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RESEARCH PAPER

Evolutionary life history theory as an organising framework for cohort studies: insights from the Cebu Longitudinal Health and Nutrition Survey

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ABSTRACT

By tracking a group of individuals through time, cohort studies provide fundamental insights into the developmental time course and causes of health and disease. Evolutionary life history theory seeks to explain patterns of growth, development, reproduction and senescence, and inspires a range of hypotheses that are testable using the longitudinal data from cohort studies. Here we review two decades of life history theory-motivated work conducted in collaboration with the Cebu Longitudinal Health and Nutrition Survey (CLHNS), a birth cohort study that enrolled more than 3000 pregnant women in the Philippines in 1983 and has since followed these women, their offspring and grandoffspring. This work has provided evidence that reproduction carries "costs" to cellular maintenance functions, potentially speeding senescence, and revealed an unusual form of genetic plasticity in which the length of telomeres inherited across generations is influenced by reproductive timing in paternal ancestors. Men in Cebu experience hormonal and behavioural changes in conjunction with changes in relationship and fatherhood status that are consistent with predictions based upon other species that practice bi-parental care. The theoretical expectation that early life cues of mortality or environmental unpredictability will motivate a "fast" life history strategy are confirmed for behavioural components of reproductive decision making, but not for maturational tempo, while our work points to a broader capacity for early life developmental calibration of systems like immunity, reproductive biology and metabolism. Our CLHNS findings illustrate the power of life history theory as an integrative, lifecourse framework to guide longitudinal studies of human populations.

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Epidemiology; evolution; reproduction; growth; plasticity

Most adults alive today will, in time, die from a chronic disease that develops in response to a lifetime of exposure to a diverse set of environments and experiences. Many conditions are influenced by the chronicity of specific exposures across the lifecycle, whether beneficial or harmful. Critical periods are increasingly understood as heightening sensitivity to specific classes of exposures in defined developmental windows, thus linking early nutrition, stress and other factors with later biology and health (Barker 1990; Hanson and Gluckman 2011). By following a group of individuals longitudinally, cohort studies are ideally suited to addressing these temporal and developmental dimensions of phenotypes and disease emergence, and such studies have provided foundational knowledge about the causes of some of the globally most pressing public health issues. Framingham Heart Study that began in 1948 has provided fundamental insights into the role of biological processes like blood pressure and lipid metabolism in the development of atherosclerosis and coronary heart disease (Ho et al. 1993). The Whitehall Study similarly helped lay the foundations for contemporary understandings of the role of social class as a driver of health inequality within society (Marmot et al. 1991). The Dunedin Longitudinal Study has provided key insights into the long term psychological and health effects of early psychosocial adversity (Poulton et al. 2015). Cohort studies in countries like the Gambia (Hennig et al. 2017), Guatemala (Stein et al. 2008), South Africa (Cameron et al. 1998; Richter et al. 2007), the Philippines (Adair et al. 2011), Bangladesh (Arifeen et al. 2018) and Jamaica (Walker et al. 2005) have clarified the influence of factors like nutrition, infectious disease, and infant feeding practices on infancy and childhood growth and development, and traced the long-term impacts of these early experiences on human economic and health outcomes measured in adulthood.

The longitudinal dimension of cohort studies provides powerful insights into the time course of disease

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development, and the types and timings of exposures that increase or decrease this risk. What is often less clear, and traditionally has rarely been addressed by such studies, is *why* our bodies and behaviour tend to respond predictably to our experiences. Longitudinal studies not only reveal the power of chronic experience and of sensitive or critical periods, but demonstrate that our biology and behaviours tend to co-vary and flex in predictable ways as environments change. As one example, it is intuitive that early severe stressors might lead to cognitive impairment, but it is less clear why individuals who experience such stress also tend to begin their reproductive careers earlier or have larger completed family sizes (Wilson and Daly 1997; Nettle et al. 2011). In turn, parity has been shown to predict an accelerated pace of late life functional decline, ageing and mortality (Doblhammer and Oeppen 2003; Jasienska 2009). Findings such as these illustrate how the full impact of our experience on health and wellbeing must be understood as a series of changes that cascade through the lifecycle. The coordinated nature of these changes also hints at an underlying strategy that has a capacity to adjust in response to the physical and social environments that we experience.

Life history theory (LHT) is the branch of evolutionary theory that seeks to understand the evolution of species variation in life cycles, and also how and why they vary across individuals of the same species (Charnov 1991; Hill and Kaplan 1999; Kuzawa and Bragg 2012). For the purpose of human biological investigations using cohorts, LHT provides a framework for formulating *a priori*, testable hypotheses regarding an organism's metabolism and pattern of energy allocation to the body's various functions, and focuses attention on the finite nature of resources and the resultant trade-offs that bind traits into patterns of co-variation. It also inspires hypotheses for how behaviours or experiences early in life might impact various outcomes measured in adulthood, including such traits as reproductive biology, behaviour, immunity and the pace of senescence and functional decline. Life history theory thus provides a useful scaffold for our investigations of human biology and its unfolding across the lifecourse and even across generations.

In this paper, we first briefly review some of the core organising principles of LHT as they have been used to illuminate the evolution of interspecific variation in life cycle characteristics like growth rate, body size and lifespan. The scaling of metabolic expenditure on an individual's body mass places fundamental constraints on the energy and other metabolic resources available to meet the body's many functions, leading unavoidably to trade-offs (Urlacher et al. 2019). With the body's energy budget set by body size, the optimal pattern of allocation across functions is driven in part by ambient levels of unavoidable mortality, which determine the likely future returns on investing in somatic durability and lifespan extension. After this review, we will discuss our use of life history principles as an organising framework for a subset of our investigations of the Cebu Longitudinal Health and Nutrition Survey, a birth cohort that began in 1983 and has since followed a large sample of women, their offspring and grand offspring living in metropolitan Cebu, Philippines (Adair et al. 2011). We will discuss some of our tests of life history principles, focussing on questions like the links between reproduction and markers of ageing, the role of telomeres as an intergenerational life history cue, hormones in the coordination of male life history and reproductive strategy, and developmental calibration of immune development and life history trade-offs. We will conclude by considering the limitations of LHT for use in cohort studies, and argue that they are primarily a result of our limited understanding of the functional significance of many of the biomarkers that we routinely collect, which are targeted for predictive relationships with biological dysfunction and disease.

Life history primer: metabolic scaling, trade-offs and unavoidable mortality

Organisms vary widely in characteristics like body size, growth rate, age at first reproduction, reproductive rate, and lifespan. These traits tend to co-vary such that species that are larger as adults also tend to have an extended period of relatively slower growth, invest a smaller fraction of their metabolic resources in offspring (reproduction), and have longer lifespans. Life history theory (LHT) is the branch of evolutionary theory that seeks to explain the evolution of life cycles and has helped shed light on these predictable patterns of trait co-variation (Stearns 1992).

The scaling of an organism's energy expenditure on body size, as reflected in the classic "three-quarter" scaling of a species' energy expenditure on body mass (Kleiber 1932), provides a useful starting point for considering the factors that constrain the evolution of life histories. One model to explain this regularity, proposed by West et al. (1999), posits that an organism's metabolic expenditure is limited by its ability to distribute resources. Animal circulatory systems are organised to deliver blood, enriched with oxygen, energy and other nutrients, from a single, large vessel (the aorta) to capillaries that service individual cells throughout the body. West and colleagues note that the strategy for distributing resources within a given mass that minimises hydrodynamic resistance within the system is a fractal network in which large vessels branch into smaller vessels, with nested vascular branching continuing until individual cells are reached. The authors show that such a fractal distribution network leads to 0.75 scaling of energy expenditure on mass, irrespective of the size of the organism or system (West et al. 2002), thus, potentially helping explain metabolic scaling from first principles of physics.

