PHILOSOPHICAL TRANSACTIONS B

royalsocietypublishing.org/journal/rstb

Introduction

Cite this article: Kuijper B, Hanson MA, Vitikainen EIK, Marshall HH, Ozanne SE, Cant MA. 2019 Developing differences: early-life effects and evolutionary medicine. *Phil. Trans. R. Soc. B* **374**: 20190039. http://dx.doi.org/10.1098/rstb.2019.0039

Accepted: 29 January 2019

One contribution of 18 to a theme issue 'Developing differences: early-life effects and evolutionary medicine'.

Subject Areas:
developmental biology, evolution, health and disease and epidemiology

Keywords:
developmental plasticity, predictive adaptive response, growth, parental effect, nutrition, epigenetics

Authors for correspondence:
Bram Kuijper
e-mail: a.l.w.kuijper@exeter.ac.uk
Michael A. Cant
e-mail: m.a.cant@exeter.ac.uk

Developing differences: early-life effects and evolutionary medicine

Bram Kuijper[1], Mark A. Hanson[3], Emma I. K. Vitikainen[2,4], Harry H. Marshall[2,5], Susan E. Ozanne[6] and Michael A. Cant[2]

[1]Environment and Sustainability Institute, and [2]Centre for Ecology and Conservation, Penryn Campus, University of Exeter, Penryn TR10 IEZ, UK
[3]Institute of Developmental Sciences and NIHR Southampton Biomedical Research Centre, Southampton University Hospital and University of Southampton, UK
[4]Organismal and Evolutionary Biology Research Programme, Faculty of Biological and Environmental Sciences, University of Helsinki, Helsinki, Finland
[5]Department of Life Sciences, University of Roehampton, London SW15 4JD, UK
[6]University of Cambridge - Department of Clinical Biochemistry, Hills Road, Addenbrookes Level 4, Box 232 Cambridge CB2 2QR, UK

BK, 0000-0002-7263-2846

Variation in early-life conditions can trigger developmental switches that lead to predictable individual differences in adult behaviour and physiology. Despite evidence for such early-life effects being widespread both in humans and throughout the animal kingdom, the evolutionary causes and consequences of this developmental plasticity remain unclear. The current issue aims to bring together studies of early-life effects from the fields of both evolutionary ecology and biomedicine to synthesise and advance current knowledge of how information is used during development, the mechanisms involved, and how early-life effects evolved. We hope this will stimulate further research into early-life effects, improving our understanding of why individuals differ and how this might influence their susceptibility to disease.

This article is part of the theme issue 'Developing differences: early-life effects and evolutionary medicine'.

1. Introduction

This special issue grew out of a meeting held in September 2015 in Falmouth, Cornwall, UK, which brought together evolutionary and biomedical researchers working on early-life effects. In both these fields, researchers have repeatedly demonstrated that experiences during early development can trigger developmental switches that shape anatomy, physiology and behaviour for a lifetime, while potentially also affecting future generations [1–3]. In medicine, developmental plasticity in response to various early-life exposures has been implicated in the development of many non-communicable diseases, including cardiovascular and metabolic diseases (e.g. hypertension, obesity and type 2 diabetes), as well as cancer and neurological conditions [2,4,5]. Understanding the nature of these plastic responses is therefore critical to the early prevention of these diseases and thus of huge social and economic importance.

In evolutionary biology, a substantial amount of thought has been devoted to understanding how natural selection has come to favour plastic responses and what consequences this has [6–8]: indeed, questions highly relevant to medicine—such as why organisms respond to certain environmental stimuli during specific time windows while ignoring others [9,10], why they would remain sensitive to some stimuli much longer than to others [11–13] and how exposure to novel environments affects development [14,15]—are all mainstays in evolutionary theory, with rigorous modelling leading to testable predictions (e.g. review [16] in this issue). Moreover, evolutionary theory also accommodates recent findings in which the developmental environment can

THE ROYAL SOCIETY PUBLISHING

influence subsequent generations [10,17,18], for example, when mediated through a number of pathways, including heritable epigenetic variants (see [19,20] this issue).

Our goal for the meeting was to explore what evolutionary and medical researchers could learn from the different findings and approaches in each other's fields. Conventionally, early-life effects in medicine have been studied with a strong focus on the mechanisms that underlie each pathology in question. While clinically useful, an exclusively descriptive and mechanistic agenda is unlikely to provide us with an understanding of *why* early-life exposures have the effects that they have, which is important to identify the most effective ways of mitigation and to make sense of the large amounts of variation in responses to a range of stimuli within a population [21–24]. 'Why' questions are, however, the meat and drink of evolutionary biologists.

