Developmental plasticity as adaptation:

adjusting to the external environment under the imprint of maternal capital

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Abstract

Plasticity is assumed to enable beneficial adjustment to the environment. In this context, developmental plasticity is generally approached within a two-stage framework, whereby adjustments to ecological cues in stage 1 are exposed to selection in stage 2. This conceptual approach may have limitations, because in species providing parental investment, particularly placental mammals such as humans, initial adjustments are not to the environment directly, but rather to the niche generated by parental phenotype (in mammals, primarily that of the mother). Only as maternal investment is withdrawn is the developing organism exposed directly to prevailing ecological conditions. A three-stage model may therefore be preferable, where developmental trajectory first adjusts to maternal investment, then to the external environment. Each offspring experiences a trade-off, benefitting from maternal investment during the most vulnerable stages of development, at the cost of exposure to investment strategies that maximise maternal fitness. Maternal life history trade-offs impact the magnitude and schedule of her investment in her offspring, generating life-long effects on traits related to health outcomes. Understanding the imprint of maternal capital on offspring is particularly important in species demonstrating social hierarchy. Interventions targeting maternal capital might offer new opportunities to improve health outcomes of both mother and offspring.

Keywords: Developmental plasticity; adaptation; parental investment; parent-offspring conflict; life history theory

Introduction

The importance of phenotypic plasticity in medicine is undisputed. The majority of treatments or efforts to prevent disease are based on the assumption that plastic responses will enhance health. To the extent that this promotes reproductive fitness, it may also be considered adaptive. Recently, this framework has been approached from a life-course perspective, following recognition that adult health is profoundly influenced by experience in early life (the 'developmental origins of adult health and disease' (DOHaD) hypothesis) [1]. A huge literature spanning epidemiology and mechanism has emerged in support of this hypothesis in humans [2], while across diverse species, biologists have produced compelling evidence on the phenotypic consequences of early developmental adjustments [3].

From an evolutionary perspective, it might seem intuitive that developmental plasticity likewise represents an adaptive process. Were it overtly maladaptive, it would have been diminished through natural selection, and indeed variability in the costs of plasticity may help explain inter-species variability in its magnitude [4]. Even where developmental plasticity is beneficial for fitness, however, such benefits may come at a cost to health outcomes. For example, thrifty growth patterns in early life resolve immediate energy scarcity at a cost of elevated non-communicable disease (NCD) risk in later life [5]. The relationship between developmental plasticity and adaptation is therefore complex, and remains poorly understood in the context of human medicine. Many studies that support the DOHaD hypothesis (eg [6]) do not necessarily provide insight into the nature of developmental adaptation. Without understanding *why* individuals respond to stresses and stimuli in early life, we will be unable to optimise interventions aimed at promoting long-term health and human capital.

An evolutionary perspective on developmental plasticity and human health must achieve several aims. First, it must be capable of explaining variability in diverse outcomes, including both non-communicable and communicable disease risk. Second, it must constitute a theoretical framework applicable to other species. Third, it must be capable of embracing mechanistic evidence at behavioural, physiological and molecular levels [7]. The aim of this review is to consider parent-offspring dynamics in this context, expanding the theoretical framework within which the relationships between plasticity, adaptation and health outcomes can be addressed. I focus here on physical development, but the framework may in future be extended to psychological outcomes.

Evolutionary approaches to DOHaD

Regarding human health, the first adaptive model of developmental plasticity was the 'thrifty phenotype' hypothesis [5], proposing that fetuses exposed to inadequate energy supply protected the brain by reducing investment in other vital organs. In the short-term, it was proposed, this adjustment would promote survival in the face of energy scarcity, but in the long term, such individuals would have poorer tolerance of energy-dense diets, and be susceptible to diseases such as type 2 diabetes (T2DM) [5]. This ground-breaking concept of developmental trade-offs has broader relevance to any form of phenotypic variability demonstrating sensitivity to prior experience [8].

