EVOLUTIONARY PERSPECTIVES ON HUMAN GROWTH AND DEVELOPMENT

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EVOLUTIONARY PERSPECTIVES ON HUMAN GROWTH AND DEVELOPMENT

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EDITORIAL
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Editorial: Evolutionary Perspectives on Human Growth and Development

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Keywords: evolutionary biology, growth and development, life history, fetal development, childhood

Editorial on the Research Topic

Evolutionary Perspectives on Human Growth and Development

The 10 articles in this special topic represent the fruits of an evolutionary approach to human development that spans from fetus to young adults, and across subsistence and industrialized populations. In doing so it touches on the genetic basis of human growth and development and the impact of larger environmental and social conditions. The collection will appeal to those interested in an understanding of the developmental pattern of our slowly developing and long-lived species and its variations. Below I highlight and integrate crucial elements from each of the articles in the special topic and point toward future research.

In *Why and How Imprinted Genes Drive Fetal Programming*, Crespi incorporates evolutionary ideas of genomic conflict and imprinted genes into the well-established notion of fetal programming for postnatal growth and development. Crespi's call for the inclusion of imprinted maternal genes in longitudinal studies of the effects of low birthweight and subsequent catch-up growth echoes through the other contributions.

In *Timing of the Infancy-Childhood Transition in Rural Gambia*, Bernstein et al. use patterns of weight for age z scores to place the infant-child transition among children in the Gambia at 9 months, some 3 months earlier than similar results in the U.K. This runs counter to ideas that undernutrition leads to extended infant growth. Instead, it suggests that infant growth may be cut short to allocate energy for immune development, a life history trade-off that deserves more attention in the future.

Turing to middle childhood, in *DHEAS and Human Development: An Evolutionary Perspective*, Campbell focuses adrenarche as an endocrinological marker. He argues that DHEAS acts at the IGF-1 receptor, giving it a role brain in development starting with the 5-8 transition. Given evidence that IGF-1 is stimulated by animal protein in the diet, the roots of human middle childhood may go back to the origins of meat consumption with the Genus Homo.

In their contribution, *Emerging Adulthood, A Pre-Adult Life History Stage*, Hochberg and Konner point to continued brain development after and lasting into the mid-20s, suggesting young adulthood as biologically based rather than socially constructed. Chimpanzee brain maturation ends at puberty, pointing to a unique human life history stage that needs to be characterized more fully in terms of endocrinology and its relationship to earlier development.

Young adulthood is also marked by peak bone mass as explored by Kralick and Zemel, in *Evolutionary Perspectives on the Developing Skeleton and Implications for Lifelong Health*. In fact, Kralick and Zemel suggest that the most important determinant of osteoporosis for older women life may be low peak bone mass. Bone mass is diminished by a sedentary lifestyle. Thus, osteoporosis

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is not only an evolutionary disease, but changes in activity with the advent of agriculture may have been a key factor.

The importance of the agriculture revolution to modern human growth and development is central to Wells and Stock in *Life History Transitions at the Origins of Agriculture: A Model for Understanding How Niche Construction Impacts Human Growth, Demography and Health*. The article makes a forceful case for the selective impact of the agricultural revolution human growth and development through its effects on immune defenses against infectious disease. This intriguing idea deserves much future consideration in understanding growth and development in subsequent populations as well as the paleopathology of juveniles at the origins of civilization.

Little's contribution, *Evolutionary Strategies for Body Size* focuses on what is known about factors contribution to variation in human body size in populations outside the bounds of civilization. Variation in phenotypes such the short statured pygmies of the Congo and the long lean Turkana pastoralist of Kenya are well documented. The availability of non-invasive sample collection and assay techniques means that future research may now focus on the underlying physiological growth processes.

At the other end of the environmental spectrum, in *Sexual Dimorphism of Size Ontogeny and Life History*, German and Hochberg consider differences in height over the life span across a set of national populations. Not only does sexual dimorphism emerge with puberty, but also the authors find it is maximal under good environmental conditions. Importantly, these results hold across a set of subsistence populations as well. In other words, male growth is more responsive to environmental variation than females, and in ways that are likely derived from developmental adaptations to energy constraints.

The final two papers take the topic deeper into environments not anticipated in human evolution and more fully into the realm of global public health. *People Are Taller in Countries With Better Environmental Conditions* by German et al. demonstrates differences in adult height across OCED countries as a function of modern environments, including air pollution, income inequality and stress, with males more affected than females. It will be important to elaborate how these environmental factors map onto the those experienced during our evolution history if we are to understand future developmental outcomes and safeguard human health in the years to come.

Finally, in *Nutrition Justice: Uncovering Invisible Pathways to Malnutrition*, Hanieh et al. bring attention to social and political factors contributing to the double burden of disease in marginalized populations. But at the core of their argument is an evolutionary perspective. That underfed babies exhibit growth faltering and stunting leading to metabolic complications and disease as adults IS an evolutionary adaptation for survival. One that represents the impact of environmental fluctuation during human evolutionary history in shaping human life history. It also brings us back full circle to the genetic underpinnings of fetal programming discussed by Crespi.

Together these articles demonstrate the integrative nature of an evolutionary approach to human growth and development. Though we divide growth and development into stages, each stage is related to the next, and they are all linked to fetal development. Thus, despite its responsiveness to environmental factors, the developing human body has a remarkable capacity to return to a growth trajectory set up in utero. It is a tragedy when social conditions not only disrupt that trajectory, but also cause us to lose sight of it in the first place.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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REVIEW
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Emerging Adulthood, a Pre-adult Life-History Stage

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The duration of human maturation has been underestimated; an additional 4–6-year pre-adult period of "emerging adulthood," should be included in models of human maturation. It is a period of brain maturation, learning about intimacy and mutual support, intensification of pre-existing friendships, family-oriented socialization, and the attainment of those social skills that are needed for mating and reproduction. We propose that emerging adulthood is a life-history stage that is a foundation of the high reproductive success of human beings. The period of emerging adulthood has an evolutionary context and developmental markers, and we present evidence that supports the idea that emerging adults require protection because they are still learning and maturing.

Keywords: life history, adolescence, human evolution, hominin, comparative development, brain development

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INTRODUCTION

Growing evidence suggests that an individual at the end of adolescence cannot be considered to be an adult when using physical, physiological, intellectual, social, emotional, and behavioral measures. When adolescents in developed societies mature and achieve adult body size, their behavior often remains immature. Specialists in adolescent medicine have recognized this incongruity, and have redefined adolescence to include young adults up to age 24 years, of whom many have not yet assumed adult roles (1, 2). Reproduction in contemporary forager societies also begins several years after adolescence and post-adolescent individuals are often limited in their gathering and/or hunting skills (3–5). Compared to other mammals, primates produce few offspring. Humans have an even slower growth rate than that of non-human primates of comparable size, but human growth may be even more prolonged than is generally realized.

Arnett proposed emerging adulthood as a phase of life between adolescence and full-fledged adulthood, with distinctive demographic, social, and subjective psychological features (6, 7). This life- history stage applies to individuals aged between 18 and 25 years, the period during which they become more economically independent by training and/or education. Previously, the psychodynamic theorist Erik Erikson identified a stage that he called a *prolonged adolescence* or *psychosocial moratorium* in young people in developed societies (8, 9). Much more recently, Hopwood and colleagues explored genetic and environmental influences on personality development during the transition to adulthood in same-sex male and female monozygotic and dizygotic twins assessed in late adolescence (approximately age 17 years), emerging adulthood (∼24 years), and young adulthood (∼29 years) (10). Their genetically-informed results support a life-course perspective on personality development during the transition to adulthood. In addition, the United Nations has identified youth, defined as the period from 15 to 24 years of age, as a period of vulnerability worldwide and has made it a priority for multiple interventions (11).

Here, we use an evolutionary approach in order to understand emerging adulthood, arguing that it is not just a sociological transition period but a biological life-history phase. Trait variability, whether it is molecular, cellular, physiological, morphological, or behavioral, is the leading edge of evolution. Together with genetic evolution, plasticity in developmental programming has evolved to provide the organism with traits that can secure its survival and reproductive success (12). Life-history theory is a powerful tool for understanding child growth and development from an evolutionary perspective (2, 13, 14). We provide evidence that emerging adulthood exists in some other mammals, which implies genetic evolution, and we discuss emerging adulthood in foraging as well as developed societies, which implies the occurrence of adaptive plasticity and cultural influences. We propose that genetic and cultural evolution have interacted to produce the emerging adulthood stage in human life history.

DEFINING THE TRANSITION FROM ADOLESCENCE TO EMERGING ADULTHOOD

Determining the exact time of transitions between life-history stages is challenging (13). Saltations (growth spurts) and transitions occur during human growth (15, 16), and stages have a central place in evolutionary life-history theory, but the turning points are theoretical constructions in which some aspects of a transition are highlighted.

Puberty produces an endocrine transformation with striking somatic and behavioral changes, especially in body image, sex identity, aggression, and impulsivity. To define a maturational stage between adolescence and adulthood, we need first to define the end of adolescence. During this transition, growth velocity decelerates, blood and tissue hormone levels increase, aggression becomes less overt, and learning and maturation mitigate hormonal impact.

Using maturational measures avoids the pitfalls of defining emerging adulthood according to chronological age. For example, the Tanner scale of adolescent development is based on external primary and secondary sex characteristics. Tanner stage V recognizes the conclusion of puberty in boys when the testicular volume is >20 ml and the length of the penis is >14 cm (17) and in girls when the breast reaches final adult size and the areola returns to the contour of the surrounding breast with a projecting central papilla (18).

Here, we define the transition between adolescence and emerging adulthood as occurring when growth returns to its prepubertal trajectory and the boy or girl is at Tanner stage IV (19). Boys at this stage have a testicular volume between 12 and 20 ml, their scrotal skin darkens, and the length of their penis is ∼10 cm. Girls at this stage have experienced menarche, their breasts are of adult size and elevated, and the areola and papilla form a secondary mound which projects from the contour of the surrounding breast. Body composition continues to change during emerging adulthood, in terms of relative fat mass, lean body mass, and total body bone mineral content and bone mineral density increase (20), but the most important maturational changes after adolescence, even if defined as the end of Tanner Stage 4, are in the brain.

Brain size may be a pacemaker in mammalian life history (21), and it underlies the remarkable human capacity for learning and communication, but the length of the brain's developmental trajectory was until recently underestimated. It is now clear that brain development does not stop with the completion of puberty when adult brain *size* is attained. Brain maturation continues beyond adolescence, extending until around age 25 years, and this recently discovered prolongation provides critical support for emerging adulthood as a post-adolescent maturational stage (22). Compared to other primates, human newborns are neurologically and behaviorally altricial because many aspects of brain development are protracted, including that of the prefrontal cortex (23). The cortical architectural units or minicolumns in the prefrontal cortex of humans are wider than those of the great apes, an increase that occurs after puberty in humans, but not in chimpanzees (24). In chimpanzees, but not in humans, myelination becomes complete at about the time of sexual maturity (25). Interestingly, human brain regions with protracted development are the same that have undergone the greatest degree of volumetric enlargement in primate evolution (26).

In a large-scale longitudinal pediatric neuroimaging study, brain maturation was found to continue after adolescence: post-adolescent increases in white matter are linear while the changes in the cortical gray matter are non-linear. Cortical white matter in particular continues to increase into the mid-twenties, which is likely related to the efficiency and speed of cortical connectivity (27, 28). In another study, Sowell and her colleagues spatially and temporally mapped brain maturation in North American adolescents (age 12–16 years) and young adults (age 23–30 years) using a whole-brain, voxel-by-voxel statistical analysis of high-resolution structural magnetic resonance images (29). They found that the pattern of brain maturation during these years was distinct from earlier development and was localized to large regions of the dorsal, medial, and orbital frontal cortex and lenticular nuclei. They also reported relatively little change at other brain locations. They concluded that cognitive function improves throughout adolescence, and this improvement is associated with parallel post-adolescent reductions in gray matter density (as white matter increases) in frontal and striatal regions. It has been argued that such brain changes should mitigate the guilt of adolescent delinquents who have not yet gone through them (30–32).

Asato and colleagues also investigated white matter maturation during adolescence using diffusion tensor imaging and reported that (a) pubertal hormones influence white matter development and maturation and (b) white matter connectivity and the executive control of behavior is still immature in adolescence (33). Jolles and colleagues investigated the association between whole-brain functional connectivity and cognitive and emotional functions in children (11–13 years) and young adults (19–25 years) (34). Although they found similar patterns of functional connectivity in children and young adults, there were differences in the size of the functionally connected

regions and the strength of functional connectivity. Thus, functional connectivity continues to change during and after adolescence, and these developmental differences in functional connectivity patterns were associated with higher cognitive or emotional functions and basic visual and sensorimotor functions.

In another study comparing social and emotional functioning of children, adolescents, and young adults, by analyzing the age-dependent development of five functionally distinct cingulate-based intrinsic connectivity networks (ICNs), Kelly and colleagues provide additional evidence that brain maturation extends beyond adolescence into young adulthood (35). They found that the pattern of correlation with voxels proximal to the seed region of interest was age-dependent: the pattern was diffuse in children (mean age 10.6 years), was less diffuse in adolescents (mean age 15.4 years), and showed signs of becoming focal in young adults (mean age 22.4 years). Also, the greatest development occurred in those ICNs associated with social and emotional functions. Finally, in their study of the brains of 103 healthy subjects aged 5–32 years using diffusion tensor tractography, Lebel and Beaulieu provide further evidence that brain maturation continues from childhood into adulthood (36). Association tracts show within-subject maturation of measures indicative of myelination and axon density.

Collectively, these studies provide strong evidence that brain development and maturation continue in young adulthood; the idea that brain maturation is finalized during adolescence is no longer tenable. Psychologically, emerging adulthood is a stage when an individual's cognitive abilities increase to reach their peak in their fourth decade and possibly beyond (37). Schaie and colleagues included 13 measures of crystallized abilities influenced by schooling and experience. The critical abilities from this perspective are those that enable the learning of new things, that is, working memory and fluid intelligence; these, as well as processing speed (38), peak in the mid 20s.

Emerging adulthood is also a social stage: it is a period of learning about intimacy and mutual support, intensification of pre-existing friendships, family-oriented socialization, political awareness, developing new relationships, and the attainment of biosocial skills that are needed for successful mating and reproduction. Finally, it is also a stage of understanding self-concepts and ideal concepts, emphasized interpersonal reactivity and obligation, self-expressiveness, and contempt toward particular ideologies (39). The attainment of these cognitive, emotional, and social abilities is the result of a complex interplay of maturation and interaction with the environment, but it is now possible to say that at least in the earlier years of emerging adulthood, they are correlated with and possibly caused by brain maturation. There is also evidence that brain size growth continues into the third decade in some individuals. In these individuals, hypothalamic maturation, puberty, and the resultant hormonal surges are dissociated from and even precede development and maturity of frontal cortex (40, 41).

Emerging adulthood is associated with other physiological changes, such as bone mineral accretion, the completion of growth, and [frequently] first reproduction. Hence, emerging adulthood begins as a physiological, but most importantly a neural transformation in which behavioral and social functions interact, with consequences for impulse control in domains that have put the individual at risk during puberty. We will argue that this life-history phase has unfolded throughout hominin evolution. In **Figure 1** we show the timeline of maturation of the main physical, behavioral and social traits.

GROWTH-RELATED DEFINITION OF THE TRANSITION TO EMERGING ADULTHOOD

To define the transition from adolescence to emerging adulthood, we use the age at which growth velocity returns to prepubertal levels (**Figure 2A**). The adolescent growth spurt can be identified from the growth velocity curve, and its takeoff is signaled when the rate of growth changes from deceleration to acceleration at the end of the juvenile stage (13). This inflection point marks the beginning of the adolescent growth spurt. The point at which the curvilinear growth velocity spurt returns to the pre-takeoff velocity defines for us the end of adolescence and the beginning of emerging adulthood. This refinement of the "return to [pre-]takeoff velocity," which was previously proposed by Leigh and Park (42), is essential for understanding the human pubertal growth spurt (43). This model, displayed in **Figure 2A**, explains the apparently diminished peak height velocity in delayed puberty and is the basis of adult height predictions for prepubertal children.

In an allometric analysis of 21 species of anthropoid primates, the age at return to pre-takeoff velocity and the adult body mass are positively correlated in both females and males (**Figure 2B**). The age at return to pre-takeoff velocity occurs later in human beings than other primates because of the lateness of our growth spurt when body mass is considered (42). Overall, the growth spurt in most primates is quite minimal, and little is known about the relationship between the age at return to prepubertal growth velocity and the appearance of secondary sexual characteristics at puberty. Takeoff velocity occurs early in gorillas, and despite their greater body mass, female gorillas become sexually mature at a younger age than female chimpanzees (44). Similar to humans, vervet (*Cercopithecus aethiops*) and rhesus monkeys (*Macaca mulatta*) show a relatively late return to prepubertal growth velocity. Interestingly, this positive correlation between the age at return to prepubertal growth velocity curve and body mass also exists in six small-scale societies described in Walker's Database for Indigenous Cultural Evolution (http://dice.missouri.edu/) (**Figures 2C,D**).

THE EVOLUTIONARY CONTEXT OF EMERGING ADULTHOOD

Evolutionary Life-History Theory

Life history is defined as the allocation of an organism's energy toward growth, maintenance, reproduction, raising offspring to independence, and avoiding death (45), and adaptation to environmental changes requires the selection of certain life-cycle traits (46, 47) (**Figure 3**). Evolutionary life-history theory attempts to explain and predict tradeoffs that optimize energy expenditure, reproductive advantage, and risk (2, 14, 48, 49).

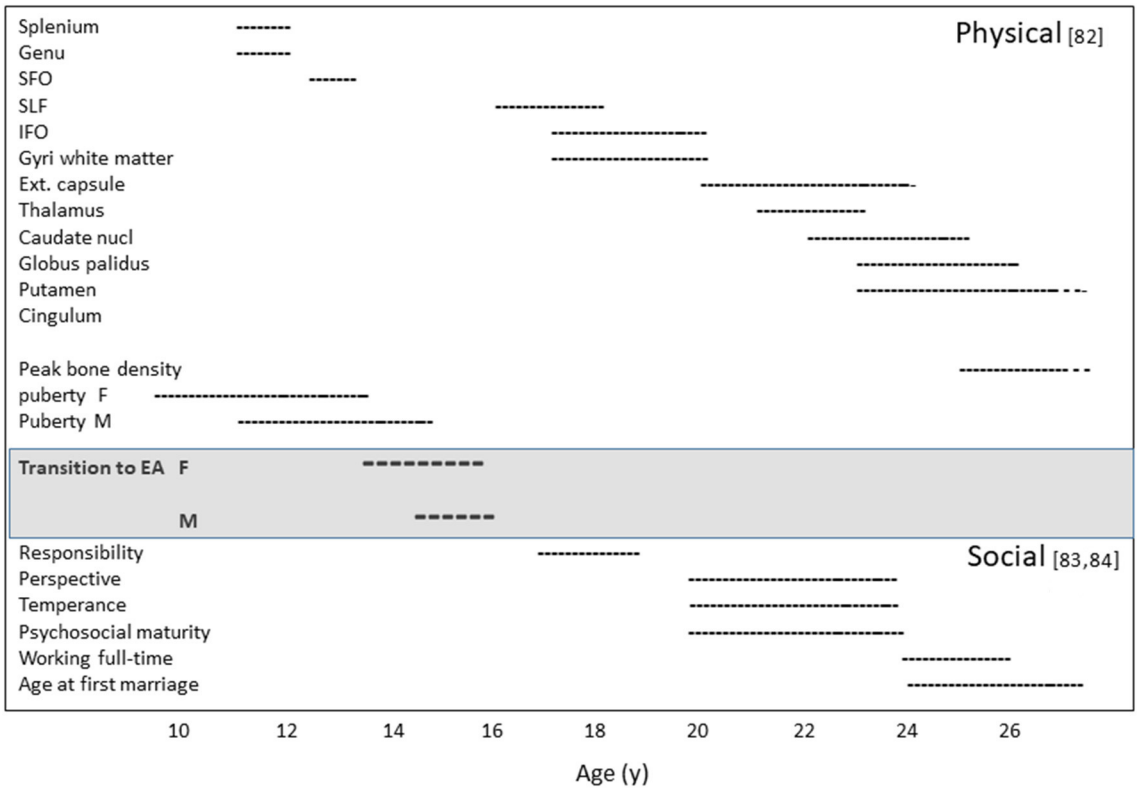

FIGURE 1 | Maturation timeline: (Upper) the age range to complete physical maturation (82). (Lower) the age range to complete social maturation (83) and US Bureau of Labor Statistics, 2014. SFO, The subfornical organ; SLF, The superior longitudinal fasciculus; IFO, anterior insula/frontal operculum complex; EA, emerging adulthood; F, female; M, male (82–84).

Central to the concept of sexual selection is the attainment and optimization of reproductive competence, and the key traits for selection are growth, maturation, and the age at transition to adulthood and sexual reproduction (12).

Human beings and the great apes share similar traits including, to some extent, emerging adulthood. We know relatively little about neurological maturation in non-human primates, but we do know that non-human great apes have a 2-year period of post-menarcheal infertility (50), extended in human foragers to 3 years (51). Low reproductive success among young females is a general primate phenomenon (52). Male preference for fully developed adult females has been described in 15 primate species (52). Goodall reported that after menarche, which usually occurs at age 10 years, female chimpanzees average 19 full-size cycles before becoming pregnant for the first time at age 12 years (53). Moreover, they will have about 60% of their lifetime sexual encounters during this post-menarcheal period. Unlike gorillas, chimpanzees (*Pan troglodytes),* and bonobos (*Pan paniscus*) live in multi-male and multi-female groups and mate more often than needed to conceive. Accordingly, primatologists have suggested that adolescent sterility is a period in which sexual and social skills are practiced without responsibility for the care of a newborn (53). In their emerging adulthood, female vervet monkeys (*Cercopithecus aethiops*) display a high degree of interest in young infants and will touch, cuddle, carry, and groom infants whenever they can. Lancaster interpreted this play-mothering by young females as an opportunity to practice maternal behavior and ease into their expected maternal role in society (54). Fecundity in males depends on age, size, and experience. Similar to humans, where reproductive success is in-line with hunting ability (55) reproductive success among the Barbary macaques (*Macaca sylvanus*) is much lower in young than adult males (56). In male chimpanzees, pre-fertility copulation is very common (53).