For evolutionary researchers, medical research on model organisms and humans brings a richness of detail on the workings of development and individual phenotypic variation that is often missing from biological studies. Moreover, biomedical research forces evolutionary biologists to think about pathologies and constraints on development, the information available to organisms at different stages of their life history, and the difficulties associated with forecasting the future. Natural selection is a process for maximizing (inclusive) fitness [25], but this is very much a constrained optimization problem—bounded by physical and energetic constraints imposed by the ecological and social environment, by constraints on information, and by the apparatus of genetic and cellular machinery. Medical research offers powerful insights into the workings and constraints of developmental processes and their phenotypic consequences.

Following on from calls by others [23,26,27], this special issue, therefore, aims to place the study of early-life effects within the growing field of evolutionary medicine, which focuses on the question *why* the body becomes susceptible to disease [23,24]. Above and beyond mechanistic studies, evolutionary medicine provides two key insights to the study of pathology: first, natural selection on a certain trait serves to enhance survival to reproduce, rather than health *per se* [23,24]. Second, the response of traits to natural selection is limited by a variety of constraints [28], particularly as natural selection acts not on single traits, but on suites of traits which often have a shared genetic or developmental architecture (pleiotropy) [29]. Taking these evolutionary viewpoints to the study of early-life effects is important, as it allows one to consider how certain adverse health outcomes that are nonetheless associated with high reproductive success can become prevalent in some populations.

In studying the evolutionary origins of early-life effects, evolutionary medicine is necessarily *integrative*, as it (i) is based on a rigorous mathematical theory of evolution that describes how natural selection acts on phenotypic variation. It does so by (ii) considering how different physiological, behavioural and genetic mechanisms drive phenotypic variation on which natural selection acts, (iii) allowing us to generate predictions about how differences in susceptibility arise between individuals and populations, and finally aims to (iv) derive general mechanistic insights by testing these predictions across a broad range of species.

The general feeling at the end of the Cornwall meeting was a combination of enthusiasm and optimism, but also recognition of how much work there is ahead to establish a coherent evolutionary understanding of early-life effects on health in humans. The first step of this task is recognizing the parallels between research in different fields, and the common aims of our endeavours. We also need a common language and set of assumptions about how we test for adaptations and how we think about evolutionary fitness in the field of human health. Hopefully, this collection of papers can help address these first steps, and set the stage for future cross-disciplinary research on the evolved mechanisms and functions of early-life effects.

2. Overview of the issue

The current issue closely follows this integrative approach that lies at the heart of evolutionary medicine to study early-life effects: to this end, the first three contributions of this issue draw on evolutionary theory to predict how organisms should respond to environmental variation throughout the life course [16,30,31]: Gluckman *et al.* [30] assess how different types of mismatches between a phenotype and environment can explain differences in disease aetiology, distinguishing between evolutionary and developmental mismatches. An evolutionary mismatch occurs when a novel environment is encountered that has never been experienced throughout evolutionary history. Suggested examples include the exposure of infants to formula milk as a substitute for breast milk, which is linked to increased rates of obesity and type 2 diabetes in later life [32]. By contrast, developmental mismatches reflect scenarios in which the cue received in early-life incorrectly predicts the future environment. Developmental mismatches build on long-standing ideas of predictive adaptive responses (PARs) and immediately adaptive responses (IARs), in which early-life cues are predictive about selective conditions in later life (PARs) or immediately after the cue has been received (IARs). For example, certain responses to early-life malnutrition (e.g. marasmus [33]) are likely to be the result of a prediction *in utero* of later-life nutritional environments, but will result in malprediction when individuals are faced with nutrition-rich diets later in life (often resulting in metabolic disorders [34]). They then discuss how evolutionary and developmental mismatches may differ in their mitigation.

Next, Frankenhuis *et al.* [16] review the statistical structures of environments which are most conducive to the evolution of early-life effects (focusing particularly on PARs) by building on previous analyses in the context of adaptive parental effects [35]. They review the recent flurry of evolutionary models on PARs, which highlight that environmental cues received in early life need to be sufficiently autocorrelated to later-life environments for such cues to be reliable. Moreover, less reliable cues may need to be sampled for longer, either selectively favouring longer sensitive periods for those cues that are more variable (e.g. [36]) or favouring no developmental plasticity at all [37]. They then highlight that most abiotic environments (e.g. temperature, rainfall) are, in fact, highly unpredictable (i.e. characterized by weak autocorrelations), raising the question of whether PARs involve abiotic cues. Rather, Frankenhuis *et al.* suggest that more future work should focus on social environments—in which the environment is shaped by the individual itself and other members of its social group—as

these are suggested to have much higher autocorrelations. Overall, the review by Frankenhuis *et al.* suggests that future studies should aim to measure many more aspects of environmental variation throughout an individual's life and beyond.