Subsequently, many researchers have focused on two competing frameworks to understand how developmental adjustments might contribute to later disease risk. Some maintain focus on the notion that environmental stresses deplete the supply of *resources* in early life,

driving trade-offs between competing biological functions [3, 9]. Here, the trade-offs underlying the thrifty phenotype are considered adaptive through generating short-term survival pay-offs, at a cost of long-term penalties that cannot be resolved even if the environment subsequently improves. These penalties may furthermore be greatest in harsh adult environments that impose further trade-offs [9]. Nonetheless, we can assume that selection has favoured developmental trade-offs in response to early-life constraints that both promote early survival advantages and reduce long-term fitness costs.

Others propose that organisms seek *information* in early life about ecological conditions, and tailor their phenotype specifically in anticipation of encountering similar conditions in later life stages [10, 11]. Here, the adjustments associated with the thrifty phenotype are considered an adaptive preparation for future famine, and the 'predictive adaptive response' (PAR) hypothesis attributes the manifestation of disease to the environment failing to match the conditions for which the phenotype was prepared [10, 11].

The merits of these two conceptual approaches remain subject to discussion, both in humans and in other species. Some studies of non-human animals support the notion of adaptive forecasting over relatively short time periods. For example, in banded mongooses, higher levels of inter-female competition were correlated with higher levels of prenatal investment, suggesting that mothers prime the phenotype of their offspring in anticipation of specific social environments [12]. For humans, Bateson and Gluckman proposed an 'acid test' for the PAR hypothesis: 'whether the small baby will be better suited to the poor environment predicted by the mother's low nutritional level than a big baby' [13]. Consistent with that hypothesis, children born small are more likely to survive severe-acute

malnutrition in early life than children with higher birth weight, due to their more efficient mobilization of protein and lipid stores [14]. Note that this evidence is also consistent with other hypotheses, as discussed below.

However, beyond such 'immediately adaptive responses' [15], it was suggested that human phenotype also developed in anticipation of expected ecological conditions in adulthood, and that mismatch between early phenotype and adult conditions was central to the emergence of NCDs [10]. Mathematical simulations suggest that such long-term phenotypic matching may be implausible [16, 17], while empirical studies of long-lived animals and humans have also been largely unsupportive of adult PARs [9, 18]. Regarding the association between developmental exposure and adult disease risk, therefore, constraints models are generally preferred [19].

Importantly, both anticipatory and conventional constraint approaches are broadly framed in terms of a two-stage process [20]. For the PAR hypothesis, the first stage involves the organism 'scanning' the environment to prepare an appropriate phenotype, whereas for the constraints hypothesis, it involves making functional trade-offs to resolve ecological stresses. My main concern in this paper is how well either of these approaches provides a valid conceptual model of the relationship between developmental plasticity and adaptation.

I argue that any adjustment during the earliest developmental period is not directly to the external environment. For placental mammals in particular, via the niches of pregnancy and lactation, but also for any organism receiving parental investment, the earliest niche is imprinted by components of parental phenotype, which generate 'parental effects' on the

offspring [21]. Any short-term adjustment by the offspring is therefore to the information and resources/constraints indexed by parental investment, which in placental mammals equates closely to maternal phenotype [7, 22]. Although paternal and grand-maternal physiological influences are also relevant [7], for simplicity I will restrict the discussion below to maternal effects.

Since maternal phenotype and the external environment may not be well correlated, I suggest that a two-stage model may have limitations for understanding the relationship between DOHaD and adaptation. This review builds on my earlier work [7, 23], arguing that an evolutionary perspective on the association of developmental plasticity with health variability requires an inter-generational perspective, in order to address both maternal and offspring fitness.

Maternal effects and the maternal capital model

'Maternal effects' refer to any maternal influence on offspring phenotype that cannot be attributed to the direct transmission of maternal genes [24]. Since these effects are experienced by offspring during periods of substantial plasticity, they have implications for the fitness of both mother and offspring. Whether maternal effects are 'adaptive' or not depends in part on which party is considered. Marshall and Uller differentiated four different scenarios [25]: maternal effects may either (A) increase maternal fitness by promoting offspring fitness, (B) increase maternal fitness at a cost to offspring fitness, (C) enhance maternal fitness by bet-hedging (producing offspring with variable phenotypes) or (D) reduce the fitness of both mother and offspring through the transmission of toxins or pathogens.