While it seems impossible to ascertain the life-history stages of early hominids, the timing of their dental maturation from the fossil record has shed some light on their stages (see below). Australopithecines are anatomical intermediates between apes and human beings and chimpanzees and bonobos are often regarded as living species that can to some extent represent the australopithecines. Based on fossil dental specimens, australopithecined resembled wild chimpanzees, not modern humans, in life-history stages (57). Fossil *Homo* species matured more slowly and the attainment of certain developmental milestones, such as the onset of puberty, adolescence, and first reproduction, probably occurred later, in parallel with their increasing longevity, body mass, and height (**Figure 3**).

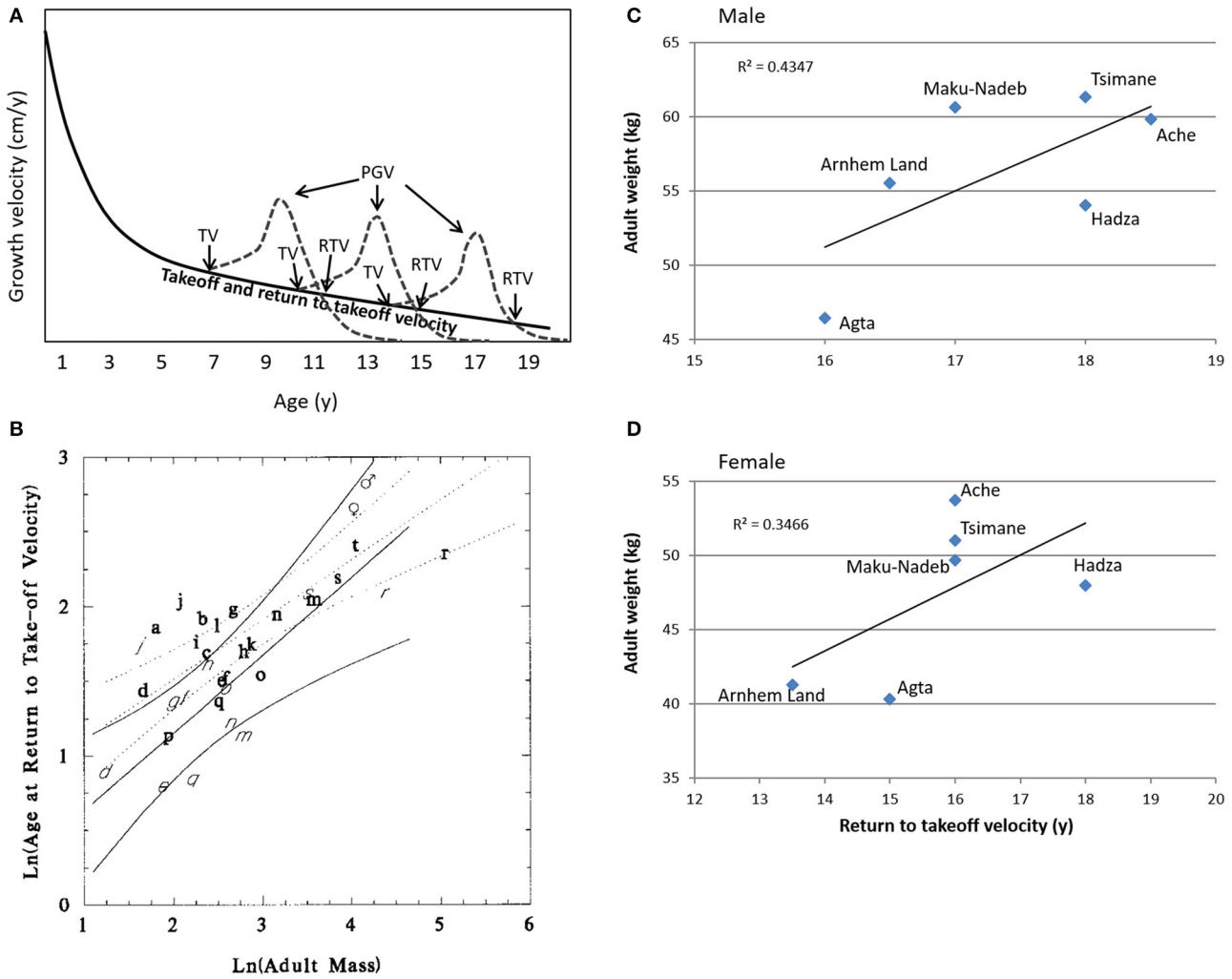

FIGURE 2 | The concept of the return to prepubertal growth velocity curve as a life history mile stone. Here, we define the return to take-off velocity as the transition from adolescence to emerging adulthood. **(A)** Schematic representation of the age-dependent pubertal take-off velocity and the return to prepubertal growth velocity curve; in girls the return to takeoff velocity coincides with menarcheal age in the early, average, and late maturers. The age-dependent decline in peak height velocity is a function of the decelerating takeoff velocity and returns to the prepubertal growth velocity curve. PGV, peak growth velocity; TV, takeoff velocity; RTV, return to prepubertal growth velocity curve. **(B)** The age of return to prepubertal growth velocity curve as a function of adult body mass in 21 primate species. Observations are derived from captive primates held at zoological parks and primate centers. With permission from Leigh and Park (42). a—*Cebus apella*, b—*Cercopithecus aethiops,* c—*Cercopithecus mitis*, d—*Cercopithecus neglectus*, e—*Erythrocebus patas*, f—*Cercocebus atys*, g—*Macaca arctoides*, h—*Macaca fascicularis*, i—*Macaca fuscata*, j—*Macaca mulatta*, k—*Macaca nemestrina*, l—*Macaca silenus*, m—*Papio hamadryas*, n—*Mandrillus sphinx*, o—*Colobus guereza*, p—*Presbytis entellus*, q—*Presbytis obscura*, r—*Gorilla gorilla*, s—*Pan paniscus*, t—*Pan troglodytes.* **(C,D)**—average adult body weight as a function of the age at return to prepubertal takeoff growth velocity of males **(C)** and females **(D)** in six predeveloped societies. Data from http://dice.missouri.edu.

A life-history tradeoff is a fitness cost that occurs when a beneficial change in one trait is linked to a detrimental change in another trait (58). According to Charnov, a life-history tradeoff also entails an invariant in an underlying parameter that the life cycle stabilizes or is constrained by (59). The *Charnov model* of mammalian life-history evolution (59) derives the flow of life-history consequences from the adult mortality rate:

Adult mortality □ *Age at maturity* □ *Adult weight* □ *Fecundity* □ *Juvenile mortality*.

In this model, any factor that decreases adult mortality, such as large adult body mass, sociality, or a low-predation environment, favors delayed maturation. Reproductive value (RV) increases with body mass while growth rates decline. The optimal age to stop investing in growth is when the expected RV starts to decline. Body mass increases during growth, which stops when body mass is optimal, so juvenile survival becomes important when maturation is delayed. Increasing juvenile survival and extending the adolescent life-history stage increases that individual's RV. Hence, emerging adulthood is highly favored.

The offspring number of most species with a large body size is small. Additionally, juvenile mortality decreases when reproduction is late, and late reproduction is associated with high fertility. Late reproduction should decrease fitness

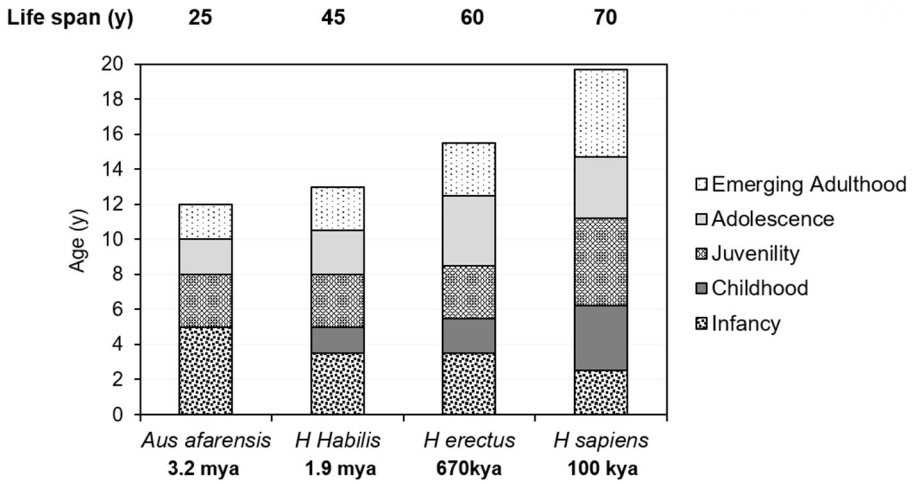

FIGURE 3 | Comparison of the life-history stages and the newly defined emerging adulthood of *Australopithecus afarensis*, *Homo habilis, H. erectus*, and *H. sapiens*.

(60), but several tradeoffs could influence the prolonged period of emerging adulthood in human life-history strategies: reproducing at an earlier or later age; reproducing at a young age or continuing to grow and develop; and being an adult parent with a large parental investment in each offspring of a small family or a young parent with a small parental investment in each offspring of a large family. The Charnov model predicts that a long life span will be associated with slow development, iteroparity (repeated reproduction), a single offspring, and long parental care (59). It was recently suggested that slow rates of growth, reproduction, and aging among primates reflect their low total energy expenditure (61). Emerging adulthood in modern societies is part of the historical lengthening of both ends of the pre-reproductive life span of human females (early puberty and late reproduction) in response to improved nutrition and decreased infection (62, 63). Microevolutionary tradeoffs that might underlie an extended emerging adulthood stage of life history include the allocation of energy to growth or reproduction, and the energy investment in courtship or parenting. Indeed, performing the sexual act in some species requires good cognitive ability and specific sexual behaviors (64). During human evolution, the acquisition of certain abilities resulted in the lengthening of maturation and development.

Brain size in mammals is correlated with longitudinal growth, and both have increased during human evolution (65). Brain size and cultural complexity have concomitantly increased over the last 2 million years with two possible periods of accelerated increase. The first occurred during the early evolution of the genus *Homo*, the second during the rise of *Homo sapiens*.

Using Charnov's model, we also suggest that emerging adulthood is a life-history stage that is a foundation of the high productivity of human beings: the metabolic potential of human beings exceeds the metabolic requirements of survival and this excess is first used to support growth and brain maturation before being allocated to reproduction. Another critical adaptation in hominin evolution was the ability to improve the food supply by establishing a rich and stable food base through the control of fire (*Homo erectus*), cooking (early *Homo sapiens* or earlier) (66, 67), and exploiting coastal food resources (shellfish) (68).

Despite the fact that the human juvenile (including emerging adulthood) and adult periods are longer than that of the chimpanzee and that human infants are larger than chimpanzee infants at birth, hunter-gatherer women characteristically have higher fertility than chimpanzee females (69). In anthropoid primates (monkeys, apes, and humans), non-maternal care predicts earlier weaning, shorter birth spacing, and higher reproductive success (70). Parental provisioning of the weaned offspring, an aspect of cooperative breeding (71), is crucial (72, 73). Here, we argue that anatomically modern human parents care for their offspring throughout their offspring's adolescence and emerging adulthood, and this extended period of care is longer than that of other primates.

The unique evolutionary path to the genus *Homo* was shaped by an increasing reliance on calorie-dense, large-package, skill-intensive food resources, "which, in turn, operated to produce the extreme intelligence, long developmental period, three-generational system of resource flows, and exceptionally long adult life characteristic of our species" (74). Kaplan and Robson emphasized the role of human males in provisioning meat to their family and tribal members (74). They also highlighted the contributions of grandmothers and other family and band members to provisioning and childcare, enhancing survival and success in emerging adulthood.

Although, the average menarcheal ages of the gorilla, the bonobo, and the chimpanzee are 7–8, 9, and 11 years, respectively, their ages at first birth are 10–12, 13–15, and 14–15 years (75). Despite their rapid development compared with humans, the great apes have a distinct period of post-menarcheal. In parallel with other great apes, the menarcheal age of human forager populations ranges from 13 to 19 years, and their first birth occurs about 4 years later when they are between 17 and 23 years of age (62, 76) (**Figure 4**). In contrast

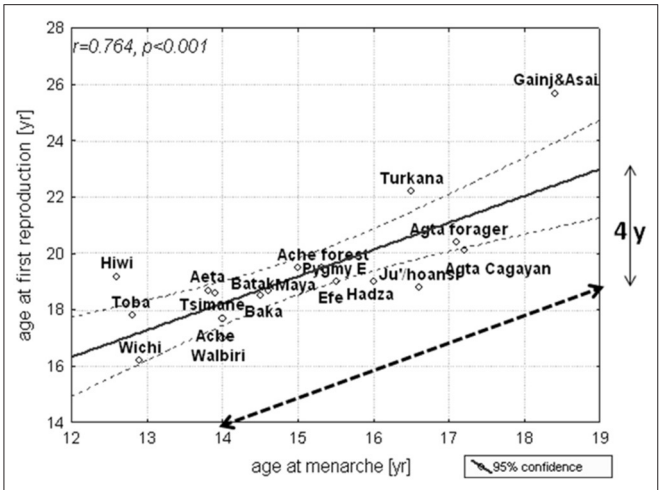

FIGURE 4 | Age at menarche and first birth among some natural fertility societies; mean and 95% confidence limits. The dashed line is the age at menarche when plotted against the age at first reproduction [reproduced with permission from Hochberg et al. (76)].

to great apes, primiparous women of human forager populations are provisioned by mature adults, such as grandmothers, who are usually post-reproductive (77, 78); their husbands, who are typically several years older and have often passed through the emerging adulthood stage of their life history before marriage; and other adults (3, 79–81).

Despite similarities among primates, the prolongation of dependency during emerging adulthood (**Figure 3**) is unique to human life history, and is part of the evolutionary success of *Homo sapiens*. In the light of the knowledge we have gained from other primates, we need to improve our existing definitions of the beginning and end of emerging adulthood in primates in terms of physical traits.

Development of the Human Reproductive Strategy

Across forager societies, there is a consistent 3–4-year period between menarche and the birth of the first child (**Figure 4**) and adult reproductive behaviors are learned during this period of emerging adulthood. The evolution of human development culminated in environment-dependent and late reproductive maturation. According to life-history theory (59, 85), a reduction in juvenile and adult mortality (86) postponed reproduction and necessitated substantial parental investment in each offspring.

Sexual behavior develops according to a species-specific, genetically controlled, maturational plan in which the age at first reproduction occurs within a specific age range (87). Darwinian theory yields testable predictions about mating strategies and behaviors, which include jealousy, fidelity, pursuit, diffidence, the number of new sexual partners per year (partner frequency), and gender roles and behaviors customarily displayed in emerging adulthood (88). These predictions also apply to adult patterns of intra- and intersexual aggression (89, 90). Here, we offer an evolutionary model for this transformative life-history stage, emerging adulthood.

Despite cross-cultural variations in the age of initiation of sexual activity and the age at marriage, the period of emerging adulthood in all cultures involves readiness for mating. Strong emotions often accompany early sexual activity. During adolescence, the frequency of depressive episodes is temporarily increased in boys and especially in girls (91–93).

Sex hormones intensify adolescent behavioral and psychological changes (94–96), but in emerging adulthood and into adulthood, average rates of depression, anxiety, and risk-taking decline. Interestingly, serum testosterone levels continue to rise after puberty and peak in the third decade in male humans (97). However, this age-dependent increase in serum testosterone levels does not occur in chimpanzees: serum testosterone levels are higher in adolescent chimpanzees (age 7–10 years) than in adults (age >11 years) (98). Male and female sex drive may be intensified and/or enabled by the activational effects of the sex steroids, as part of a switching mechanism that re-allocates resources from growth to reproductive activity during emerging adulthood (99). If the same genes allocate the energy that is required for growth and reproduction, these genes could exhibit antagonistic pleiotropy and mediate the tradeoff between growth and reproduction (100). The "fight or flight" response to perceived threat influences life-history tradeoffs during development (101, 102). As part of their readiness for mating, the bullying behavior of adolescent males diminishes at the time of transition to emerging adulthood (103, 104). This could be due to adolescents learning subtler ways of competing, they still vie for dominance and resource control. This may help explain why the mean age difference between men and women at the time of their first marriage in 191 national populations and traditional societies is 3.5 years (105).

Adolescence and Emerging Adulthood Among the !Kung and Other Foragers

Contemporary forager societies are to some extent modern representatives of pre-agricultural forager societies. The !Kung were until recently foraging people of the Kalahari Desert, whose demography and life history have been extensively studied (81, 106). Their average age of menarche is 16.6 years (range 16–18 years), and about 50% were married before menarche to men averaging 10 years older. Their age at first childbirth was 19 years (range 17–22 years) (106). This 3-year period of between the age of menarche and the age at first birth is probably due to subfertile ovarian cycling. Although their husband's sexual advances were supposed to be delayed until menarche, women reported that this period was often stressful (107). This 3-year period is important for a newly married !Kung woman for at least two reasons. First, she gradually learns to adopt adult roles and acquire adult sexuality without having to deal with the consequences of pregnancy and feeding a family. Second, she usually lives near her mother, even after the first birth, because she is dependent on her mother, father, and extended family before moving to her husband's village-camp after a second child (81, 107). Although !Kung women become socially responsible mothers with two or more children by their mid-20s, they are typically still being provisioned by their families (81). Psychosocial development

during emerging adulthood is substantially longer in boys than in girls, and the transition from adolescence to adulthood is gradual (108). !Kung boys learn hunting and other subsistence skills and are permitted to accompany adult men on hunting trips from their mid-teens. But the husband's obligation to provision his family with meat is also aided by relatives during the period of emerging adulthood.

To what extent do the !Kung resemble other hunter-gatherer societies? The acquisition of subsistence skills is a very long process among the closely related San of the Okavongo Delta, Botswana (5). Mongongo nuts are a staple food (as for the !Kung) and the ability to crack these nuts is age-specific because nut-cracking requires skill; arm strength is less important than age. Plotted against age, the ability follows an inverted U-shaped function across the lifespan, and this time-dependent function is a good example of the adaptive evolutionary value of emerging adulthood beyond adolescence. Success at nut-cracking is minimal until the late teens and then this skill improves until midlife.

The Hiwi Indians of Venezuela and the Aché Indians of Paraguay are traditional hunter-gatherer groups whose hunting and subsistence skills gradually increase throughout young adulthood (109). Although Aché girls collect insect larvae for subsistence, children of the two tribes under age 10 years do almost no foraging and especially no hunting until their teenage years. Specifically, the skill of gathering honey and palm fiber of Aché boys and Hiwi girls progressively increases to levels that are about half of their peak adult values in adolescence. The age at which the hunting skills of Hiwi and Aché men are at their best is the late 30s, and the age at which Hiwi and Aché men and women reach their peak gathering skills for honey and palm fiber occurs is even later.

Tsimane foragers of Bolivian Amazonia are also relevant to the long pre-adult life history of modern humans (4). Based on hunting returns and specific skill tests, the peak performance of hunters is only reached several years after the completion of a long childhood and adolescence; hunters must first learn to recognize the sounds, smells, tracks, and feces of critical prey species, and then learn to hunt by sightings, pursuits, and attempted kills. The hunting performance and ability of Tsimane foragers is another example of a skill whose acquisition depends more on age than strength.

Thus, the evidence from foraging societies and the conditions to which humans became adapted during our evolution show that neither reproductive behaviors (i.e., parenting and the ability to manage the relationship with a spouse) nor subsistence skills are mastered by the end of adolescence. Even in societies where children forage from an age as young as four, their efficiency as young adults remains lower than that of their mothers (110). Blurton Jones and Marlowe confirmed increases in skill and performance with age in the Hadza, hunter-gatherers of northern Tanzania. For example, the accuracy when shooting with a bow and arrow among men Hadza people increases with age and reaches its peak at age 25 years (111). From such findings, Blurton Jones and Marlowe concluded that one cannot assume that the age-dependent increase in performance and ability is entirely due to learning and/or practice; the increase may also be due to increases in an individual's size and strength (111). The importance of size and strength is confirmed by a study of spearfishing and shellfishing efficiency among the Meriam, who live on the Mer and Dauer islands in the eastern Torres Strait. For fishing and spearfishing, which are cognitively difficult, Bird and Bird found no significant amount of variability in return rates because experiential factors correlated with age. However, for shellfish collecting, which is relatively easy to learn, they found strong age-related effects on efficiency (112). From the evidence collected from various foraging societies around the globe, performance proficiency of subsistence skills of individuals increases with age and only peaks when they transit from emerging adulthood into adulthood in their twenties or later. These findings confirm that the period of emerging adulthood is marked by age-dependent maturation, ongoing brain development, strength accrual, and learning, and is a key adaptation for human survival and reproduction.

SECULAR TRENDS IN ADOLESCENCE AND EMERGING ADULTHOOD

Menarcheal age has declined in the U.S. and Europe for over a century (113, 114). It has declined by 4 years over the past 150 years, and the age at peak height velocity in the pubertal growth spurt has also decreased by 4 months per decade (114). An evolutionary approach to this secular trend challenges the concept that early adolescence is a disease process, and suggests that contemporary reproductive and life-history strategies are reflected in the substantial increase in the presentation of females with early-onset adolescence (115–118). Part of the misconception that early adolescence is a pathological condition is related to the assumption that the transition from adolescence to adulthood is direct. The subfertility of emerging adulthood can be explained by the period between the age at menarche, which is 12.5 years, and the modeled optimal age at first birth of 18 years (119). Indeed, puberty is followed by subfertility in adolescence and emerging adulthood (120) due to a high proportion of non-ovulatory cycles (121). Currently, there is no evidence for a secular trend in the age at first consistent ovulation.

