maternal-offspring strategy because maternal condition, on average, is likely to be a better proxy for successful development as well.[24]

While maternal condition can serve as a buffer against stochastic sources of environmental adversity, this buffer may fail in more extreme environments. In such cases, mothers might act selfishly to curtail parental investment and preserve energy for future reproduction at a cost to current offspring.[22,54] Thus, offspring costs under extreme conditions are viewed as inevitable outcomes of adaptively relinquishing their ability to counter maternal decisions.[50] The unifying theme of this model is that mothers are in control and can allocate resources to benefit or hinder offspring development, depending on their own cost-benefit analyses.

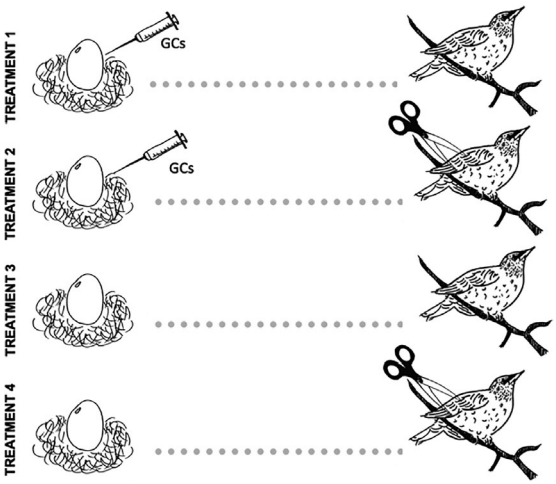
Empirical data support this hypothesis. For instance, in humans, maternal body condition at conception consistently predicts offspring birth weight.[22] By contrast, early pregnancy exposure to famine has little effect on offspring birth weight,[55] suggesting that mothers can buffer infants from external conditions. Similarly, in wild baboons, maternal social status—which is likely correlated with maternal condition—can buffer the fitness effects of being born in a drought year.[2] Finally, studies across mammals have demonstrated that the stress response pathway is blunted during pregnancy[56,57] (and possibly also lactation[58,59]), suggesting that maternal physiology has evolved the capabilities of attenuating ecological signals while offspring are dependent.

At the same time, a vast literature on maternal reproductive suppression demonstrates that mothers often curtail investment or even abandon offspring in response to adverse ecological or social conditions. This may improve maternal fitness by delaying reproductive investment until conditions have improved.[60] Such strategies include fetal loss in response to drought or infanticide risk, and other forms of curtailed postnatal maternal investment (e.g., early weaning) in response to similar conditions.[61–63] Studies on birds provide some of the best evidence for such parent-offspring conflict (Box 3). In European starlings, experimental stress applied during egg-laying resulted in smaller offspring who begged less and were more likely to die; however, mothers with smaller offspring were able to accelerate their next reproduction, leading to greater reproductive success across clutches.[64] Thus, mothers appear to have substantial control over the development and survival of offspring.

Despite this degree of control, the maternal capital model suggests that offspring can still make ancillary resource allocation decisions that improve immediate survival given the initial constraints imposed by the mother.[50] In other words, unlike the developmental constraints model, the maternal capital model posits that the source of constraint is the mother rather than the external environment.

With regard to health, the maternal capital model proposes that later-life disease can ensue via two processes. First, adaptations to survive early life in the face of poor maternal condition may catalyze life history tradeoffs. If phenotypes that promote early life survival are

BOX 3 Maternal matching and parent offspring conflict in European starlings



Despite the central role of parent-offspring conflict[54] within the developmental and life history literature, studies examining developmental programming from a maternal perspective have been rare.[22] An elegant study performed in birds, however, highlights the complexity of developmental plasticity when both maternal and infant perspectives are considered. Love and Williams[64] combined manipulations of yolk GCs with manipulations of postnatal maternal condition (via feather-clipping) in European starlings (*Sturnus vulgaris*) to create four treatments representing matched versus mismatched prenatal versus postnatal maternal chick-rearing ability. These treatments included: GC-clipped, GC-nonclipped, control-clipped, and control-nonclipped parent-offspring conditions (control individuals did not receive GC treatment). Their goal was to examine whether elevated yolk GCs, a known maternal response to nutritional stress, would exact fitness returns for the mother during matched versus mismatched pre- and posthatching conditions. Love and Williams found that increases in yolk GCs reduced offspring size and begging behavior in sons. Furthermore, sons in the GC-clipped condition were more likely to die. Although these offspring modifications were clearly costly (both for the mother and chicks), they appeared to benefit maternal fitness when prenatal and postnatal maternal conditions were matched. Compared to mothers in the control-clipped treatment, mothers in the GC-clipped treatment were in better body condition when they initiated their next reproductive event, and were more than two times as likely to successfully fledge at least one offspring in their second brood. These changes resulted in a greater cumulative number of fledged offspring and thus higher maternal fitness for mothers in the GC-clipped treatment. Love and Williams propose maternal manipulation of yolk GCs as a strategy to match offspring demand with expected postnatal maternal condition, allowing mothers to accelerate energetic recovery and increase lifetime reproductive success. This study thus illustrates how predictive adaptive models may be applied to maternal rather than offspring fitness. Predictive models appear more intuitive in this context because prenatal and postnatal environments can take place within the same year. More importantly, this study highlights how optimal maternal strategies may trump those of each individual offspring. Such a nuanced consideration of parent-offspring conflict should be adopted in future studies of adaptive plasticity.

prioritized at the expense of those that promote long-term survival, organisms may, for example, lack fully developed immune components essential to maintaining health in later life. Second, evolutionarily or developmentally mismatched maternal signals have also been proposed to explain disease.[65] As an example, bottle-feeding replaces nutritional and biochemical signals in breast milk with artificial supplements. This not only disrupts maternal influence on offspring development, but can contradict signals received during the prenatal period that are consistent with true maternal interests.