144

145 To explore the dynamics of maternal effects, I developed a conceptual model termed the
146 'maternal capital' hypothesis. Building on the 'embodied capital' model of Kaplan and
147 colleagues [26], I defined maternal capital as the sum total of maternal traits that enable
148 investment in offspring [22]. These include physical traits such as body size, nutrient stores
149 and homeostatic physiology, but also social and educational components along with
150 material assets, all of which may promote the capacity for maternal reproductive
151 investment. For example, mothers with more somatic capital tend to produce larger
152 offspring [27], while mothers with lower social capital tend to produce smaller offspring with
153 higher mortality risk [28].

154

155 Maternal capital mediates any exposure of the fetus to external ecological stresses and
156 stimuli. Like other species, humans occupy ecological niches characterised by diverse
157 sources of variability, signalling a wide variety of stimuli and stresses. These signals relate to
158 factors such as temperature, altitude, local infectious disease burden, food availability and
159 diet composition, and the psychosocial environment. There may also be transient but
160 powerful shocks such as floods and droughts. Each of these ecological signals may vary
161 independently in its magnitude and periodicity [29], but the mammalian fetus lacks the
162 physiological apparatus to adapt directly to multiple and potentially conflicting external
163 factors. However, it has no need to, instead it simply samples maternal phenotype, which
164 provides a relatively stable homeostatic niche representing a 'safe harbour' during the most
165 vulnerable periods of offspring development [30]. This niche may benefit from social
166 support, representing both the mother's 'extended phenotype' [31] and her social capital
167 [32]. The multiple components of maternal capital allow short-term ecological fluctuations

168 to be smoothed into a more stable signal [33], and it is how the mother resolves any
169 ecological stress through such smoothing that best describes the initial niche experienced by
170 the offspring.
171
172 For example, fetuses gestated during famines have reduced birth weight and an elevated
173 risk of T2DM in adulthood, though the magnitude of these associations also varies by the
174 trimester of exposure [34]. However, while the energy supply of pregnant women may fall
175 by >50% during famine, birth weights are typically reduced by only <10% [35, 36]. This
176 reminds us that offspring are not exposed, not can they adapt, to famine itself, rather they
177 respond to variability in maternal capital. A similar scenario relates to many other ecological
178 stresses, such as extreme temperatures, infectious disease, and social stresses [7].
179
180 Nonetheless, the 'safe harbour' may itself become compromised. For example, in a recent
181 study from South Africa, 40% of young mothers (mean age 29 years) were overweight, 30%
182 anaemic, 10% had gestational diabetes and 32% had HIV, while 8% of mothers had all four
183 penalties (Norris, personal communication). Here, maternal metabolism is less favourable to
184 the offspring - either because it incorporates adjustments promoting maternal survival, or
185 because the quality of homeostasis has declined. Under such circumstances, the fetus can be
186 exposed to multiple depletions of maternal capital, adversely impacting its developmental
187 trajectory. For example, gestational diabetes results in excessive fuel transfer across the
188 placenta causing fetal pancreatic hypertrophy and beta-cell hyperplasia [37], while maternal
189 infections during pregnancy such as malaria also elevate NCD risk in the offspring [38].
190

Considering such a population of mothers, in which individuals vary in the number of beneficial or deleterious traits, reiterates the point that each offspring does not receive accurate signals of the quality of the external environment. Rather, each offspring receives signals about the magnitude and quality of maternal capital – the mother's nutritional reserves, the efficiency of her homeostasis, and the extent to which her metabolism has adjusted to promote her own survival. Other factors relevant to maternal fitness include the birth order of the offspring, the age at which the mother commenced reproduction, and her current age, all of which influence the magnitude of maternal investment in the current offspring, but which are at best weakly correlated with environmental conditions.