Metabolic scaling shows that the energy available to an organism of a particular size is finite, which implies that any expenditure of a metabolic resource (e.g. a gram of glucose, an amino acid or molecule of ATP) on one function leaves fewer resources available to be allocated to the body's other functions and needs. As demonstrated empirically in humans, constraints on energy budgets lead unavoidably to functional trade-offs (Kuzawa et al. 2014; Urlacher et al. 2019), which the metabolic and physiologic architecture of the human body has been designed to balance. This concept of trade-offs is central to LHT-focussed analyses, which

emphasise both immediate or concurrent resource trade-offs, as illustrated for instance by the fact that testosterone boosts muscle anabolism (in males a form of mating effort) but at a cost to immunity (a maintenance function) (Muehlenbein and Bribiescas 2005), or lagged trade-offs in which expenditures at one point in the lifecycle influence future phenotypes.

As a result of finite energy, complex multi-cellular organisms face a fundamental decision: what fraction of their metabolic resources to invest in growing new tissue (becoming bigger during growth, or growing the tissue of the next generation during reproduction) – versus repairing and maintaining the tissues and organs that are already present (extending lifespan). The idea that reproduction carries costs to survival, thus reducing future reproduction, is a long-standing assumption in evolutionary biology (Williams 1966) and is a key inspiration for the "disposable soma" model for the evolution of senescence (Kirkwood and Rose 1991). The disposable soma posits a trade-off between reproduction and maintenance expenditures, such that species that invest a greater fraction of their metabolic budget in reproduction have fewer resources to invest in functions that help maintain durability and function of the body and brain into later life. Although the disposable soma has gained support from some animal models (Bouwhuis et al. 2010), applicability to human senescence has been mixed; for instance, in some historical data, lifespan is inversely related to fertility (Westendorp and Kirkwood 1998), while in others the two measures are positively related (see Mitteldorf 2010). Although the reason for these inconsistencies is uncertain, human studies have shown that trade-offs can be obscured when individuals vary widely in nutritional sufficiency or resource access (Hill and Hurtado 1996). It has also been noted that the costs of reproduction may be minimised in some recent high socioeconomic cohorts owing to reduced reproductive costs associated with the use of infant formula (Jasienska 2009).

A second assumption of many LHT frameworks is that unavoidable or "extrinsic" mortality, such as is approximated by predation or unpredictable features of the environment that impact survival, influences the optimal strategy of partitioning resources across these various functions, while also helping determine the optimal age at maturity. According to this principle, mice mature earlier than elephants, and attain a much smaller final size, in large part because they are subjected to high rates of predation, making it risky to delay maturity further. Once mature, they also invest a greater fraction of the body's metabolism to reproducing now (and, thus, less to maintenance effort), given that chances of surviving to reproduce in the future are reduced by high unavoidable mortality. Another way of stating this is that the high likelihood of predation among mice makes them pessimistic about their futures, forcing them to adopt a "live fast, die young" strategy.

Because organisms often face substantial variability in their environments and experiences, natural selection generally does not set an individual's LH trajectory genetically but instead allows some degree of flexibility in the form of developmental and phenotypic plasticity (Stearns and Koella 1986; Kuzawa and Bragg 2012). Most notably, the experience of local cues reflecting mortality or environmental unpredictability have been predicted to motivate a "fast" life history strategy in which reproduction is initiated earlier and the rate of investment in each offspring (as reflected for instance in birth size, duration of breastfeeding or interbirth interval) is reduced. This increase in reproductive expenditure, in turn, is predicted to increase the costs of reproduction and accelerate functional decline and senescence. Other capacities to adjust life history priorities play out in an ongoing fashion across the lifecycle, such as through the dynamic effects of hormones that mediate trade-offs between functions like reproduction and immunity.

Testing LHT with the CLHNS

During the past several decades, we and our collaborators and students have used principles from LHT to help organise our work on the Cebu Longitudinal Health and Nutrition Survey (CLHNS). The CLHNS was initiated in 1983 by a team that included Barry Popkin and Wilhelm Flieger, with the recruitment of 3327 women who were pregnant (for an overview of study design and timeline, see Adair et al. 2011). Their offspring were followed after birth, and surveys during the first 2 years recorded information on infant feeding, including breastfeeding and supplemental foods, maternal reports of infectious disease symptoms (e.g. diarrhoea or respiratory infections), and length and weight growth. Linda Adair later spearheaded an effort to relocate the original birth cohort in 1991, when they were an average of 8.5 years old. The original mothers, their offspring, and now the grand offspring, have been followed periodically to the present, representing more than 35 years of data collection across three generations (Adair et al. 2011; Eisenberg et al. 2019). Standardised modules on diet, income, health, sexual activity and a wide range of other individual, household and neighbourhood characteristics were recorded regularly until the cohort was in young adulthood. Surveys since 2005 have focussed on longitudinal follow-up of males to measure salivary hormones and reproductive ecology (Rosenbaum et al. 2018), while adult females were tracked to locate new pregnancies and to obtain information during the pregnancy and on birth outcomes of offspring (Kuzawa et al. 2017). Other recent surveys have focussed on ageing in the mothers of the CLHNS birth cohort, and on adult cognition and well-being in the offspring. These data have provided a rich resource to address a wide array of questions of interest to fields like economics, sociology, and demography. In addition, our own anthropologically-oriented work has harnessed these data to address many questions in population biology, including a subset inspired by evolutionary LHT. Here we will review some of this work as it applies to questions around the biology of ageing, male reproductive ecology and life history, the role of early experiences as cues that set life history strategy, and the developmental ecology of human immunity.

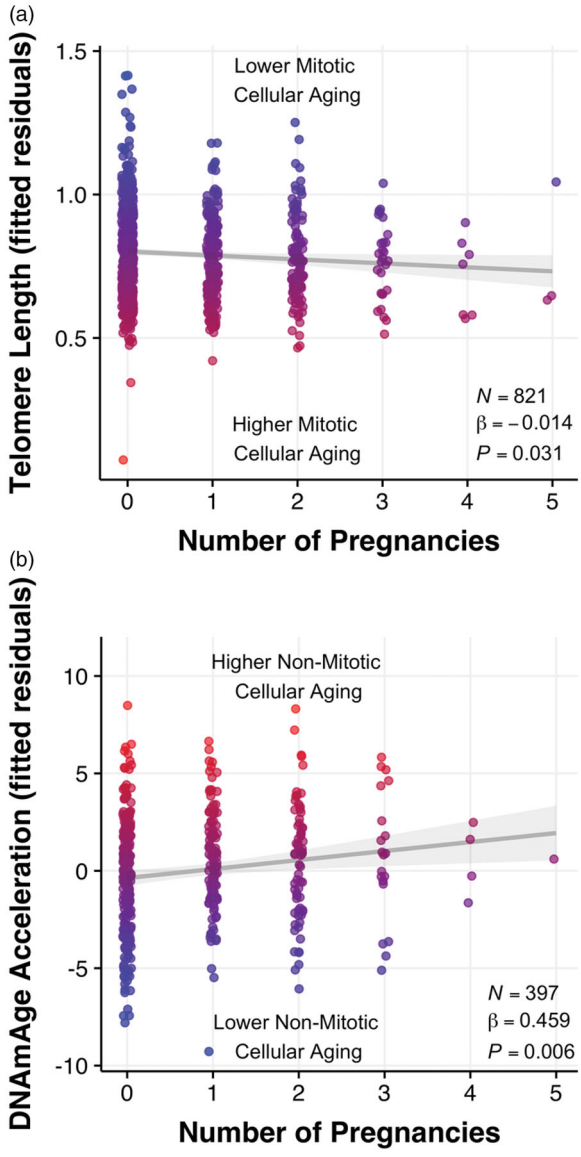

Figure 1. Evidence for costs of reproduction in 20–22-year-old female participants in the Cebu Longitudinal Health and Nutrition Survey. Figure reprinted with permission from Ryan et al. (2018).