Although these proposed pathways for disease may not appear much different from those predicted by offspring-centric models (Figure 1a), the hypothesis that development is initially constrained by maternal interests has broader implications for treating or preventing disease. For example, recent public health efforts to reduce maternal energy expenditure by installing water taps in Ethiopian villages worsened childhood malnutrition, but improved maternal fertility, possibly because mothers used the additional energy to prioritize reproductive rate rather than infant health.[66] Thus, understanding the multi-player nature of developmental decisions and the time frame in which fitness benefits might accrue is of utmost importance from both clinical and evolutionary perspectives.

2.3 | Testing existing possibilities

In light of these theoretical possibilities, we advise researchers interested in examining adaptive models of developmental plasticity to consider two major questions prior to making specific predictions. First, given the study system and the adversity under consideration, is

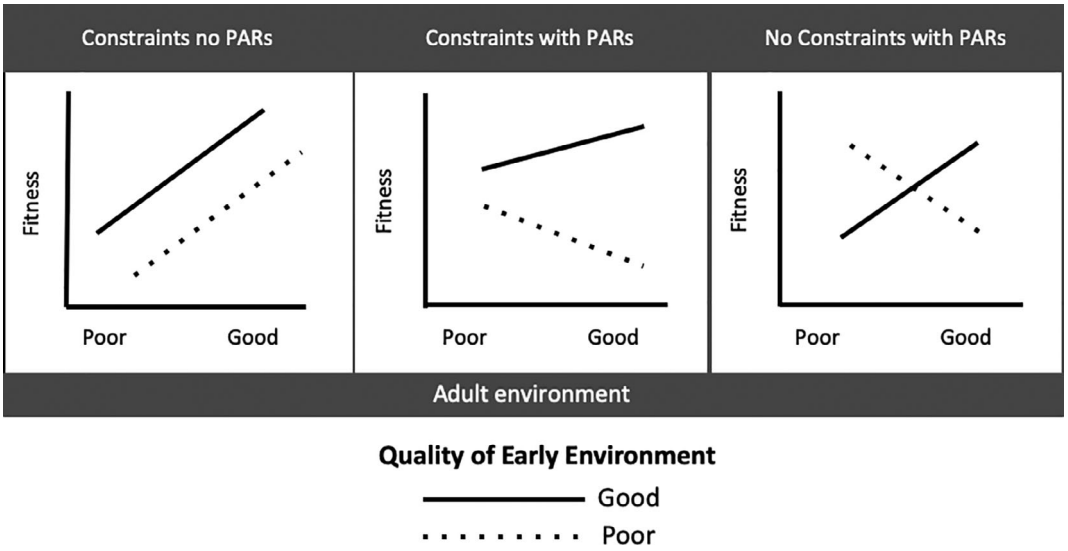


FIGURE 2 Factorial models commonly used to examine developmental constraints versus predictive adaptive responses. All proposed predictions assume that different individuals initiate similar responses to gradients in environmental quality. The left panel illustrates cases where constraints are present (individuals raised in poor environments always perform worse than those raised in good environments) and are not improved when later-life conditions are matched and equally poor. This condition supports the existence of general constraints only and is not consistent with PAR. The middle panel illustrates the case where general constraints exist; however, individuals raised in adverse early-life circumstances do better in matched later-life conditions, supporting PAR. The right panel illustrates a situation with no initial constraints, and only the presence of adaptively calibrated responses

developmental plasticity expected to benefit maternal fitness, offspring fitness, or both? Second, under what social systems and forms of adversity are adaptive developmental adjustments likely to be immediate or delayed?

The answer to the first question- "who benefits?" - likely depends on the degree of parent-offspring conflict within a given system. Because the fitness interests of mothers and offspring are expected to be at least somewhat aligned, we might expect benefits to accrue for both players when parent-offspring conflict is low. In addition, certain taxa may have evolved to be more sensitive to internal rather than external cues (e.g., capital breeders), allowing mothers to use maternal condition as a buffer against current ecological conditions. Here, mothers may attenuate external signals, but to the offspring's (and mother's) benefit. However, as parent-offspring conflict increases, the fitness interests of mothers and offspring are expected to diverge.[67] Under such conditions, mothers are expected to manipulate offspring development and conserve energy for future reproduction by providing inaccurate signals of the external environment, investing less, and creating "cheaper" offspring.[52] Consequently, offspring development is unlikely to be optimally calibrated to external conditions. Although existing empirical data suggest that mothers are more likely to "win" this conflict, experimental studies by Kuijper and Johnstone[52] found that maternal signals might remain at least partially informative of the current environment when alternative offspring phenotypes exact similar investment costs on the mother (as opposed to having a more expensive phenotype that benefits the offspring but is more energetically demanding on the mother). Moreover, despite presumed maternal control, neither side may reach a fitness optimum. Thus the answer to the question - "who benefits?" - may be hardest to identify during conditions of exaggerated parent-offspring conflict.