The call by Frankenhuis *et al.* to consider the social environment also dovetails with a theoretical model by Kuijper & Johnstone [31], which considers why social behaviours are commonly found to depend on the level of social adversity experienced in early life. Focusing on an example scenario on the evolution of cooperative breeding, they show that the tendency to help others commonly evolves to depend on social experiences in early life. Moreover, this form of developmental plasticity can have intergenerational consequences: in taxa with non-overlapping generations, a positive feedback occurs, where individuals who received little help themselves are found to be less likely to help others later in life, while individuals who received more help are more likely to help others later. Hence, this leads to intergenerational feedbacks where an individual's helping behaviour may resemble that of previous generations. The situation is, however, more complex in the context of overlapping generations, where such feedbacks are negative instead, with individuals who received little help being more likely to help themselves later. Overall, the model adds weight to the consideration by Frankenhuis *et al.* [16] that social interactions and the composition of the social group should be considered more widely when studying the causes and consequences of developmental plasticity.

Wells [38] argues that the maternal phenotype itself may hamper the evolution of PARs: although offspring stand to benefit from extensive maternal investment during the initial most vulnerable stages of their lives, the flipside is that they open themselves up to investment strategies that benefit maternal, rather than offspring fitness [39]. Wells reviews evidence where interventions that overlook such differences between maternal and offspring optima can lead to counter-intuitive outcomes: for example, a study performed in an Ethiopian population showed that the energy saving measure of installing water taps did not improve child nourishment as intended: rather, the higher energy levels resulted in a higher birth rate and subsequent offspring undernourishment [40], suggesting that the contribution of biological processes to birth rates (particularly in areas without access to modern contraception) has been overlooked. To account for maternal impacts on early-life effects, Wells suggests a three-step model in which offspring developmental plasticity is initially influenced by the maternal phenotype, then the early-life external environment and finally the later-life selective environment. Wells suggests that such a three-stage model is particularly important in scenarios where there is substantial inequality among mothers in resource availability (e.g. social hierarchies). To sum up, these four papers give an overview of how evolutionary processes leading to adaptive predictions of environmental change lie at the forefront of thought in the study of early-life effects.

Continuing with this integrative approach, the issue then moves on to review the *mechanisms* that underlie the relationship between an environmental stimulus in early life and its long-term phenotypic consequences: in this context, Vukic *et al.* [19] review how DNA methylation, histone modification and non-coding RNAs are the major epigenetic mechanisms that mediate gene regulation changes in response to environmental exposures. While the majority of these modifications are reset either during the development of the primordial germ cells or during early embryonal development [41], some modifications can survive this reprogramming stage, potentially paving the way for long-term inheritance (e.g. [42]), although few findings exist, so far, of this phenomenon in humans. Vukic *et al.* discuss how nutritional influences and stress in mammalian model systems change epigenetic modifications; data on differential DNA methylation in humans points in the same direction, although a causal link between epigenetic modifications and later-life phenotypes is yet to be made. Vukic *et al.* make several recommendations for future analyses, noting in particular that repetitive regions are often excluded from bioinformatic analyses, whereas those regions appear to be particularly resistant to epigenetic reprogramming during development.

While most of the current work on intergenerational and transgenerational effects focuses on maternal transmission, Baxter & Drake [20] review recent research on the epigenetic mechanisms that facilitate transgenerational effects through fathers. An emerging message is that exposure of males to some (but not all) early-life environmental insults indeed produces epigenetic modifications in sperm, and changes in the phenotypes of offspring sired by these. However, a causal link between sperm epigenetic modifications and offspring phenotypic variation is yet to be established: for example, it is hitherto unknown whether and how paternally inherited histone modifications can indeed survive the epigenetic reprogramming stages in early development. More recent studies suggest that RNAs might well be the more important epigenetic mechanism that mediates paternal influences on the offspring's phenotype. However, Baxter and Drake also argue the need to consider other, non-epigenetic mechanisms (e.g. paternal influences on maternal behaviour) by which fathers may affect offspring phenotypes and which currently receive little consideration.

Hormones are another major mechanism with which mothers influence offspring phenotypes. Hence, Groothuis *et al.* [43] focus on maternal hormones in avian systems. As in birds the embryo develops outside the mother, they are particularly amenable to study the effect of maternal hormones, illustrating why an integrative approach that relies on inferences taken across a broad range of species may provide insights above and beyond studies taking a singular, human-centred focus. Groothuis *et al.* highlight that the time of postulating simple, univariate hypotheses about the phenotypic consequences of hormones is now well and truly over, urging for a framework that embraces the complexity inherent to hormone-mediated maternal effects. There is now an accumulation of studies which find interactions among hormones themselves (or between hormones and other allocation components such as egg yolk), which suggest that hormones are not necessarily cost-free (as is the assumption in many models) but that trade-offs between hormones and other allocation components needs to be considered. Hence, evolutionary models which assume that a single maternal hormone predicts the prevalent environment may be too simplistic; hence, a multivariate theory of hormonal effects is needed in order to make more realistic predictions.

