RICKARD, I.J. & LUMMAA V. 2007: The Predictive Adaptive Response and metabolic syndrome: Challenges for the hypothesis. Trends in Endocrinology & Metabolism. 18 (3): 94-99

The Predictive Adaptive Response and metabolic syndrome: Challenges for the hypothesis

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In humans, and other mammals, maternal undernutrition or stress during gestation results in small offspring with permanently altered metabolism and tissue composition. It has been suggested that such responses may exist because *in utero* conditions provide a reliable 'prediction' of the environmental conditions that fetuses will eventually be exposed to during adulthood. Thus some developmental responses to early environment may improve an individual's evolutionary success in a similar future environment. We consider the evidence in favour of predictive adaptive responses in the light of competing hypotheses and suggest testable predictions for distinguishing between them.

Introduction

Variation in the environmental conditions experienced by fetuses and neonates can have extensive and permanent consequences for their phenotype (see Glossary) in adulthood[1]. Numerous studies have reported inverse relationships between measures of prenatal growth, such as weight and length at birth, and the risk of developing diseases such as coronary heart disease and type II diabetes in adulthood (collectively known as metabolic syndrome)[2]. Experimental manipulation of laboratory animals has confirmed the general pattern that such relationships are causal and occur largely because of increased insulin resistance in those poorly nourished in early life[3]. An intriguing additional observation is that the effects appear to be exacerbated when the individual is well-nourished postnatally[4, 5].

One hypothesis that has been proposed recently to account for these observations is that rather than being an inevitable consequence of a poor early environment, insulin resistance is actually deliberately induced during development because it confers an advantage. According to this view, genes promoting the induction of insulin resistance in response to some early fetal environments, along with other co-occurring traits (Table 1), have been favoured in ancestral humans because they collectively form a phenotype which would have improved survival under sub-optimal conditions[6, 7]. For example, insulin resistance would reduce basal metabolic requirements[6]. Most importantly, it is proposed that the advantages of this 'survival phenotype' are gained not immediately but during reproductive life[6, 8] so that a fetus which 'chooses' to develop according to this pathway uses current circumstances to predict future environmental conditions.

It has been proposed that there would be negative consequences of the 'survival phenotype' strategy only when the adult environment, provided, an abundant food resource (a mismatch between the predicted and realised environments)[6, 9]. Thus individuals who based their development on the expectation of poor conditions but found themselves in a resource-rich environment would experience both insulin resistance and high plasma levels of glucose, a risk factor for the development of metabolic syndrome and type II diabetes. This hypothesis thus would account for the abundance of metabolic syndrome in societies undergoing rapid industrialisation[8] and for the observations that incidences of adult coronary heart disease[4] and type II diabetes[5] correlate on a continuous scale with childhood growth rate, i.e. the greatest risks befalling those who were small at birth but received good nutrition postnatally.

It has also been suggested[10] that a mismatch between pre- and postnatal conditions may explain the differences in adulthood disease risk of those who were *in utero* during two separate World War II civilian famines, the Dutch Hunger Winter (1944-1945) and the Siege of Leningrad (1941-1944). In the case of the former, those who were starved prenatally had impaired glucose tolerance in adulthood[11], whereas no comparable effects occurred in the latter case[12]. One interpretation of this is that while in both cases, fetuses 'predicted' a poor postnatal environment, and initiated development of the 'survival phenotype', the prediction only proved to be accurate in the case of Leningrad, where the famine lasted for years rather than months, and nutrition remained poor in subsequent years[10]. The Dutch Hunger Winter was

Glossary

Phenotype	The characteristics of an organism, resulting from the combination of genotype and environment
Trait	A single phenotypic character
Prediction	An assessment of future environmental conditions
Adaptive	The quality of a given trait of increasing fitness in a specific environment
Plasticity	The capacity of a trait to be influenced by environmental variation. Here, used in the context of developmental plasticity, in which the environmental influence on a trait is permanent
Fitness	The contribution of an individual's genotype to the next generation, relative to that of other genotypes. A function of both survival and reproductive success.
Selective pressure	An aspect of environment or demography that imposes selection for or against traits
Life-history	The pattern of allocation of resources into growth, somatic maintenance and reproductive events across lifetime

relatively brief by comparison, and nutrition improved quickly, leading to a 'mismatched' and disease-prone adult phenotype in this group.