Insights into the biology of ageing: testing the trade-off between reproduction and somatic maintenance

The trade-off between reproduction and somatic maintenance that is central to LHT inspired models of ageing can be understood as a decision between investing energy in current reproduction versus investing in functions that promote survival and thereby allow reproduction in the future. Costs of reproduction are central among trade-offs in LHT, and as noted, are also fundamental to the disposable soma model for the evolution of senescence. In Cebu, we have tested for costs of reproduction using two complementary measures of biological ageing: telomere length and epigenetic age acceleration (Ryan et al. 2018). Telomeres are repeating DNA sequences that cap the ends of chromosomes and are required for normal cell replication. With each replication telomere length is shortened and cells undergo programmed cell death (apoptosis) when a critically short telomere length is reached (Eisenberg 2011). Epigenetic age is a measure of molecular ageing based on predictable changes to DNA methylation in the genome. While epigenetic age is closely tied to chronological age, accelerated epigenetic age relative to chronologic age is associated with elevated mortality risk and a range of adverse health outcomes independent of other risk factors.

Using telomere length and epigenetic age as measures of cellular ageing and predictors of mortality and health, we found evidence that women's cells "age" with each additional pregnancy (Figure 1). This effect was not attributable to a range of social factors, such as urbanicity, parental education, household assets, or income, supporting the theorised trade-off between reproduction and bodily maintenance at the cellular level (Ryan et al. 2018). Moreover, neither measure predicted the number of pregnancies over the subsequent four years, implying that reproductive effort is likely driving cellular ageing in these women rather than increasing in response to an intrinsically accelerated pace of ageing more generally. These findings support the assumption that reproduction carries costs among women. In an unrelated earlier analysis, we also found evidence that anti-Mullerian hormone, a marker that reflects follicular reserve, was reduced in relation to parity, also potentially pointing at a cost of reproduction (Bragg et al. 2012). What is less clear is whether these relationships will still be detectable at older ages when cellular senescence leads to functional decline (or in the case of anti-Mullerian hormone, as declining follicular counts impairs fecundity).

The paternal age at conception effect on telomere length as a form of genetic plasticity in life history allocation

While increasing reproductive effort during early adulthood may accelerate blood telomere shortening in females, the dynamics of telomere length in the germline allow for a unique form of intergenerational genetic plasticity that could link male reproduction to patterns of life history allocation in future generations. Telomere length shortens with age in most human tissues, but spermatocyte telomere length increases with age (Eisenberg and Kuzawa 2018), which appears to be driven by the continuous production of sperm in the presence of high levels of testicular telomerase (an enzyme that lengthens telomeres). Correspondingly, offspring of older fathers have longer telomere length (Eisenberg and Kuzawa 2018). Our work with the CLHNS demonstrated that this effect of paternal age at conception persists cumulatively across at least two generations – that is, the age at which paternal grandfathers sired fathers and maternal grandfathers sired mothers predicts the grandchild's telomere length additively and independently to the effect of their own father's age on their telomere length (Eisenberg et al. 2012, 2019).

These findings are important because they suggest that telomere length in any given generation is partially a reflection of the *average* age of reproduction among recent generations of male ancestors. Because the age at reproduction is

a key life history parameter, this integrative quality of the paternal age at conception effect hints at a capacity to calibrate a dimension of maintenance expenditure in response to a signal of the likely ages of reproduction in that population (for a similar example involving nutrition, see Kuzawa 2005). Because longer telomere length allows cells to replace themselves more readily, longer telomere length is implicated as a cause of improved immune function, better wound healing, and improved cardiovascular function (likely due to improved blood vessel repairs). All of these cell replication-dependent processes are likely to be energetically expensive and from an LHT perspective longer inherited TL may thus be viewed as a cause of increased maintenance effort (Eisenberg 2011). Increasing allocation to somatic maintenance may thus be an adaptive shift in allocation priorities in demographic and cultural settings in which reproduction typically occurs later in life.

Because telomeres are DNA, the telomerase-driven changes in sperm telomere length that accrue with paternal age are highly heritable, which underlies the paternal age at conception effect. Emerging evidence suggests that sperm telomere length could be modified by other environmental or behavioural factors aside from male age, and these changes should similarly be highly heritable. In Cebu, we find that the offspring of men with shorter leg length tend to have longer telomeres (Eisenberg et al. 2020). Although mechanistic explanations for this finding remain tentative, it is notable that short leg length – a measure of early developmental adversity – has been associated elsewhere with earlier puberty (Schooling et al. 2008), perhaps reflecting the maturation-accelerating effect of early growth deficits followed by catch-up growth (Gluckman and Hanson 2006). Because individuals who experience puberty earlier likely also begin increasing their sperm telomere length at a younger age, the physiology of earlier puberty could increase the rate of age-related increase in sperm telomere length (Eisenberg et al. 2020). This is particularly intriguing as age at puberty is influenced by nutritional availability (Bribiescas 2006), including among the younger (cohort) generation at Cebu (see below). The general take away is that the telomere lengths that men pass on to their offspring might be adjusted not only in response to the age at reproduction, but also to their childhood nutritional circumstances and growth dynamics – paralleling intergenerational effects on other systems observed along the matriline (Kuzawa and Quinn 2009).

Relationships, fatherhood and male reproductive effort

Across cultures, men provide varying levels and types of parental care and investment (Marlowe 2000; Lamb 2004; Gray and Anderson 2010; Hewlett and Macfarlan 2010; Gettler 2016). While this most commonly takes the form of providing resources, depending on the cultural context and individual family setting, men may regularly be involved in direct childcare (Hewlett 1991; Anderson et al. 2007; Rosenbaum et al. 2019; Alvergne et al. 2009; Winking et al. 2009; Mattison et al. 2014; Boyette et al. 2018). This is a vast departure from the behaviour of most other mammals, a taxonomic class in which males provide paternal care in roughly 5% of species (Kleiman and Malcolm 1981; Lukas and Clutton-Brock 2013). The rarity of this behaviour, along with the importance of cooperative care – including paternal care – to the suite of life history traits that make humans unique, has generated great interest in whether physiological and behavioural expressions of mating-parenting trade-offs in humans are similar to those of other species.

Though it is unusual in mammals, bi-parental cooperation in caring for young is quite common in many seasonally breeding bird species. An extensive body of work has demonstrated that male birds' testosterone rises during the time of year when males are competing for mates and defending their territories but falls dramatically once it is time to care for nestlings (Wingfield et al. 1990). Across vertebrate species, testosterone commonly enhances mating-related somatic investment (e.g. skeletal muscle mass; ornamentation), dampens the fear response, and increases competitive-aggressive tendencies, all of which are desirable traits when fending off competitors. These tendencies, however, are largely incompatible with the very different demands that direct care and male-female cooperation involve (Gettler, McDade, Feranil et al. 2014; Gray et al. 2017; Muller 2017). The physiological switch male birds experience presumably helps ensure that they have the physical capacity to deal with intraspecific challengers when necessary, but also that they are behaviourally capable of taking care of young once they arrive.

This 'challenge hypothesis' aligns with the basic tenets of LHT because of its emphasis on the biological mechanisms that underpin the allocation of limited resources to competing demands. It has become the dominant framework for understanding the physiological trade-offs males make between mating and parenting effort in a much wider assortment of organisms (Wingfield 2017; Grebe et al. 2019). The CLHNS cohort has provided a unique opportunity to test the applicability of the challenge hypothesis in humans and to explore the role of endocrine change as a coordinator of men's changing social roles across adulthood. Though prior studies had observed that fathers had lower testosterone than non-fathers, it was unclear whether fatherhood caused a reduction in testosterone, as seen in birds, or alternatively, whether men with lower testosterone might be more likely to end up in stable relationships and become fathers (Gray et al. 2002; Kuzawa et al. 2009). In Cebu, testosterone predicts muscle and strength in early adulthood, consistent with the hormone's expected role in promoting costly components of mating effort (Gettler et al. 2010), although there was no evidence for testosterone's proposed suppressive effects on immunity (Gettler, McDade, Agustin et al. 2014). We also found that single non-partnered men with high testosterone at baseline (~21 years of age) were more likely to have entered a stable relationship and become a father during a 4.5-year follow up period. The newly-partnered, new fathers then experienced large decreases in testosterone concentrations to end up with lower testosterone than men