Vukic *et al.* [19], Baxter & Drake [20] and Groothuis *et al.* [43] review findings where parents influence the phenotypes of their offspring or later descendants through epigenetic

modifications or hormones (see also other reviews in this issue, e.g. [5,44]). These intergenerational effects (or transgenerational effects when effects last until generation F_3 and beyond [45]) thus give rise to acquired inheritance, where an environmental exposure has phenotypic consequences that spans more than one generation. Danchin *et al.* [46] ask how such ideas of acquired inheritance can be reconciled with classical gene-centric views of inheritance, suggesting that each of these inheritance systems reflects adaptation to variable environments that change at different timescales (see also [47]). Anticipatory parental effects driven by hormones, for example, allow for adaptation to environments that fluctuate extremely rapidly, while the stable transmission of genetic variants facilitates adaptation to environments that fluctuate over the course of 1000s of generations. Owing to its inherent stability, genetic variation is therefore often considered to be the only factor underlying adaptation (see [48] for an essential review that brings a healthy dose of scepticism to studies of acquired inheritance). However, Danchin *et al.* [46] point out that it is exactly because of the stability of genetic inheritance that we are able to observe different genetic variants (as they persist for numerous generations) and measure their long-term impact on adaptation. By contrast, measuring how epigenetic variants affect long-term adaptation is much more difficult, as their instability implies that any fitness effects play out over the short term. This does not necessarily imply that epigenetic variants are therefore unimportant to adaptation, as spontaneously arising epigenetics that may currently seem neutral may well do the leg work of adaptation during an environmental perturbation, only to become selectively neutral again after genetic accommodation. Overall, more work thus remains to be done to assess the relative importance of acquired inheritance in populations that adapt to a changing world.

Following these mechanistic insights, we then move on to testing evolutionary predictions about early-life effects, both in the laboratory and the wild. Crucially, at the heart of evolutionary medicine lies a comparative approach, in which insights are obtained by comparing early-life effects and their consequences across multiple species. To this end, the current issue contains novel work on early-life effects in organisms ranging from nematode worms, cichlid fish, wild populations of meerkats and mongooses, to humans. Novel work from Lev *et al.* [49] focuses on how exposure to liquid versus solid environments in the nematode model organism *Caenorhabditis elegans* has effects on morphology on subsequent generations. They show that worms grown in a liquid environment produce offspring that are much longer than controls, even when those offspring themselves grown in a solid environment. Moreover, these effects are immediately apparent upon hatching, suggesting that it is not just a matter of a more rapid rate of development that affects the morphology of offspring born from liquid-grown worms. To understand the mechanism, they repeated the experiments using a broad variety of mutant strains, focusing on mutants that are either impaired in their ability to obtain cues about the environment (e.g., pheromone biosynthesis or chemosensation), or mutants which have an impaired ability to transmit any inter- or transgenerational signals through small RNAs or chromatin modifications (*C. elegans* lacks conventional forms of DNA methylation). Interestingly, none of the mutants affected this intergenerational phenotype in the offspring of liquid-grown worms, suggesting that another mechanism (e.g., metabolites or hormones) is mediating this effect. Lev *et al.* [49] also assessed and investigated the presence of any transgenerational effects (lasting up to generation F_3 or longer), finding that effects on morphology were either much weaker or absent. Overall, this study shows that intergenerational effects may be conveyed by an even broader range of molecular mechanisms (e.g., metabolites vs hormones vs small RNAs vs chromatin modifications), raising the question why particular traits become affected by one mechanism versus another.

Next, Reyes-Contreras *et al.* [50] use pharmacological manipulations in a cooperatively breeding cichlid (*Neolamprologus pulcher*) to determine the causal mechanisms by which early-life stress affects later life behaviour. Fish were either exposed to the stress hormone cortisol or to the glucocorticoid-receptor blocker mifepristone in early life, which both impact on the main physiological stress axis in fishes (the HPI axis – analogous the HPA axis in mammals and birds). Interestingly, neither exposure to cortisol and mifepristone affected behaviour in early life. By contrast, in later life, cortisol-treated fish were more aggressive and had longer contests with others. Effects of mifepristone were more complex, as neither later life aggression nor the duration of contests were relative to controls. However, mifepristone influenced the likelihood that a fish would win contests, dependent on the individual's inherent stress responsiveness. Finally, the early-life exposure to both cortisol and mifepristone affected the expression of key genes (*mr* and crf) of the HPI axis during later life. This work is an important step towards understanding the mechanisms that mediate how early life stresses affect later life behaviour.