In a broader context, the 'survival phenotype' is just one proposed example of a 'Predictive Adaptive Response' (PAR), whereby a developing individual makes permanent changes to aspects of its physiology or anatomy that are advantageous in a predicted future reproductive environment. The PAR model has been alluded to in a number of empirical and theoretical papers addressing not just characteristics of the metabolic syndrome[13] but also ovarian suppression[14], the aetiology of Down syndrome[15] and variation in menarcheal age[16].

However, there is a notable lack of direct tests of the PAR model and consideration of competing hypotheses that are also consistent with the above observations[17, 18]. Thus, using the 'survival phenotype' as an example, we here: (i) place the PAR hypothesis in the context of adaptive developmental processes observed in other species, (ii) stress the need to evaluate both the benefits and costs of the developmental changes suggested to be associated with PARs when evaluating the likelihood that such long-term predictions of the adulthood environment could evolve; (iii) specify competing hypotheses for the developmental origins of metabolic syndrome and; (iv) describe the predictions of these hypotheses and suggest the means of testing them.

We hope that in this short article, we will encourage interdisciplinary efforts to investigate the evolutionary significance of variation in human developmental processes, as well as improved mutual understanding at the interface of evolutionary biology and human epidemiology.

Adaptive developmental plasticity

Adaptive developmental plasticity, by which developing individuals adopt permanently different phenotypic characteristics in response to prevailing

Table 1: 'survival phenotype' traits and their proposed adaptive benefits.

Compiled from reference [6].

Trait	**Possible adaptive value**
Insulin resistance	Reduces energy invested into growth and metabolism
A preference to lay down visceral fat	Emergency fuel reserve, acting as a buffer in unpredictable conditions
Reduced skeletal muscle mass	Decreases energetic demands of maintaining adult body and frees up resources for survival and reproduction
Reduced capillary density in some tissues	Reduced postnatal food availability equates to less exchange of nutrients and hormones between organs and tissues
Reduced nephron number	Appropriate to smaller body size and smaller kidneys
Reduced negative feedback in the hypothalamic-adrenal axis	Heightened stress response allows greater chance of survival in a nutrient-deprived and therefore predator rich environment

environment to increase survival and reproductive success has been documented in many animal species[19]. A special case of such plasticity occurs when the benefits of the alternative developmental pathways are not gained at the time the developmental 'decision' is made, but at a subsequent time. Such examples satisfy the one criterion that distinguishes PARs from other instances of developmental plasticity, specifically that they lead to an improvement in fitness in a predicted reproductive environment[6, 8]. However, these examples come from organisms which are significantly more short-lived than humans, such that either the environment remains relatively constant between development and reproduction, or relationships between environmental characteristics covary reliably. Such circumstances provide 'foolproof' circumstances under which predictions can be made. Considering that in humans, the start of reproduction is separated from early development by more than a decade, and that reproductive lifespan is decades long, is it likely that PARs could evolve in our species?

In the context of the 'survival phenotype', the answer to this question has implications for both evolutionary biology and epidemiology. Regarding the former, prediction of environmental conditions made during early life would need to remain reasonably accurate for decades. This implies a degree of foresight rare in any analogous process in other species, and thus demands investigation from an evolutionary perspective. Regarding the latter, prevention and treatment of type II diabetes and coronary heart disease rests on understanding the relationship between developmental and adult environments. The question of whether an attempt by a fetus to predict the adult environment is worthwhile can be addressed by comparing the future benefits against the immediate (and potential future) costs.

Benefits and costs of PARs

Both the potential benefits and the costs of the developmental changes suggested to be associated with PARs need to be considered when evaluating the likelihood that predictive processes can evolve. The benefits of forecasting the future environment are dependent on the probability that the forecast will be accurate, because the costs of inaccurate prediction will be high[20]. Individuals who incorrectly 'choose' a metabolism 'designed' for a nutritionally poor environment, but who find themselves in a rich one, would be at a competitive disadvantage when compared to individuals who do not make such an inaccurate prediction. Furthermore, maintaining the developmental pathways necessary for plasticity itself carries a physiological cost[21] and therefore plastic traits are not always favoured over fixed traits. In short, for the capacity for choice to be maintained, each choice must offer particular advantages under particular conditions.