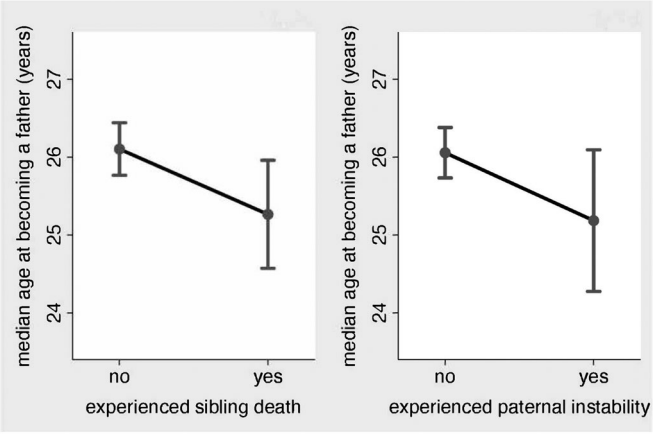

Figure 2. Early cues of mortality and familial instability predict an earlier transition to fatherhood among 21–23-year-old male participants in the Cebu Longitudinal Health and Nutrition Survey. Figure reprinted with permission from Gettler et al. (2015).

who remained single (Gettler, McDade, Feranil et al. 2011). Furthermore, the fathers who engaged in more direct care had lower testosterone than less involved fathers (Gettler, McDade, Feranil et al. 2011). These critical findings demonstrated the applicability of the general concepts of the challenge hypothesis framework to humans.

Other CLHNS work has further illuminated the physiological underpinnings of humans' remarkably flexible mating and parenting strategies. For example, parenting status is associated with lower testosterone not only in men, but also in women (Kuzawa, Gettler et al. 2010), and in fathers, specific partnering and parenting behaviours can mediate the relationship between paternal status and a man's testosterone (Gettler et al. 2013; Gettler, McKenna, McDade et al. 2012). Moreover, we also found that other hormones (e.g. cortisol, prolactin) differ between CLHNS fathers and non-fathers, likely reflecting shifting priorities across life history transitions (Gettler, McDade et al. 2012; Gettler, McDade, Kuzawa, 2011). Although there is little evidence that a common polymorphism in the androgen receptor alters regulation of testosterone production in the sample (Ryan et al. 2017), we did find that this polymorphism interacted with testosterone to influence traits like pairbond stability (Gettler et al. 2017). Additionally, in contrast to the predictions of the challenge hypothesis, men's testosterone does not appear to be closely tied to at least some measures of mating effort (Rosenbaum et al. 2018; Gettler et al. 2019). These results highlight the many nuances of human mating-parenting trade-offs. Our current work is focussed on understanding how developmental experience influences later-life psychobiological profiles (e.g. Sarma et al. 2018), and the broader caretaking context in which male parenting effort occurs in Cebu (Rosenbaum et al. 2019).

The role of early environmental cues as influences on life history strategy

Beyond the dynamic role of hormones in mediating trade-offs across the lifecycle, LHT also leads to an expectation that experiences early in development serve as informative cues that allow a calibration of the trajectory of development and life history strategy. Consistent with this concept, an extensive literature, much of it focussed in psychology, provides evidence that individuals exposed to early life cues of mortality or environmental unpredictability tend to adopt features of a "fast" life history strategy, including traits like an earlier age at maturity, earlier onset of first reproduction, greater likelihood of risk taking and a shortened interbirth interval (Belsky et al. 1991; Wilson and Daly 1997; Ellis et al. 2009). Our CLHNS findings provide partial support for these expectations. Although we have yet to explore these specific relationships in females, we find that males who experienced early life cues of mortality or environmental harshness have sex for the first time and become fathers at an earlier age (Figure 2; Gettler et al. 2015). However, counter to the expectations of past evolutionary psychology oriented studies in other populations, in both males and females early cues of harshness predict *delayed* sexual maturity, while – consistent with most past work in other lower resources settings (e.g. Eveleth and Tanner 1990) – multiple measures of favourable nutrition were strong predictors of maturational acceleration (Gettler et al. 2015; Kyweluk et al. 2018).

This set of findings confirms the long-appreciated role of nutrition (and more proximately, growth rate) as a fundamental constraint on timing of maturity (Eveleth and Tanner 1990), while sexual behaviours may be largely uncoupled from physical maturity and thus influenced independently by cues of mortality or environmental harshness (Kuzawa and Bragg 2012). It is notable that most past evidence for maturational acceleration in high stress environments has come from populations in which inequality, and the maturity-accelerating effects of overweight and obesity, are common, raising doubt about the evolutionary relevance of those findings (Kyweluk et al. 2018).

We have additional evidence that favourable – not stressful – nutritional environments are the key to early physical maturity among study participants. Following earlier work in the cohort linking birth proportions to menarcheal timing among cohort females (Adair 2001), we reported that rapid late-infancy weight gain, which in this population is an indicator of nutritional adequacy and a reduced burden of infancy infections, disproportionately impacts male adult phenotypes, as reflected in larger adult size, lean mass, muscle, grip strength and heightened testicular sensitivity to luteinizing hormone, leading to higher adult testosterone (Kuzawa, McDade et al. 2010). The age when rapid weight gain has these long-term predictive relationships is specific to the first half year of postnatal life, which corresponds with the "mini puberty" of temporarily high T production that newborn boys experience. The finding that adult males who grew rapidly during this period also reported having more recent sex, had more lifetime sex partners, and an earlier age at first sex, suggests potentially broad long-term impacts of nutrition and endocrine regulation during this narrow early developmental window. These findings thus support the hypothesis that the mini puberty could serve as a critical or sensitive period for males, when nutrition and growth are predictive of subsequent growth trajectories and life history,

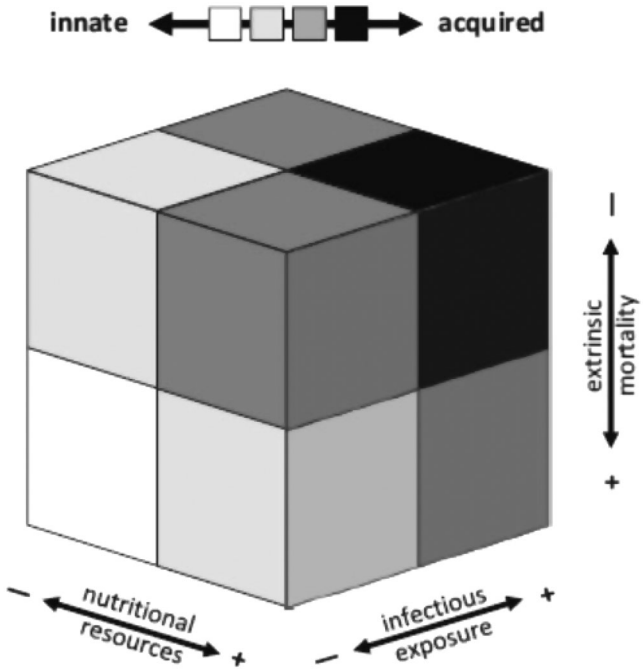

Figure 3. Higher levels of nutritional resources, more intense pathogen exposure and lower extrinsic mortality risk should promote higher levels of investment in acquired immune defences (darker grey to black). Lower levels of nutritional resources and infectious exposures, and higher extrinsic mortality, will promote more investment in innate immunity (lighter grey to white). Absent from view is the condition with low nutritional resources, high infectious exposure, and high extrinsic mortality, which should bias investment towards innate immunity (lighter grey) (figure reprinted with permission from McDade et al. 2016).

including effects on regulation of testicular hormone production (Kuzawa 2007). In Cebu, we find modest evidence that rapid growth during this window is associated with a more androgenic 2D:4D ratio (the so-called "digit ratio"), hinting that this ratio reflects not only exposure to testosterone during the prenatal period, as typically assumed, but possibly also to levels of the hormone during the early postnatal months (Georgiev et al. 2017). Growth during this window was found not to be a strong predictor of female outcomes, consistent with this being a critical period specific to male development (Kuzawa et al. 2010b). What is less clear at present is whether there are critical periods that are specific to females, or during which nutrition or growth processes have particularly strong effects on adult reproductive effort, as would be predicted to impact outcomes like offspring birth size.