The issue also includes two studies of early-life effects in wild animal populations. Studies of wild animals living in the environment in which they evolved are a powerful complement to laboratory studies of model organisms [51]. They offer a way to measure the fitness impacts of variation in early life conditions, and test evolutionary hypotheses about the causes and consequences of developmental responses. Dantzer *et al.* [52] show that a manipulation of early-life maternal hormone exposure affects later-life cooperative behaviour in a female, but not male, meerkats (*Suricatta suricatta*). Their findings suggest that these early-life effects may be in the interests of parents, but not offspring. Vitikainen *et al.* [53] show that banded mongoose offspring (*Mungos mungo*) that receive more care and attention from helpers during a six week period in early life are heavier at sexual maturity, and in the case of females, go on to produce more surviving offspring across their lifetime. These 'durable benefits' of care are manifest long after the initial helping act, often after the helper has died, which has important implications for the evolution of parental and alloparental care.

Moving on from wild animal populations, the next collection of studies takes a more human-oriented focus. First, the review by Nicholas & Ozanne [44] shows how mouse models can help us obtain insights about the mechanisms that mediate how maternal obesity affects metabolic programming in offspring and what interventions are likely to be most effective. Giving mice a high-fat/high-sugar diet (HFD) induces various metabolic changes in their offspring (e.g., increased adiposity, hyperinsulinaemia/hyperglycaemia), but the precise effects depend on the timing of the

maternal nutritional exposure as well as on the sex of the offspring (potentially mediated by sex hormones). Underlying mechanisms may involve changes in DNA methylation (as demonstrated by the well-studied agouti viable yellow locus Kazachenka *et al.* [54]), but Nicholas & Ozanne also raise the exciting possibility that epigenetic modifications in the mtDNA or changes in miRNAs play a role in metabolic programming.

Next, Fall & Kumaran [5] review patterns of metabolic programming in humans, along with current knowledge about the effect of interventions and the underlying epigenetic mechanisms. Long-term consequences of fetal undernutrition, carryover effects of maternal overweight and diabetes and how they relate to patterns of post-natal weight gain are a key research focus. A general finding is that the highest risk of metabolic disease is consistently found in those individuals who started off with a low birth weight but became relatively heavy in later life. Fall & Kumaran [5] highlight that most studies which assessed the effect of metabolic interventions in early-life lack follow-up studies throughout the life course of children. Where a follow-up study exists, evidence that interventions affect metabolic outcomes in offspring is mixed. As it emerges that many early-life effects originate around the time of conception [4], Fall & Kumaran [5] suggest that future studies should focus on an earlier timing of these interventions (e.g. before or around conception). Regarding the study of the underlying mechanisms, Fall & Kumaran [5] also stress that despite accumulating research, there are currently no studies in humans that have demonstrated the full chain of events, starting from an intervention which results in an epigenetic modification to modifications in gene expression and a resulting disease-related phenotype.

As undertaking such causal studies will be difficult in humans, Hannon *et al.* [55] use an epigenomic association study (EWAS; [56]) to assess whether epigenomic modifications could mediate the relationship between maternal smoking and offspring birth weight using an existing collection of neonatal blood spot samples collected shortly after birth from over 1300 neonates. Measuring differential DNA methylation, they find 18 differentially methylated positions (DMPs) that are associated with birth weight, and 110 DMPs which are associated with maternal smoking. They then use a mediator-approach, derived from structural equation modelling [57], to find that three DMPs are likely to mediate how maternal smoking leads to low birth weight, shedding light on the mechanism with which early-life environmental insults change regulation. They suggest that differential DNA methylation, when measured as early as possible in life, can serve as a biomarker of early-life exposure that would be highly valuable to the study of early-life effects.

The studies by Sear *et al.* [58] and Williams & Drake [59] use published data on human health and fertility from across the globe to evaluate evidence that human life history has been shaped by adaptive early-life effects. Sear *et al.* [58] examine the relationship between father's absence and age at first menarche in girls, and in particular the hypothesis that father's absence should be associated with earlier age at menarche because it is an indicator of an unstable social environment [60]. Sear *et al.* [58] show that previous empirical support for this hypothesis is largely restricted to WEIRD human datasets (Western, Educated, Industrialised, Rich, Democratic [61]), and that data on hunter–gatherers and other small scale human societies offer a more complex picture. Williams & Drake [59] present a wide-ranging review of the literature on preterm birth (i.e. birth prior to week 37 of gestation) and ask whether variation in rates of preterm birth and its consequences can be explained if early birth is an IAR to conditions experienced *in utero*, or a PAR to anticipated future conditions. They show that preterm birth is associated with predictable changes in adult physiology. However, as with many other studies, testing whether these changes are adaptive remains difficult given the lack of detailed information about life-history trajectories and fitness in human datasets.

We hope that, taken together, the papers in this special issue demonstrate the benefits of interdisciplinary research between the fields of developmental effects and evolutionary biology, as applied to evolutionary medicine. Such collaborations have great potential not only for understanding the processes underlying the evolution of developmental plasticity but also for current and future human health and the prevention of disease.

Data accessibility. This article has no additional data.