Despite liberal mores and adolescent sexual activity, early childbearing was uncommon in pre-agricultural societies. In a non-industrial traditional society, a girl who begins to menstruate at age 15 years can take her place in that society at age 19 years as a young mother after a 4-year period of emerging adulthood and be supported by the institutions of marriage and an extended family (**Figure 4**) (76). In developed societies, the period of emerging adulthood of a girl who begins to menstruate at 12 years is prolonged, with slow maturation of the prefrontal cortex and other brain structures and late myelination until at least age 25, producing the mismatch between early-onset of puberty and late mental maturation in contemporary developed societies (116). It is the later part of this period of mismatch that we define as emerging adulthood, a time when young adults are still immature in their judgment and incapable of performing adult tasks (82).

SUMMARY AND CONCLUSIONS

The idea that one of the outcomes of human evolution is a very prolonged period of adolescent growth and delayed maturity is old, and is consistent with life-history theory, comparative primatology, and the hominin fossil record. We suggest in addition that emerging adulthood is a life-history stage that is part of the foundation the high productivity of human beings: our metabolic potential exceeds the metabolic requirements of survival and this excess is first used to support growth and brain maturation before being allocated to reproduction. We contend that the duration of human maturation has been underestimated, and that an additional 4–6-year pre-adult period, which (following Arnett) we call emerging adulthood, should be included in human life history. Recent imaging studies have shown that brain development continues throughout emerging adulthood; maturation of the neocortical association areas, notably the frontal lobes, extends into the mid-twenties, and is still incomplete long after the end of puberty and linear body growth. There is now abundant evidence that the frequency of behavioral disturbances of adolescence, such as unplanned sexual activity, risk-taking, impulsivity, depression, and delinquency, declines after adolescence despite persistent high levels of gonadal hormones. The most likely explanation for the transient nature of these behavioral disturbances of adolescence is continuing myelination of the frontal cortex and other brain regions that are involved in the executive control of impulses and emotions.

Adolescence is often delayed in foraging societies, resembling our human environments of evolutionary adaptedness. Since the women in these societies have late menarche and are subsequently subfertile, the age of these young women at the time of first birth is 19 years and their husbands are generally several years older. These young parents are strongly supported by older family members, who supply needed food and advice. The mastering of subsistence skills takes many years and an individual generally becomes proficient in these skills in their fourth decade. These realities highlight the adaptive advantages of a post-adolescent or emerging adulthood phase of human maturation, which requires substantial brain maturation and learning.

Secular trends indicate that the duration of pre-adolescent growth and development has shortened over the past two centuries and a further decoupling between pubertal/hormonal maturation and brain maturation has occurred in adolescents in developed societies. The nutritional and social conditions which drive this trend have been previously discussed and reviewed (2). While the mental maturation of adolescents and emerging adults in developed societies is as slow or slower than that of those in predeveloped societies, the onset of puberty in the developed societies now occurs at a younger age than that in the predeveloped societies. Many people in advanced developed states have increasingly recognized the need for prolonged period of education and support beyond adolescence. Others in contrast, especially those in the developing world where traditional structural support systems have collapsed, are often not able to provide the experience of a protected emerging adulthood to their children, leading the United Nations to identify youth, defined as 15–24 years of age, as a demographic group at risk and a special target for intervention (11). The period of emerging adulthood has an evolutionary context and a prolonged maturational underpinning, and we present evidence that supports the idea that emerging adults require protection because they are still both learning *and* maturing. Yet, A literature review and hypotheses of that sort are based on associations. The prolonged dependency and frequent confusion of emerging adults in modern societies is not solely attributable to the complexity of our societies, but also to the fact that they are, intrinsically and physiologically, not yet adults.

AUTHOR CONTRIBUTIONS

ZH and MK jointly conceived the article, drafted the manuscript, read, and approved the final version.

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Why and How Imprinted Genes Drive Fetal Programming

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Imprinted genes mediate fetal and childhood growth and development, and early growth patterns drive fetal programming effects. However, predictions and evidence from the kinship theory of imprinting have yet to be directly integrated with data on fetal programming and risks of metabolic disease. I first define paternal-gene and maternal-gene optima with regard to early human growth and development. Next, I review salient evidence with regard to imprinted gene effects on birth weight, body composition, trajectories of feeding and growth, and timing of developmental stages, to evaluate why and how imprinted gene expression influences risks of metabolic disease in later life. I find that metabolic disease risks derive primarily from maternal gene biases that lead to reduced placental efficacy, low birth weight, low relative muscle mass, high relative white fat, increased abdominal adiposity, reduced pancreatic β-cell mass that promotes insulin resistance, reduced appetite and infant sucking efficacy, catch-up fat deposition from family foods after weaning, and early puberty. Paternal gene biases, by contrast, may contribute to metabolic disease via lower rates of brown fat thermiogenesis, and through favoring more rapid postnatal catch-up growth after intrauterine growth restriction from environmental causes. These disease risks can be alleviated through dietary and pharmacological alterations that selectively target imprinted gene expression and relevant metabolic pathways. The kinship theory of imprinting, and mother-offspring conflict more generally, provide a clear predictive framework for guiding future research on fetal programming and metabolic disease.

Keywords: genomic imprinting, fetal programming, metabolic syndrome, type 2 diabetes, mother-offspring conflict

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INTRODUCTION

The deleterious effects of metabolic syndrome, comprising some combination of central obesity, insulin resistance, hypertension, and dyslipidemia, represent a primary health challenge of our generation (1). The majority of research on these problems addresses the "how" questions of proximate, mechanistic causation, and treatment. A complementary question, and one that can directly guide such work, is the ultimate, evolutionary question of why humans are so vulnerable to this particular suite of diseases, with this set of manifestations.

Addressing the evolutionary causes of human disease risks requires analysis of human-specific adaptations salient to growth, early development, and metabolism (2–4). Such adaptations center on selection for maximization of inclusive fitness, in the context of social resource-related interactions with other humans.

For the fetus, infant, and child, interactions with the mother guide development. These interactions involve mixtures of cooperation and conflict, because mothers and offspring are related

by only one half (for most autosomal genes), leading to selection for offspring to solicit more fitness-related resource from the mother than she is selected to provide (5). Relatedness asymmetries are higher still for imprinted genes, such that paternally expressed alleles in offspring are predicted, under the kinship theory of imprinting, to exert even more "selfish" solicitation; maternally expressed imprinted genes in offspring by contrast, are predicted to constrain such increased demand (6, 7). Mother-offspring and paternal-maternal gene conflicts typically generate molecular level tugs-of-war that lead either to dynamic equilibria, or to one party "winning," more or less (8–10).

The functional haploidy, conflictual dynamics, dosage sensitivity, and direct links to fitness variation of imprinted genes make changes in their expression an important cause of human disease risks, especially through impacts on offspring growth and development (2, 11). These health-related considerations dovetail directly with fetal programming effects, which are predominantly disease-related sequelae of growth patterns during fetal and childhood development (12). Despite the large body of previous work on fetal programming, no previous studies have used the kinship theory of imprinting as a framework for understanding fetal programming and its connections with metabolic disease.

In this Perspective article, I evaluate the roles of genomic imprinting in fetal programming of metabolic disease, from theory to evidence. I first describe relevant background concerning genomic imprinting effects in the context of human development. I then describe three domains of evidence showing how, and why, genomic imprinting drives fetal programming.

ADAPTIVE AND CONFLICTUAL HUMAN DEVELOPMENT

Humans develop through the fetal-placental stage, infant growth, and differentiation fueled by breast milk, early weaning (for an ape) facilitated by complementary feeding (baby foods) in childhood, and juvenile and adolescent stages, when food is obtained from the family, local group, and oneself (2, 11, 13, 14). Under the kinship theory of imprinting, we can define relative paternal-gene and maternal-gene optima for each stage of development. These relative optima define axes of genomic conflict, and axes of potential maladaptation in disease due to dysregulation. The optima are relative, rather than absolute, because, from theory and evidence, the paternal and maternal imprinted genes are engaged in physiological "tugs" or "webs" of war, with each party "pulling" in the context of the other party "pulling back" in dynamic equilibrium. Losses of "pull" on either side will thus lead to maladaptation for both parties rather than optimality for one (15). This maladaptation is directly reflected in the syndromic disorders caused by major germline, chromosomal or epigenetic disruptions to imprinted genes, that indicate the "pull points" of imprinted gene effects: the set of traits that reflect effects of maternal or paternal pull unopposed [e.g., (2, 6, 15)]. Typical development is expected to manifest in some level of demand intermediate between the maternal and paternal optima, with mothers, offspring, and paternal genes and maternal genes in offspring, being subject to deviations from their inclusive fitness optima to some degree.

Placental development is driven by paternal gene expression, constrained by maternal genes (12, 16–18). Optimal placentation for paternal genes involves successful modification of maternal spiral arteries, and a relatively effective placenta that directly reflects the anatomical basis of fetal demand for maternal resources. A well-developed placenta leads to an optimally large baby, as regards parturition success, optimal birth weight and body length, and an optimal body composition, where "optimal" refers to expected effects on inclusive fitness of the offspring, in comparison to inclusive fitness of the mother. Optimal body composition will involve relatively high lean mass including bodily organs, bone, and muscle (the "lean-mass working parts" of the body). This set of traits corresponds closely with the concept of "metabolic capacity" described by Wells (1, 19, 20): the engine that powers human physiological, psychological, and mechanical systems.

Optimal post-natal development for paternal genes engenders vigorous and frequent sucking and rapid early growth (when growth is food-limited rather than hormone-regulated, and involves growth in lean mass as well as fat), delayed weaning, enhanced solicitation of both complementary foods and later, other-provided "family" foods (in comparison to self-feeding), and delayed puberty that lengthens the overall period of dependence (11, 14, 21, 22).

Optimal offspring growth and development for maternal genes involves the relative opposite of the phenotypes above: reduced (though "adequate") placentation, smaller birth weight and length, reduced lean mass and subcutaneous fat, and so on. As regards body composition at birth, the maternal optimum should involve reduced relative investment in lean mass (especially muscle, pancreas, kidneys, bone, and liver) to help spare energy for the brain and allow for relatively increased abdominal white fat accumulation, partially in the context of surviving infection and periods of restricted food in infancy and childhood (23). Maternal genes are also expected to favor relatively high levels of brown adipose tissue in infants (which comprises about 10% of birth weight) (24), because it generates high levels of heat that can contribute to the energy budget of the mother, at some cost to the child. This apparent maternal-gene effect on human infant thermiogenesis is directly comparable to increased heat contributions caused by maternal gene expression biases in the communal huddling of offspring, among rodents (25).

Maternal gene optima also involve postnatal growth that does not involve statural "catch-up" during early infancy, which is energetically costly via lactation. Such offspring are instead expected to put on relatively more fat (white adipose tissue) in infancy and childhood, as a low-metabolic rate store of food; they are also expected to reduce and delay acceptance of complementary foods (which are also costly to mothers), instead transitioning relatively early to self-foraging and self-feeding (6, 22). Overall, these maternal-gene optima reflect the maternal energetic tradeoff between investment in current vs. future

offspring, whereby the inclusive fitness of mothers is maximized by producing more offspring but investing less in each.

Maternal and paternal imprinted genes in offspring mediate levels and patterns of demand for resources imposed upon mothers, from conception until independence. Supply of resources from the mother depends, in turn, on her ability to meet demand, which is some function of her internal physical, physiological, and psychological state, and external, ecological conditions that may constrain resources available; for example, shorter mothers have notably lighter babies (26), and food restriction in the latter two trimesters of gestation causes low birth weights [e.g., (27)]. Such limitations, as well as imprinted gene effects and other genetic effects, activate the "fetal programs" that reallocate available developmental resources to different structures and functions, via a hierarchical, cascading series of tradeoffs (3, 4, 28, 29). Most generally, fetal programs themselves can be considered as reaction norms subject to effects of conflicts, with distinct maternal gene vs. paternal gene inclusive fitness optima for fetally programmed trajectories of cell and tissue investment. How, then, are imprinted genes, and phenotypic axes of imprinted-gene actions, related to fetal programs and their effects on human health in childhood and later life?

THREE DOMAINS OF ASSOCIATION BETWEEN FETAL PROGRAMMING AND GENOMIC IMPRINTING

Fetal programming is linked with genomic imprinting effects because both are determined by resource provision and restriction in early development. As such, variation in imprinted gene expression, and the differing optimal fetal program trajectories of paternal vs. maternal genes, are predicted to represent major determinants of advantageous and deleterious programming effects, especially those that involve insulin resistance, visceral obesity, and other manifestations of the metabolic syndrome. This supposition is supported most directly by the high frequency of imprinted genes among the top risk factors and causes of type 2 diabetes and obesity [e.g., (30, 31)].

I describe below three major connections of genomic imprinting with the causes and effects of fetal programming, with emphasis on the links of theory with evidence across proximate and ultimate domains of research. **Figure 1** summarizes the primary impacts of imprinted genes on fetal programming effects, as described from previous studies.

Birth Weight

Weight at birth integrates effects of placental and fetal development as regards resource demand and restriction. It represents the major correlate of adverse fetal programming effects on health, since the first studies by David Barker back in the 1980s. Birth weight is also strongly influenced by expression of imprinted genes, from analyses of large-scale naturally-occurring loss and gains of imprinting (32, 33), studies of SNPs, methylation and expression levels of imprinted genes [e.g., (34, 35)] and GWAS meta-analysis of birth weight [e.g., (36)]; for example, St. Pierre et al. (37) found that 31% of human birth weight variance could be accounted for by genetic and epigenetic variation at the *IGF2/H19* locus. These studies support the kinship theory prediction that higher birth weight should be associated with biases toward paternal gene expression; in turn,

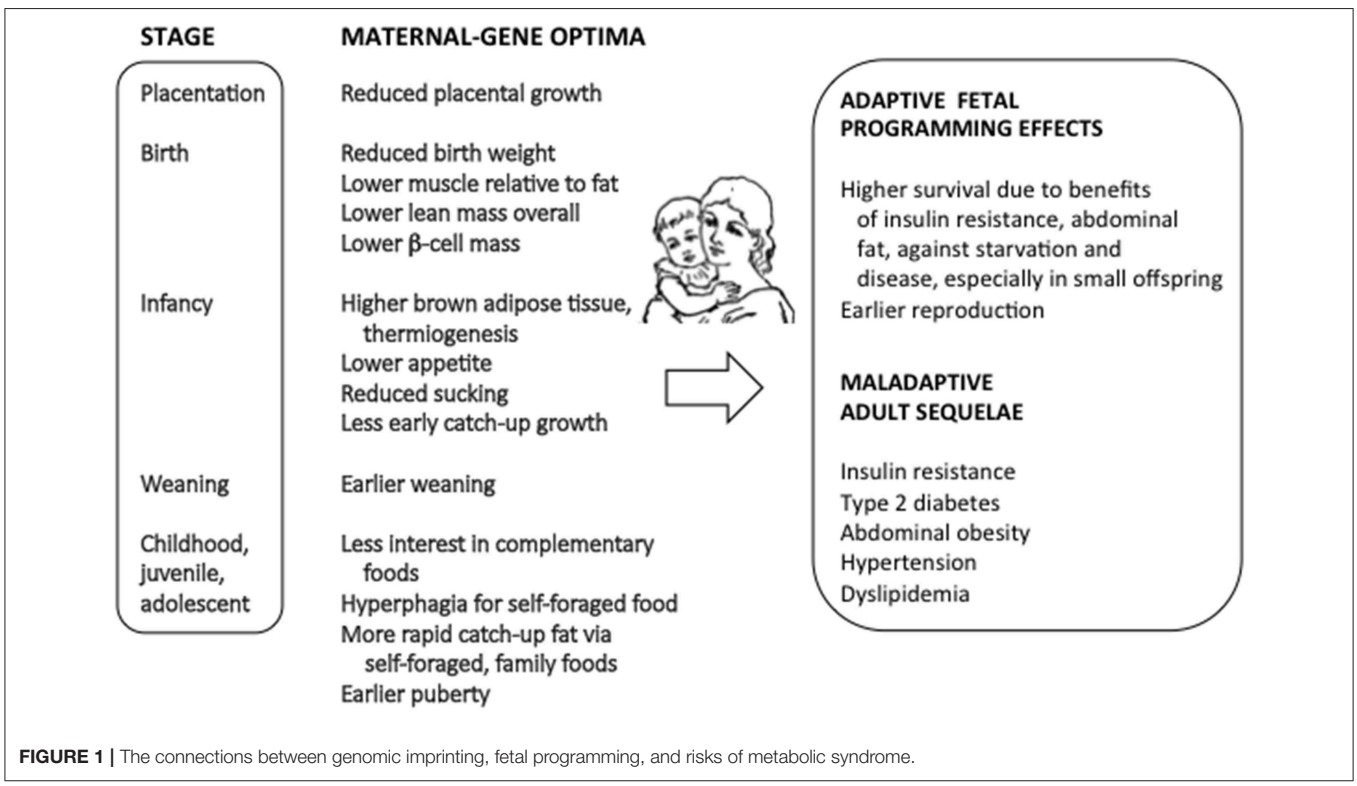

FIGURE 1 | The connections between genomic imprinting, fetal programming, and risks of metabolic syndrome.

lower birth weight is associated with biases toward maternal gene expression and its fetally programmed sequelae.

Beaumont et al. (38) showed that genes with strong GWAS effects on birth weight (including the imprinted *INS-IGF2* locus) mediate risk of type 2 diabetes, thus providing clear evidence of pleiotropy and a genetic basis to fetal programming effects. One of the primary means to analyze the role of imprinted genes in future work on fetal programming effects would be to test effects of specific imprinted SNPs and transcripts on both fetal, infant, and childhood traits including birth weight and composition, and adult traits associated with the metabolic syndrome. This has yet to be done. Prospective, longitudinal studies of individuals with imprinted gene disorders are also required, that can link gene expression and birth phenotypes with later metabolic syndrome effects.

Body Composition

Bodies can be partitioned into fat mass vs. lean mass (mainly skeletal muscle, bone, and internal organs), and brown fat (for thermiogenesis) vs. white fat (in labile abdominal stores for energetic reserve), among other bodily components.

Studies of imprinted gene alteration, and SNP variation effects, indicate that biases toward paternal imprinted gene expression favor increased skeletal muscle mass, bone mass, and pancreatic β-cell mass, and reduced white fat mass [e.g., (31, 39–48)]. This paternal-gene tissue allocation pattern involves high demands on the mother for the protein, fat, minerals, and carbohydrates that lead to extensive insulin-fueled growth in lean mass, which is expected to benefit offspring inclusive fitness through large overall size, better physiological function, better early survival, and higher reproduction [e.g., (1, 11)]. Enhancements to metabolic health are expected to follow most directly from large skeletal muscle mass, and pancreatic β-cell mass (leading to more effective glucose metabolism), and reduced abdominal fat deposition (leading to reduced susceptibility to other dimensions of metabolic syndrome).

The optimal maternal-gene tissue-allocation pattern involves, conversely to the paternal one, lower lean mass, notably less skeletal muscle and a smaller β-cell mass, and higher levels of white fat, expressed mainly in abdominal white adipose tissue. This pattern of allocation takes place in the context of reduced overall resources (and lower birth weight), and appears to reflect tradeoffs that alleviate some of the deleterious effects of small body size, especially low early-life survivorship (19, 20, 49–55). Thus, less skeletal muscle and a smaller β-cell mass promote insulin resistance that can enhance survival and protect the brain during periods of starvation or infection, and white abdominal fat serves, in turn, as an energy reservoir, linked tightly with the immune system, for fighting infectious disease (23, 56–58).

This set of conditional, best-of-bad-job adaptations (28) in babies born small, and/or subject to maternal-gene biases, is attuned to premodern environments of relative resource scarcity. In current, novel environments with food available *ad libitum*, this programmed system generates mismatch, promoting type 2 diabetes, abdominal obesity, and other effects of the metabolic syndrome (**Figure 1**). The most severe metabolic syndrome effects are found when light, skinny neonates exhibit extensive catch-up growth after about 1 year of age, and are subject to high levels of nutrition during later development and adulthood [e.g., (1, 49, 59–61)].

Phenotypes optimal for maternal genes need not, and do not, align exactly with deleterious fetal programming effects. Thus, an important bodily tissue allocation trait favored by maternally expressed imprinted genes is higher levels of brown adipose tissue, which undergo energy intensive thermiogenesis. In humans and/or mice, higher expression of the maternally expressed genes *CDKN1C* and *H19*, and lower levels of the paternally expressed genes *DLK1, NDN,* and *XLas*, promote increased non-shivering thermiogenesis of neonates (25, 62–64), which in mice benefits maternal genes in the context of offspring cooperative huddling (25), and in humans should benefit the mother energetically (65). Extension of high brown fat thermiogenesis and high metabolic rate throughout childhood, and into the adult stage, can prevent the development of diet- and age-induced obesity (66), as evidenced, for example, by the general lack of catch-up growth, obesity, or metabolic syndrome in Silver-Russell syndrome, and the high energy expenditure and lean phenotypes associated with loss of *XLαs* expression (in contrast to low energy expenditure, obesity, and insulin resistance, with reduced expression of Gs*α*) (18, 39). Manipulation of imprinted gene systems affecting thermiogenesis and metabolic rate offers exciting opportunities for therapeutic alleviation of metabolic syndrome. Elucidation of the adaptive significance of such effects in humans, in the context of the kinship theory, requires further study of the roles of thermiogenesis in the energetics of mother-infant interactions, especially given the life-history differences between humans and mice.

Trajectories of Post-natal Feeding, Growth and Development

Lui et al. (67) and Finkielstain et al. (68) showed that post-natal growth acceleration and deceleration are mediated by expression of a suite of imprinted genes. Among infants, appetite and sucking ability are increased by higher paternal imprinted gene expression, with the clearest evidence from paternal gene knockouts in mice and humans that reduce sucking [e.g., (11, 35, 69)]. For offspring born below optimal weight, paternally expressed genes are expected to favor rapid early catch-up growth, especially via lactation (with high costs to the mother), and especially when growth in lean mass is still mediated by insulin and *IGF2* (11), although catch-up at any point may be expected if it involves increased demands on the mother. As such, postnatal paternally biased gene expression effects that follow environmentally induced intrauterine growth restriction may be an important cause of catch-up growth and metabolic disease.