Gestation and lactation are increasingly understood as an additional source of cues that convey information about local ecologies, and thus might allow calibration of life history strategy in offspring (Kuzawa and Quinn 2009), and our work with the CLHNS has also explored these links. During pregnancy, maternal metabolism undergoes major shifts to help facilitate the delivery of nutritional resources to the foetus, including a late gestation rise in glucose and triglycerides (Fried et al. 2017). In a sample of CLHNS participants, among whom birth weights are relatively light by comparative standards, we find that placentas ($n = 22$) are disproportionately small and efficient, producing more foetal mass per unit placental mass than is typically the case in more affluent populations; this increased efficiency of placental nutrient transport may be an important mechanism to buffer the foetus from maternal chronic undernutrition (Rutherford et al. 2019). In pregnant women in the sample, fasting glucose is a stronger predictor of birth weight in males compared to females (Fried et al. 2017), which parallels evidence for a similar male-biased effect of maternal cortisol during pregnancy on offspring birth weight (Thayer et al. 2012). These findings suggest that male offspring may place higher demands for resources on maternal metabolism and have heightened sensitivity as a result. We have speculated that these findings could help explain why measures of the gestational environment, such as birth weight or prematurity, have stronger relationships with cardiovascular risk factors, including adolescent lipid profiles (Kuzawa and Adair 2003), blood pressure (Adair et al. 2001) and adult diurnal cortisol levels in this cohort (Lee et al. 2014). In contrast, there is no evidence that the composition of breast milk, or frequency of suckling, varies in relation to offspring sex among young mothers in the sample (Quinn 2013). However, metabolic hormones in maternal milk vary in relation to the mother's body composition, and predict variation in offspring growth rate (Quinn et al. 2015; Anderson et al. 2016), possibly hinting at a capacity to set aspects of life history trajectory in response to measures of ecological quality such as the mother's chronic energy status.

Life history trade-offs and the developmental ecology of human immunity

As noted above, life history theory underscores the importance of maintenance to survival, and in shaping life history trade-offs and allocation strategies. However, with the exception of research on ageing, most studies applying an LHT framework focus on issues related to reproduction and growth, with relatively little attention given to investments in the preservation and repair of the soma. Immunity plays central roles in host defence and repair, and therefore, provides opportunities to operationalise a major component of maintenance effort (McDade 2003). With the addition of several immune markers, beginning in 1999 and continuing today, Cebu data have made important contributions to our understanding of the developmental ecology of human immunity.

Investments in immune defences are costly, and resources allocated to immunity are therefore not available for other developmental or physiological processes (McDade 2003, 2005). A life history approach underscores that trade-offs are therefore inevitable and that investments in immunity are likely to be shaped by the availability of nutritional resources. Furthermore, one might hypothesise that nutrition early in development, during the establishment and rapid expansion of immune tissues and cells, will have disproportionate and lasting impact to the extent that current nutritional conditions forecast future environmental quality.

Using data from the 1998 survey, we showed that individuals born small-for-gestational age were less likely to respond to typhoid vaccination in adolescence (McDade

et al. 2001). This study was important in that it was the first to demonstrate a long-term effect of prenatal undernutrition on immune function in humans, whereas prior work motivated by the "Barker hypothesis" was focussing primarily on cardiovascular and metabolic outcomes. Subsequently, we have shown that prenatal undernutrition is associated with reduced thymic hormone production in adolescence, as well as a lower proportion of B lymphocytes and CD4 helper T lymphocytes in young adulthood (McDade et al. 2001, 2018). Overall, this pattern of results suggests that prenatal undernutrition leads to reduced investment in key aspects of human immunity.

Life history theory provides a theoretical framework for understanding when, and why, low nutrition environments should reduce long term investments in aspects of immunity. This framework also encourages us to move beyond the prevailing emphasis on birth weight and consider other ecological inputs that might be important determinants of allocation decisions related to maintenance effort. The intensity of pathogen exposure is a likely candidate: the immune system is primarily responsible for protecting us against infectious disease, yet immune defences are costly. Therefore, one might hypothesise that – all things being equal – investments in immunity will be higher in environments with higher levels of pathogen exposure. We tested this hypothesis in Cebu, taking advantage of one of the study's unique features: multiple measures of sanitation, microbial exposure, and infectious disease symptoms in infancy. We find that higher levels of infectious exposure in infancy are associated with a more robust antibody response to typhoid vaccination, and marginally higher proportions of CD4 and CD8 T lymphocytes in young adulthood (McDade et al. 2001, 2018).

Interestingly, we have also discovered that higher birth weight and higher levels of microbial exposure in infancy are associated with lower concentrations of C-reactive protein (CRP), an endpoint measure of systemic inflammation (McDade et al. 2010). A subsequent analysis identified DNA methylation as a potential mechanism linking early exposures and the regulation of inflammation in young adulthood (McDade et al. 2017). While these results may seem to run counter to the hypothesis that the body should prioritise investment in immunity when infectious disease risk is high (when payoffs are high) and/or when nutrition is abundant (when costs/trade-offs are minimised), they remind us that immunity is comprised of multiple subsystems of defence. No single measure can provide an indication of overall investment in immunity, and trade-offs across subsystems of immune function are likely based on the relative costs and benefits of each.

To further elaborate this idea, we recently proposed, and tested, an "immunocalibration" hypothesis (Figure 3) to explain variation in patterns of investment in innate (non-specific) and acquired (specific) immunity (McDade et al. 2016). While both subsystems play important, and complementary, roles in host defence, their functional profiles and associated costs are distinct. The development of acquired immunity is a time-dependent, antigen-driven process with relatively high upfront costs, but the costs of maintaining and activating specific defences upon secondary antigen exposures are relatively low. Innate immunity provides rapid, generalised responses to novel (as well as secondary) pathogens that impose lower upfront developmental costs, but higher operating costs – including damage to host tissues. We therefore might expect that relative levels of investment in innate versus acquired immune defences will be optimised in response to local ecological cues that motivate "fast" versus "slow" life history strategies, along the lines of our explorations of similar questions predicting timing and intensity of reproductive investments discussed above.

To test this idea, we hypothesised that abundant nutritional resources, higher levels of pathogen exposure, and low signals of extrinsic mortality risk would favour relatively higher levels of investment in acquired immunity. Using CRP as an indicator of innate immunity, and antibodies against the Epstein-Barr virus as an indirect measure of an aspect of cell-mediated, acquired immunity, we found general support for these predictions among the Cebu cohort in young adulthood (Georgiev et al. 2016). Additional tests with more in-depth measures of immunity are needed, but these findings – as well as those described above – highlight the value of life history theory for providing an explanatory framework that organises prior empirical findings and generates novel hypotheses regarding the impact of developmental environments on human immunity.

Discussion

Working with the CLHNS, we have used LHT to frame a wide array of hypotheses, which we have explored using the lifetime of longitudinal data available for study participants. Our efforts are by no means complete, and there are obvious gaps in our analyses to date. Perhaps most notably, we know more about male than female life history, in part because of the challenges of studying female reproductive endocrinology in a setting in which participants are distributed across urban and rural areas of a large metropolitan area of 3 million people, and in which the repeat sample collections typically needed to accurately characterise female reproductive function are not feasible. We find support for many key LHT assumptions, such as that reproduction carries "costs," and that cues of unstable or dangerous environments motivate an accelerated onset of first reproduction, along with a shift to an immune system oriented around defending against immediate challenges. Patterns of adult male reproductive behaviour and biology unfold as predicted by observations in other species with similar mating systems. The timing and age of reproduction, in turn, appears to have intergenerational consequences for patterns of life history allocation in the next generation, manifesting as inheritance of longer telomeres (and we can surmise, enhanced allocation to lifespan-extending maintenance effort) when multiple recent generations of male ancestors have conceived at older average ages.