Competing interests. We declare we have no competing interests.

Funding. The workshop in Cornwall that resulted in this special issue was funded by NERC grant no. NE/J010278/1 to M.A.C. B.K. is funded by a Leverhulme Trust Early Career Fellowship (ECF 2015-273), and E.I.K.V. by the Ella and Georg Ehrnrooth Foundation. M.A.H. is supported by the British Heart Foundation.

Acknowledgements. We thank all authors for their contributions to this theme issue. We are indebted to the senior commissioning editor Helen Eaton for all her support and hard work during the preparation of this theme issue.

References

1. Barker DJP, Thornburg KL. 2013 The obstetric origins of health for a lifetime. *Clin. Obstet. Gynecol.* **56**, 511–519. (doi:10.1097/GRF.0b013e31829cb9ca)
2. Hanson MA, Gluckman PD. 2014 Early developmental conditioning of later health and disease: physiology or pathophysiology? *Physiol. Rev.* **94**, 1027–1076. (doi:10.1152/physrev.00029.2013)
3. Godfrey KM, Reynolds RM, Prescott SL, Nyirenda M, Jaddoe VW V, Eriksson JG, Broekman BFP. 2017 Influence of maternal obesity on the long-term health of offspring. *Lancet Diabetes Endocrinol.* **5**, 53–64. (doi:10.1016/s2213-8587(16)30107-3)
4. Fleming TP *et al.* 2018 Origins of lifetime health around the time of conception: causes and consequences. *Lancet* **391**, 1842–1852. (doi:10.1016/S0140-6736(18)30312-X)
5. Fall CHD, Kumaran K. 2019 Metabolic programming in early life in humans. *Phil. Trans. R. Soc. B* **374**, 20180123. (doi:10.1098/rstb.2018.0123)
6. Scheiner SM. 1993 Genetics and evolution of phenotypic plasticity. *Annu. Rev. Ecol. Syst.* **24**, 35–68. (doi:10.1146/annurev.es.24.110193.000343)
7. West-Eberhard MJ. 2003 *Developmental plasticity and evolution*. New York, NY: Oxford University Press.
8. Chevin L-M, Lande R, Mace GM. 2010 Adaptation, plasticity, and extinction in a changing environment: towards a predictive theory. *PLoS Biol.* **8**, e1000357. (doi:10.1371/journal.pbio.1000357)