The crucial influence of maternal capital, which may be only weakly correlated with prevailing ecological conditions, on offspring developmental trajectory is demonstrated by longitudinal studies of mothers whose metabolic state varies across successive pregnancies. For example, research on Pima Indians showed that the risk of developing type-2 diabetes is much greater among those offspring born after the maternal diagnosis of diabetes compared to those born before the diagnosis [39]. A similar study showed that, following bariatric surgery to reduce body fat, mothers had a lower risk of delivering large infants, and the offspring themselves had lower adiposity, insulin resistance and blood pressure, compared to their siblings born before maternal surgery [40]. In each case, a change in the quality of maternal homeostasis affected the developmental trajectory of the offspring.

Other studies show that maternal capital mediates the impact of environmental change on fetal development. A study of nutritional supplementation during pregnancy showed that its effect on weight of the placenta and neonate depended on the rate of maternal fat

accretion during mid-pregnancy [41]. Among mothers with inadequate fat accretion, compared to a control supplement containing only vitamins, protein-energy-vitamin supplementation increased both placental and neonatal weights. However, no such increases occurred among mothers with adequate fat accretion, indicating that the additional nutrients were in this case retained by the mother.

These studies indicate that there is no direct signal from the external environment to the fetus, rather its magnitude depends on maternal phenotype. Such findings are not restricted to humans: in birds, for example, experimental cross-fostering studies show that offspring adapt to parental signals of supply (androgen levels deposited in eggs at the time of laying), rather than the external food supply provided by the foster parents after hatching [42]. This interpretation may apply to the human study of severe-acute malnutrition described above [14], where offspring smaller at birth remain less costly for the mother during the period of lactation.

Maternal effects and developmental plasticity in the offspring are inherently connected, to the extent that in early life they could essentially be defined in terms of each other. During pregnancy, for example, a maternal non-genetic effect could be defined as anything that elicits a plastic response in the fetus, while fetal plastic responses could be defined as the consequence of maternal effects [43]. This integral relationship generates the prediction that components of developmental plasticity should close as the 'safe harbour' provided by maternal physiology is withdrawn [29], which for some traits may occur at birth, and for others at weaning. For example, maternal buffering of offspring hemodynamics ceases when placental nutrition ends, and this may explain why components of renal plasticity such as

239 nephrogenesis cease at birth. In contrast, nutritional buffering of offspring growth continues
240 through lactation, and this may explain why linear growth only undergoes canalisation in
241 late infancy [29].
242
243 **Fitness conflicts**
244 Beyond buffering the fetus from short-term ecological stresses, the imperfect correlation
245 between maternal phenotype and the external environment additionally opens the
246 opportunity for the mother to manipulate, in her own interests, any signals transmitted to
247 the fetus.
248
249 The notion that maternal and offspring fitness may be subject to competition was originally
250 proposed by Trivers [44]. According to this approach, mothers maximise fitness by dividing
251 their investment across multiple offspring, whereas each offspring would maximise its own
252 fitness by receiving substantially more than its fair share of resources [44]. Regarding
253 placental nutrition, there is no 'objective' availability of resources to the offspring, instead
254 mother and offspring contest nutrient transfers through physiological mechanisms. Neither
255 party may win this negotiation out-right, rather the final magnitude of investment may be a
256 compromise between the respective optima [45]. On this basis, each offspring is initially
257 exposed to a fundamental trade-off: the protection provided by the safe harbour comes at
258 the cost of submitting developmental trajectory to the influence of maternal fitness-
259 maximising strategy [33].
260
261 That maternal effects may impose costs on individual offspring is well illustrated by analysis
262 of a public health intervention, intended to reduce maternal under-nutrition in Ethiopia. The