The degree of parent-offspring conflict can vary between and within species. First, in polyandrous or polygynandrous species, parent-offspring conflict may be more pronounced because mothers conceive successive offspring with different males. The resulting half-siblings are, on average, 50% less related than full-siblings, which may create greater selfishness on the part of offspring and a tug-of-war between maternal and offspring interests.[54] Thus, clear fitness benefits for offspring might be better supported in monogamous or polygynous systems, where siblings are more closely related and less conflict exists between parent and offspring optima.[52]

Second, within a given system, parent-offspring conflict is expected to be pronounced when individuals are faced with the most extreme forms of adversity.[60] Take, for example, famine: for offspring, a smaller body size and/or reduced growth rate might be beneficial to some extent in order to avoid starvation. For the mother, however, the optimal amount of maternal divestment might include complete offspring abandonment. Similarly, under conditions of extreme social adversity (e.g., warfare, infanticide risk), substantially curtailing parental investment may be in the best interest of mothers, but not offspring.[60,61]

Counterintuitively, recent research on primates suggests that parent-offspring conflict may also be pronounced under resource-rich conditions.[66,68–71] For example, female chimpanzees in the best energetic condition prioritized reproductive rate by weaning offspring earlier, thereby accelerating investment in the following offspring. However, offspring that were younger when their mothers reconceived grew slower as juveniles, suggesting that offspring paid a cost for this maternal strategy. This lack of congruency between maternal body condition and

parental investment suggests that parent-offspring conflict might be exaggerated in the worst and best environments (Figure 3).

Finally, the likelihood of parent-offspring conflict will be determined by the developmental timing of adversity.[50] Early-life adversity can potentially influence development from conception through reproductive maturation,[72] with maternal effects at their strongest during earlier life phases and weakening after weaning as maternal dependence sharply declines. In utero, offspring are completely dependent on nutritional and biochemical input via the placenta. Although offspring independence increases during the postnatal period, mothers still contribute substantial nutritional and biochemical input via lactation as well as behavioral input via direct forms of care. Thus, during fetal and infant life, mammalian mothers have greater agency to direct offspring development, creating greater opportunities for conflict. Under such conditions, developmental responses are likely to reflect the outcome of parent-offspring conflict, rather than a simple optimum for either individual. By contrast, developmental responses to adversity following weaning are more likely to reflect offspring optima. Thus a number of inter- (e.g., mating system) and intraspecific (e.g., environmental quality, developmental time frame) characteristics must be considered to anticipate whether developmental plasticity will primarily benefit mother, infant, or both.

A second major question facing future research is: under what conditions will fitness benefits associated with developmental plasticity be immediate or delayed? Although immediate versus delayed benefits have mostly been considered in relation to offspring fitness, they could also pertain to maternal fitness. In European starlings, prehatching, stress-induced reductions in nestling weight and begging behavior only benefitted maternal fitness if posthatching maternal condition was also impaired.[64] Similar short-term adaptive calibrations for mammalian mothers and offspring may occur between the prenatal and early postnatal period—when maternal condition and/or the external environment are more likely to be matched. However, adaptive calibrations over longer time scales for offspring or mothers (e.g., fetal life to adulthood, mother: gestation to later postnatal parenthood) may be less likely in species with longer life histories. This hypothesis can be bolstered by autocorrelation tests to examine the predictability of early- and later-life environmental variables.[73,74]

Given the long-term perspective of maternal fitness strategies and the potential immediate and future benefits for offspring and mothers, the developmental, survival, and reproductive data required to examine these hypotheses must span the life course of study subjects — a difficult task for long-lived animals such as primates. Importantly, this expanded approach unifies both offspring- and maternal-centric models of developmental plasticity by considering the conditions in which immediate and/or future benefits to mother and/or offspring are likely. A more expansive view of developmental plasticity as a battleground between mother and offspring is critical to understanding both the evolutionary forces shaping plasticity, as well as the proximate mechanisms mediating such plasticity. For example, although a number of maternal-origin bioactives are now known to influence offspring development, increasing evidence also suggest that these signals have co-evolved with offspring physiological counterstrategies that limit maternal control.[67,75,76]

3 | PROXIMATE MECHANISMS OF DEVELOPMENTAL PLASTICITY

Plastic responses to environmental input during early life can be mediated by a number of complex behavioral and physiological mechanisms, including maternal care behaviors, as well as the actions of hormones, enzymes, immune factors, and microbiota. These physiological mechanisms are thought to "developmentally program" infant and adult phenotypes.[77]

One potential mechanism through which physiological responses to adversity can induce long-lasting phenotypic change is through epigenetic modifications—changes to the DNA structure, not the DNA sequence, that affect how genes are expressed. Indeed, recent studies in humans and nonhuman primates have found evidence for maternal effects on the offspring's epigenome.[78–80] For instance, changes in DNA methylation (the most well-studied epigenetic change) may mediate the link between prenatal adversity and disease risk in adulthood in offspring born to malnourished mothers.[78] Such epigenetic changes are covered in detail in other recent reviews,[17,18,80] and are not discussed further here.