9. McNamara JM, Dall SRX, Hammerstein P, Leimar O. 2016 Detection vs. selection: integration of genetic, epigenetic and environmental cues in fluctuating environments. *Ecol. Lett.* **19**, 1267–1276. (doi:10.1111/ele.12663)
10. Rivoire O, Leibler S. 2014 A model for the generation and transmission of variations in evolution. *Proc. Natl Acad. Sci. USA* **111**, E1940–E1949. (doi:10.1073/pnas.1323901111)
11. English S, Fawcett TW, Higginson AD, Trimmer PC, Uller T. 2016 Adaptive use of information during growth can explain long-term effects of early life experiences. *Am. Nat.* **187**, 620–632. (doi:10.1086/685644)
12. Frankenhuis WE, Panchanathan K. 2011 Balancing sampling and specialization: an adaptationist model of incremental development. *Proc. R. Soc. B* **278**, 3558–3565. (doi:10.1098/rspb.2011.0055)
13. Fischer B, Van Doorn GS, Dieckmann U, Taborsky B. 2014 The evolution of age-dependent plasticity. *Am. Nat.* **183**, 108–125. (doi:10.1086/674008)
14. Lande R. 2009 Adaptation to an extraordinary environment by evolution of phenotypic plasticity and genetic assimilation. *J. Evol. Biol.* **22**, 1435–1446. (doi:10.1111/j.1420-9101.2009.01754.x)
15. Snell-Rood EC, Kobiela, ME, Sikkink, KL, Shephard AM. 2018 Mechanisms of plastic rescue in novel environments. *Annu. Rev. Ecol. Evol. Syst.* **49**, 331–354. (doi:10.1146/annurev-ecolsys-110617-062622)
16. Frankenhuis WE, Nettle D, Dall SRX. 2019 A case for environmental statistics of early-life effects. *Phil. Trans. R. Soc. B* **374**, 20180110. (doi:10.1098/rstb.2018.0110)
17. Kuijper B, Hoyle RB. 2015 When to rely on maternal effects and when on phenotypic plasticity? *Evolution* **69**, 950–968. (doi:10.1111/evo.12635)
18. Leimar O, McNamara JM. 2015 The evolution of transgenerational integration of information in heterogeneous environments. *Am. Nat.* **185**, E55–E69. (doi:10.1086/679575)
19. Vukic M, Wu H, Daxinger L. 2019 Making headway towards understanding how epigenetic mechanisms contribute to early-life effects. *Phil. Trans. R. Soc. B* **374**, 20180126. (doi:10.1098/rstb.2018.0126)
20. Baxter FA, Drake AJ. 2019 Non-genetic inheritance via the male germline in mammals. *Phil. Trans. R. Soc. B* **374**, 20180118. (doi:10.1098/rstb.2018.0118)
21. Omenn GS. 2010 Evolution and public health. *Proc. Natl Acad. Sci. USA* **107**, 1702–1709. (doi:10.1073/pnas.0906198106)
22. Wells JCK, Johnstone RA. 2017 Modeling developmental plasticity in human growth: buffering the past or predicting the future? In *The Arc of life* (eds G Jasienska, D Sherry, D Holmes), pp. 21–39. New York, NY: Springer New York.
23. Gluckman P, Beedle A, Buklijas T, Low F, Hanson M. 2016 *Principles of evolutionary medicine*. Oxford, UK: Oxford University Press.
24. Stearns SC, Medzhitov R. 2015 *Evolutionary medicine*. Oxford, UK: Oxford University Press.
25. West SA, Gardner A. 2013 Adaptation and inclusive fitness. *Curr. Biol.* **23**, R577–R584. (doi:10.1016/j.cub.2013.05.031)
26. Gluckman PD, Hanson MA. 2004 Living with the past: evolution, development, and patterns of disease. *Science* **305**, 1733–1736. (doi:10.1126/science.1095292)
27. Wells JCK, Nesse RM, Sear R, Johnstone RA, Stearns SC. 2017 Evolutionary public health: introducing the concept. *Lancet* **390**, 500–509. (doi:10.1016/S0140-6736(17)30572-X)
28. Arnold SJ. 1992 Constraints on phenotypic evolution. *Am. Nat.* **140**, S85–S107. (doi:10.1086/285398)
29. Walsh B, Blows MW. 2009 Abundant genetic variation + strong selection = multivariate genetic constraints: a geometric view of adaptation. *Annu. Rev. Ecol. Evol. Syst.* **40**, 41–59. (doi:10.1146/annurev.ecolsys.110308.120232)
30. Gluckman PD, Hanson MA, Low FM. 2019 Evolutionary and developmental mismatches are consequences of adaptive developmental plasticity in humans and have implications for later disease risk. *Phil. Trans. R. Soc. B* **374**, 20180109. (doi:10.1098/rstb.2018.0109)
31. Kuijper B, Johnstone RA. 2019 The evolution of early-life effects on social behaviour—why should social adversity carry over to the future? *Phil. Trans. R. Soc. B* **374**, 20180111. (doi:10.1098/rstb.2018.0111)
32. Victora CG *et al*. 2016 Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. *Lancet* **387**, 475–490. (doi:10.1016/S0140-6736(15)01024-7)
33. Shetty P. 2006 Malnutrition and undernutrition. *Medicine* (*Baltimore*) **34**, 524–529. (doi:10.1053/j.mpmed.2006.09.014)
34. Boyne MS, Francis-Emmanuel P, Tennant IA, Thompson DS, Forrester TE. 2017 Cardiometabolic risk in Marasmus and Kwashiorkor survivors. In *Handbook of famine, starvation, and nutrient deprivation* (eds V Preedy, VB Patel), pp. 1–23. Cham, Switzerland: Springer International Publishing.
35. Burgess SC, Marshall DJ. 2014 Adaptive parental effects: the importance of estimating environmental predictability and offspring fitness appropriately. *Oikos* **123**, 769–776. (doi:10.1111/oik.01235)
36. Panchanathan K, Frankenhuis WE. 2016 The evolution of sensitive periods in a model of incremental development. *Proc. R. Soc. B* **283**, 20152439. (doi:10.1098/rspb.2015.2439)
37. Nettle D, Frankenhuis WE, Rickard IJ. 2013 The evolution of predictive adaptive responses in human life history. *Proc. R. Soc. B* **280**, 20131343. (doi:10.1098/rspb.2013.1343)
38. Wells JCK. 2019 Developmental plasticity as adaptation: adjusting to the external environment under the imprint of maternal capital. *Phil. Trans. R. Soc. B* **374**, 20180122. (doi:10.1098/rstb.2018.0122)
39. Marshall JD, Uller T. 2007 When is a maternal effect adaptive? *Oikos* **116**, 1957–1963. (doi:10.1111/j.2007.0030-1299.16203.x)
40. Gibson MA, Mace R. 2006 An energy-saving development initiative Increases birth rate and childhood malnutrition in rural Ethiopia. *PLoS Med.* **3**, e87. (doi:10.1371/journal.pmed.0030087)
41. Tang WWC, Kobayashi T, Irie N, Dietmann S, Surani MA. 2016 Specification and epigenetic programming of the human germ line. *Nat. Rev. Genet.* **17**, 585–600. (doi:10.1038/nrg.2016.88)
42. Guo F *et al*. 2015 The transcriptome and DNA methylome landscapes of human primordial germ cells. *Cell* **161**, 1437–1452. (doi:10.1016/j.cell.2015.05.015)
43. Groothuis TGG, Hsu B-Y, Kumar N, Tschirren B. 2019 Revisiting mechanisms and functions of prenatal hormone-mediated maternal effects using avian species as a model. *Phil. Trans. R. Soc. B* **374**, 20180115. (doi:10.1098/rstb.2018.0115)
44. Nicholas LM, Ozanne SE. 2019 Early life programming in mice by maternal overnutrition: mechanistic insights and interventional approaches. *Phil. Trans. R. Soc. B* **374**, 20180116. (doi:10.1098/rstb.2018.0116)
45. Skinner MK. 2008 What is an epigenetic transgenerational phenotype? F3 or F2. *Reprod. Toxicol.* **25**, 2–6. (doi:10.1016/j.reprotox.2007.09.001)
46. Danchin É, Pocheville A, Huneman P. 2019 Early in life effects and heredity: reconciling neo-Darwinism with neo-Lamarckism under the banner of the inclusive evolutionary synthesis. *Phil. Trans. R. Soc. B* **374**, 20180113. (doi:10.1098/rstb.2018.0113)
47. Rando OJ, Verstrepen KJ. 2007 Timescales of genetic and epigenetic inheritance. *Cell* **128**, 655–668. (doi:10.1016/j.cell.2007.01.023)
48. Charlesworth D, Barton NH, Charlesworth B. 2017 The sources of adaptive variation. *Proc. R. Soc. B* **284**, 20162864. (doi:10.1098/rspb.2016.2864)
49. Lev I, Bril R, Liu Y, Ceré LI, Rechavi O. 2019 Intergenerational consequences for growing *Caenorhabditis elegans* in liquid. *Phil. Trans. R. Soc. B* **374**, 20180125. (doi:10.1098/rstb.2018.0125)
50. Reyes-Contreras M, Glauser G, Rennison DJ, Taborsky B. 2019 Early-life manipulation of cortisol and its receptor alters stress axis programming and social competence. *Phil. Trans. R. Soc. B* **374**, 20180119. (doi:10.1098/rstb.2018.0119)
51. Clutton-Brock T, Sheldon BC. 2010 Individuals and populations: the role of long-term, individual-based studies of animals in ecology and evolutionary biology. *Trends Ecol. Evol.* **25**, 562–573. (doi:10.1016/jtree.2010.08.002)
52. Dantzer B *et al*. 2019 The development of individual differences in cooperative behaviour: maternal glucocorticoid hormones alter helping behaviour of offspring in wild meerkats. *Phil. Trans. R. Soc. B* **374**, 20180117. (doi:10.1098/rstb.2018.0117)
53. Vitikainen EIK, Thompson FJ, Marshall HH, Cant MA. 2019 Live long and prosper: durable benefits of early-life care in banded mongooses. *Phil. Trans. R. Soc. B* **374**, 20180114. (doi:10.1098/rstb.2018.0114)