Maternal imprinted gene expression, by contrast, should favor catch-up growth only after weaning (relative to before weaning), and only when it involves modes of feeding with relatively low costs to mothers; this later catch-up growth predominantly involves white, abdominal adipose tissue. For example, deletions of the paternally-expressed genes *PEG3, DLK1, MAGEL2,* and *NNAT* (leading to maternal gene biases and poor early feeding)

result in catch-up white fat, and are associated with adult obesity (35, 70).

In humans, lactation is normally supplemented by feeding of 'baby foods' (so-called "complementary" foods) (13, 71) some months after birth. Individuals with Angelman syndrome, involving a paternal gene bias, show evidence of 'picky' eating with preference for such foods, which are costly to mothers to acquire and process (22). By contrast, individuals with Prader-Willi syndrome, involving a maternal-gene bias, show highly indiscriminate food choice and high rates of self-foraging, in association with hyperphagia. Haig and Wharton (72) interpreted these latter findings in terms of reduced feeding demand being imposed on mothers by children with Prader-Willi syndrome, after weaning. Hyperphagia after weaning, which is also found in mice with deletions of the paternally expressed gene *Nnat* (35), will notably exacerbate fetal programming effects, especially given that it follows prenatal and early postnatal restrictions on growth.

Finally, theory and evidence indicate that maternally expressed imprinted genes favor fast childhood development and early menarche, which reduce demands on the mother (21). In turn, early menarche is associated with higher risk of metabolic syndrome later in life [e.g., (73)]. These considerations of timing emphasize the benefits of early-infancy catch-up in lean mass under paternal gene effects, compared to the long-term metabolic costs of later, maternal-gene mediated, catch-up fat.

CONCLUSIONS

Conflicts in biology are all about control of fitness-related resources. Genomic imprinting thus originated and evolves in the context of gene expression that controls levels and patterns of resource demand, by offspring, for maternal investments. This is ultimately why genomic imprinting drives fetal programming. Proximately, the causal devils are in the molecular details, that are explicable only in terms of opposing, distinct inclusive fitness optima, some of which also mediate variation in human health and risks of disease.

An evolutionary-medical approach to understanding metabolic syndrome requires integration of evolutionary biology, for the study of tradeoffs, genomic conflicts, and mismatches, with genetic, developmental, and physiological data on mechanisms. The perspective provided here indicates that maternal imprinted-gene phenotypic optima parallel the deleterious fetal programming effects of early growth restriction, though with important exceptions. These findings provide insights into potential new therapies and preventatives via manipulation of imprinted gene expression and effects, and patterns of feeding, that should encourage studies of fetal programming that test hypotheses inspired by evolutionary theory.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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DHEAS and Human Development: An Evolutionary Perspective

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Adrenarche, the post-natal rise of DHEA and DHEAS, is unique to humans and the African Apes. Recent findings have linked DHEA in humans to the development of the left dorsolateral prefrontal cortex (LDPFC) between the ages of 4–8 years and the right temporoparietal junction (rTPJ) from 7 to 12 years of age. Given the association of the LDLPFC with the 5-to-8 transition and the rTPJ with mentalizing during middle childhood DHEA may have played an important role in the evolution of the human brain. I argue that increasing protein in the diet over the course of human evolution not only increased levels of DHEAS, but linked meat consumption with brain development during the important 5- to-8 transition. Consumption of animal protein has been associated with IGF-1, implicated in the development of the adrenal zona reticularis (ZR), the site of DHEAS production. In humans and chimps, the zona reticularis emerges at 3–4 years, along with the onset of DHEA/S production. For chimps this coincides with weaning and peak synaptogenesis. Among humans, weaning is completed around 2 ½ years, while synaptogenesis peaks around 5 years. Thus, in chimpanzees, early cortical maturation is tied to the mother; in humans it may be associated with post-weaning provisioning by others. I call for further research on adrenarche among the African apes as a critical comparison to humans. I also suggest research in subsistence populations to establish the role of nutrition and energetics in the timing of adrenarche and the onset of middle childhood.

Keywords: brain, DHEAS, growth and development, human evolution, middle childhood

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INTRODUCTION

Adrenarche, the post-natal rise in androgen production by the adrenal gland, including both (DHEA) dehydroepiandrosterone and its sulfated form (DHEAS), has attracted increasing attention for its role in middle childhood (1). Once thought to be involved in the initiation of puberty (2), it is now clear that the rise in DHEAS is an independent event (3). Once thought unique to humans, it now known to be shared with chimps (4), bonobos (5), and gorillas (6). Previously considered for its actions as sex steroid, or a sex steroid precursor (7), DHEAS it is now known to act through a variety of non-genomic mechanisms (8). Yet the functional significance of adrenarche remains little understood.

Together DHEA and DHEAS are the most abundant hormone in human circulation, with DHEAS the more abundant of the two (9). DHEA is generally considered the active form, but DHEAS can be converted to DHEA within cells (7). In addition, DHEAS is the form produced by the adrenal gland (10) making it a marker of adrenal function. Thus, in what follows I will use DHEA/S as a general term, but will differentiate between DHEA and DHEAS where their specific effects have been demonstrated.

In fact, DHEA has a wide variety of physiological effects, including promoting immune function (11), and endothelial function (12), as well as altering brain function (13). At the organismal level DHEA, has documented effects on brain development (14–16), sexuality, mood and cognition (17), cardiovascular disease (18, 19), stroke (20), and mortality [(21, 22), but see (23)]. More recently, DHEA has been linked to follicular development (24–26), with some studies implicating the impact of DHEA on mitochondrial function (27, 28).

Ironically, the wide-ranging physiological impact of DHEA/S makes it hard to focus on a single primary function and has impeded a more systematic understanding of this important hormone. In addition, the most common animal models, the rat and the mouse do not exhibit adrenal production of DHEA/S. However, both mice and rats produce DHEAS within the brain (29), as do humans (30–32). Hence the term neurosteroid for DHEA/S (33). However, neural production of DHEA/S can't explain the origins of adrenal production of DHEA/S and its circulation throughout the body.

More recently, the spiny mouse has been reported to develop an adrenal zona reticularis from post natal day 8–20, a possible analog to human adrenarche, in addition to producing DHEAS in the brain throughout life (34). Interestingly, the species also exhibits high level of fetal adrenal production and menstruates (35) suggesting that it may be a useful rodent model for studying the effects of DHEA/S in humans.

Thus, current results beg the question of what is evolutionarily novel and adaptive about the high and increasing level of circulating DHEAS in humans at the onset of middle childhood around 6–7 years. I suggested that the primary effect (among others) of increasing DHEAS is the maintenance of plasticity in the developing brain (36, 37), a point since elaborated by others (38, 39). Recent finding showing an impact of DHEA on cortical development and cortical-limbic connectivity in children (14–16, 40–43) provide strong support for this argument.

Here I extend my argument about the evolutionary origins of adrenarche in humans to include both the social and nutritional context of the infancy—early child transition as well as the shift from early childhood to middle childhood. More specifically, I suggest that the higher titers of DHEA/S in humans relative to apes may reflect increasing levels meat in the diet with advent of the genus Homo (44). Consumption of meat in early hominids is generally agreed to provide increased energy to support a larger brain, whether this includes a reduction in gut size (45), or not (46), and regardless of when the role of cooking became important (47).

Importantly, consumption of animal protein intake has been related to increased IGF-1 levels in human adults (48, 49) and children (50, 51) and mice (19). At the same time IGF-1 has been implicated in the development of the zona reticularis (52) the layer of the adrenal gland responsible for DHEA production.

I hypothesize that increased meat consumption over the course of human evolution played a role in increasing production of DHEA/S as a part of the extended development of an energetically costly brain (53). Starting with the genus Homo meat consumption would have lead to increased IGF-1 and elevated DHEA/S levels beyond those in the African apes. After weaning, meat provided by males (54) would have provisioned children (55, 56) and supplied protein and energy for cortical synaptogenesis (53, 57). Increased DHEA/S would have acted as a co-factor in promoting cortical maturation, including in the right temporal parietal junction (rTPJ) leading to increased capacity for mentalizing and perspective-taking before the onset of reproductive maturation, a useful trait for a species with pair-bonding and biparental care (58).

I forward this argument in three parts. In the first section, I lay out a series of steps potentially linking intake of animal protein to brain development. These start with the consumption of animal protein which has been associated with higher IGF-1 levels in adults (48, 49) and children (59). IGF-1 also has been implicated in the development of zona reticularis (52), suggesting that higher IGF-1 titers could promote a thicker zona reticularis and increased DHEAS production. IGF-1 itself plays a key role in brain development, both *in utero* and post-natally (60, 61), promoting neurogenesis, neurite growth, and synaptogenesis (62, 63). DHEA has been show to increase energy available in neurons through mitochondrial respiration (64–66), potentially providing additional energy for the metabolic costs of early brain development (53).

In the second section I compare the timing of adrenarche in humans and the great apes. I present evidence showing that while the zona reticularis begins to mature around the age of 3–4 years in both humans (67) and chimpanzees (68), its relationship to other developmental landmarks varies between the two species. Most importantly, in chimpanzees the onset of weaning and peak synaptogenesis in the prefrontal cortex at 3–4 years (69) occur roughly in concert with the emergence of the ZR. In comparison, in humans weaning is completed around 2 ½ years (70, 71), while the peak of synaptogenesis is around 5 years (72) years. Thus, in chimpanzees, early cortical maturation is tied to weaning, while in humans it is more closely associated with DHEAS production.

In the third section, I integrate the timing of DHEA impacts on cortical thickness (14) with social and behavioral markers to present a picture of DHEAS's potential role in the evolution of human childhood stages. Most obviously, the 5-to-8 transition to middle childhood, referred to as the "age of reason and responsibility" by White (73), maps onto the effects of DHEA on LDLPC from 4 to 8 years. Lancy and Grove (74) point out that in many societies children are considered incapable of learning before this age, consistent with the importance of LDLFC for the development of executive function (75).

The impact of DHEA on the rTPJ during middle childhood and its consequences for mentalizing is harder to interpret. Hrdy (76) emphasizes the importance of child care by girls, as practice for their own infants, during human evolution. Mentalizing is an important part of such skills (77, 78). Child care would presumably have been less important for males, but mentalizing may have been useful in learning the skills of cooperative hunting (79). In addition, mentalizing might be beneficial for developing an understanding of one's self in relationship to the opposite sex (1, 80) before puberty exaggerates sexually dimorphic physical and behavioral characteristics that can lead to misunderstandings and tension between the sexes.

Based on the first three sections I end with suggestions for future research directions in the comparative study of adrenarche and middle childhood among both the great apes and humans. Current evidence for adrenarche and its relationship to differences in hormonal (81), cranial (82), and brain (83–85) traits in these two related species (86) is quite limited. A simple direct comparison of adrenarcheal timing in the two species would add immensely to our understanding.

In addition, the onset of middle childhood is thought to be consistent across human populations (74, 87) the evidence regarding adrenarche in subsistence populations (88–91) is scattered and incoherent. A better understanding of variation in adrenarche in the context of poor nutrition, high disease burdens and traditional child care practices would help to ground evolutionary perspectives on adrenarche in a more realistic context. It would also set the foundation of a better understanding of the role of adrenarcheal timing in cognitive development (37).

IGF-1 AND DHEA/S

IGF-1 (Insulin-like Growth Factor 1), as the name suggests, is closely related to insulin. Like insulin, IGF-1 plays a role in glucose regulation (92), and both hormones impact mitochondrial function, protecting against oxidative damage while promoting oxidative capacity (93). However, IGF-1 is most directly associated with protein metabolism, including cell proliferation and differentiation (72) as well as protein synthesis (92). At an organismal level, variation in circulating IGF-1 levels has been related to differences in protein consumption across the life cycle, including during infancy (94), childhood (59), and adulthood (48, 49). In fact, early protein consumption may lead to programing of the IGF-1 axis that becomes apparent during adolescence (95).

IGF-1 is of special interest because it plays an important role in the development of the adrenal gland, including the zona reticularis (52, 96). The zona reticularis develops as primordial stem cells located at the surface of the adrenal cortex move from the zona glomerosa through the zona fasicularis to their final residence in the zona reticularis (52, 96). IGF-1, given its ability to inhibit apoptosis (97) is thought to enhance the survival of the migrating cells. Higher levels of IGF-1 during the formative period of the adrenal gland before the age of 6 years when the zona reticularis is established (67) may lead to increased numbers of progenitor cells reaching the ZR. More ZR cells would presumably lead to increased DHEA/S production. Thus accelerated early somatic growth, linked to increased IGF-1 (98, 99) may be associated with greater DHEA/S as well.

DHEA is generally classified as a weak androgen, i.e., a sex steroid. However, DHEA acts on a variety of cells types and receptor making it more difficult to characterize a single mode of action. For instance in prostate-derived LNCaP tumor cells, DHEA acts at the androgen receptor (AR) and beta estrogen receptor beta (ER-beta) at similar affinities, but the effects at ER-beta appear to be more physiologically relevant (100). In contrast, DHEA does appear to have demonstrable effects on AR mRNA expression in ovarian granulosa cells (101). Thus, the actions of DHEAS are unlikely to be sufficiently characterized as that of a weak androgen alone, and it is important to consider the specific tissue and/or organ involved.

DHEAS has also been suggested to act primarily as a sex-steroid precursor because of its conversion into testosterone and/or estrogen within peripheral target tissues (102). However, the importance of peripheral conversion of DHEAS is most obvious in post-menopausal women for whom ovarian steroid production has ceased. In this case, DHEAS is responsible for 100% of estrogens and 70% of circulating androgens (7). In men and premenopausal women gonadal sources of estrogen and testosterone may obscure the contribution of peripheral conversion of DHEAS to the sex hormones.

More recently, non-genomic mechanisms of DHEA action have been clearly demonstrated, including actions through the IGF-1, sigma 1, TrkA, and GABA receptors as well as the DHEA specific GCPR (8, 103). I specifically mention Sigma-1, TrkAR, and IGF1R because of their role in the brain. The sigma-1R is a chaperone that brings molecules from the cell membrane to the mitochondrial associated membrane (MAM) at the nexus of the mitochondria and endoplasmic reticulum (ER) (103). Sigma-1R has been related to axonal guidance and dendritic arborization (104). The TrkA receptor is important in transducing the effect of nerve growth factor (NGF) and has been related to neuronal differentiation and survival (105). As already mentioned the IGF-1R is related to mitochondrial energy production in neurons (106).

Regardless of the specific receptors involved, DHEA/S has demonstrable effects in the brain. DHEAS regulates the IGF-1 system in the rat hypothalamus by down regulating IGF-1 levels (107). DHEAS is also known to modulate the release of neurotransmitters such as GABA, 5-HT, glutamate and dopamine [see (108) for a review], effects that may involve the Sigma-1R. DHEA, on the other hand, has also been shown to modulate glucose and lactate uptake (109), glucose metabolism (110) and increase mitochondrial energy production in the rat brain (65, 66). A fuller picture of the metabolic effects of DHEA/S' on the brain await future research.

Nonetheless, DHEAS-related impact on neurotransmitter production and release has important implications for patterns of neural activity and brain development. DHEA administration in adults has been shown to inhibit connectivity between the amygdala, the hippocampus and the insula (13) regions connected by glutamatergic and dopaminergic pathways. In addition, individual variation in DHEA from the age of 4–23 years has been linked to differences in connectivity of the amygdala with both the anterior cingulate cortex and the visual cortex (14, 16). Such differences in connectivity may reflect the impact of increasing levels of DHEA on neurotransmitter release and the subsequent production and maintenance synaptic connections.

Taken as a whole, findings on DHEA and the Sigma-1R, TrkAR, and IGF-1Rs in neurons suggest that DHEA/S may be one thread in a non-genomic metabolic pathway linking protein intake and brain development in humans, as follows. Increased protein intake would lead to increased

IGF-1 production by the liver. Increased IGF-1 would act directly to increase mitochondrial energy production within brain neurons. At the same time, increased levels of IGF-1 during development would promote the growth of the adrenal zona reticularis and with it DHEA/S production. DHEA/S would act on the brain to augment mitochondrial energy production (65, 66) while protecting neurons against related mitochondrial production of oxygen free-radicals and apoptosis (64), with the net income of increasing neurotransmitter release. See **Figure 1** for a diagrammatic representation of how meat consumption might play a role in neurotransmitter release acting through the sigma-1 receptor.

ADRENARCHE IN THE AFRICAN APES

DHEAS produced by the fetal adrenal is present prenatally in a wide variety of primate species (111). The fetal adrenal is very large *in utero* and then atrophies after birth, meaning DHEAS levels decline rapidly post-natally, with levels among adults generally low across primate species (112). In rhesus macaques, close examination of the adrenal gland indicates that the zona reticularis develops during the period just after birth while the fetal zone of the adrenal is atrophying (113), leading to a transient post-natal increase in DHEAS production (114).

Many primate species, including rhesus and pigtailed macaques and yellow baboons (115) show detectable levels of circulating DHEAS post-natally (112). In fact, across primate species circulating adult DHEAS levels are strongly related to life span (115, 116). Interestingly in the common marmoset (Callithrix jacchus) female show increased levels of DHEAS during adulthood, while adult males do not (117, 118).

However, clear and sustained post-natal increases in DHEAS are limited to humans (119, 120) chimps (4), and bonobos (5). In fact, DHEAS levels appear to be much higher in chimps and bonobos compared to gorillas, which would make adrenarche a derived trait <10 million years old (121). At the same time, substantially higher levels of DHEAS have been documented in human females relative to chimpanzees (68), suggesting that the human pattern is derived from that of chimpanzees and bonobos.

The timing of increases in DHEA/S production across humans, bonobos and chimpanzee species appear to be generally similar. Recently published longitudinal results based on 53 wild chimpanzees from birth to 20 years of age show that urinary DHEAS, after declining from birth, starts to rise around 2–3 years (4). This rise continues until at least 20 years of age, with no significance in urinary DHEAS between the sexes. These findings are consistent with those from a cross-sectional study of 86 captive chimpanzees, ages 1–12 years (122) in which females showing higher serum levels of DHEA starting at 2–4 (122). Males from the same study showing increases in DHEAS starting at 4–6 years.

In humans, a recent cross-sectional study of almost 2,000 ($m = 1{,}031$; $f = 926$) individuals using a sensitive LC-MS/MS system demonstrate an increase in serum DHEA (119) starting at 3–5 years and continuing into the 20's. Remer et al. (120) show a similar pattern based on LC-MS/MS measurements of urinary DHEA & metabolites in 400 children 3–17 years of age. The data on age patterns of DHEAS for bonobos is much more limited. A single cross-sectional study of 53 captive animals, ages 1–18 years, shows an increase in urinary DHEA-S after 5 years of age (5). As with chimpanzees the values appear to be still increasing at the upper end of the age range.

Taken together, these studies suggest very similar patterns of DHEAS in humans, bonobos and chimpanzees, with onset around 3–5 years and continued increase into at least the late teens. Comparison of age related cortisol patterns re-enforces the similarity of adrenal development between of humans and chimpanzees. In humans, urinary cortisol declines from birth and then starts to increase at 10 years of age with higher levels for males (123). Sabbi et al. (4) show a similar pattern for the wild chimpanzees with an increase from 10 years, but no sex differentiation. Comparable results are not available for bonobos.

It is important, however, to point out that the phenotypic signs used to define adrenarche (presence of acne, body odor, and hair) appear on average at about 8 years for girls (124) and 9 years for boys (125). Phenotypic signs of adrenarche have not be been characterized in either of the two ape species. Thus, while chimpanzees show similar pattern of age related DHEAS and cortisol to humans, the timing of adrenarche as defined by phenotypic markers and associated behavioral changes in chimps and bonobos remains to be investigated.

Current Research on Adrenarche in Subsistence Populations

Up to this point, I have drawn from results among WEIRD (white educated, industrialized rich and democratic) populations (126) to characterize human adrenarche. However, these populations are generally well-nourished, largely sedentary, and with low disease burdens leaving abundant energy to fuel the development of the brain, confounding any comparison with wild chimpanzees. Nonetheless, Shi et al. (127) report that animal protein intake and fat mass explained a small but significant amount of variation in adrenal androgen secretion (5 and 1% respectively) in a sample of 137 pre-pubertal (ages 3–12 years) German children. Thus, given the existence of undernutrition, high disease burdens and habitual physical activity we might expect that adrenarche, like puberty, would be delayed in subsistence populations. Furthermore, given energetic constraints, the relationship between DHEA/S, fat depots and animal protein intake might be more sharply drawn.

A previous set of studies in subsistence populations based on older sample collection and assay techniques (88, 91, 128) could not adequately address the timing of adrenarche. These studies conceptualized adrenarche as a part of puberty and as a consequence didn't sample individuals young enough to be able catch adrenal onset.