In order for PARs to evolve, fluctuation in the appropriate environmental variable(s) must fulfil specific criteria: The variation must be of a frequency high enough to maintain the selective advantage of plasticity[22] but low enough to ensure relative stability across a small number of generations. For example, predictable high frequency variation in the form of seasonality impacts upon mortality rates of children and adults in agricultural[23] and industrialised[24] societies, and is likely to have been a constant influence throughout hominid evolution[25]. However, given that human gestation lasts nine months and the most vulnerable periods of postnatal life immediately follow this[26-28], seasonal variation in environmental conditions is more

Box 1: Human life-history

Reconstructing ancestral human life-history is problematic because of (i) the relatively rapid demographic changes since the advent of agriculture in the middle east 10,000 years ago, (ii) the variability of some key life-history traits in populations living under 'natural conditions' and (iii) the unreliability of deducing population age-structure from skeletal remains[29]. However, progress can be made on this question by considering life-history characteristics conserved amongst primates. First, because primates tend to practice extended parental care, natural selection should select for parents to survive for the dependent portion of their offspring's lifetime. Second, in mammals that tend to produce one offspring per reproductive event, selection must favour several reproductive episodes per female, multiplying the power of selection on parental survival. Third, survival during early life is particularly important (Figure I). This additionally increases selection for parental survival further. Finally, there is also evidence that survival beyond reproductive years in humans may be selected for to provide assistance with the rearing of grandchildren[30].

We can pursue this question still further by considering differences between the life-histories of humans and the other primates. In the context of the PAR hypothesis, it has been argued that as recently as the late Pleistocene (126,000-10,000 years ago), age at reproductive competency was reached between the ages of 9 and 14 years, with life expectancy of 25 years, implying a life-history pattern more similar to that of chimpanzees than that observed in any contemporary human population[31]. In contrast, a recent meta-analysis of 22 hunter-gatherer and small-scale societies worldwide revealed female ages of first reproduction varying between 16 years and 26 years, with female life expectancy (at age 15) varying between 27 and 50 years[32]. The high degree of variation complicates estimating the ancestral human life-history pattern. However, the observed ranges, together with other shared life-history characteristics such as early weaning and shorter interbirth intervals compared with other primates, a prolonged juvenile period, and similar age at menopause across populations, suggest a broadly conserved distinct pattern of human life-history[33]. This indicates that selection on reproductive lifespan of humans begins approximately at age 15 and can last for decades. Both the long delay between prenatal life and the first reproduction and the length of reproductive lifespan itself decrease the likelihood that foetal environmental conditions experienced will match those experienced during reproductive life, increase the probability of mismatches, and thus lower the potential adaptive value of the 'survival phenotype' in this life stage.

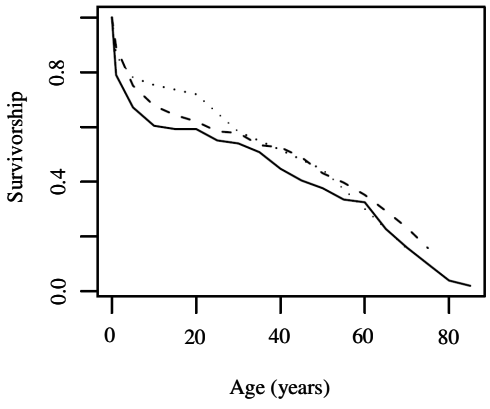


Figure I: Cumulative survivorship probability for three hunter-gatherer populations, living in conditions considered representative of those that all humans experienced prior to the advent of agriculture and western industrialisation. Demographics of these populations are not influenced by (i) reliable medical care and (ii) the increased influence of infectious disease and nutritional deficiencies associated with intensive agriculture and sedentism[34]. Although patterns of survivorship vary slightly between groups, the broad pattern is that mortality risk is greatest in the youngest age groups due to high infant mortality. !Kung (southern Africa) = Solid line, Ache (Paraguay) = dashed line, Yanomamo (Brazil) = dotted line. Reproduced with permission from Jones (2005)[35].

likely to confound the evolution of PARs than aid it. What are the other possible explanations?

Competing hypotheses

Alternative hypotheses for the PAR model to explain the origins of 'survival phenotype' characteristics are offered here, which arise from considering how natural selection interacts with the different stages of human-life history (Box 1). The null hypothesis proposes that prediction does not occur, whilst the 'infancy prediction' hypothesis proposes that 'prediction' occurs but is targeted at the first year of an infant's postnatal life. It is important to consider that any one of these two hypotheses could also apply to each individual 'survival phenotype' trait (see Table 1), e.g. some may be adaptive whereas others may not be.