54. Kazachenka A *et al*. 2018 Identification, characterization, and heritability of murine metastable epialleles: implications for non-genetic inheritance. *Cell* **175**, 1259–1271.e13. (doi:10.1016/j.cell.2018.09.043)
55. Hannon E *et al*. 2019 Variable DNA methylation in neonates mediates the association between prenatal smoking and birth weight. *Phil. Trans. R. Soc. B* **374**, 20180120. (doi:10.1098/rstb.2018.0120)
56. Murphy TM, Mill J. 2014 Epigenetics in health and disease: heralding the EWAS era. *Lancet* **383**, 1952–1954. (doi:10.1016/S0140-6736(14)60269-5)
57. Baron RM, Kenny DA. 1986 The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J. Pers. Soc. Psychol.* **51**, 1173–1182. (doi:10.1037/0022-3514.51.6.1173)
58. Sear R, Sheppard P, Coall DA. 2019 Cross-cultural evidence does not support universal acceleration of puberty in father-absent households. *Phil. Trans. R. Soc. B* **374**, 20180124. (doi:10.1098/rstb.2018.0124)
59. Williams TC, Drake AJ. 2019 Preterm birth in evolutionary context: a predictive adaptive response? *Phil. Trans. R. Soc. B* **374**, 20180121. (doi:10.1098/rstb.2018.0121)
60. Draper P, Harpending H. 1982 Father absence and reproductive strategy: an evolutionary perspective. *J. Anthropol. Res.* **38**, 255–273. (doi:10.1086/jar.38.3.3629848)
61. Henrich J, Heine SJ, Norenzayan A. 2010 The weirdest people in the world? *Behav. Brain Sci.* **33**, 61–83. (doi:10.1017/S0140525X0999152X)