Although a useful framework, there are notable challenges to testing LHT predictions in longitudinal human cohort studies. Most broadly, much of the theoretical

foundations of LHT were developed to explain between-species variation in life histories. Although these principles have been used fruitfully to gain insights into human developmental plasticity (Kuzawa and Bragg 2012), they may not always translate to helping explain within-species variation (Stearns and Rodrigues in press). As we discuss in detail elsewhere (Kyweluk et al. 2018), the important role of extrinsic mortality as a predictor of timing of maturity across species (Charnov 1991) may be less applicable to within-species plasticity in humans, in which factors like nutritional sufficiency may play a more central role.

The idea that finite energy leads to functional trade-offs is a core assumption of LHT, for these link functions to one another in predicted patterns of co-variation. Methodologically, identifying trade-offs can be challenging owing to the fact that individuals often vary in resource acquisition and energy budget. Because individuals with larger energy budgets will tend to expend more on all functions compared to less well-nourished individuals, this can lead to positive correlations between different classes of expenditure when groups of individuals are compared. It is possible that such "phenotypic correlations" (Hill and Hurtado 1996) help explain some of our unanticipated findings, such as the positive association between testosterone and measures of immunity (Gettler, McDade, Agustin et al. 2014). More generally, physiological trade-offs that evolved under ancestral conditions of resource scarcity, which are mediated by adaptive patterns of genetic pleiotropy (Finch and Rose 1995), may be less easy to identify when studied under contemporary conditions of chronic energy excess.

Life history theory focuses on functional trade-offs, and, thus, has greatest applicability when studying phenotypes with clear functional significance. Because many disease risk factors and processes studied using cohort designs have ambiguous functions, it is often not straight-forward to link such measures to theoretical expectations from LHT. Thus, it is rarely simple to integrate studies of widely-studied biomarkers of pathophysiology, such as elevated LDL cholesterol or hypertension, into LHT inspired hypotheses. Future work demonstrating the functional significance of such measures, inspired for instance by their role in support of cellular turnover, metabolism or growth (Kuzawa et al. 2006), could help broaden the applicability of theoretical predictions from evolutionary frameworks like life history theory. These limitations aside, we feel that CLHNS work that has been motivated by LHT helps illustrate the power of this integrative framework to inspire testable hypotheses addressing key domains of human population biological research, including growth, reproduction, behaviour and ageing.

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References

Adair LS. 2001. Size at birth predicts age at menarche. Pediatrics. 107(4): E59–E59.

Adair LS, Kuzawa CW, Borja J. 2001. Maternal energy stores and diet composition during pregnancy program adolescent blood pressure. Circulation. 104(9):1034–1039.

Adair LS, Popkin BM, Akin JS, Guilkey DK, Gultiano S, Borja J, Perez L, Kuzawa, CW, et al. 2011. Cohort profile: the Cebu longitudinal health and nutrition survey. Int J Epidemiol. 40(3):619–625.

Alvergne A, Faurie C, Raymond M. 2009. Variation in testosterone levels and male reproductive effort: insight from a polygynous human population. Horm Behav. 56(5):491–497.

Anderson J, McKinley K, Onugha J, Duazo P, Chernoff M, Quinn EA. 2016. Lower levels of human milk adiponectin predict offspring weight for age: a study in a lean population of Filipinos. Matern Child Nutr. 12(4):790–800.

Anderson KG, Kaplan H, Lancaster JB. 2007. Confidence of paternity, divorce, and investment in children by Albuquerque men. Evol Hum Behav. 28(1):1–10.

Arifeen SE, Ekstrom EC, Frongillo EA, Hamadani J, Khan AI, Naved RT, Rahman A, Raqib R, et al. 2018. Cohort Profile: the maternal and infant nutrition interventions in Matlab (MINIMat) cohort in Bangladesh. Int J Epidemiol. 47(6):1737–1738e.

Barker DJ. 1990. The fetal and infant origins of adult disease. BMJ. 301(6761):1111.

Belsky J, Steinberg L, Draper P. 1991. Childhood experience, interpersonal development, and reproductive strategy: an evolutionary theory of socialization. Child Dev. 62(4):647–670.

Bouwhuis S, Charmantier A, Verhulst S, Sheldon BC. 2010. Individual variation in rates of senescence: natal origin effects and disposable soma in a wild bird population. J Anim Ecol. 79(6):1251–1261.

Boyette A, Lew-Levy S, Gettler L. 2018. Dimensions of fatherhood in a Congo Basin village: a multi-method analysis of intra-cultural variation in men's parenting and its relevance for child health. Curr Anthropol. 59:1–33.

Bragg JM, Kuzawa CW, Agustin SS, Banerjee MN, McDade TW. 2012. Age at menarche and parity are independently associated with Anti-Mullerian hormone, a marker of ovarian reserve, in Filipino young adult women. Am J Hum Biol. 24(6):739–745.

Bribiescas RG. 2006. Men – evolutionary and life history. Cambridge (MA): Harvard University Press.

Cameron N, De Wet T, Ellison GT, Bogin B. 1998. Growth in height and weight of South African urban infants from birth to five years: the Birth to Ten Study. Am J Hum Biol. 10(4):495–504.

Charnov EL. 1991. Evolution of life history variation among female mammals. Proc Natl Acad Sci USA. 88(4):1134–1137.

Doblhammer G, Oeppen J. 2003. Reproduction and longevity among the British peerage: the effect of frailty and health selection. Proc R Soc Lond B. 270(1524):1541–1547.

Eisenberg D, Rej P, Duazo P, Carba D, Hayes MG, Kuzawa CW. 2020. Testing for paternal influences on offspring telomere length in a human cohort in the Philippines. Am J Phys Anthropol. 171(3): 520–528.

Eisenberg DT. 2011. An evolutionary review of human telomere biology: the thrifty telomere hypothesis and notes on potential adaptive paternal effects. Am J Hum Biol. 23(2):149–167.

Eisenberg DT, Hayes MG, Kuzawa CW. 2012. Delayed paternal age of reproduction in humans is associated with longer telomeres across two generations of descendants. Proc Natl Acad Sci USA. 109(26): 10251–10256.

Eisenberg DTA, Kuzawa CW. 2018. The paternal age at conception effect on offspring telomere length: mechanistic, comparative and adaptive perspectives. Philos Trans R Soc Lond B Biol Sci. 373:20160442.

Eisenberg DTA, Lee NR, Rej PH, Hayes MG, Kuzawa CW. 2019. Older paternal ages and grandpaternal ages at conception predict longer telomeres in human descendants. Proc R Soc B. 286(1903):20190800.

Ellis BJ, Figueredo AJ, Brumbach BH, Schlomer GL. 2009. Fundamental dimensions of environmental risk. Hum Nat. 20(2):204–268.

Eveleth PB, Tanner JM. 1990. Worldwide variation in human growth. Cambridge, England, New York: Cambridge University Press.

Finch CE, Rose MR. 1995. Hormones and the physiological architecture of life history evolution. Q Rev Biol. 70(1):1–52.

Fried RL, Mayol NL, McDade TW, Kuzawa CW. 2017. Maternal metabolic adaptations to pregnancy among young women in Cebu, Philippines. Am J Hum Biol. 29:626–631.

Georgiev AV, Kuzawa CW, McDade TW. 2016. Early developmental exposures shape trade-offs between acquired and innate immunity in humans. Evol Med Public Health. 2016(1):256–269.

Georgiev AV, Ryan CP, Borja JB, Kuzawa CW. 2017. Is early postnatal growth velocity, a proxy of minipubertal androgen action, related to adult second-to-fourth digit (2D:4D) ratios in men? A test in Cebu, Philippines. Am J Hum Biol. 29:e23047.

Gettler LT. 2016. Becoming DADS: considering the role of cultural context and developmental plasticity for paternal socioendocrinology. Curr Anthropol. 57(S13):S38–S51.

Gettler LT, Agustin SS, Kuzawa CW. 2010. Testosterone, physical activity, and somatic outcomes among Filipino males. Am J Phys Anthropol. 142(4):590–599.