263 intervention installed water taps in some villages, in the expectation that reducing maternal
264 energy stress would additionally reduce child malnutrition. Contrary to expectations,
265 however, child malnutrition increased relative to control villages, mediated by a rise in
266 maternal fertility [46]. The energy 'spared' by the intervention was therefore allocated to
267 maternal fitness, at a cost to the health of individual offspring. This finding contradicts the
268 PAR hypothesis, since the offspring developed a phenotype in early life already mismatched
269 to the improved environment, and it is equally challenging for conventional constraints
270 models to explain why trade-offs worsened at a time when ecological conditions improved.
271 The interpretation provided by the maternal capital model is that mothers re-allocated their
272 reproductive investment in order to maximise fitness, capping investment in the short term
273 to maximise their future opportunities, and this is supported by a mathematical model [47].
274
275 The notion that maternal investment strategy can favour maternal fitness, potentially at
276 some cost to the fitness of individual offspring, is also supported by studies of non-human
277 animals [3]. For example, a study of birds demonstrated corticosterone-mediated sex-biased
278 investment, resulting in rapid male-biased mortality and hence a reduction in brood size.
279 Overall, this adjustment improved the match between maternal capacity to provision and
280 offspring demand [48]. Similarly, studies of primates have shown that concentrations of milk
281 bio-actives vary in association with maternal parity, social rank and infant sex [49], while the
282 age at which reproduction commences was associated with the capacity to synthesise milk
283 [50]. All of these studies indicate that mothers may vary their investment strategy in ways
284 that do not necessarily match offspring phenotype with external ecological conditions,
285 instead the constraints experienced by the offspring relate to maternal fitness-maximising
286 strategy.

In humans, the importance of demographic factors for maternal investment variability is demonstrated by birth order associations. First-born offspring tend to have lower average birth weight than those born subsequently, but often show catch-up in infancy. In a Brazilian cohort, for example, firstborns were shorter and lighter than their later-born peers at birth, but by 6 months they had already overtaken them, and from 1 year remained taller and heavier [51]. In adulthood, firstborns may be taller and fatter, and may have higher NCD risk [52], though the magnitude of these associations appears to depend on the opportunity for early catch-up.

Birth order contains no 'useful' information about the long-term environment, but represents a maternal effect whereby mothers vary the magnitude of their investment through their reproductive career. Neither conventional constraints nor adaptive forecasting approaches have considered how this variability may relate to maternal fitness-maximising strategy.

A recent mathematical model of signalling between mothers and offspring found that parent-offspring conflict often disrupts information transfer, resulting in the offspring failing to acquire accurate information about external environmental conditions [53]. Although not targeted specifically at human characteristics, this model is consistent with the perspective outlined above, and supports the notion that when there is a conflict of interest between maternal and offspring fitness (particularly the case for offspring growth trajectory) the fetus cannot adapt directly to ecological signals, but rather to those relating to maternal investment, which is tailored in the interests of maternal as well as offspring fitness.

311

312 **Variability in the timing of exposure**

313 It might be assumed that the maternal capacity for buffering offspring is greatest at the start
314 of pregnancy (when the offspring generates a relatively low metabolic cost) and then
315 reduces in efficacy through pregnancy and lactation as the offspring becomes more costly.
316 On this basis, minimal information about the external environment would be available to the
317 fetus during the earliest windows of development. However, associations of maternal
318 phenotype around the time of conception with epigenetic traits in the offspring suggest a
319 more complex scenario.

320

321 Among rural Gambian women, seasonal variability in maternal blood substrates and methyl-
322 donors, measured around the time of conception, predicted methylation patterns of the
323 offspring [54]. Given that such maternal phenotypes are cyclical and transient, it is not clear
324 how they could facilitate long-term adaptation by the offspring. Moreover, the poorer
325 outcomes of offspring conceived in harsher seasons [55] suggest that mothers may transmit
326 adverse effects to their offspring. Both maternal obesity and micro-nutrient deficiency in the
327 peri-conceptional period may cause subsequent metabolic dysfunction in the offspring [56],
328 indicating adverse consequences of exposing the small number of cells present at this
329 developmental stage to extremes of maternal phenotype, reducing the fitness of both
330 parties.

331

332 Later in pregnancy, maternal buffering becomes more effective, though studies of exposure
333 to fasting or famine during late pregnancy show that the protection is not perfect [36].