Instead, we will focus on two physiological mechanisms known to have powerful effects on the developing phenotype (potentially by inducing epigenetic change[81,82]): (a) GCs, a well-studied class of steroid hormones that regulate metabolism and the vertebrate stress response,[8] and (b) the gut microbiome, a system that is highly responsive to maternal and environmental input and known to play a role in metabolism, growth, immunity, behavior, and the emergence of later-life disease (Figure 3).[83–85] The rich history of GC research, coupled with increasing evidence for the involvement of the gut microbiome in development, makes these two systems ideal avenues for research on developmental plasticity. Moreover, GCs and gut microbes are easily quantified in noninvasive samples (see Supporting Information for details on methodological approaches), offering plausible research avenues for human biologists and primatologists studying development in both captive and wild settings. We focus mainly on the prenatal and early postnatal period, when adversity is influenced by maternal interests and is also expected to have the most profound effects on offspring phenotype (Figure 4).[86] While later postnatal adversity may impact organisms directly without maternal input, these mechanisms are outside the scope of this review.

3.1 | Glucocorticoids

GCs are end-products of the hypothalamic–pituitary adrenal (HPA) axis and best known for their role in the vertebrate stress response.[8] The stress response is initiated when exposure to a challenging stimulus (or "stressor") jumpstarts the HPA axis, beginning with increased corticotropin releasing hormone (CRH) secretion by the hypothalamus and ending with increased GC secretion by the adrenal cortex. Elevated GCs increase respiratory and heart rates, enhance cardiovascular tone, decrease digestive function, and primarily suppress the immune system[8]—changes that are viewed as adaptive in the face of an immediate stressor. Beyond their roles in the stress response, GCs

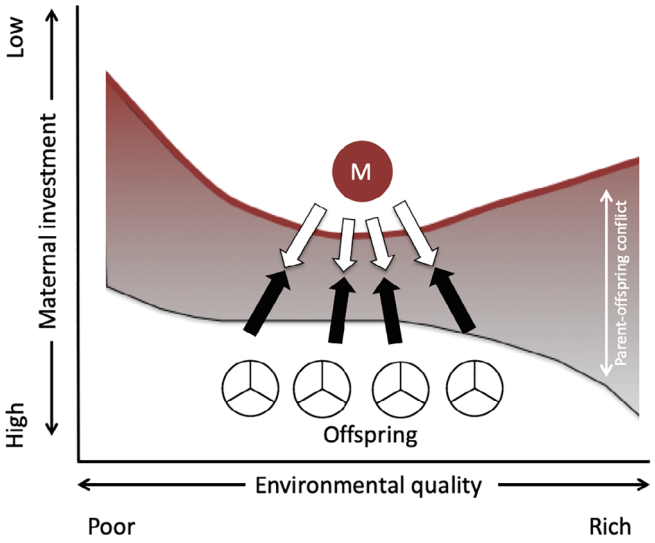


FIGURE 3 Parent-offspring conflict across environmental gradients. Each offspring faces resource allocation tradeoffs across its own developmental systems (indicated by pie graphs), while each mother (M) faces resource allocation tradeoffs across successive offspring. At poor and rich environmental extremes, the optimal amount of resources allocated to offspring is expected to diverge from the perspective of mothers versus offspring (see text for details). When such parent-offspring conflict is high, maternal signals of environmental quality are expected to be less accurate, leading to offspring developmental trajectories that may benefit the mother at a cost to the infant. Maternal manipulation is in part counteracted by infant physiological mechanisms (e.g., 11B-HSD2) that have the potential to filter maternal signals (indicated by black and white arrows), potentially resulting in developmental trajectories that are suboptimally calibrated for both parties [Color figure can be viewed at wileyonlinelibrary.com]

are essential to energy regulation and metabolism, affecting the availability of glucose at specific tissues, maintaining body mass, and mediating locomotor, foraging, and even parenting behaviors, which can be energetically costly.[8,87] These stress-related and energetic functions position GCs as one of the central biochemical mediators of developmental responses to environmental adversity.

One major way in which GCs can influence offspring development is by altering maternal behavior. In studies of wild nonhuman primates and humans, maternal GCs during gestation and lactation increase maternal responsiveness[88,89] and time spent grooming and nursing infants.[90] However, opposite patterns have been found in captive populations, with GCs inversely related to measures of maternal investment[91,92] and positively related to the frequency of abuse and rejection toward offspring.[93,94] These patterns may suggest that intermediate concentrations of GCs within a more naturalistic range (e.g., in the wild) enhance maternal care through arousal mechanisms, but extreme environments (e.g., constraints of captivity)[87] may trigger abandonment behaviors.