(i) Prediction does not occur (null hypothesis)

The most parsimonious explanation for developmental responses to poor nutrition or maternal stress during prenatal life is that such changes occur because they represent the only choice that a fetus can make if it wishes to survive. Attrition rates of implanted embryos show that most of the selection on human survival probably occurs before birth[36]. This suggests that dynamic adjustment to changes in nutrient supply may be strongly favoured by natural selection.

Thus poor nutrition may not be a 'signal' (indicating assessment), but in fact the constraining factor in development and the inevitable precursor to the development of 'survival phenotype' traits. For example, poor fetal nutrition may lead to reduced muscle mass and lower bone mineral content, traits proposed to be adaptive components of the 'survival phenotype'[6]. However, responses such as this could occur simply because the fetus has no choice when maternal nutrition is limiting and must reduce expenditure in the growth of some tissues.

(ii) Prediction is targeted at infancy

The PAR hypothesis explicitly proposes that 'survival phenotype' acts primarily to improve fitness during reproductive life[8], i.e. the 'survival phenotype' is 'designed' for adulthood. This is despite the fact that the individual must face the challenges presented by infancy before it confronts those of childhood and reproductive life. Gaining any reproductive success is dependent on an individual surviving to reproductive age, and we must therefore consider the selective pressures early in postnatal life when evaluating the adaptive value of 'survival phenotype' traits.

For two reasons early, rather than late (cf. PAR), selection for plasticity provides the more parsimonious adaptive explanation. Firstly, the reliability of a prediction will inevitably decline with time, as more opportunity arises for conditions to deviate further from those that have been predicted. Secondly, early survival is a crucial component of human life-history. Only approximately 60-75% of born children survive to reproductive age in most pre-medical care populations[26-28], a fact that may be overlooked in studies focusing on evaluating the adaptive value of PARs using data from modern western countries. Consequently, 'survival phenotype' traits can be beneficial in adulthood only if they do not impose prior costs that outweigh later benefits, whereas traits that increase the probability of early survival could be favoured by selection even if they also bring substantial downstream costs.

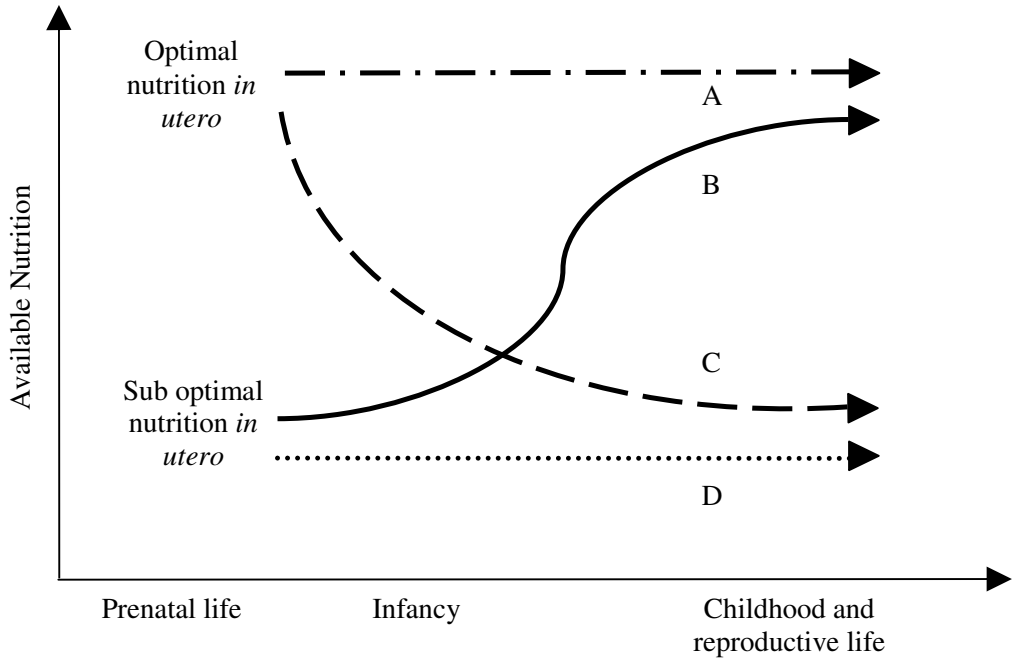
It is possible that a slower metabolism in a poor nutritional environment may bring with it a survival advantage (and be favoured by natural selection) in infancy, the most crucial stage of postnatal life, regardless of what is experienced after this. In particular, reduced nutritional demand may render the infant less susceptible to early mortality as a result of nutritional shortfalls or to energetically costly exposure to pathogens. Identifying the mechanistic basis behind associations between 'survival phenotype' traits, e.g. adiposity and insulin resistance, is important in gaining an understanding of which traits may be adaptive and which may not. For example, it has been suggested that fat reserves may be beneficial to the short-term survival of small and vulnerable infants[37]. Some recent data suggest that permanent insulin resistance may be partly a direct result of this[38, 39], thus one 'survival trait' with long-term consequences could in fact be a side-effect of another adaptive trait with early benefits.