Gettler LT, Kuo PX, Rosenbaum S, Avila JL, McDade TW, Kuzawa CW. 2019. Sociosexuality, testosterone, and life history status: prospective associations and longitudinal changes among men in Cebu, Philippines. Evol Hum Behav. 40(2):249–258.

Gettler LT, McDade TW, Kuzawa CW. 2011. Cortisol and testosterone in Filipino young adult men: evidence for co-regulation of both hormones by fatherhood and relationship status. Am J Hum Biol. 23(5): 609–620.

Gettler LT, McDade TW, Agustin SS, Feranil AB, Kuzawa CW. 2013. Do testosterone declines during the transition to marriage and fatherhood relate to men's sexual behavior? Evidence from the Philippines. Horm Behav. 64(5):755–763.

Gettler LT, McDade TW, Agustin SS, Feranil AB, Kuzawa CW. 2014. Testosterone, immune function, and life history transitions in Filipino males (Homo sapiens). Int J Primatol. 35(3–4):787–804.

Gettler LT, McDade TW, Bragg JM, Feranil AB, Kuzawa CW. 2015. Developmental energetics, sibling death, and parental instability as predictors of maturational tempo and life history scheduling in males from Cebu, Philippines. Am J Phys Anthropol. 158(2):175–184.

Gettler LT, McDade TW, Feranil AB, Kuzawa CW. 2011. Longitudinal evidence that fatherhood decreases testosterone in human males. Proc Natl Acad Sci USA. 108(39):16194–16199.

Gettler LT, McDade TW, Feranil AB, Kuzawa CW. 2012. Prolactin, fatherhood, and reproductive behavior in human males. Am J Phys Anthropol. 148(3):362–370.

Gettler LT, McDade TW, Feranil AB, Agustin SS, Kuzawa CW. 2014. Salivary estradiol and testosterone in Filipino men: diurnal patterns and relationships with adiposity. Am J Hum Biol. 26(3):376–383.

Gettler LT, McKenna JJ, McKenna TW, Agustin SS, Kuzawa CW. 2012. Does cosleeping contribute to lower testosterone levels in fathers? Evidence from the Philippines. PLOS One. 7(9):e41559.

Gettler LT, Ryan CP, Eisenberg DTA, Rzhetskaya M, Hayes MG, Feranil AB, Bechayda SA, Kuzawa CW. 2017. The role of testosterone in coordinating male life history strategies: the moderating effects of the androgen receptor CAG repeat polymorphism. Horm Behav. 87:164–175.

Gluckman PD, Hanson MA. 2006. Evolution, development and timing of puberty. Trends Endocrinol Metab. 17(1):7–12.

Gray PB, Anderson KG. 2010. Fatherhood: evolution and human paternal behavior. Cambridge (MA): Harvard University Press.

Gray PB, Kahlenberg SM, Barrett ES, Lipson SF, Ellison PT. 2002. Marriage and fatherhood are associated with lower testosterone in males. Evol Hum Behav. 23(3):193–201.

Gray PB, Mchale TS, Carré JM. 2017. A review of human male field studies of hormones and behavioral reproductive effort. Horm Behav. 91: 52–67.

Grebe NM, Sarafin RE, Strenth CR, Zilioli S. 2019. Pair-bonding, fatherhood, and the role of testosterone: a meta-analytic review. Neurosci Biobehav Rev. 98:221–233.

Hanson M, Gluckman P. 2011. Developmental origins of noncommunicable disease: population and public health implications. Am J Clin Nutr. 94(Suppl_6):1754S–1758S.

Hennig BJ, Unger SA, Dondeh BL, Hassan J, Hawkesworth S, Jarjou L, Jones KS, Moore SE, et al. 2017. Cohort profile: the Kiang West Longitudinal Population Study (KWLPS)-a platform for integrated research and health care provision in rural Gambia. Int J Epidemiol. 46(2):e13.

Hewlett BS. 1991. Intimate fathers: the nature and context of Aka Pygmy paternal infant care. Ann Arbor (MI): University of Michigan Press.

Hewlett BS, Macfarlan SJ. 2010. Fathers' roles in hunter-gatherer and other small-scale cultures. In: Lamb, ME, editor. The role of the father in child development. Hoboken (NJ): John Wiley & Sons, Inc.

Hill K, Hurtado AM. 1996. Aché life history: The Ecology and Demography of a Foraging People. New York: Aldine de Gruyter.

Hill K, Kaplan H. 1999. Life history traits in humans: theory and empirical studies. Annu Rev Anthropol. 28(1):397–430.

Ho KK, Pinsky JL, Kannel WB, Levy D. 1993. The epidemiology of heart failure: the Framingham Study. J Am Coll Cardiol. 22(4 Suppl A): 6A–13A.

Jasienska G. 2009. Reproduction and lifespan: trade-offs, overall energy budgets, intergenerational costs, and costs neglected by research. Am J Hum Biol. 21(4):524–532.

Kirkwood TB, Rose MR. 1991. Evolution of senescence: late survival sacrificed for reproduction. Philos Trans R Soc Lond, B, Biol Sci. 332(1262): 15–24.

Kleiber M. 1932. Body size and metabolism. Hilg. 6(11):315–353.

Kleiman DG, Malcolm JR. 1981. The evolution of male parental investment in mammals. In: Gubernick, D, Klopfer, P, editors. Parental Care in Mammals. New York (NY): Plenum Press.

Kuzawa C, Snodgrass J, Leonard W. 2006. Evolutionary medicine and human cholesterol. Am J Hum Biol. 18(2): 261.

Kuzawa CW. 2005. Fetal origins of developmental plasticity: are fetal cues reliable predictors of future nutritional environments? Am J Hum Biol. 17(1):5–21.

Kuzawa CW. 2007. Developmental origins of life history: growth, productivity, and reproduction. Am J Hum Biol. 19(5):654–661.

Kuzawa CW, Adair LS. 2003. Lipid profiles in adolescent Filipinos: relation to birth weight and maternal energy status during pregnancy. Am J Clin Nutr. 77(4):960–966.

Kuzawa CW, Bragg JM. 2012. Plasticity in human life history strategy: implications for contemporary human variation and the evolution of genus Homo. Curr Anthropol. 53(S6):S369–S382.

Kuzawa CW, Chugani HT, Grossman LI, Lipovich L, Muzik O, Hof PR, Wildman DE, Sherwood, CC, et al. 2014. Metabolic costs and evolutionary implications of human brain development. Proc Natl Acad Sci USA. 111(36):13010–13015.

Kuzawa CW, Fried RL, Borja JB, McDade TW. 2017. Maternal pregnancy C-reactive protein predicts offspring birth size and body composition in metropolitan Cebu, Philippines. J Dev Orig Health Dis. 8(6): 674–681.

Kuzawa CW, Gettler LT, Huang Y-Y, McDade TW. 2010. Mothers have lower testosterone than non-mothers: evidence from the Philippines. Horm Behav. 57(4–5):441–447.

Kuzawa CW, Gettler LT, Muller MN, McDade TW, Feranil AB. 2009. Fatherhood, pairbonding and testosterone in the Philippines. Horm Behav. 56(4):429–435.

Kuzawa CW, McDade TW, Adair LS, Lee N. 2010. Rapid weight gain after birth predicts life history and reproductive strategy in Filipino males. Proc Natl Acad Sci USA. 107(39):16800–16805.

Kuzawa CW, Quinn EA. 2009. Developmental origins of adult function and health: evolutionary hypotheses. Annu Rev Anthropol. 38(1): 131–147.

Kyweluk MA, Georgiev AV, Borja JB, Gettler LT, Kuzawa CW. 2018. Menarcheal timing is accelerated by favorable nutrition but unrelated to developmental cues of mortality or familial instability in Cebu, Philippines. Evol Hum Behav. 39(1):76–81.

Lamb ME. 2004. The Role of the Father in Child Development. New York: John Wiley & Sons.

Lee J, Fried R, Thayer Z, Kuzawa CW. 2014. Preterm delivery as a predictor of diurnal cortisol profiles in adulthood: evidence from Cebu, Philippines. Am J Hum Biol. 26(5):598–602.