Maternal GCs can also influence offspring development more directly by binding to the placenta or to offspring tissues during the pre- and postnatal periods. During gestation, maternal GCs bind at the placenta and alter carbohydrate metabolism,[95] thus decreasing the amount of energy transferred to the fetus. Maternal GCs can also pass through the placenta directly into fetal circulation (10–20% of maternal circulating GCs in humans[96]), binding to fetal target tissues and initiating changes in development. In the postnatal period, GCs from maternal circulation reach the offspring through the transfer of milk, a process presumed to occur via passive diffusion across the mammary gland.[97] Once ingested, milk GCs can influence intestinal permeability and the transport of macromolecules by binding directly to the offspring gut, where GC receptor density is highest during infancy.[98] Ingested milk GCs are also able to cross the intestinal wall and enter circulation, where they can ultimately bind to other body tissues.[99]

Although the relative contributions of direct and indirect (i.e., maternal care behavior) effects of maternal GCs are difficult to tease apart, numerous studies have linked these hormones to offspring growth, immunity, and behavior during the pre- and postnatal periods. During gestation, maternal GCs have contrasting effects on pre- and postnatal growth. In humans and captive rodents, exposure to elevated prenatal GCs primarily restricts fetal growth[10] (but see Petrullo and Lu for opposite results in vervet monkeys[100]). By contrast, recent studies on captive and wild mammals have shown accelerating effects of prenatal GCs on postnatal growth,[28,38,86] an effect that may be similar to catch-up postnatal growth found in human infants exposed to nutritional stress in-utero[101] (but see Berghänel and colleagues[86]).

The effects of prenatal GCs on offspring immune development are primarily immunosuppressive. In captive rodents, elevated maternal gestational GCs are associated with atrophied lymphoid tissues and reduced *lymphocyte* production and activation in response to immune challenge.[102,103] In vitro studies on human immune cells exposed to elevated GCs show similar effects, with fetal immune cells experiencing more drastic lymphocyte reduction, and a greater shift from *Th1* to *Th2* immunity compared to adult immune cells.[104] While comparable studies have not been conducted in nonhuman primates, a single study on wild macaques found that infants born to mothers with high gestational GCs took longer to recover from conjunctivitis,[28] supporting similar suppressive effects of prenatal GCs on immunity.

Prenatal GCs also have wide-ranging effects on offspring behavior and cognition. Across mammals, both experimentally-induced and naturally-occuring elevations in prenatal maternal GCs have been associated with less sociable, more introverted, and more reactive temperaments,[105,106] slower motor development,[28,106,107] and altered HPA axis reactivity.[108] However, these effects do not always persist into adulthood, with some outcomes (e.g., reactivity) either disappearing or even reversing later in life.[109]

Compared to the case for prenatal maternal GCs, the effects of postnatal maternal GCs on offspring phenotype remain poorly understood. This is particularly the case for the direct effects of milk GCs, which have been studied for less than a decade. With regard to growth, the only study on humans focusing on milk GCs found a negative relationship between GCs and offspring BMI,[110] while a similar study on captive rhesus macaques found a positive relationship between milk GCs and offspring weight gain during "peak," but not

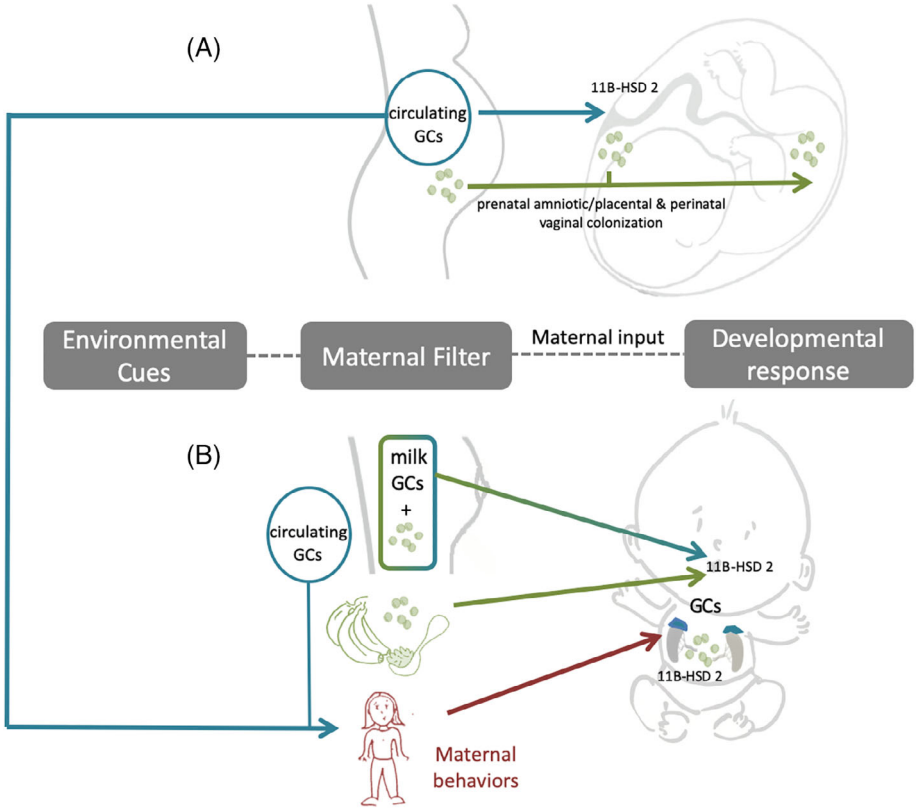


FIGURE 4 Glucocorticoids (GCs) and the infant gut microbiome are proximate regulators of developmental responses to early-life adversity. (a) During fetal life, maternal-origin GCs reach the fetus by passing through the placental barrier. Maternal-origin vaginal microbiota can also exert developmental effects by colonizing the perinatal infant gut microbiome. (b) During infancy, maternal effects continue via GC-mediated caretaking behaviors as well as through direct transmission of GCs and bacteria that are ingested by the infant via breastmilk. During both time periods, maternal GCs may also be neutralized by 11B-HSD 2 at the placenta and in the mouth and gastrointestinal tract of infants. Finally, postnatal development can also be influenced by maternal behaviors, which are under the influence of preparatory and activational effects of circulating maternal GCs during the pre- and postnatal periods [Color figure can be viewed at wileyonlinelibrary.com]