However, three recent studies yield results speak to variation in the timing of adrenarche in subsistence populations and its possible causes. In the study most comparable to that of wild chimps, Helfrecht et al. (89) compared cross-sectional age-related patterns of DHEAS and cortisol derived from hair among

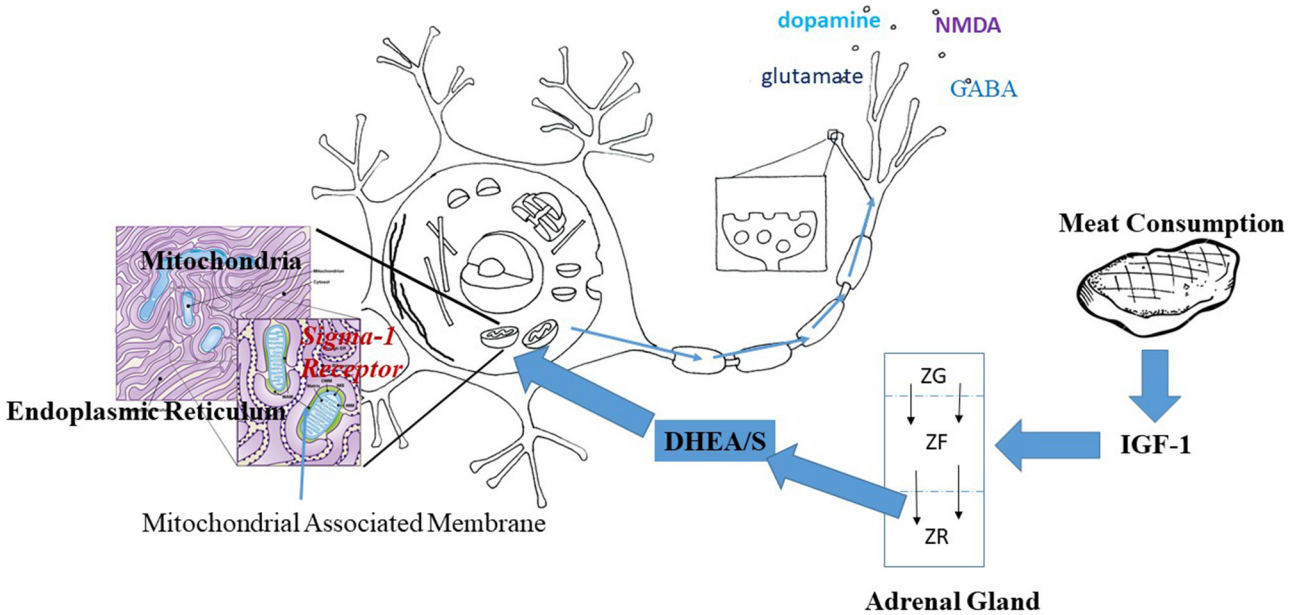

FIGURE 1 | Hypothesized pathway linking meat consumption and neuronal activity. IGF-1 increases with the consumption of animal protein. Within the adrenal gland, IGF-1 prevents apoptosis of cells thus increasing the centripetal movement of cells from the Zona Glomerulus (ZG) and Zona Fascularis (ZF) into the Zona Reticularis (ZR). Increased IGF-1 would result in a thicker ZR and greater production of DHEA/S. DHEA/S crosses the blood brain barrier and enters into neurons. Within the neuron, DHEA acts at the Sigma-1 Receptor located on the mitochondrial associated membrane between the mitochondria and the endoplasmic reticulum. Activation of the Sigma-1 receptor acts to increase energy production and alleviate stress-related production of oxygen free radicals. The result is the increased production and release of neurotransmitters as suggested by the arrows along the axon.

Aka pygmies and Ngandu farmers of the Congo with those of Sidama agriculturalist from Ethiopia. The authors used GM models to determine the transition point at which DHEAS levels start to increase again after declining from birth, based on 160 individuals (80 m; 80 f) ages 3–18 years from any all three populations. Results indicate an average age of adrenarche of about 8 years for the Ngandu, and Sidama and 9 years for the Aka, with no significant sex differences in any of the three groups. In addition, age patterns of cortisol among Aka females and Sidama males appear to include a nadir around the age of 10 years.

Importantly, all three of these subsistence populations exhibit high rates of growth stunting (89). Stunting has been associated with lower DHEAS among children in a single study from rural Malawi (59), so undernutrition alone might account for later age at adrenal onset among Aka, Ngandu and Sidama children. In addition, the Aka and the Ngandu, as residents of a tropical forest, presumably carry high parasite burden (89), which could play a role in adrenarche time relative to the non-forest dwelling Sidama.

However, Hlefrecht et al. (89) don't include anthropometric measures to test the relationship of DHEAS with stunting or other nutritional status indices. No do they have measures of animal protein consumption that might be used to test the hypothesis that meat consumption is important to variation in in adrenarcheal timing. Thus, the results are tantalizing, but without reference values for hair DHEAS from industrialized populations for comparison as well as measures of dietary intake and nutritional status they simply beg further investigation.

In a study of the impacts of migration on reproductive maturation (also cross-sectional), Houghton et al. (124) compared the timing of adrenarche in girls among British natives, Bangladeshi natives and both 1st and 2nd generation Bangladeshi immigrants to the U.K., using salivary DHEAS. Average age at adrenarche (determined by a Wiebell regression as a measures of estimating when 50% of the sample passed a threshold value of 400 pg/ml) was 7.1, 7.2, and 7.4 years for the British, Bangladeshi Natives, and 2nd generation immigrants, respectively, while for 1st generation immigrants the average was 5.3 years.

Houghton et al. also analyzed their DHEAS results with regard to nutritional status, reporting that BMI quartiles predicted onset of adrenarche, with the highest quartile showing a significant difference from the others. However, BMI quartiles did not predict DHEAS levels subsequent to adrenarche, suggesting that earlier onset of DHEAS is not related to higher levels of DHEAS during middle childhood and adolescence. In other words, the earlier emergence of the zona reticularis did not appear to be related to the development of a thicker zona reticularis, as indexed by DHEAS production, contrary to my argument above.

The population comparison in Houghton et al.'s study is instructive in two important ways. An earlier study, based on serum DHEAS, reported an average age of adrenarche of 7.7 years among school girls in Taiwan (129). Thus, the timing of adrenarche among the British, Bangledeshi and Taiwan natives

provides a clear baseline for the onset of adrenarche among adequately nourished girls at 7–8 years. The results from the Bangledeshi immigrants also shows that adrenarche can vary substantially across populations. On the other hand, the results do not suggest a clear reason for substantially earlier onset of adrenarche among the 1st generation migrants nor do they speak to adrenarche in boys.

Hodges-Simeon et al. (90) investigated the relationship of salivary DHEAS with energetic status in a sample of 90 boys and 81 girls, aged 8–23 years, from the Tsimane of lowland Bolivia, a horticultural/foraging population,. They found higher salivary DHEAS associated with greater superiliac skinfolds and grip strength, among the males, but not the females. The youngest participants in Hodges-Simeon et al.'s sample were 8 years old so estimating adrenarcheal timing was not possible. In fact, 8–23 years is more reflective of pubertal than adrenarcheal changes. Thus, the reported relationship of DHEAS with energy stores and grip strength may be more reflective of the effects of testosterone during puberty, as reported by Campbell and Mbizvo (130) among 441, 12–18 year old, Zimbabwe school boys.

Together these three studies provide clear evidence that the timing of adrenarche can vary across populations and may be related to nutritional status. However, they say little about potential causes for such differences, including differences in energy stores (131), diet (132), and/or heavy parasite burden (133), or protein consumption as proposed here, that characterize subsistence populations. They also leave open potential sex differences in adrenarcheal timing, which may be involved in the development of attachment and gender roles (1).

Comparative Timing of Zona Reticularis, Brain, and Weaning

Examination of adrenal glands from chimpanzees suggest the ZR begins to emerge around the age of 3 years and continues to broaden into adulthood (134), similar to the pattern found in humans (67). Unfortunately, data regarding the maturation of the zona reticularis is not available for bonobos.

The emergence of the zona reticularis in chimpanzees appears co-incident with the eruption of the deciduous (baby teeth) M1 molar at 3.3 years of age in both wild and captive animals (135, 136). Deciduous M1 eruption is of specific interest because it is related to the age of weaning across mammals in general (137). At the same time a period of elevated synaptogenesis lasts from 3 to 5 years (69) paralleling the process of weaning starting around 3 and finishing at ca. 4.5 years (135). Thus it appears that increased synaptogenesis, with its elevated energy requirements (138), takes place while energy availability from breast milk declines, and DHEA/S levels rise.

In humans the emergence of the ZR at age 3 (67) is similar to that seen in chimpanzees (134). However, the relationship of ZR emergence with the timing of molar eruption, the period of elevated synaptogenesis and weaning differ from that observed in the chimpanzee. Deciduous M1 eruption, at 5.5 years, is delayed by a couple of years relative to chimps. The period of peak brain glucose utilization, associated with synaptogenesis, is reached at about 5 years (53, 57). In contrast, age at weaning in natural fertility populations is close to 2 1/2 years, although the data are poor (70, 71).

In all, it appears that in humans the onset of weaning has been accelerated relative to chimps, with delayed dental maturation and a later peak in synaptogenesis. Thus, the human pattern of early development appears to separate the integration of breast-feeding and brain development from its ancestral roots. This comparison makes it clear that breast feeding intervals have been shortened to increase reproductive rates, while at the same time humans show slower growth rates consistent with our extended life spans, a point made previously by Bogin (55, 56), Bogin et al. (139), Kramer (140), and Kramer and Otárola-Castillo (141).

It has been suggested on the basis of deciduous M1 eruption timing that humans would be expected to exhibit weaning somewhere between 5 and 7 years (137). If this were so, weaning in humans would be associated with a period of declining glucose utilization (53) as in chimps. Instead the temporal advance of weaning means that the period of peak glucose utilization and increased synaptogenesis from the age of 4–8 years falls outside of the period of breastfeeding.

DHEAS AND HUMAN DEVELOPMENT

The association of DHEA with the development of the LDLPC is notable for two reasons; 4–8 years is a period of elevated glucose utilization (53, 57) and increased synaptogenesis (138). The timing also maps onto the so-called 5-to-8 transition when children begin to develop cognitive skills that allow for great individual independence (142) White (73) point out that children become cognitively and socially capable of carrying out basic social tasks during this period. Among hunter-gatherer groups this shift is associated with increasing play directed toward subsistence activities [see examples in (143)], as well as the care of younger siblings (144).

The association of DHEA with the rTPJ from 7 to 12 years of age is even more striking because it suggests DHEA's importance to the development of theory of mind (ToM). ToM is well-developed in humans [for whom it is associated with activity in the rTPJ (145)], but rudimentary in chimpanzees (146). During middle childhood, the differentiation of thinking about the thought of others, rather than their actions or feelings is associated with the development of the rTPJ (147, 148).

Thus, DHEA appears to play a role in two key transitional periods; that from infancy to early childhood and from early childhood to the juvenile stage or middle childhood. The first of these steps represents a standard transition in mammals from dependent infants to largely self-sufficient juveniles. As such one might expect that the pattern of DHEAS production during this period would differ between human and chimpanzees primarily by magnitude or timing. The second transition, on the other hand, is thought to be unique to humans as is middle childhood itself (55). Hence the role of DHEA in the development of the rTPJ may be a relatively recent phenomenon in evolutionary terms and as such associated with other novel physiological, neurological or genetic differences between humans and both chimps and bonobos.

The dramatic changes in secondary sexual characteristics during puberty brought on by testosterone and estrogen overshadow any of the physical effect of DHEAS, including acne, body odor, oily skin, and body hair [see (37) for a review]. As

mentioned earlier DHEA and DHEAS can be converted into testosterone and/or estrogen and act through the AR (100) or the ER (149). So it possible that DHEA contributes to the effects of testosterone and estradiol. However, given the lack of strong affinity for the AR and ER, DHEA/S it is unlikely to have much discernable impact on secondary sexual characteristics during puberty when testosterone and estrogen levels are rising.

Nonetheless, DHEA/S may continue to have effects on brain development throughout puberty. In fact, among prepubertal children, Nguyen et al. (14) found an interaction of DHEA with testosterone on cortical thickness in the right cingulate cortex and occipital pole while Barendse et al. (150) report an interaction of testosterone and DHEA on white matter microstructure. These findings presumably reflect different modes of action for the two hormones, with testosterone acting through the AR while DHEA acts at other receptors, including sigma-1, TrkA, and IGF-1 (103). If so, prolonged cortical maturation starting at 6 years and continuing into the 20's would appear to reflect increasing levels of DHEA/S as a separate but interrelated process with that of the impact of reproductive maturation on brain development.

Less attention has been given to the implications for the end of the steady rise in DHEAS in the 20's (151, 152). One study reported a peak for females about 25 years, with males showing a peak at 30 (152). This timing is roughly consistent with the end of cortical maturation in the 20's as judged by myelination (153–155). Such continued maturation presumably underlies the emergence of young adulthood as a human developmental stage [see (156) for a discussion of young adulthood].

In contrast, myelination in the chimp appears to reach a peak during puberty, around 12 years (157). However, it is unclear how this timing corresponds to age patterns of DHEAS. Bernstein et al. (112) show a peak in serum DHEAS at 10 years of age for a sample they label PAN, i.e., both chimpanzees and bonobos. In contrast, Behringer et al. (5) report increases in urinary DHEAS among Bonobos until at least the age of 20 years, as do Sabbi et al. (4) for chimpanzees.

More precise measures of both age-related DHEA/S and cortical changes in humans are needed to determine if the cessation of significant myelinization and increases in DHEA/S in humans are in fact related. Nonetheless, the current findings are consistent with a role for DHEA in the prolonged development of the human cortex starting at age 6, continuing through puberty and into the 20's. On the other hand, the relationship of the timing of DHEA/S and cortical maturation for chimps and bonobos remains an important question for investigation.

EVOLUTION OF EARLY AND MIDDLE CHILDHOOD

Up to this point I have focused on physiological and cellular mechanisms underlying adrenarche and the effects of DHEA on the brain, including increased cortical thickness in the LDLPFC from 4 to 8 years, and the rTPJ from 7 to 12 (14). Together these brain changes underlie the behavioral and cognitive changes of the 5-to-8 transition and middle childhood (1, 37). The evolutionary question is the nature of the selection pressures that created this novel human life stage of early and middle childhood, inserted between infancy and adolescence (55, 56, 139).

Bogin (55) suggests three possible hypotheses for the evolutionary benefits to early and middle childhood against the backdrop of generally longer development in humans. These include; (1) a reproductive and feeding strategy for the mother, (2) a way of eliciting child care for older children, (3) a way of reducing the energetic cost of juvenile children. All of these factors appear to apply to early childhood. While a nursing mother is pre-occupied by a nursing infant, toddlers can look to other adults and old siblings for both food and social interaction, while their small size makes them less expensive to feed.

With the advent of middle childhood the focus of development shifts to the role of socialization and cultural learning for the child itself (87). Hrdy (76) stresses the importance of child care experience during middle childhood for girls among hunter-gather societies, such as the Ju'Hoansi. The development of mentalizing would be especially helpful for such mothers in training, as recent findings documenting changes in the social brain during pregnancy emphasize (158). But girls of this age are also encultured in women's subsistence activities, as well as morality and religion (87).

Boys are solicitous of their younger siblings as well. However, among subsistence societies childhood activities start to become gender specific during the 7–12 year stage, with girls expected to do childcare (144). Thus, among H-Gs, pre-pubertal boys will start to spend more time practicing and playing hunting skills [see (159, 160) for examples]. As part of this, mentalizing would be important for coordinating behavior during a hunt. In fact, mentalizing can include understanding the mind of prey animals [see (161) for such accounts among the San].

In addition, mentalizing would be useful for developing an understanding of one's self in relationship to the opposite sex. Del Guidice (1) has argued that middle childhood is a time when attachment becomes sexually differentiated and the increase in DHEAS stimulate genetically-based sexually related behaviors that will be more fully developed with puberty. The fact that DHEAS has been related to amygdala connectivity and emotion in prepubertal children (40) together with the role of amygdala in human chemosensory processing (162, 163) provides a potential link by which body odor at adrenarche might be related to the emergence of sexual awareness. Specifically, the development of body odor as a function of sebaceous glands (37) may be synchronous with the development of the emotional salience of body odor as a signal.

HUMAN EVOLUTION, WEANING, AND MEAT

To be convincing arguments about the evolution of unique human traits like mentalizing (148) or the emergence of a novel life stage like middle childhood (55) require both a physiological substrate and evidence for a phylogenetic precursor. The onset of DHEAS production during early childhood (119, 120), and its impact on brain development during both early and

middle childhood (14, 42, 43), together with the emergence of mentalizing from 9 to 11 years (147) fits both criteria. Adrenarche is a physiological process with neurological consequences related to behaviors during middle childhood, and the increase in DHEAS is linked to the development of the adrenal ZR. A similar increase in DHEA/S among chimpanzees provides a phylogenetic precursor, though the behavioral consequences of adrenarche for chimpanzees are unclear.

Evidence for the role of meat in human brain evolution starting with the origins of the genus *Homo* can only come from the hominid evolutionary record. Recent findings based on analysis of barium/calcium isotopic ratios from five Australopithecus Africanus teeth suggest weaning around 1 year (164). Furthermore, the isotopic analysis show cyclic changes in the barium/calcium ratios after apparent weaning suggesting renewed period of milk intake in response to environmental fluctuations, similar to that observed among orangutans.

These finding are important in suggest that provisioning by non-material family members during early childhood development may have started alongside an increase in endocranial volume with Homo Habilis (165). In other words, provisioning of weaned infants with meat would have helped to alleviate seasonal undernutrition, thus promoting growth and survival while allowing for energetically expensive brain development during this period as discussed above for modern humans.

It is generally agreed that increased meat consumption was critical to early Homo adaptations, including increased brain size (166, 167). The importance of specific factors, such as the role of cooking in making meat especially energy rich (47, 168) and timing of the habitual use of fire for cooking is a topic of much discussion (169–171). As are the roles of essential fatty acids (172, 173) and vitamins and minerals (174). I am not arguing that DHEA/S supplants those factors, i.e., this is not a case of endocrinological "newcomer bias" with regard to metabolic regulation (175), but that DHEA/S represents a previously unrecognized pathway promoting increased brain size, one that seems to fits the specific trajectory of human brain development.

FUTURE RESEARCH DIRECTIONS

Because direct experimentation is not possible, arguments about evolutionary history are by their nature speculative. However, evolutionary arguments can be substantiated by what Wilson (176) referred to as consilience, the jumping together of relevant elements, each subject to empirical investigation, to bear on the central question. In this case, I highlight two related areas where further research can generate empirical results that can then to applied to the interpretation of the fossil record. These are; (1) better characterization of adrenarcheal timing and its association with behavior in the Africa apes; and (2) the role of protein consumption and nutritional status in adrenarcheal timing among human subsistence populations and its potential implications for behavioral and cognitive development.

Adrenarche in Chimpanzees and Bonobos

For the great apes, given the longitudinal results available from wild chimpanzees (4) the immediate focus of inquiry shifts to a more complete characterization of adrenarche among bonobos. On-going work at the Kokolopori and Luikotali study sites in the Democrative Republic of Congo by researchers at the Max Planck Institute for Evolutionary Anthropology in Leipzig (https://www.eva.mpg.de/primat/research-groups/bonobos/main-page) are ideally positioned to produce results for wild bonobos. The value of such results would be greatly increased by comparison with an on-going project among captive bonobos and chimpanzee also on-going at the Max Planck Institute. Most specifically, the availability of a well-tested urinary IGFBP-3 (IGF binding protein 3) assay, as proxy for IGF-1 (5) would make it possible to test the mechanism put forward here. Does individual variation in IGFBP-3 predict variation in DHEAS and the timing of adrenarche? Do longitudinal increases in IGFBP-3 predict increases in DHEA/S within individuals?

If bonobos show age-related increases in DHEA/S similar to those clearly documented for wild chimpanzees by Sabbi et al. (4), together the two species would represent a common pattern useful as a single comparison for humans. On other hand, if patterns of adrenarche are different, it is possible that DHEAS may have some role in reported differences between chimpanzee and bonobo brains (83–85). This is a topic worthy of investigation in its own right.

Adrenarche in Subsistence Populations

As discussed previously, current results suggest that adrenarche may be delayed by a year or two in subsistence populations, but the possible causes and potential implications have yet to receive much attention. The hypothesis advanced here, that meat consumption plays a role is adrenarche, can be tested by using measures of animal protein intake as well as skinfold measures as a marker of energy stores as predictors of DHEA/S in a lean subsistence population much as Shi et al. (127) found among children in Germany. If the results show a significant relationship with animal protein intake, controlling for measures of energy stores, the next step is test IGF-1 as a possible mechanism mediating protein consumption and DHEA/S.

The question remains as to whether differences in timing of adrenarche associated with undernutrition have a demonstrable impact on the timing of cognitive processes associated with the 5-to-8 transition and middle childhood. In WEIRD populations, in addition to underlying process of brain development, cognitive development is scheduled by age-related progression through school which plays an important role in entraining attention (177–179). In fact, cross-cultural studies suggest that the timing of the 5-8 transition is consistent across societies (74, 87), implying that underlying brain maturation, including peak glucose utilization (53) and associated synaptogenesis (138) show similar timing across populations.

Thus, a significant delay in adrenarcheal timing would seem mostly like to shift the relative impact of increasing DHEA/S

levels away from maturation of the LDLPFC at 4–8 years and toward the maturation of the rTPJ from 7 to 12 years. As a consequence, delayed adrenal timing might bias brain development away from impulse control and decision-making during the 5-to-8 transition and more toward mentalizing during middle childhood.

Such a brain might end up producing a mind characterized more by attention to the thoughts of others than to abstract thoughts and rules, as suggested by reports of important differences in attentional style in subsistence vs. WEIRD populations (178, 180). Furthermore, greater emphasis on mentalizing might lead to metalizing about the thoughts of animals, especially among hunter-gatherers who are so intimate with their prey (181–183). Or, in the words of Hallowell (184), animals might be come be seen as non-human persons.

CONCLUSION

Recent evidence that DHEA/S plays a role in the development of the human brain calls for an evolutionary explanation of adrenarche among both humans and the African Apes. I hypothesize that increasing consumption of meat among our hominid ancestors promoted increased IGF-1 leading to increased growth of the adrenal reticularis and increased production of DHEA/S. In turn, DHEA/S may promote mitochondrial energy production critical for synaptogenesis and brain development.

Comparison of the timing of brain development relative to weaning and dental eruption patterns suggests that unlike for chimps, in humans the maximal brain energy demands are not supported by maternal energy stores. Thus, provisioning of young children by kin with meat may have to the increased important of DHEA/S in brain development during the 5-to-8 transition along with the later development of a middle childhood stage.

Results from wild chimpanzees demonstrate age related patterns of DHEAS and cortisol very similar to those displayed in humans, providing a baseline from which to understand how DHEAS may have played a role in childhood development over the course of human evolution. More work is needed to determine adrenarcheal timing among wild bonobos, and whether differences in DHEA/S is related to developmental differences between the two ape species.