Lukas D, Clutton-Brock TH. 2013. The evolution of social monogamy in mammals. Science. 341(6145):526–530.

Marlowe F. 2000. Paternal investment and the human mating system. Behav Process. 51(1–3):45–61.

Marmot MG, Stansfeld S, Patel C, North F, Head J, White I, Brunner E, Feeney A. 1991. Health inequalities among British civil servants: the Whitehall II study. Lancet. 337(8754):1387–1393.

Mattison SM, Scelza B, Blumenfield T. 2014. Paternal investment and the positive effects of fathers among the matrilineal Mosuo of Southwest China. Am Anthropol. 116(3):591–610.

McDade TW. 2003. Life history theory and the immune system: steps toward a human ecological immunology. Am J Phys Anthropol. 37: 100–125.

McDade TW. 2005. Life history, maintenance, and the early origins of immune function. Am J Hum Biol. 17(1):81–94.

McDade TW, Beck MA, Kuzawa CW, Adair LS. 2001. Prenatal undernutrition and postnatal growth are associated with adolescent thymic function. J Nutr. 131(4):1225–1231.

McDade TW, Georgiev AV, Kuzawa CW. 2016. Trade-offs between acquired and innate immune defenses in humans. Evol Med Public Health. 2016(1):1–16.

McDade TW, Jones MJ, Miller G, Borja J, Kobor MS, Kuzawa CW. 2018. Birth weight and postnatal microbial exposures predict the distribution of peripheral blood leukocyte subsets in young adults in the Philippines. J Dev Orig Health Dis. 9(2):198–207.

McDade TW, Rutherford J, Adair L, Kuzawa CW. 2010. Early origins of inflammation: microbial exposures in infancy predict lower levels of C-reactive protein in adulthood. Proc R Soc B. 277(1684):1129–1137.

McDade TW, Ryan C, Jones MJ, Macisaac JL, Morin AM, Meyer JM, Borja JB, Miller GE, et al. 2017. Social and physical environments early in development predict DNA methylation of inflammatory genes in young adulthood. Proc Natl Acad Sci USA. 114(29):7611–7616.

Mitteldorf J. 2010. Female fertility and longevity. Age (Dordr). 32(1): 79–84.

Muehlenbein MP, Bribiescas RG. 2005. Testosterone-mediated immune functions and male life histories. Am J Hum Biol. 17(5):527–558.

Muller MN. 2017. Testosterone and reproductive effort in male primates. Horm Behav. 91:36–51.

Nettle D, Coall DA, Dickins TE. 2011. Early-life conditions and age at first pregnancy in British women. Proc R Soc B. 278(1712):1721–1727.

Poulton R, Moffitt TE, Silva PA. 2015. The Dunedin Multidisciplinary Health and Development Study: overview of the first 40 years, with an eye to the future. Soc Psychiatry Psychiatr Epidemiol. 50(5): 679–693.

Quinn EA. 2013. No evidence for sex biases in milk macronutrients, energy, or breastfeeding frequency in a sample of Filipino mothers. Am J Phys Anthropol. 152(2):209–216.

Quinn EA, Largado F, Borja JB, Kuzawa CW. 2015. Maternal characteristics associated with milk leptin content in a sample of Filipino women and associations with infant weight for age. J Hum Lact. 31(2): 273–281.

Richter L, Norris S, Pettifor J, Yach D, Cameron N. 2007. Cohort Profile: Mandela's children: the 1990 birth to twenty study in South Africa. Int J Epidemiol. 36(3):504–511.

Rosenbaum S, Gettler LT, McDade TW, Bechayda SS, Kuzawa CW. 2018. Does a man's testosterone "rebound" as dependent children grow up, or when pairbonds end? A test in Cebu, Philippines. Am J Hum Biol. 30(6):e23180.

Rosenbaum S, McDade TW, Agustin S, Kuzawa CW, Gettler LT. 2019. Facultative fatherhood? Parental and alloparental caretaking tradeoffs in Cebu, the Philippines. Am J Phys Anthropol. 168(s68):208.

Rutherford JN, Victoria AD, Ragsdale HB, Avila JL, Lee NR, Kuzawa CW. 2019. Global population variation in placental size and structure: evidence from Cebu, Philippines. Placenta. 85:40–48.

Ryan CP, Hayes MG, Lee NR, McDade TW, Jones MJ, Kobor MS, Kuzawa CW, Eisenberg DTA. 2018. Reproduction predicts shorter telomeres and epigenetic age acceleration among young adult women. Sci Rep. 8(1):11100.

Ryan CP, McDade TW, Gettler LT, Eisenberg DT, Rzhetskaya M, Hayes M, Kuzawa CW. 2017. Androgen receptor CAG repeat polymorphism and hypothalamic-pituitary-gonadal function in Filipino young adult males. Am J Hum Biol. 29(1): e22897.

Sarma MS, Kuo PX, Bechayda SA, Kuzawa CW, Gettler LT. 2018. Exploring the links between early life and young adulthood social experiences and men's later life psychobiology as fathers. Physiol Behav. 193: 82–89.

Schooling CM, Jiang CQ, Heys M, Zhang WS, Lao XQ, Adab P, Cowling BJ, Thomas GN, et al. 2008. Is leg length a biomarker of childhood conditions in older Chinese women? The Guangzhou Biobank Cohort Study. J Epidemiol Community Health. 62(2):160–166.

Stearns SC. 1992. The evolution of life histories. Oxford; New York: Oxford University Press.

Stearns SC, Koella JC. 1986. The evolution of phenotypic plasticity in life-history traits: predictions of reaction norms for age and size at maturity. Evolution. 40(5):893–913.

Stearns SC, Rodrigues AMM. in press. On the use of "life history theory" in evolutionary psychology. Evol Hum Behav.

Stein AD, Melgar P, Hoddinott J, Martorell R. 2008. Cohort Profile: the institute of nutrition of Central America and Panama (INCAP) Nutrition Trial Cohort Study. Int J Epidemiol. 37(4):716–720.

Thayer ZM, Feranil AB, Kuzawa CW. 2012. Maternal cortisol disproportionately impacts fetal growth in male offspring: evidence from the Philippines. Am J Hum Biol. 24(1):1–4.

Urlacher SS, Snodgrass JJ, Dugas LR, Sugiyama LS, Liebert MA, Joyce CJ, Pontzer H. 2019. Constraint and trade-offs regulate energy expenditure during childhood. Sci Adv. 5(12):eaax1065.

Walker SP, Chang SM, Powell CA, Grantham-Mcgregor SM. 2005. Effects of early childhood psychosocial stimulation and nutritional supplementation on cognition and education in growth-stunted Jamaican children: prospective cohort study. Lancet. 366(9499):1804–1807.

West GB, Brown JH, Enquist BJ. 1999. The fourth dimension of life: fractal geometry and allometric scaling of organisms. Science. 284(5420): 1677–1679.

West GB, Woodruff WH, Brown JH. 2002. Allometric scaling of metabolic rate from molecules and mitochondria to cells and mammals. Proc Natl Acad Sci USA. 99(Supplement 1):2473–2478.

Westendorp RG, Kirkwood TB. 1998. Human longevity at the cost of reproductive success. Nature. 396(6713):743–746.

Williams GC. 1966. Adaptation and natural selection; A Critique of some Current Evolutionary thought. Princeton (NJ); Princeton University Press.

Wilson M, Daly M. 1997. Life expectancy, economic inequality, homicide, and reproductive timing in Chicago neighbourhoods. BMJ. 314(7089):1271–1274.

Wingfield J, Hegner R, Ball G, Duffy A. 1990. The 'challenge hypothesis': theoretical implications for patterns of testosterone secretion, mating systems, and breeding strategies. Am Nat. 136:829–846.

Wingfield JC. 2017. The challenge hypothesis: where it began and relevance to humans. Horm Behav. 92:9–12.

Winking J, Gurven M, Kaplan H, Stieglitz J. 2009. The goals of direct paternal care among a South Amerindian population. Am J Phys Anthropol. 139(3):295–304.