early lactation.[111] Importantly, the latter study controlled for the effects of milk quality, separating out the potential effects of GC-induced differences in maternal energetic investment, but not necessarily maternal care-taking behaviors, on offspring growth. Although we are unaware of any studies examining the indirect or direct effect of lactational GCs on offspring immunity, experimental injection of GCs into infant rhesus macaques suppresses cellular immune responses and decreases lymphocyte activity,[112] suggesting similar effects would be induced if milk-origin GCs entered infant circulation. With regard to neurobehavioral development, moderate increases in maternal GCs or the ingestion of milk GCs by rodent pups are associated with improved memory and learning and reduced fear behaviors.[11,113,114] However, among primates, elevated milk GCs appear to have opposite effects. In human and macaque offspring, high concentrations of milk GCs are associated with greater rather than reduced fearfulness, nervousness, and impulsivity.[11,111,115–117] Thus, lactational, and milk-origin GCs appear to induce many of the same developmental changes as prenatal GCs, but some patterns remain contradictory and are difficult to interpret in the absence of further study.

Intriguingly, offspring may buffer the input of maternal GCs both pre- and postnatally via the enzyme 11B-hydroxysteroid dehydrogenase 2 (11B-HSD2), which converts cortisol and corticosterone into the biologically inactive molecule cortisone.[10] This conversion results in the passage of only a small fraction of maternal-origin GCs to the developing fetus, potentially buffering the fetus from deleterious maternally-induced effects.[96] Indeed, recent studies have shown that stress-induced effects on offspring phenotype are contingent upon downregulated levels of placental 11B-HSD2.[118] Further, 11B-HSD2 is active in the offspring intestine (ileum and colon)[98] and parotid gland,[119] suggesting that localized buffering against maternal milk GCs during lactation is also likely. Given the presence of 11B-HSD2 at these critical locations during development, the programming effects of maternal GCs can potentially be offset in favor of offspring strategies. Thus, 11B-HSD2 represents a physiological embodiment of parent-offspring conflict,[76] where maternal interests can be directly modified by offspring at a molecular level.[5,67] As a tissue with shared maternal and fetal origins, the placenta may be one of the most intriguing sites of coevolutionary conflict between mother and offspring, especially given recent evidence in rodents and domestic sheep that maternal malnutrition can also reduce placental 11B-HSD2.[120,121]

3.2 | Gut microbiome

Complementing the rich research on GCs and developmental plasticity, the gut microbiome has recently emerged as another mechanism through which early-life adversity can translate into developmental and adult outcomes. The adult human gut microbiome contains trillions of bacteria,[122] including health-promoting *symbionts*, neutral *commensals*, and potentially harmful *pathobionts* that activate the host immune system.[123] Key functions of symbiotic bacteria include regulating digestion, gut permeability, energy balance, and nutrient absorption[124]—processes that generate energy that can then be allocated toward growth.[83] Accordingly, alterations in microbial composition

have been associated with changes in weight, BMI, and stature growth in human infants and children.[125,126] In addition, the diversity and composition of the gut microbiome have also been linked to metabolic (e.g., obesity) and inflammatory (e.g., arthritis, irritable bowel syndrome) disease, mucosal immunity, neurodevelopmental disorders (e.g., autism spectrum disorder, and depression), and temperament.[84,127] Thus, a myriad of connections have been drawn between gut microbes and physiological and psychological traits that are also strongly associated with early-life adversity.

The composition, diversity, and abundance of gut bacteria are constantly in flux and responsive to environmental input, particularly during the prenatal and early postnatal periods.[128] Factors such as stress, diet, and social partners can alter the composition of the gut microbiome and may perturb the system into dysbiosis.[123,129] When this occurs, the balance of symbionts and putative pathobionts can shift, affecting growth, immunity, and neurobehavioral development. Further, the trajectory of the developing gut microbiome is heavily influenced by maternal vertical transmission. Maternal skin, fecal, and vaginal microbes are some of the first to colonize the infant's gut at birth, followed by milk-origin microbes and bacteria-modifying factors (e.g., probiotic oligosaccharides) that further shape the infant's gut microbiome during lactation.[128,130–132]

These earliest periods of bacterial colonization are highly sensitive to disturbance. Clinical evidence from human infants demonstrates that antibiotics, Caesarean section (C-section) delivery,[133] and formula feeding all disrupt the infant gut microbiome,[128,134] with reductions in microbial diversity and changes in composition that may persist into adulthood.[135] Furthermore, experimental studies using *germ-free* and microbiome *transplant models* have shown that the developing immune system and HPA axis are altered by microbial disruptions during infancy, with phenotypic development reversed by restoring the "normative" microbiome early in life, but not during adulthood.[136–138]