In addition, findings among subsistence populations are tantalizing in suggesting delayed age at adrenarche relative to the industrialized world. But the current results are subject to interpretation and specific factors behind apparent delays call for investigation. To test the hypothesis suggested here, collect data on animal protein consumption as well as anthropometric measures of energetic status in energetically constrained populations are needed. Such work may have important implications for understanding the impact of adrenarcheal timing on the development of cognition in subsistence populations and by inference among humans generally.

AUTHOR CONTRIBUTIONS

BC was responsible for the entire production of this manuscript.

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REVIEW
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Evolutionary Perspectives on the Developing Skeleton and Implications for Lifelong Health

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Osteoporosis is a significant cause of morbidity and mortality in contemporary populations. This common disease of aging results from a state of bone fragility that occurs with low bone mass and loss of bone quality. Osteoporosis is thought to have origins in childhood. During growth and development, there are rapid gains in bone dimensions, mass, and strength. Peak bone mass is attained in young adulthood, well after the cessation of linear growth, and is a major determinant of osteoporosis later in life. Here we discuss the evolutionary implications of osteoporosis as a disease with developmental origins that is shaped by the interaction among genes, behavior, health status, and the environment during the attainment of peak bone mass. Studies of contemporary populations show that growth, body composition, sexual maturation, physical activity, nutritional status, and dietary intake are determinants of childhood bone accretion, and provide context for interpreting bone strength and osteoporosis in skeletal populations. Studies of skeletal populations demonstrate the role of subsistence strategies, social context, and occupation in the development of skeletal strength. Comparisons of contemporary living populations and archeological skeletal populations suggest declines in bone density and strength that have been occurring since the Pleistocene. Aspects of western lifestyles carry implications for optimal peak bone mass attainment and lifelong skeletal health, from increased longevity to circumstances during development such as obesity and sedentism. In light of these considerations, osteoporosis is a disease of contemporary human evolution and evolutionary perspectives provide a key lens for interpreting the changing global patterns of osteoporosis in human health.

Keywords: osteoporosis, evolution, growth, skeleton, nutrition, physical activity, longevity

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INTRODUCTION

Globally, musculoskeletal disorders are one of the five leading causes of years lived with disability, affecting an estimated 1,270,630,000 people (1). While the contribution of osteoporosis to this global statistic is uncertain, the magnitude of the burden is reflected by the fact that in the U.S., osteoporosis-related fractures are responsible for more hospitalizations than heart attacks, strokes and breast cancer combined (2). Osteoporosis is primarily a disease of aging whereby age-related losses in the mass and structural properties of bone lead to increased bone fragility and risk of

fracture (3, 4). Clinically, osteoporosis in adults is defined as a bone mineral density measurement at least 2.5 standard deviations below the mean at the spine, femoral neck or total hip for young, healthy adults (5), or the occurrence of an osteoporotic (low-trauma) fracture of the hip, vertebra, proximal humerus, pelvis, and some wrist fractures in the context of low bone density (1–2.5 standard deviations below the mean) (6).

Although osteoporosis is primarily a disease of aging, it is thought to have origins in childhood. The bone mineral content of the body increases as the size of the skeleton expands during growth (**Figure 1**). During the second to third decades, gains in bone mineral content and density reach a plateau, referred to as peak bone mass. This process has a strong genetic component, but is also sensitive to the physiological milieu and behaviors that can influence bone accretion and result in suboptimal peak bone mass. Peak bone mass is a strong predictor of osteoporosis in later life. Because childhood and adolescence are periods of rapid bone accrual leading up to peak bone mass, they are believed to be critical for optimizing peak bone mass and preventing or delaying the onset of osteoporosis in older age.

Here we will describe the relationship of growth, body composition, maturation, and behaviors to peak bone mass attainment in contemporary populations, what is known from skeletal populations, and the evolutionary implications of skeletal development and osteoporosis.

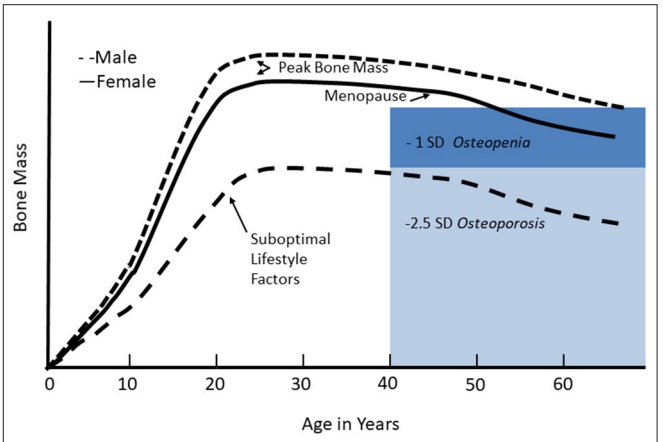

FIGURE 1 | Changes in bone mineral mass across the life cycle. Bone mineral mass increases during growth and reaches a plateau, referred to as peak bone mass, in young adulthood. Women lose bone rapidly in the first few years of the menopausal transition, and then both men and women continue to lose bone gradually in older age. For adults, low bone mass, or osteopenia, is defined as 1–2.5 standard deviations below peak bone mass; osteoporosis is defined as bone mass <2.5 standard deviations below peak bone mass. With suboptimal lifestyle factors, failure to achieve optimal peak bone mass reduces the age of onset of osteopenia or osteoporosis given the usual age-related bone mass. Reproduced from Weaver et al. (7) under the Creative Commons CC-BY License.

DEVELOPMENT OF PEAK BONE MASS AND PEAK BONE STRENGTH

Bone accrual and the development of peak bone mass occurs through the delicately coordinated actions of bone deposition and resorption that are sensitive to genetics, hormones, mechanical loading through physical activity, other behaviorally mediated factors (e.g., diet), and insults from the internal (e.g., inflammatory cytokines), and external environments (e.g., low sunlight exposure) (7). During childhood, the rate of bone accrual is relatively constant, but changes as puberty progresses. As shown in **Figure 2**, prepubertal children (Tanner breast/genital stage 1) and those in early puberty (Tanner stage 2) show similar rates of bone accrual. In mid-puberty, i.e., Tanner stages 3 and 4, the rate of bone accrual increases markedly, and even in the later stages of puberty (Tanner stage 5), bone accrual rates are still at their peak for some youth. The rate of bone accrual reaches a maximum 6 months to 2 years after peak height velocity, depending on the skeletal site examined (9). Approximately 33% of adult total bone mass is accrued in the 2 years before and 2 years following peak height velocity. Bone accrual continues after cessation of linear growth; in fact, 7–11% of adult bone mass is gained after the cessation of linear growth (9). Bone accrual is completed and peak bone mass attained earlier in females than in males (9, 10), although the exact timing at the individual level is uncertain.

Peak bone mass could be the single most important factor to prevent osteoporosis later in life (11, 12). Two lines of evidence support this hypothesis. First, the variability in bone mass and density at the time of peak bone mass is large compared to age-related bone loss in older adulthood. So, attaining a higher peak bone mass mitigates against age-related bone loss to a level that poses risk for fracture (13, 14). Secondly, a computer simulation study of bone remodeling showed that at the population level, shifts in peak bone mass have a greater impact on delaying the onset of osteoporosis than shifting the age at menopause, a major cause of age-related bone loss in women. Indeed, this simulation showed that an increase of 10% in the magnitude of peak bone mass can delay the onset of osteoporosis by 13 years for much of the population (12).

Bone strength is determined, in part, by bone mineral mass and density. The structural properties of bone also contribute to bone strength. Characteristics such as the thickness, density and porosity of cortical bone, and trabecular microarchitecture (trabecular thickness, number, and spacing), together determine the structural strength of bone. It is unknown whether peak bone strength occurs at the same time as peak bone mass attainment. Recent studies suggest redistribution between the trabecular and cortical bone compartments after the age at which peak bone mass is attained. One of the first studies using high-resolution peripheral quantitative computed tomography (a technology that can quantify the properties of trabecular and cortical bone) demonstrated fairly rapid trabecular bone density loss in the tibia, radius and spine in females and to a lesser degree in males after peak bone mass attainment. However, increases in cortical bone occurred through the 3rd decade. The increases in cortical bone density into the third decade have been confirmed in other studies, with inconsistent results for trabecular bone density (15–17).

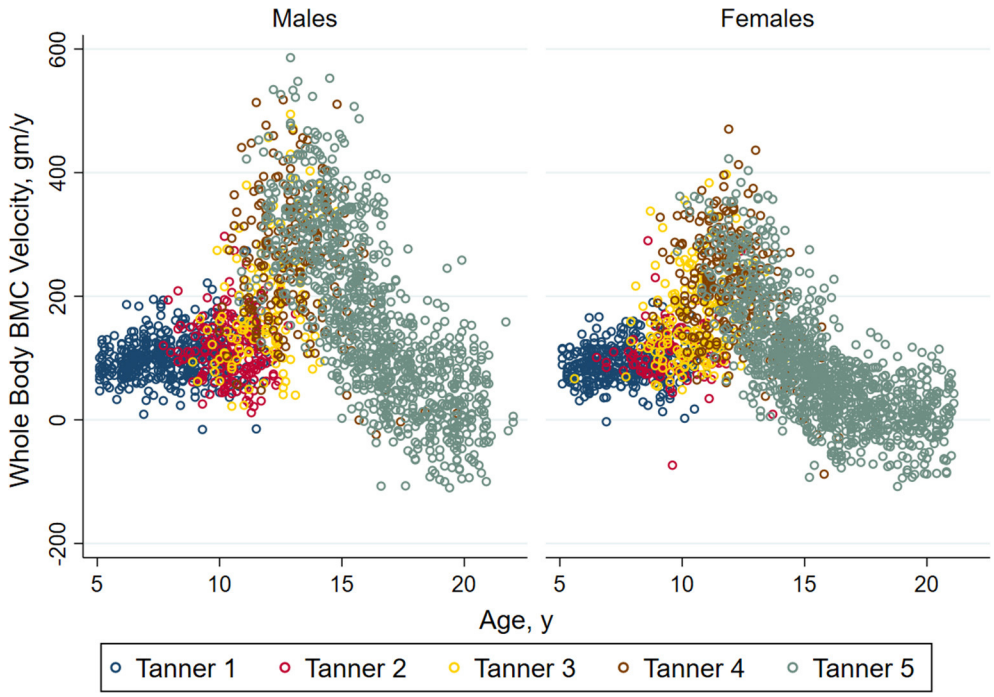

FIGURE 2 | Annual velocity (bone accrual) in whole body bone mineral mass in healthy non-African American children and adolescents according to Tanner stage of sexual maturation (breast stage for girls and testicular volume for boys). Individual values for bone accrual are shown relative to age with different colors representing the stages of sexual maturation. For both males and females, children in Tanner stages 1 and 2 have similar whole body bone accrual. Annual velocity is highest in Tanner stages 4 and 5, and declines with age among children in Tanner stage 5. Reproduced from Kelly et al. (8) with permission.

FACTORS THAT INFLUENCE DEVELOPMENT OF PEAK BONE MASS AND STRENGTH

The development of peak bone mass during adolescence is influenced by heredity, growth, sexual maturation, physical activity, diet, nutritional status, and other behaviors such as sleep, and overall health. These factors have important implications for understanding temporal and geographic variation in osteoporosis.

Heredity and Genetics

Differences between some population ancestry groups in bone density distributions are present during both childhood and adulthood. Areal bone mineral density is greatest for African Americans, and Europeans have higher areal bone mineral density than Asians and Hispanics (18–20); these differences are thought to be due to differences in genetic potential for peak bone mass (21). The population ancestry differences are also mirrored by differences in fracture rates among both children and adults (22, 23). For example, in the Women's Health Initiative study, African American women had a 49% lower risk of fracture than white women (22) similar to other reports (24–27), Asian populations also have a lower incidence of hip fractures than white US populations (28–30). During development of peak bone strength, African Americans have greater maturation-specific trabecular density and cortical structural strength (31–33). The evolutionary basis for these population ancestry differences in bone density and strength are unknown.

Familial studies show that ∼60–80% of osteoporosis risk is attributed to heredity (11, 34). Familial concordance is strong (35, 36), and is expressed prior to puberty (37). More recently, genome wide association studies in adults have discovered more than 60 loci associated with bone density (38–41) and 14 loci associated with fracture risk (41). An additional 518 loci have been associated with ultrasound heel estimated bone mineral density by heel ultrasound (42, 43). Genetic risk scores, calculated as a tally of the number of risk alleles at these loci, associate with bone density during childhood (21, 44–47). Combined, these many loci only explain about 20 percent of the variability in bone density and related outcomes (43), so a large portion of the estimated heritability of low bone density remains to be identified.

Growth and Maturation

The bone mineral content of the total body and subregions increases along with skeleton size during growth and maturation. Most pediatric studies have used dual energy x-ray absorptiometry (DXA) to measure bone mineral content and density and the association with height in growing children is very strong. More importantly, for children of the same age, those who are taller for age have greater bone mineral content and areal bone mineral density (48). **Figure 3** illustrates the rate of bone accretion relative to the timing of the pubertal growth

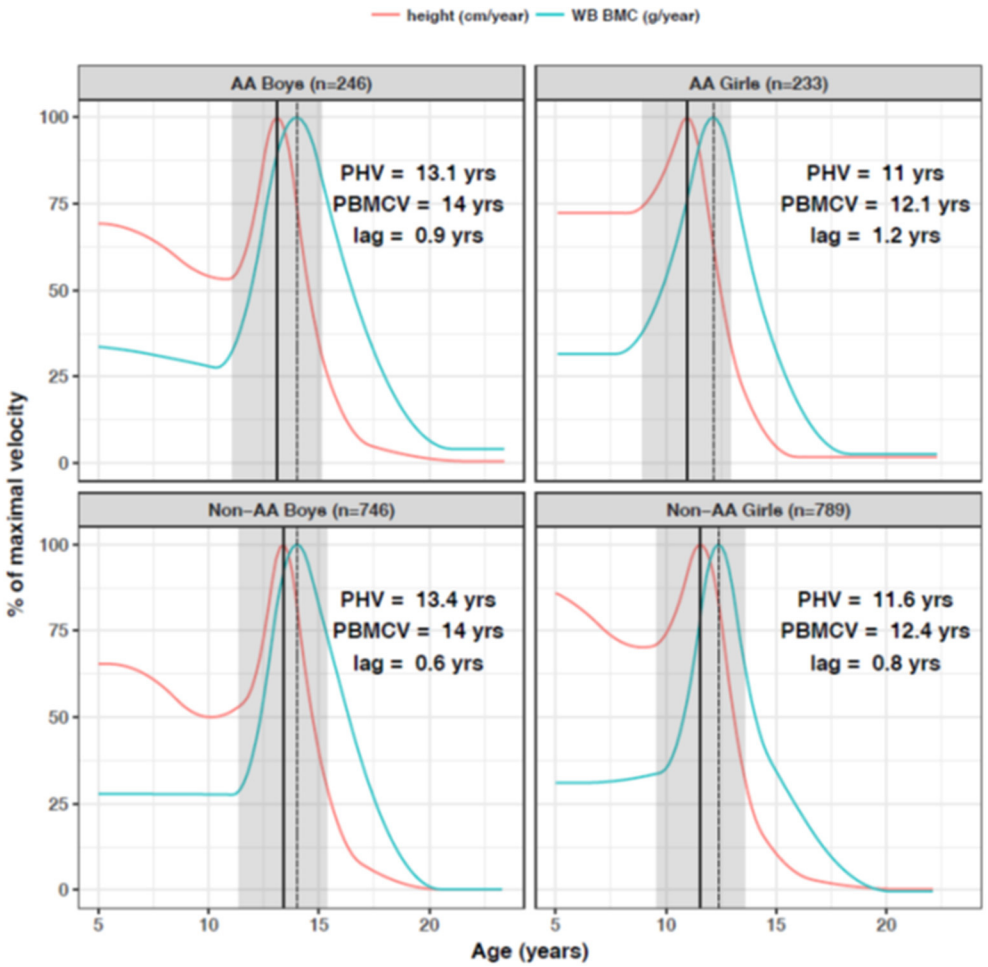

FIGURE 3 | Peak bone accretion occurs after the pubertal growth spurt in height in African American (AA) and non-African American (non-AA) boys and girls. In the 2 years before and 2 years after the growth spurt in height, children gain about 33% of adult total bone mass. Bone accrual continues after cessation of linear growth. Reproduced from McCormack et al. (9) with permission.

spurt in height (9). The maximum rate of bone accretion is preceded by peak height velocity which occurs 6 months to 2 years depending on the skeletal site. Cortical dimensions, such as periosteal circumference and cortical thickness also increase profoundly during growth, and scale to the length of growing long bones in order to sustain structural competency (33).

As described above, pubertal maturation has a profound effect on bone accretion. The rate of bone accretion in childhood and early puberty is fairly constant. By puberty stage 3, defined breast development in girls and genital development in boys (49), the rate of bone accrual for the whole body, spine and hip begins to increase and is greatest in stages 4 and 5 (8). At the end of puberty, male cortical thickness is greater than in females (50). While sex differences in bone mass are small prior to puberty, it is the sex differences in pubertal gains in bone mass, dimensions and strength that establish the sex-based differences in osteoporosis and fracture later in life. Osteoporosis disproportionally affects women, who have a two-fold greater lifetime risk of bone fracture (51).

Pubertal timing has long lasting effects on bone mineral content and density. One longitudinal study of prepubertal girls followed to young adulthood showed that earlier maturing girls had greater bone density prior to menarche and into adulthood (52). A population based cohort also found later age at maturation associated with lower bone density in both males and females in young adulthood (53), but another study suggested that later-maturing males eventually catch up to their earlier maturing peers (54). A genetic study demonstrated that genetic risk scores based on variants associated with later pubertal timing in boys and girls were associated with lower bone mineral density, supporting a causal relationship between later puberty and osteoporosis risk in both sexes (47). The detrimental effect of later pubertal timing on bone accrual in women appears to be sustained well into adulthood (52).

Physical Activity

Physical activity is perhaps the single most important lifestyle factor influencing peak bone mass. Bone responds to loads

and mechanical use resulting from physical activity. This phenomenon was first described as Wolff's law (55), which proposed that bone morphology adapts to mechanical forces from muscle load (56, 57). Building upon this law, the "mechanostat theory" developed by Frost explained how bones adapt their strength to the mechanical loads to which they are exposed (58). Bone turnover occurs throughout the lifecycle to maintain healthy bone through the delicately coordinated action of osteoblasts and osteoclasts which control bone formation and resorption. When bone formation exceeds bone resorption, bone modeling occurs. During longitudinal bone growth, mechanical stimulation increases the bone modeling process to reshape bone in a manner that minimizes risk of fracture (58). Mechanical stimulation from high magnitude strains produces more bone modeling than lower strains at higher frequency. Modeling is less effective after skeletal maturity. The relationship between mechanical loads and cortical development was best documented in tennis players. Professional tennis players show marked asymmetry due to about 20% more bone mineral content and muscle mass in the dominant arm (59–61). The benefit of playing tennis or squash on the bones of the playing arm was approximately doubled for females who started playing at or before menarche compared to those who began training at a later age, demonstrating the increased responsiveness of bones to adapt to loading forces earlier during development (60). Numerous studies have confirmed the effects of physical activity on bone mineral content and density, dimensions and strength during childhood and adolescence for those engaged in other sports, such as gymnastics (62), as well as non-competitive weightbearing physical activity (46, 63, 64). Even in young adulthood, the benefits of weight-bearing physical activity on increasing or sustaining bone strength have been documented (65–67).

Several studies suggest that the increased bone mass and strength derived from physical activity in childhood may not be sustained at the same level (bone loss can occur) if physical activity levels decline. However, the advantage in bone mass and strength remains compared to those who never engaged in high levels of physical activity during growth. This has been demonstrated, for example, in studies of female soccer players (68), retired gymnasts (69), and former weightlifters (70).

Diet and Nutritional Status

There are several dietary constituents that are essential for bone health. The mineral matrix of bones is made of hydroxyapatite, a compound of calcium and phosphate. Bones are the primary reservoir for calcium, an essential nutrient that is tightly regulated in the blood to sustain important physiologic functions such as nerve conduction. Vitamin D is needed for calcium homeostasis. Thus, calcium and vitamin D are among the most important nutrients for sustaining bone mineral accrual and optimizing peak bone mass. Young children are particularly vulnerable to nutritional rickets from either calcium or vitamin D deficiency (71). Some randomized control trials of calcium and/or vitamin D support the importance of these nutrients for optimizing bone accretion during childhood (7). The importance of these nutrients during the most rapid phase of bone accretion during adolescence is uncertain (72). The effects of very low calcium intake during childhood may be long lasting; women who reported consuming less than one serving of milk per week during childhood and adolescence had lower hip bone mineral density compared to those who consumed more milk, and fracture risk was greater in those with low milk consumption (73).

Other nutrients are also important for bone accretion based, including but not limited to copper, zinc, magnesium, vitamin C and K, and protein (74). The effects of these individual nutrients on bone accretion during growth and development in humans has been difficult to discern in the absence of frank deficiency states since many of these nutrients are combined in overall dietary patterns. For example, higher fruit and vegetable consumption is associated with greater bone accretion in young children (75) and adolescents (76). A supplementation study using a prebiotic inulin type of dietary fiber showed increased calcium absorption and greater gains in bone mineral content in peripubertal children (77). A "prudent/healthy" dietary pattern (high intakes of vegetables, fruits, low-fat milk and dairy products, whole grains, fish, beans, and nuts) was associated with lower risk of fracture in adolescents (78). Thus, while diet is clearly an important factor, the role of many individual dietary constituents has not been fully delineated, but diets rich in fruit and vegetables with adequate calcium intake will support optimal bone accretion.