However, lactation is metabolically more costly than pregnancy for mothers, and parent-offspring conflict is expected over the schedule of weaning.

Maternal effects and life history trajectory

The generation and consequences of the maternal effects described above can be examined through the lens of life history theory (LHT). This theory assumes that organisms are under selective pressure to harvest resources from the environment throughout the life-cycle, and to allocate them to biological functions to maximise fitness. The most important resources are time and energy, hence the organisms making the best use of energy over the life-span should receive the highest fitness payoffs. Energy is allocated in competition between four functions, namely *maintenance* (broadly equivalent to homeostasis), *growth*, *reproduction* and *defence* against pathogens and predators [57].

First, LHT helps explain variability in maternal investment patterns. The optimal strategy for maternal investment depends on numerous factors, including threats to maternal survival (eg infection), challenges to maternal homeostasis, the stage of her reproductive career, and the mortality risk facing her offspring. Such factors may favour her withholding resources to protect her own survival, or allocating resources across multiple offspring to the detriment of the allocation favoured by each individual offspring. Once again, such variability is not addressed by either conventional constraints or anticipatory approaches.

For example, it is well established that maternal obesity increases the risk of obesity re-occurring in the offspring. However, this inter-generational transmission of phenotype is further mediated by the mother's capacity for homeostasis, which reflects her own

developmental trajectory. A study in Sweden found that the risk of obese mothers having obese offspring was three times greater if the mother had herself been born with low birth weight, compared to normal birth weight [58]. Similarly, maternal developmental trajectory mediates the capacity to invest in offspring across pregnancy versus infancy [59]. These findings highlight how maternal metabolic effects on offspring are sensitive to the mother's own developmental trade-offs.

Second, LHT can be linked with physiological models of disease aetiology to understand associations between the developmental trajectory of offspring and a range of health outcomes. The capacity-load model relates NCD risk to the interaction of two generic traits, 'metabolic capacity' which promotes homeostasis, and 'metabolic load' which challenges homeostasis [60]. Since 'metabolic capacity' primarily develops during early critical windows, it is strongly imprinted by the magnitude and quality of maternal investment.

Low maternal investment constrains the offspring's long-term capacity for homeostasis, making it more susceptible to infections and accelerated aging [23, 61]. Under these circumstances, the best response for the offspring may be to discount the long-term future, and to shunt energy towards reproduction in order to maximise fitness before mortality occurs [61, 62]. This approach helps understand the 'thrifty phenotype' as an evolved developmental strategy. NCDs such as T2DM typically emerge from middle-age onwards, in association with the accumulation of metabolic load that promotes metabolic dysfunction. In environments with high extrinsic mortality risk, a high proportion of individuals would not live long enough to benefit from investing in homeostasis to an extent that would minimise metabolic deterioration in old age. Instead, fitness would be maximised by investing in

382 reproduction, at the cost of ‘maintenance’, and only a small proportion who by random
383 chance survived past middle-age would pay the long-term costs, developing NCDs at post-
384 reproductive ages [63].
385
386 The prediction that offspring should respond to low maternal investment by favouring
387 reproduction at a cost to growth and maintenance was supported in a study of South Asian
388 women living in the UK. Those with lower birth weight showed faster pubertal maturation,
389 shorter adult height, higher adiposity and higher blood pressure. These patterns indicate
390 that daughters developed variable life history strategies in response to their exposure to
391 maternal capital, and that growth and health were traded off in favour of reproductive
392 fitness among those receiving low investment [61]. Rather than the offspring matching their
393 phenotype to prevailing conditions, they demonstrated trade-offs during childhood, that
394 were contingent on prior trade-offs elicited by maternal effects.
395
396 **Developing a multi-stage model**
397 The concept of ‘adaptation’ is closely associated with that of the ecological niche [64].
398 However, while the relationship between niches and species has been discussed extensively,
399 less attention has been paid to the successive niches occupied by individuals through their
400 development [65]. Models of ‘adaptive calibration’ assume that an individual’s
401 developmental trajectory is continually shaped to match the local conditions of the social
402 and physical environment [66]. My aim in this review has been to highlight that exposure to
403 maternal capital during early critical windows of development partially disrupts this
404 calibration process.
405