Taken together, these data support two tantalizing hypotheses. First, similar to organizational effects often attributed to hormones, there appear to be early critical periods during which microbes exert profound effects on the developing phenotype. During this time, normative gut microbial succession—and thus offspring phenotype—might be disrupted by adversity. Second, at least some of these phenotypic effects may be modulated by stress-induced alterations in the maternal microbial community that are vertically transmitted to offspring during parturition and lactation. Indeed, in a study of non-human primates, maternal stress during gestation altered microbial communities in the infant; however, the role of vertically transmitted bacteria was not explicitly demonstrated, and there was no follow-up research on possible effects on offspring phenotype.[14]

By contrast, a handful of recent studies on prenatal adversity in rodents have provided the strongest support for vertical microbial transmission as a mechanism directing offspring development in response to adversity. Stress-induced changes in maternal gestational gut and vaginal microbial communities, for instance, have consistently predicted the composition of infant gut microbial communities and a suite of other phenotypic traits after birth, including altered immunity, impaired neurodevelopment, higher blood pressure, greater HPA reactivity, and increased anxiety-like behavior, with some of these traits persisting into adulthood.[139–141] Furthermore, maternal microbial transplants prior to birth can directly influence offspring postnatal phenotype, suggesting that these changes are likely causal, not just correlational.[142] Finally, in perhaps the strongest demonstration of maternal microbial effects, pregnant mouse mothers with stress-induced vaginal microbiome dysbiosis gave birth to neonates with distinct changes in their gut microbiome and metabolism.[13,141] Analyses of neonatal gut tissue further revealed an abundance of host metabolites involved in oxidative stress, nutrient absorption, and mitochondrial regulation, processes linked to life history and neurodevelopment. However, the same differences were not found for infants delivered via C-section, demonstrating clearly that vertical maternal transmission of stress-induced vaginal dysbiosis directly influenced offspring metabolic differences.

Despite the known transmission of bacteria and bacteria-modifying factors from mother to offspring via milk, there is comparatively little direct evidence for *postnatal* vertical transmission as a mechanism by which mothers can alter infant development in response to adversity. A handful of studies on humans have linked maternal health (obesity, celiac disease, and HIV, and infection)[143–145] to individual differences in milk microbial composition; however, thus far there has been no research on the impact of social and nutritional stressors on the milk microbiome or how potential alterations might shape the infant gut flora and phenotype. Experimental studies mimicking the methodology employed in stress-induced vertical vaginal transmission studies are now necessary to test such hypotheses.

A major mechanism that should be considered in tandem with milk microbiota is the transfer of milk *oligosaccharides*, which are small sugar molecules that have the capacity to drive the growth of preferred microbial taxa over others in the infant gut.[146] Instead of being processed by host-specific enzymes, milk oligosaccharides are only digested by specific microbes residing in the infant's gut, providing an avenue by which mothers can promote the proliferation of certain bacterial strains over others. In humans, milk oligosaccharide composition appears to shift in response to food availability. A recent study on Gambian women,[147] for instance, found that oligosaccharide abundance decreased during the lean season, and that specific oligosaccharides and their correlated infant microbial communities were associated with faster growth and greater protection against illness in infants. Similar associations between milk oligosaccharide profiles and infant health (e.g., gastroenteritis and respiratory infection) have been demonstrated in other human populations.[148] Finally, mouse models of infant nutrition and growth found that supplementation with specific types of oligosaccharides increased lean body mass, bone density, and metabolism.[149] Thus, there is compelling evidence that research on milk oligosaccharides is integral to establishing a comprehensive picture of how seeding of the infant gut microbiome shapes development.

More generally, investigating how the organization of the gut microbiome acts in conjunction with GCs to direct developmental plasticity appears increasingly important, given the emerging view that the gut microbiome and HPA axis are bidirectionally linked in what is often referred to as the "gut-brain-axis."[150] While the central role of

GCs in the stress response suggests that the gut microbiome is simply another downstream system under its influence, gut microbiome composition can impact signaling pathways in the hypothalamus,[12] directly impacting GC concentrations.[151] This dynamic interaction suggests that the relationship between stress, microbial perturbations, and development is exceedingly complex.

The importance of the gut microbiome for both the host stress response and the developmental phenotype has theoretical implications for understanding developmental plasticity. From an evolutionary perspective, microbial involvement in the stress response suggests that developmental plasticity is the result of coevolution between host physiology and dynamic changes in the gut microbiome, which in turn may be influenced by maternal and offspring interests. This multi-player tug-of-war should encourage future researchers to consider the composition and functions of the gut microbiome as potentially benefiting maternal, offspring, and even microbial fitness.[15] One clear example of these conflicts is the transfer of probiotic maternal milk oligosaccharides allowing mothers to preferentially support certain microbe strains over others.[152] Although we are unaware of any research suggesting that infants can counteract these measures, competitive exclusion (i.e., microbial competition for available niches and resources) can, in theory, also be driven by offspring gut motility and the biochemical makeup of the mucosal lining of the offspring gut.[153,154] Further, offspring intestinal immune responses to maternal microbes can result in the selective seeding of certain maternal microbial strains over others.[155,156] Thus, despite the magnitude of maternal microbiota and oligosaccharide transmission, offspring physiology ultimately shapes the maternal microbes that successfully colonize and proliferate within the infant gut. Whether microbial strains might have similar mechanisms to counter offspring or maternal interests is fodder for future studies.