Nutritional status in terms of extremes of underweight and overweight have adverse consequences for bone accretion and development of optimal bone strength. Adolescents with anorexia have low bone density and reduced strength compared to normal weight peers, and these effects can be long lasting (79, 80). At the other end of the spectrum, children with obesity have greater bone mineral content and density and greater cortical thickness than non-obese children (81). However, they experience greater risk of fracture (82) and greater complications from fractures (83) than peers who are not obese.

In sum, genetic differences between and within populations suggest that selective pressures may have influenced the development of bone fragility in some populations. However, the nature of these evolutionary forces remains unknown. Developmental patterns of growth and maturation, especially timing of sexual maturation, have long lasting effects on bone health through the life cycle. Lifestyle factors such as physical activity patterns, diet, and nutritional status also influence bone mineral accretion and the development of peak bone mass. The implications through human history are considered below.

DEVELOPMENT OF PEAK BONE MASS AND STRENGTH IN SKELETAL POPULATIONS

From early human history to today, changes in subsistence strategy, physical activity pattern, and occupation have been inferred in archaeological skeletal collections using the relationships between physical activity patterns and musculoskeletal stress markers, cross-sectional bone properties,

bone mass, and skeletal strength. While there is some caution to these interpretations because of the osteological paradox, i.e., the uncertainty in inferring cause of death in skeletal remains because most skeletal markers of disease require prolonged disease duration, these conclusions have implications for the interpretation of osteoporosis as a disease of modern human evolution.

Differences between skeletal collections in bone mass and strength are not uniform across all skeletal sites due to activities patterns and resulting mechanical loading at each skeletal site (84). Most skeletal research is represented by adult samples, but a few skeletal collections include infants and children. Childhood activity patterns are inferred from adult characteristics based on the greater responsiveness to mechanical loading of bone during childhood, and the need to sustain physical activity throughout life to maintain bone's structural competency. The relationship between skeletal features and biomechanical stimuli is used to reconstruct past lifeways from skeletal collections (85).

Musculoskeletal Stress Markers

Subsistence strategy, occupation, and socioeconomic status for past peoples have been linked to musculoskeletal stress markers (enthesiopathies) based on interpretations of the effects physical activity on bone (86, 87). The enthesis is the area where a tendon or ligament attaches to bone, so enthesopathies, also known as a musculoskeletal stress markers, are changes to that region which are assumed to reflect changes in the attaching musculature (88). Studies of musculoskeletal stress markers and habitual activities began in the 1950s, but received greater attention in the 1980s (89). A meta-analysis of these studies concluded that agriculturalists had the lowest entheseal changes in the upper body, followed by hunter gatherers, and then by those working in industry, for both males and females. These findings suggest that individuals from industrialized populations were not as adequately adapted to adult workloads as were individuals from other subsistence groups, although age-related differences between populations were unknown (87). Confounding factors in studies that use entheseal changes to interpret effects of habitual physical activity on bone include the difference in responsiveness to loading forces in growing vs. older bone (56); the difference between fibrous and fibrocartilaginous entheses (88), and age-related changes (90, 91). More robust methods of interpreting physical activity from skeletal collections are based on cross-sectional area and geometry of long bones using imaging technologies such as x-ray, MRI, and CT scanning.

Cross-Sectional Bone Geometry

Studies of cross-sectional bone geometry began in the late 1970s (89). Here we offer some examples describing characteristics of bone strength at a number of skeletal sites. Ruff compared geometric properties of the femoral midshaft (such as cross-sectional area, polar moment of area, etc.) in pre-agricultural and agricultural young adult skeletons (both males and female) from the Georgia coast. The agricultural sample had significantly lower values for nearly every geometric property measured, such as cortical area, medullary area, and polar second moment of area in the midshaft and subtrochanteric regions. To some degree, this was due to smaller bone length in the agricultural sample, but after adjusting for the smaller bone length in the agricultural samples, numerous differences remained significant especially in subtrochanteric cross-sectional properties. Results were more pronounced for females. These findings are consistent with a decline in mechanical loading associated with the transition to agriculture (92). A subsequent study of more than 1,800 specimens across Europe, from the Upper Paleolithic (11,000–33,000 years BP) to the twentieth century showed a large decline in anteroposterior bending strength in the femur and tibia that began during the Neolithic period (∼4,000–7,000 years BP), continued through the Roman period (∼2,000 years BP), and then stabilized (93). They found little change in humeral strength measures. Declining lower limb strength appears to be due to lower mobility (distance and speed of travel, and roughness of terrain) and increasing sedentism, which was gradual over time with the transition to sedentism and agriculture, and has not changed substantially with industrialization.

The upper body is subject to different lifestyle factors than the lower body. Differences in the cross-sectional structure of the humerus midshaft were examined in a skeletal collection from medieval York England (eleventh to sixteenth centuries) (94). The sample compared remains of lay benefactors (both males and females) from a church burial ground to later remains of brethren from when the church became a priory. Asymmetry in the polar moment of area between the right and left humeri was measured as an indicator of habitual loading of one limb compare to the other, such as would occur with iron working, carpentry or stone working. Monastic and lay males did not differ in the magnitude of asymmetry between right and left humeri, but both groups of males had significantly greater asymmetry compared to females. This is consistent with documented sex-specific patterns of participation in very different trades and habitual activities. However, average bone strength from polar moment of area values were greater for lay males than monastic males, which was likely a result of overall lesser physical activity levels of the monk brethren (94).

Vertebrae from Swedish and English medieval archaeological samples were compared to clinical samples in Sweden, showing an increase in vertebral height and reduction of vertebral width and vertebral cross-sectional area from medieval to post-medieval to modern time. The secular trend for increased stature in Europe over this time period accounted for increased vertebral height. The reduced vertebral width likely reflects declining physical activity in childhood and adolescence coincident with the increase in technological development and decreased strenuous physical activity (95).

Few studies have included children. Neolithic and Byzantine era samples of adults and children from Turkey were compared to contemporary data from the Denver Growth Study. Both Turkish skeletal collections had larger cortical and total areas in their femora than American urban adults, and these differences were established by age 6 years (96). These results emphasize the importance of physical activity patterns established in childhood for lifelong skeletal strength.

Lastly, a major study compared trabecular microstructure of the proximal femur by microcomputed tomography from

32 non-human primate species and archeological collections of mobile foragers (∼5,000–7,000 years BP) and sedentary agriculturalists (∼700–860 years BP) from North America. The forager population had significantly higher bone volume fraction, thicker trabeculae, and lower relative bone surface area in the proximal femur compared to the agriculturalists, and were similar to other primate species relative to estimated body mass (97). However, the agricultural specimens had the lowest bone volume fraction (bone volume to total volume) and thinnest trabeculae across species. These findings provide evidence of the effects of subsistence strategy on trabecular microarchitecture that is likely due to differences in physical activity levels, although diet may also be a contributing factor.

Overall, these studies demonstrate that declining physical activity levels attributable to sedentism and agricultural practices resulted in lower cortical dimensions and strength, and less favorable trabecular microstructure in lower limbs (97–101). Upper limb bone strength is influenced by activity patterns that are more occupation specific, rather than dependent on larger trends in recent human evolutionary history. The limited evidence from skeletal collections that include children support contemporary studies showing that the developing skeleton is responsive to highly mechanical adaptation, with differences in skeletal populations emerging at a young age.

Evidence of Osteoporosis and Fractures in Skeletal Collections

Evidence of osteoporosis and age-related bone loss in archeological skeletal collections is limited. Awareness of osteoporosis dates back at least to the mid eighteenth century as it was first described in 1751 by Joseph Guichard Duverney (102). A historic population from 1700 to 1850 from London showed patterns of age-related trabecular bone loss in vertebral bodies similar to that of contemporary populations (103). Indeed, vertebral crush fractures are the most commonly reported osteoporotic fracture found in archaeological material, although wrist and hip fractures are documented occasionally (104). Age-related cortical bone loss has been reported; in a skeletal collection from Nubia dating between 350 BC and 1400 AD, the femoral cortical thickness significantly declined with age in females but not in males, and the decline in females began earlier than in modern females (105). In a sample of British medieval adult skeletons age-dependent cortical bone loss was broadly similar to modern Europeans, particularly for post-menopausal women, using metacarpal radiogrammetry (106). Moreover, low metacarpal cortical index was significantly associated with rib and vertebral crush fractures, but hip and wrist fractures were rare. In sum, patterns of bone loss were similar between these medieval women and contemporary populations, but the nature of osteoporotic fractures differed.

Determining elements of lifestyle that might contribute to osteoporosis from archeological samples is challenging. A study of osteoporosis among ancient Egyptians of different social classes in the Old Kingdom of Giza offers some insight. Bone density by DXA and microarchitecture by scanning electron microscopy were used to examine the radius, femoral head, and fourth lumbar vertebra. Rates of osteoporosis varied by occupation and sex. Overall, bone density was lower in females than in males. Among males, osteoporosis was more frequent in workers than in high officials, whereas in females, osteoporosis was more prevalent in high officials compared to workers. This may have been a result of higher workload and nutritional stress for male workers compared to male high officials and a more sedentary lifestyle for female high officials compared to female workers (107).

Low bone mass is reported in bioarcheology studies of historic skeletal collections, but evidence of osteoporotic fracture itself is uncommon (108). However, evidence of their incidence in the archaeological record is growing (109). It is important to consider that most skeletal populations do not have known age and that age determination of older skeletons comes with challenges (106).

The Osteological Paradox

Interpreting the health of skeletal population requires consideration of the osteological paradox. The osteological paradox refers to the problems in reconstructing characteristics of once alive people from those who died (110). Three key issues that complicate attempts to evaluate the health of past human populations using archaeological skeletons: (1) demographic non-stationarity, (2) selective mortality, and (3) hidden heterogeneity in risk. In terms of osteoporosis, those who showed evidence of severe osteoporosis and osteoporotic fracture were those who survived with the disease for a period of time. There may have been individuals with the disease that died at an earlier age. We must consider what conditions were survived and which may have caused death and other factors related to individual mortality when attempting to interpret the incidence of a historic disease based on the individuals in a population who died. This is very different from contemporary methods for diagnosing osteoporosis in living populations making it difficult to compare deceased skeletal populations with those living today.

EVOLUTIONARY IMPLICATIONS

The human skeleton is gracile compared to earlier hominin fossil skeletal evidence as well as living great ape skeletons. A number of evolutionary explanations have been proposed to explain this trend. First, past populations show skeletal evidence of higher physical activity levels (93, 111). Prehistoric bronze age agriculturalist women had tibial rigidity exceeding that of living modern athletes in Europe, and Neolithic men had similar tibial rigidity and shape ratios to that of modern cross-country runners (112). In lower limbs, declining bone dimensions, density and strength were not evident in human populations until the transition from hunting and gathering to food production and sedentism in the Neolithic around 10,000–12,000 years ago (113). In other words, the agricultural transition signaled changes in the mechanical forces that shape the human skeleton.

From the archeological record, it is difficult to estimate the effect of lesser bone dimensions, density and strength on prevalence of osteoporosis, mainly because of the osteological paradox. Evidence of osteoporosis from skeletal and historic populations exists, but osteoporotic fracture mainly manifests as vertebral crush fractures rather than osteoporotic fractures of the wrist and proximal femur. As simulations have shown, at the population level small increments in peak bone mass

and strength can profoundly delay the onset of osteoporosis. Maintaining physical activity through adulthood also prevents or delays the onset of age-related declines in bone density. Physical activity levels in modern people, and in particular children for whom responsiveness to physical activity is greatest, may be reaching an unprecedented low, and is likely the primary reason for increasing cases of osteoporotic fracture (111) and the contemporary pattern of more devastating, life-altering fractures of the wrist and hip.

The transition to agriculture also brought dietary changes. Reconstructed paleolithic diets relied on varied resources, containing larger amounts and types of fruits, vegetables, nuts, seeds, tubers, and fish/game (114–116). This diet differed in fiber content, micronutrient and antioxidant capacity compared to contemporary diets, and would have more favorably supported bone health as suggested by current studies of diet and bone health described above (7).

Another consideration for the propensity for osteoporosis in modern people is the evolution of human longevity. Humans live the longest of any primate and are the longest living mammal (117). In the 1970s, the maximum human lifespan was 113 years while the maximum chimpanzee lifespan in ideal zoo conditions was 55 years (118). Maximum human lifespan was close to 95 years in medieval England, in classic Rome and Greece, in the Neolithic, and even in the Mesolithic and upper paleolithic (118). However, a sizeable portion of the population living into old age is a relatively recent change as early as the nineteenth and twentieth centuries (118).

One possible explanation for the evolution of increased human longevity is the role that grandmothers play in caring for grandchildren (119). Post-menopausal women, the demographic group most affected by osteoporosis, have completed their reproductive life and no longer contribute to the gene pool by bearing more children. However, they have great potential to contribute significantly to the survival of their progeny, so their evolutionary significance continues. Provisioning of food and childcare by grandmothers in a non-reproductive period of life favors longer lives and greater survival over generations (120). Maternal grandmothers improve the nutritional status of children and survival probabilities in rural Gambia (121). Among the Hadza hunter gatherers, grandmothers spend the most time foraging when the grandchildren are receiving the least from mothers, and they forage least when the grandchildren receive the most from mothers (122). Following a lifetime of high physical activity in hunter-gatherer subsistence, these grandmothers continue to engage in physical activity to provision for their families thereby continuing to maintain skeletal bone strength. Extended human longevity, particularly for women, speaks to the importance of continued physical activity to delay the onset of bone fragility.

CONCLUSION

The developing skeleton is highly responsive to lifestyle patterns. Peak bone mass and strength are major determinants of bone fragility later in life and are shaped during childhood and adolescence. Growth, timing of pubertal maturation, physical activity and diet are among the factors that influence the magnitude of peak bone mass. In the context of adequate health and nutrition, physical activity is the most important *modifiable* factor promoting lifelong bone strength. Studies of skeletal populations demonstrate declines in skeletal robusticity, cortical dimensions, and trabecular microarchitecture in association with changing subsistence strategies and accompanying lifestyle changes. These changes in subsistence strategy constituted a shift for many human populations from foraging or hunting and gathering for sustenance to food production and agriculture. The activity of hunting and gathering involved obtaining sustenance from the collection and/or hunting of a wide variety of wild foods that provided adequate nutrients to support a robust skeletal phenotype. While there are still a number of hunter gatherers today, most foragers began using some cultivation strategies around 13,000 years ago and eventually started using agriculture. These different subsistence strategies entail different activity patterns, with agriculture typically characterized by more sedentary lifestyles. The confluence of increased longevity and reduced physical activity throughout the lifecycle exacerbate the problem of osteoporosis. As such, osteoporosis is a disease of contemporary human evolution and a growing public health concern in contemporary human populations.

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Evolutionary Strategies for Body Size

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Humans show marked variation in body size around the world, both within and among populations. At present, the tallest people in the world are from the Netherlands and the Balkan countries, while the shortest populations are central African Pygmies. There are genetic, genetic plasticity, developmental, and environmental bases for size variation in *Homo sapiens* from the recent past and the present. Early populations of *Homo* species also have shown considerable size variation. Populations from the present and the past are also marked by sexual dimorphism, which, itself, shows group variation. There is abundant evidence for the effects of limited food and disease on human growth and resultant adult body size. This environmental influence has been reflected in "secular trends" (over a span of years) in growth and adult size from socioeconomic prosperity or poverty (availability of resources). Selective and evolutionary advantages of small or large body size also have been documented. Heritability for human height is relatively great with current genome-wide association studies (GWAS) identifying hundreds of genes leading to causes of growth and adult size variation. There are also endocrinological pathways limiting growth. An example is the reduced tissue sensitivity to human growth hormone (HGH) and insulin-like growth factor (IGF-1) in Philippine and African hunter-gatherer populations. In several short-statured hunter-gatherer populations (Asian, African, and South American), it has been hypothesized that short life expectancy has selected for early maturity and truncated growth to enhance fertility. Some island populations of humans and other mammals are thought to have been selected for small size because of limited resources, especially protein. The high-protein content of milk as a staple food may contribute to tall stature in East African pastoral peoples. These and other evolutionary questions linked to life history, male competition, reproduction, and mobility are explored in this paper.

Keywords: human body size, height, human evolution, growth and development, heredity, life history

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Human adult body size shows remarkable variation. In evolutionary and biogeographical contexts, this almost certainly results from the widespread distribution of human populations across the globe, their exposure to varying environments, evolutionary forces, and from complex forms of cultural behavior. In addition to non-cultural environmental selection, human culture diversity can lead to limited gene flow and population isolation, genetic drift, variable selection, and other factors that contribute to human biological diversity and complexity. Hence, human adaptation to the environment entails both cultural and other environmental selective forces that have contributed not only to population variation in body size and morphology, but to all of the uniquely-human attributes that we see in our present species. In addition to the fundamental evolutionary forces of mutation, genetic drift, gene flow, and selection leading to genetic variation, there are the factors of developmental adaptation and genetic plasticity that constitute the total

adaptive "package." In body size and morphology, the adult human is thus an adaptive summation of developmental steps toward maturity—each of the steps in response to the developmental environments acting via the genome through time. Evolutionary strategies involving section may then act through growth and development or be targeted toward maturity and adulthood with important survival and reproductive outcomes.

GROWTH TO ADULTHOOD

Humans are born after a 38-week gestation in what is known as an *altricial* state; that is, the newborn is helpless and totally dependent on the mother for nutrition, warmth, and protection (1, 2). This state persists through infancy and early childhood, during which time motor and perceptual skills, feeding, and cognition continue to develop. Infant growth in size, which is very rapid during the first year, begins to slow down, while brain growth only slows by ages 7 or 8 years, at which time a mature brain weight (but not brain function) is achieved (3). Some degree of independence is reached by 7 or 8 years during this childhood period of steady, but relatively slow, growth in height. Puberty and adolescence are marked by a rapid growth spurt and the beginning of sexual maturation. In girls from developed societies, adolescence begins, on average, at age 10 years and in boys, at age 12 years. Sexual and size maturation are achieved by 16 years in girls and 18 years in boys (see **Figure 1**). In this generalized figure, size or distance is the accumulation of growth rates (velocity) at different ages; or as Franz Boas (4) first described them, different "tempos of growth." Also, differences in rates of growth of specific structures (e.g., brain, lower limbs) will produce allometric changes in proportions and size at different ages. Therefore, any hereditary or environmental influence on growth rate at a given age, particularly infancy or adolescence when linear growth rates are high, can enhance or retard adult size. There is considerable variation in these ages of growth and maturation in populations throughout the world, and a number of steps in this trajectory where growth can be enhanced or retarded. Adult body size results from the cumulative growth at each of the stages (fetal, infancy, childhood, adolescence). Recent research has suggested that the prolonged growth to human maturity is a trade-off between the energy needs to fuel somatic (body) growth vs. the energy needs of the large growing brain. Kuzawa et al. (5) showed that peak human brain glucose demands occur during childhood (ages 4–10 years) when somatic growth is slow and prolonged; hence, allowing greater amounts of energy to be devoted to the rapid growth rate of the brain.

Enhanced fetal growth is limited by the size of the maternal pelvic birth canal, but large women who have large pelves are capable of delivering larger (>3,500 g) full-term fetuses. Hence, selection for human birth size is linked to maternal pelvic size and body size, a form of co-evolution that occurred as a part of human fetal evolution. There is, of course, a co-dependency between the mother and fetus during gestation that is based on both the maternal and fetal genomes and the maternal intrauterine environment. Smaller than average mothers tend to deliver the fetus at a slightly earlier gestational age and have smaller infants (6) and there is a clear relationship between birth weight and length and adult weight and height (7–9). Birth order also has an influence on height of children, where later parity children are successively shorter than early parity children (10). Meredith (11) compiled birth weights for different populations around the world. The average range of variation was between 2.4 kg in the New Guinea Lumi (an average below the "low birth weight" cutoff of 2.5 kg) and 3.6 kg in United States Native Americans. In addition to suggested ethnic differences, there were a host of likely socioeconomic, environmental, and health influences.

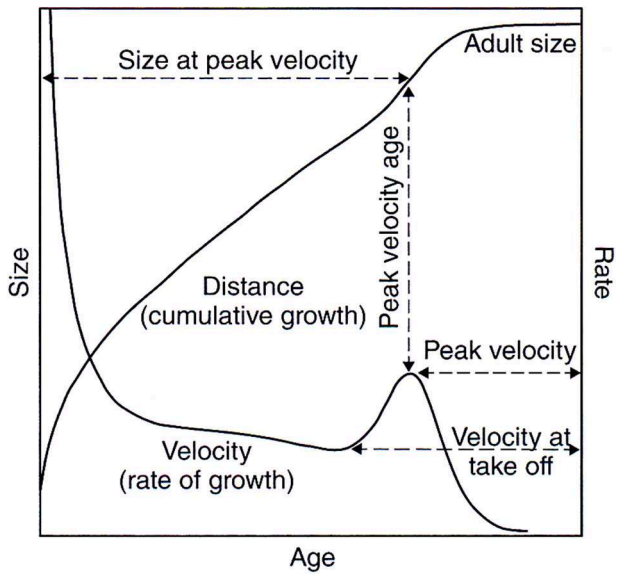

FIGURE 1 | Distance and velocity growth curves that show the generalized human pattern of growth from birth to maturity. Girls are slightly smaller than boys at all ages until adolescence that is 2 years earlier than boys. Girls' peak velocity is less than boys and they reach maturity about 2 years earlier than boys.

Both genetic and environmental variations play a role in structuring growth during childhood and adolescence, and in complex ways. For example, during adolescence, the onset, duration, intensity, and completion of the adolescent growth spurt (marked by velocity changes) can affect adult height. Late maturers begin adolescent growth at a slightly taller height than early maturers, which partly contributes to the greater height of adult males over adult females. Other factors contributing to height differences between the sexes are the slightly greater size of boys than girls at birth that persists throughout infancy and childhood, and the substantially greater amplitude in boys of the adolescent growth spurt when compared with girls (12). Despite these relationships, the correlation between early and late maturation and adult size is weak and it is possible for both early and late maturers to reach the same stature (13).