Predictions and tests

Distinct predictions can be drawn from these hypotheses, although there are empirical difficulties with testing them. All other things being equal, individuals with the 'survival phenotype' will have different fitness in different postnatal nutritional environmental regimes. Figure 1 shows four individuals experiencing different nutritional regimes across their lifetimes (A-D). A and C receive optimal nutrition *in utero* and do not develop the 'survival phenotype', and experience good and poor postnatal conditions respectively. B and D experience poor nutrition *in utero* and hence develop the 'survival phenotype'. Nutrition improves after infancy for B, but remains low for D. According to all hypotheses outlined above, the fitness of A will be greatest. The null hypothesis predicts that both B and C will have greater fitness than D because D has lower access to energy and nutrients across its lifetime. By contrast, the PAR hypothesis predicts that D will have greater fitness than both B and C because a match between early and late environment confers an advantage to the 'survival phenotype'. Finally, the 'infancy prediction' hypothesis predicts that B will have greater fitness than D, who will have greater fitness than C, because only the match between prenatal and infancy environments is advantageous.

Designing empirical studies to test these predictions is obviously difficult and long-term data that combine detailed knowledge of early conditions with outcomes across all ages are rare. Nevertheless, such tests are possible, although it is important to remember the need to compare individuals for whom nutrition either improves or deteriorates early in life, whilst other environmental variables remain constant. In addition, it is essential not to rely upon any single physiological characteristics or on survival outcomes as reliable indicators of likely evolutionary success. Natural selection ultimately operates on variation in reproductive success between individuals, and although this may often be directly related to health or survival, this cannot be taken for granted. Evolutionary theory states that organisms are expected to trade-off health and longevity in favour of successful reproduction[40], and this is supported by evidence for costs that are suffered as a result of reproduction[41]. Thus it is important that the effects of early conditions should be considered not in terms of their impact on isolated components of evolutionary success, but rather in their relationship to reproductive function and offspring viability. It is assumed that the 'survival phenotype' increases viability without affecting reproductive performance[6], but this

Figure 1: Three hypothetical lifetime nutrition regimes



Four individuals experiencing different nutritional regimes across their lifetimes, paying particular attention to prenatal life and infancy (A-D). Individuals B and D experience poor nutrition in utero and hence develop the 'survival phenotype'. Nutrition improves after infancy for B, but remains stable at a low level for the lifetime of D. A and C experiences optimal nutrition in utero and do not develop the survival phenotype, but experiences good and poor nutrition from after birth respectively. The null hypothesis predicts that Fitness (B) > Fitness (D) and Fitness (C) > Fitness (D) because of differences respective levels of total access to energy and nutrients across lifetime. By contrast, the PAR hypothesis predicts that Fitness (D) > Fitness (C) and Fitness (D) > Fitness (B) because the phenotypes of B and C are mismatched to their later environments whereas the phenotype of D and its later environment are matched. Under a modified version of the PAR hypothesis, in which the 'survival phenotype' is favoured specifically because it increases the probability of survival through infancy, it is predicted that Fitness (B) > Fitness (D) > Fitness (C). This is because, according to this hypothesis, the 'survival phenotype' is useful when the infancy environment matches the prenatal environment, but it will not confer any advantages in a continued poor environment beyond this. According to all hypotheses, A has the greatest fitness. Comparison of the fitness of A with that of C enables calculation of the cost of an individual predicting a good postnatal environment, but experiencing one that is poor. These predictions are testable in populations where individuals differ across their lifetime in terms of their access to resources.

assumption has not been tested directly in humans or the model animals. In fact, evidence suggests the opposite: the reduced size of individuals with the 'survival phenotype' may be disadvantaged in competition for mates[42]. Reduced lifetime child numbers in men[43] and in women with the tendency to give birth to smaller babies with a higher risk of early mortality[44].