By definition, capital breeders detach the magnitude and scheduling of maternal investment to some degree from on-going ecological conditions [67], and thereby expose their offspring to other factors. This means that the very concept of how organisms adjust to prevailing ecological conditions deserves reconsideration. To the extent that the genome provides 'information' to each new generation, this relates to traits (including the capacity for plasticity) that promoted fitness in ancestral environments. Phenotypic plasticity then allows more 'contemporary' information to be incorporated into developmental trajectory, but the initial 'unknown' for each offspring comprises the quality and quantity of maternal investment, and adjusting to this information and the associated transfer of resources precedes any direct adjustment to external conditions. It has been suggested that maternal smoothing of ecological signals during early life improves the prediction of adult environments [68], but this was not supported by a mathematical simulation [69].

A three-stage model may therefore offer a better framework for understanding the developmental origins of phenotypic variability. Such a model would recognise a distinction between (a) plastic responses that occur within the period of maternal physiological buffering, and (b) those that occur subsequently through direct exposure to external ecological conditions, whilst also acknowledging that plasticity in the first stage has implications for maternal as well as offspring fitness. Selective pressures in the third stage then act on the cumulative shaping of phenotype in these earlier stages. As discussed above, this approach acknowledges that maternal metabolic effects on offspring during pregnancy may vary in association with the mother's own developmental trajectory and reproductive scheduling [58]. There is increasing understanding that unique maternal signals, such as

429 those deriving from the maternal microbiome and breast-milk oligosaccharides, may be key
430 to these maternal effects.
431
432 I highlight three issues emerging from this approach, which can be tested in future studies
433 on both animal and humans. First, studies could focus in more detail how within a given
434 ecological environment, maternal signals to offspring are mediated by the mother's own
435 developmental trajectory and reproductive career. Maternal life history traits such as size at
436 birth, infant growth rate, age at puberty, adult size and reproductive scheduling all merit
437 attention in this context [22, 50].
438
439 Second, maternal effects on developmental trajectory of the offspring are particularly
440 important to consider when variability in maternal capital relates to social relationships
441 *between* mothers. Both in non-human primates and our own species, maternal rank has
442 been shown to predict contrasting developmental trajectories among offspring [22, 49].
443 Instead of this representing direct adaptation to external conditions, offspring are adjusting
444 their phenotype in relation to their mother's position in the hierarchy. These contrasts in
445 early-life experience have major significance for variability in health through the life course.
446
447 Third, while mechanistic studies in the DOHaD field have tended to focus on 'one exposure
448 at a time', more global indices of maternal capital might prove the best predictors of
449 offspring developmental trajectory. During early life, mothers not only smooth over
450 variability within individual ecological signals, but also provide a composite metabolic niche
451 that reflects exposure to multiple factors acting through the mother's entire life-course.
452 Recognising the composite nature of maternal capital may open up new opportunities to

453 intervene to improve maternal and child health. For example, most efforts to promote fetal
454 and infant nutrition have focused on increasing maternal nutritional intake. An alternative
455 approach, however, is to 'reorganise maternal life history decisions'. For example, a
456 randomized controlled trial aimed to reduce stress and anxiety among healthy first-time
457 mothers, in order to benefit growth of the offspring. The intervention comprised only
458 'relaxation therapy' (regular use of an audio-tape). Those in the intervention group reported
459 lower levels of stress compared to controls, and demonstrated lower levels of cortisol in
460 their breast-milk, while the infants of these mothers gained significantly more weight [70].
461 This study highlights how changing the maternal strategy for transferring capital may benefit
462 the offspring, without any direct alteration to the external environment.
463
464 Finally, an improved understanding of how maternal effects in early life impact both
465 maternal and offspring fitness may also help develop strategies for intervention that benefit
466 both parties. Notably, the relaxation therapy described above did not merely benefit infant
467 growth, but also improved maternal well-being.
468
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