4 | LOOKING TOWARD THE FUTURE

To date, the vast majority of research on early-life adversity has focused on the evolutionary scenarios potentially explaining the developmental origins of health and disease ("DOHaD") in humans,[20] or on the proximate mediators of early-life adversity using laboratory model species such as rodents[10] or macaques.[112] Apart from captive macaques, there has been very little research examining developmental plasticity in nonhuman primates as a whole (but see[28]), or in similarly large-bodied social mammals, particularly in naturalistic settings. However, nonhuman primates can serve as excellent models for studying developmental plasticity for several reasons.

First, as long-lived mammals that share broad reproductive similarities (e.g., invasive placenta, some capital breeding) and a long evolutionary history with humans, research on the evolutionary underpinnings of developmental plasticity in nonhuman primates has clear implications for understanding human evolution. While adaptive models are often invoked as explanations for disease in the human epidemiological literature, direct empirical support is largely lacking. More to the point, the presence of disease does not always indicate that a developmental decision was maladaptive; indeed, disease in later life can sometimes arise from an adaptive tradeoff in early life. Thus, the prevalence of disease is not an adequate test of adaptive models. To progress, studies must explicitly consider which adaptive scenarios are likely given the socioecology of a given system, and test fitness predictions associated with those scenarios. While data such as fertility and survival might be difficult to obtain and interpret in modern humans, they are more widely available from nonhuman primate populations under long-term study.

Distinguishing the precise adaptive scenarios that pertain to modern humans may have important ramifications for treating disease. For example, if developmental plasticity is less sensitive to current ecology than to maternal condition, we should not expect quick improvements in the living environment to improve offspring health outcomes. Furthermore, even improving maternal condition directly may not be sufficient if mothers utilize those resources to benefit reproductive rate over offspring fitness.[66] By contrast, Wells[50] has recently argued that "relaxation" treatments that alleviate stress might "reorganize maternal life history decisions"[157] by shifting resource allocation strategies toward greater offspring investment. Determining whether offspring phenotypes might be adaptively calibrated to benefit maternal or offspring fitness during a later time period (e.g., pre- to postnatal; prenatal to childhood) will be equally informative for public health. Although the existence of some parent-offspring signal incongruence and extended life histories in humans may render adaptive calibrations across longer time scales less likely, any demonstration of short-term adaptive calibrations (e.g., pre- to early postnatal period) may suggest that modern practices such as bottle-feeding exacerbate costs for offspring and mothers by creating a developmental mismatch. However, if early-life induced fitness effects are not influenced by later-life conditions, then bottle-feeding may not matter and interventions should focus solely on the initial culprits: maternal condition and the early-life environment itself.

Second, from a proximate perspective, integrating experimental research on captive primates with long-term research on wild nonhuman primates and humans will advance our understanding of how the HPA axis, the developing gut microbiome, and other key regulators of developmental plasticity link early-life adversity to growth, reproduction, health, and survival—knowledge that has broad translational value. A more detailed understanding of how stress-induced gut microbial change mediates later-life health, for instance, is critical toward developing treatments for disease, especially because the impact of bacterial strains on host health and behavior may be lineage-specific.[158] Furthermore, efforts to determine how offspring development is mediated by maternal GC production in conjunction with placental 11B-HSD2, which limits the transplacental passage of GCs, would have broad salience for understanding the mechanistic aspect of parent-offspring conflict. Such efforts would provide critical information for evaluating how GC treatments for illnesses such as asthma or lupus might be given safely to pregnant mothers to help mothers while limiting effects on the fetus.

Finally, as nonhuman primates face challenges such as climate change and habitat degradation, ongoing research may be able to shed light on how novel and extreme forms of adversity, such as rapid

habitat loss, climate change, and human encroachment, might impact developmental responses that have evolved in the context of more evolutionarily common stressors. Although such novel forms of adversity may not be relevant for testing adaptive hypotheses per se, insights into how threatened populations developmentally respond to increasing habitat degradation is critical to shaping conservation strategies. Furthermore, such research can offer a window into how ecologically novel environments can unveil extremes of phenotypic variation that might then be subject to selection at a later date.[159]

In conclusion, we encourage biological anthropologists to pursue research programs on developmental plasticity, focusing on evolutionary, proximate, and applied angles—particularly in naturalistic populations where animals are more likely to face strong resource allocation tradeoffs. The development of novel morphometric, physiological, and molecular measures that can be readily applied to studies of wild animals will help advance this cause (see Supporting Information), providing researchers with the opportunity to examine how the early-life environment may initiate developmental changes on multiple levels (e.g., immunity, somatic growth, HPA axis). Applying these methods to studies of nonhuman primates will provide key insights into the link between early-life experiences and adult fitness consequences, ushering in an exciting new era of studies on developmental plasticity.

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DATA SHARING STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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