One possibility is to compare data from cohorts who after a famine experienced good conditions (i.e. the Dutch Hunger Winter[45]) with those who continued to experience bad conditions (i.e. the Leningrad siege cohort[12]). However, such comparisons are qualitative, and subject to the influence of multiple unknown confounding variables. Ideally comparisons need to be made within the same population, but suitable data are rare.

Because of the limited availability of suitable human data, the most appropriate route to explore how the accurate versus inaccurate prediction of the future environment affects individual lifetime reproductive success may be the further use of animal models. Laboratory approaches, such as have been already used in this field, can exploit controlled conditions, the ability to conduct essential cross-fostering experiments and the short generation times of laboratory organisms allowing the measurement of both survival and reproductive success across the whole individual lifespan. However, there is a limit to the extent that the use of short-lived mammals is relevant to approximating human life-history (Box 1), and to which the laboratory environment can reflect natural conditions and demonstrate variation in reproductive success. One complementary approach may be found in using life-history data of relatively long-lived mammal species living under natural, variable conditions, such as that collected for sheep[46], red deer[47] and non-human primates such as chimpanzees[48]. Comparison of survival and reproductive success can be made between cohorts that are poorly nourished for different durations of their lifetime.

Conclusion

In addition to the predictions above, we have identified several questions that should be addressed when considering the adaptive value of 'survival phenotype' traits (See Box 2). There are several evolutionary pathways that could account for the early origins of traits associated with the 'survival phenotype'. Prediction, if it occurs, may be targeted at infancy or later life. Some of the proposed characteristics of the 'survival phenotype' may have adaptive value, whereas others may have none.

The PAR hypothesis proposes that the fetus responds to maternal undernutrition or stress by inducing the 'survival phenotype', which it predicts will benefit it in its postnatal life. Specifically, it proposes that the characteristics of this phenotype, such as 'thrifty' metabolism, altered stress response, and smaller size, are naturally selected for during the reproductive phase of an individual's life[6, 8]. When considering if PARs are useful and thus likely to have evolved, the benefits of making such a prediction correctly need to be weighed against the costs of getting the prediction wrong. In addition, an understanding of the current success of individuals that adopt PAR versus those that do not must be considered. For example, if individuals that adopt PAR are out-competed early in life by those that do not adopt PAR, the reproductive potential of the former may be irrelevant. Furthermore, it needs to be considered how likely it is that a match or a mismatch will occur between the environment experienced during development and that experienced in adulthood. Most importantly, understanding the

developmental 'decisions' of a fetus relies on the rigorous testing of competing alternative hypotheses for the development of a given 'survival phenotype' trait. Future work should centre on critically evaluating these problems by considering human data on individual reproductive success alongside that from laboratory and field species.

Although we have referred throughout specifically to the metabolic changes associated with the 'survival phenotype', this is one proposed example of a PAR. However, the general principles extend to every application of the PAR model in humans, and are summarised here: (1) Prediction requires stability; (2) Natural selection must balance benefits against costs; (3) Natural selection does not optimise just survival or reproductive ability, but the trade-off between reproduction and survival that will ultimately determine an individual's relative genetic contribution to the next generation.

Acknowledgements

I.R. is supported by the Natural Environment Research Council and V.L. by a Royal Society fellowship. Thanks to Andy Russell, Charlotte Faurie, Duncan Gillespie and Stewart Plaistow for their comments on earlier versions of this manuscript.

Outstanding questions
What is the cost of maintaining the ability for plasticity in 'survival phenotype' traits?
On what temporal scale did food availability typically vary in ancestral human populations?
Does plasticity in a given 'survival phenotype' trait confer a fitness advantage?
How is the evolution of adaptive traits constrained by multiple functions of agents or the functional overlap of metabolic processes?
What is the cost of inaccurate prediction?
How strongly does selection on a given survival trait occur at each stage of human life-history?
How are both survival and reproductive success affected by 'survival phenotype' traits?

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