At all prenatal and postnatal ages, the primary drivers and regulators of growth are nutrient and energy intake and hormones (14–17). Variations in the output of human growth hormone (HG), insulin-like growth factors (IGF-I, IGF-II), insulin-like growth factor binding proteins (IGFBP), and

TABLE 1 | Heights and weights of several short-statured foraging and horticultural populations.

Population	Males		Females		References
	Ht (cm)	Wt (kg)	Ht (cm)	Wt (kg)	
Aché (Paraguay)	158	60	149	54	(40)
Aeta (Philippines)	150	40	140	38	(41)
Agta (Philippines)	153	45	144	38	(42)
Batak (Sumatra)	153	47	143	41	(43)
Bundi (Papua New Guinea)	150	52	146	–	(44)
Hiwi (Venezuela)	154	56	145	48	(45)
Ju'/hoansi (Botswana, Namibia)	159	55	149	50	(46)
!Kung (Botswana, Namibia)	160	49	150	41	(47)
Onge (Andaman Islands)	148	–	138	–	(48)
Pygmy (Efe, Ituri Forest, Congo)	143	43	136	38	(49)
Pygmy (Mbuti, CentralAfrican Republic)	144	42	136	37	(33)
Pygmy (Twa, Congo)	160	46	150	42	(50, 51)
Yanomamo (Venezuela, Brazil)	152	52	142	45	(52)

other hormones, and the metabolic pathways leading to tissue receptivity, contribute to human growth within the parameters of the fundamental human growth curve (18). Evolutionary changes in the genetic control of these growth regulatory pathways can produce changes in the duration or velocity of growth at any age and can produce allometric changes and changes in overall body size. An excellent review of these regulatory hormonal pathways and their influence on human size during growth and development and through evolutionary time is found in (19).

Environmental influences on growth to adulthood can produce a range in variation in stature within a given population, but any single population does not display the full range in variation expressed in human populations throughout the world. Hence, in addition to environmental influences on stature, genetic, and epigenetic factors are shown when population averages are compared. These population differences will be discussed below.

HUMAN POPULATION VARIATIONS IN BODY SIZE

Our Hominin Ancestors

Within a given taxonomic category (such as *Hominini*, the taxonomic Tribe or evolutionary clade that includes all members of the genera *Australopithecus* and *Homo*), there are often larger and smaller body-sized representatives of species and of populations within species. In an evolutionary context, there are both selective advantages to being small and selective advantages to being large (20). Large body size tends to be associated with higher fecundity, reproductive success in male vs. male competition, greater protection against predators, and ability to combat cold climates. These advantages are countered by selection against large body size from a number of pressures. For example, viability costs are great when the time to sexual maturation increases (greater cumulative mortality) and are less with rapid growth and shorter maturation time. Also, larger bodies increase metabolic needs and intensification of food acquisition (with associated risks) and are linked to size-selective hunger and starvation. Finally, heat stress in hot climates or with physical activity is intensified with larger bodies and there may be reduced agility or increased detectablity (20, 21). In these cases, selection operates through differential survival or mortality and differential fecundity/fertility and reproduction, and a probable equilibrium in size is achieved according to any given set of ecological conditions under which a species or population is living. These principles have been identified and tested for invertebrate and vertebrate species, but apply to human species, as well (22, 23).

Ruff (24) identified several patterns of body size and shape variation in our Pliocene and Pleistocene hominin ancestors. In the transition from *the* Australopithecines to early *Homo* (*Homo habilis*/*rudolfensis*) about 2 to 2 1/2 million years ago, and the later species, *H. erectus*/*ergaster*, after 2 million years ago, there were significant increases in body size, brain size, and allometric form of the limbs. Australopithecine species body mass ranged from about 35 kg to 50+ kg, with the more robust species at the higher range. Early *Homo* body mass ranged from about 35 to 70 kg and was highly variable in stature (between 145 and 184 cm; similar to a modern population range). Shifts in locomotion, foraging, and diet were suggested as some of the selective pressures leading to these changes.

The second transition was around 500,000 years ago with a further increase in body size (mass) that Ruff (24) attributed to hominin populations moving to higher latitudes and colder climates. The estimated body mass of these mid-Pleistocene specimens ranged broadly from about 50 to 90 kg. An unusual exception to this is the diminutive *Homo floresiensis*, who lived on the tropical Flores Island (Indonesia) about 80,000 years ago (Late Pleistocene), and who had a stature of about 106 cm and a body weight of about 30 kg. Also, a more recent Late Pleistocene discovery from the Philippines (Callao

Cave, Luzon Island) was identified as a new species, *Homo luzonensis*, and thought to be as diminutive as the Flores Island population (25). The third transition occurred about 50,000 years ago in the late Pleistocene, in which there was a decline in body size (mass), particularly among higher-latitude (northern) populations, perhaps associated with increased technology (tool production) and cultural factors that led to less male-male competition.

A fourth transition (Neolithic Revolution) about 10,000 years ago led to a further reduction in body size with the shift from a hunting-gathering (foraging) subsistence pattern to a food production pattern. In addition to dietary changes, technological advancements may have contributed to this latter transition. It should be noted, however, that with the Neolithic and later dominance of cultivation and animal domestication, many populations continued foraging subsistence patterns up to the present.

A more recent interpretation of body size variation in our early ancestors arose from a Wenner-Gren Foundation symposium in 2011 (26). They noted that smaller-bodied versions of *Homo erectus* have been found in Kenya and the Republic of Georgia, and the diversity in other populations of *Homo* has been less appreciated, perhaps, in an emphasis to characterize *stages* of evolution. This newer approach to understanding human evolution has centered on the variation in forms of this genus in response to "shifting environments" and how early *Homo* can be better understood in the context of "how extant humans, non-human primates, and social carnivores respond energetically, physiologically, and socially to changes in resource availability and to stress from climatic, environmental, and other factors" [(26), p. S270]. In addition, Kuzawa and Bragg (27) concluded that developmental plasticity contributes to considerable human variation in contemporary populations, and it is assumed, then, that corresponding plasticity has contributed to variability in past populations, as well. Also, since selection operates on the phenotypic expression of developmental plasticity, then environmental modification of human biology and behavior is a major evolutionary force.

Living and Recent Populations

We know a great deal about body size and morphology of both adult and young members of contemporary human populations. The compilations of anthropometric measurements taken around the world during the late 19th and 20th centuries, and particularly those taken during the International Biological Programme (IBP) surveys from the Human Adaptability research (28), have been summarized by Eveleth and Tanner (29, 30) according to ethnicity, geographic location, and migration patterns. These measures of height, weight and different body proportions show marked variation, both within and among populations. The studies compiled by Eveleth and Tanner (29, 30) tend to describe numerically small populations, worldwide, with indications of variation listed in appended tables.

More recent worldwide compilations of body size in stature are found in Bentham et al. (31) and Roser et al. (32). These two global works are extensive, but the data are limited because reporting is done according to larger population units (nations and regions), and much of the population-specific human variation is lost. For example, Roser et al. (32) list the shortest men on record at 160 cm in stature from Timor in island Southeast Asia, whereas Cavalli-Sforza (33) and Dietz et al. (34) identify Congo men with the pygmy phenotype (short stature; usually <155 cm in men and 150 cm in women) from the Ituri Forest as averaging slightly <145 cm tall, a difference of 15 cm. However, despite the large population units surveyed, these two latter global reports are quite valuable because of the long-term data collected on stature changes according to birth cohorts. The Bentham et al. (31) compilation (NCD-RisC) provided data on mean adult heights of birth cohorts from 1896 to 1996. These data then allow global analyses of what is known as "secular changes" in growth and maturation; that is, those increases or decreases in body size over the short-term that are largely a function of environmental changes in health and nutrition affecting growth to adulthood [(35, 36), p. 116].

If we consider African men with the pygmy phenotype at an average stature of 145 cm and pygmy woman at a stature of 136 cm as the shortest contemporary populations on record (33), and the tallest as the average Netherlands' man at 184 cm and the average Netherlands' woman at 171 cm (37), then the mean difference in the population average range for our species is a remarkable 39 cm for men and 35 cm for women! Other European nations with very tall populations include Bosnia, Herzegovina, and Croatia, where average young men from a widespread survey of these three Balkan countries ranged in height from 180 to more than 184 cm (38, 39). In addition to the African pygmy phenotype, other short-statured populations, largely foraging or horticulturalist peoples, can be found in enclaves in South America, Southeast Asia, Papua-New Guinea, and equatorial Africa. **Table 1** lists several of these populations with recorded heights and weights. Many of the shortest-statured populations are from either tropical forest environments or tropical islands. Exceptions are the Ju'/hoansi San and !Kung San populations (formerly Bushmen) from semi-arid lands in southern Africa, but these populations are at the higher range of short-statured peoples. Another population at the higher range of heights is the Twa, from the Lake Tumba region of the Democratic Republic of the Congo, who are highly admixed with neighboring Bantu farmers (50).

Within these extremes of height from the shortest to the tallest populations, there is considerable variation by geography, ethnicity, nationality, and socioeconomic levels. Roser et al. (32) listed global averages of the height of men born in 1996 as 171 cm and women from the same cohort as 159 cm. The average sexual dimorphism in height is thus about 12 cm, although sexual dimorphism varies substantially for populations around the world. These authors identify the shortest men and women from South Asia and the tallest from Europe and Central Asia, although there are exceptions to these generalizations in each of these large geographic areas. In sub-Saharan Africa, for example, there are many short-statured populations (e.g., Pygmies and San), yet some of the East African populations are quite tall (e.g., Maasai and Turkana) (53, 54). NHANES data from 2007–2010 in the United States provides some reference statistics to demonstrate ethnic (and probably socioeconomic) variation in

height for a large national population (55). Young men and women aged 20–39 years were listed as Non-Hispanic White, Non-Hispanic Black, and Hispanic. The White American group's heights for men and women were 178 and 165 cm, respectively; the Black American group's heights were 176 and 164 cm; and the Hispanic group's heights were 171 and 158 cm. These ethnic differences reflect just some of the variability found in any national or large-scale population.

Environmental Factors in Body Size Variation

The variation displayed in this single variable, height, in contemporary populations is based on numerous influences from the environment, genetics (the genome and gene pool), and the genetic plasticity tied to the interaction of genes and environment. In many cases, it is easier to demonstrate environmental than genetic causality. Major environmental factors that can lead to developmental variations in body size are diet and nutrition, disease history, general sanitation and clean water availability, infant and child care, and cultural practices that can influence all of these other variables. Each of these environmental factors will contribute to human health, where optimizing health throughout the period of growth and development to maturity will lead to an optimal body size according to individual genome constitutions.

Diet, Nutrition, and Disease

Human societies/populations have highly varied diets and cuisines, and it is a characteristic of humans that they have a broad adaptive capacity for dietary diversity. However, not all diets are optimal for human growth, and food intake variations can have a profound influence on general health and body size at all ages. We know, also, that human diets are not always stable and there are periods of hunger and dietary deficiencies linked to climatic, political, economic, and other factors. For example, at an early stage of development, maternal malnutrition will negatively impact fetal growth (intrauterine growth restriction, IUGR) and may have long-term impacts leading to metabolic health disorders in middle age (56, 57). Acute respiratory and gastrointestinal disorders in children can also have profound negative effects on growth, particularly in infancy and early childhood (58–60). Poverty or limited access to resources can lead to inadequate dietary intake, disease, and anorexia, all of which will result in stunted growth and small body size in adults (61, 62). A cascade of effects of poverty leading to stunted growth (>2.0 SD below the mean of WHO standards) is diagrammatically and dramatically illustrated in **Figure 2**. Another indirect cause of disease in the lower income countries is poor sanitation in densely-populated areas, also linked to poverty. For example, Spears (63) demonstrated a strong correlation in India between open defecation (with a lack of toilets or latrines and presumed spread of fecal pathogens) and stunting in children. The average child fell 2.0 SD below the mean for child height when only 20 percent of the population had access to toilets or latrines.

Quantitative and qualitative protein intakes are important in contributing to stature variation in humans (64). A qualitatively important protein source is cow's milk, a staple food in many Western societies. Although milk is an excellent source of protein and calcium, it also contains lactose, a milk sugar that cannot be digested by many adult peoples around the world. Most native peoples from Asia, West Africa, the Pacific Islands, Australia, and the New World are unable to produce the intestinal enzyme, lactase, to break down the milk sugar, lactose, into its constituent (and digestible) monosaccharide sugars, galactose and glucose. In many Europeans, populations from the Near East, and East African herding peoples, the ability to digest lactose as adults is under genetic control; hence, selection has operated in favor of "lactase persistence" in these milk-producing populations. Tishkoff et al. (65) found that independent selection for different genetic systems produced convergent evolution for African pastoral and European people's genetic systems. It is also the case that, in addition to the value of milk as a dietary item, milk intake beyond infancy and weaning, may contribute to increased height in some populations. Cow's milk has as much as three times the protein content and four times the calcium content of human breast milk (although with some variation), and there is evidence that cow's milk consumption contributes to increased height if consumed after weaning and during late childhood and adolescence (66, 67).

A case in point is East African pastoralists, who are tall and lean in physique, and who consume significant amounts of milk in their diets as a staple food (68). Using the Turkana nomads of northwest Kenya as an example, cow's, goat's, camel's, and sheep's milk constitute as much as 80 percent of the diet during the wet seasons when forage is abundant and livestock milk production is high (69). Because of the availability of animal milk, Turkana women, who breastfeed their infants for an average of 20 months, begin to supplement infants' diets with animal milk at 5–6 months of age (70). This is consistent with the pattern described by Wiley (67) that contributes to accelerated height in other populations in later years. At 6 months of age, Turkana infants

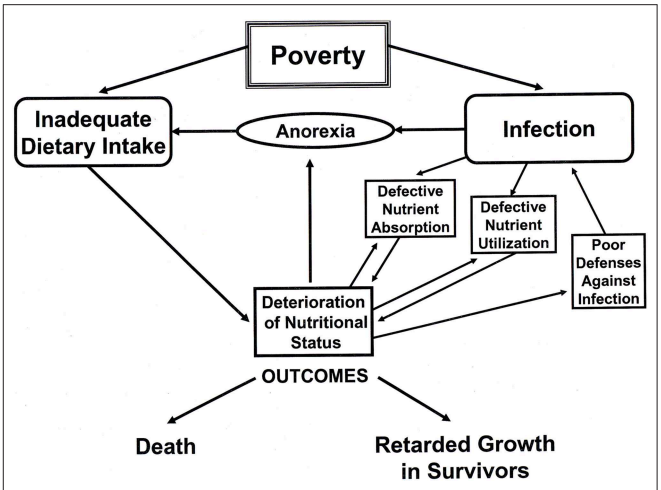

FIGURE 2 | A diagram illustrating the cascade of effects of poverty, such as limited food resources, infectious diseases, and poor sanitation. Redrawn from a diagram by Martorell (61).

begin faltering in weight (behind Western norms), but length is equivalent to U.S. standards. Although adolescent growth is not extraordinary, growth in stature is attenuated and continues into the early 20s, such that adult height by age 23 or 24 years in both men (174 cm) and women (161 cm) is close to U.S. African-American standards (54). Hence, despite the Turkana experiencing seasonal and other short-term bouts of hunger, and with average daily energy intakes well below international standards, but protein intakes at 3- or 4-times minimum daily requirements, they are able to achieve tall statures that are substantially greater than non-pastoral native populations in Africa and other parts of the lower income countries. They are, however, extremely lean in physique, with young adult body mass indices (BMI) between 17.0 and 18.5 kg/M^2 (71).

Socioeconomics and Culture

Socioeconomic status can be defined by a complex variety of factors including family history, social position, role definition, ascribed and achieved status, occupation, material wealth, and other variables. Different levels of socioeconomic status carry with them a variety of health advantages and disadvantages that are a part of the life experience as noted above. Social mobility can influence some of the factors (72) related to health status, but within-generation mobility cannot transform life history.

Influences of socioeconomic class on body size were demonstrated in a study of Scottish children aged 11 years in the early 1950s [Tanner (73), p. 138]. A gradient existed where children of professional class fathers were about 3 cm taller and 1–2 kg heavier than children of manual workers. Lasker and Mascie-Taylor (74) based their study on data drawn from the National Child Development Study of all children in England, Scotland and Wales during the 3rd−9th of March 1958. Longitudinal follow-up studies were conducted of children at 7, 11, and 16 years of age on a sample size of ∼16,000. Social class designations were based on the occupation of the male head of household (highest occupational class = professionals, lowest occupational class = unskilled laborers). Differences in height between children from difference occupational classes were achieved by 7 years of age and very little height differential was acquired after that age. Mascie-Taylor (72) showed that upwardly mobile children were smaller than their next higher class but larger than the previous socioeconomic class. Social mobility, like geographic mobility or migration (75), can contribute to body size differences both within and accross generations (76).

Secular Trends in Growth and Maturation

Secular trends in human growth are short-term trends (years, decades, and transgenerational periods) in growth patterns, proportions, and maturation. The assumption is that a secular trend, even over 100 years or more, is reversible, and hence, is largely a function of environmental, sociocultural, and general health conditions. In an early study of age cohorts of children from the Horace Mann School of Columbia University, Franz Boas (35, 77) found that children had become taller between 1909 and 1935. He attributed these changes to improvements in socioeconomic conditions leading to a modification of the "tempo of development," that is, the rate of growth of the children. This phenomenon has been documented repeatedly since that time and has been referred to as "secular trends in growth" [(73), p. 143–155, (36), p. 116, (78)]. Secular trends can be either positive (e.g., increases in size, earlier maturation) or negative (e.g., decreases in size, later maturation). In the former case, improved nutrition and health are the proximate causes, while in the latter case, a downturn in or worsening of health and nutrition are the principal causes. Because the time period is relatively short, it is unlikely that these changes in growth, maturation, and adult sizes are evolutionary changes. Economic upswings and downswings are reflected in corresponding conditions of relative health and welfare; for example, as existed before, during, and after the great depression in the early half of the 20th century.

A marked secular trend in Western nations began in the mid-18th century with the Industrial Revolution and economic improvements for workers and their families. In addition to increases in average heights of children at all ages during the 19th century, there were dramatic declines in age of menarche from 17 years of age in 1800 to 13 years of age in 1960 (earlier reproductive maturation) [(73), p. 153]. This trend has continued in contemporary populations undergoing economic expansion and experiencing economic prosperity (79). For boys, Daw (80) demonstrated a secular trend in voice change associated with puberty in J.S. Bach's early- to mid-18th century Leipzig choristers, where choir boys experienced voice changes around 17 or 18 years of age in contrast to modern choir boys who show voice changes at about 13 or 14 years of age. Although there are no records of height for Bach's choristers, late maturation was likely to be linked to short stature. Another good example is the record of heights of boys who were recruits at the Royal Military Academy at Sandhurst and the Marine Society of London between 1750 and 1950 (most were poor boys aged 13–18 years) (81). There were marked differences by social class and height changes through time that reflected secular trends in economic prosperity and life styles. For example, 15-year-olds who were 140 cm tall in 1750, were nearly 30 cm taller at the same age in 1950. This displayed a generally positive secular trend in height over that 200-year period (but with several short negative trends due to economic downturns in the late 1700s and mid-1800s).

Another major episode of secular changes in growth and adult size occurred after World War II in Europe (31, 82). The result of this post-WW II secular trend in height was the genesis of some of the tallest people in the world from the Netherlands and the Balkan States (as noted above). This trend appears to have slowed or stopped at present, perhaps reaching, what Cameron (78) has called, a "genetic ceiling."

GENETIC AND EVOLUTIONARY FACTORS IN BODY SIZE VARIATION

There are abundant examples of environmental, socioeconomic, cultural, and health influences on body size and stature/height. But what evidence do we have for hereditary and possible

evolutionary, selective, and adaptive factors associated with body size?

Human height is a complex, quantitative variable that is based on cumulative increments of growth over a prenatal and postnatal maturational period of up to 20 or more years. It is a useful variable for hereditary analysis because there is a wealth of data that have been collected over the years. The variable is polygenic and involves multiple genetic loci with punctuated genetic expression over this maturational period. Although the heritability of height is great [$h^2 = 0.80$, (83)], height is also subject to substantial environmental modification and plasticity; hence, identifying the genetics of height has been difficult using traditional methods such as family and twin analysis.

Genome-Wide Association Studies (GWAS)

More recent work has included genome-wide association studies (GWAS) and meta-analyses combining data from a number of independent studies to provide more detailed data on height-associated genetic loci and single nucleotide polymorphisms (SNPs), some of which may be quite rare. The earliest GWAS studies discovered 47 loci with SNPs associated with height (83). Most recent meta-analyses have found hundreds of loci with several thousand SNPs that are connected to biological pathways, in turn, associated with adult height and growth factors (84, 85). The SNPs associated with human growth are linked to chondrocyte proliferation and differentiation, growth plate formation, and bone development (83, 86), and later growth spurt in males and later puberty in females (87).

While much of the research has been conducted on living European populations (88, 89), some research has been done with ancient DNA derived from skeletal remains (90). Cox et al. (90) observed a decrease in stature between Early Upper Paleolithic and Mesolithic and Neolithic peoples (transition from hunting and gathering subsistence to early farming and herding), but an increase in height between the Neolithic and the Bronze Age (about 5,000 years ago). They also found that higher geographic latitude peoples were taller than lower latitude peoples. Finally they stated that with all height-associated genetic variants combined, it is now possible to predict about 30 percent of the phenotypic variance in the height variable.

Evolutionary Processes and Strategies

A productive way to study evolutionary strategies of human body size variation is through life history theory (27, 91, 92). Life history studies attempt to answer questions about evolutionary processes leading to the origins of and variations in human attributes, such as: body size; timing and events of growth to maturity; fertility and reproduction; mortality; energy allocation to growth, maintenance, reproduction, and longevity; and all in the context of the human life cycle. Energy allocations to (1) growth, (2) maintenance, (3) reproduction, and (4) longevity (= reduced mortality), require evolutionary trade-offs or compromises through natural selection for favorable outcomes. The question to be explored for human body size is: What is a favorable body size (or body sizes) to optimize these four main variables considering evolutionary trade-offs?

Figure 3 illustrates some of the variables to be considered in analyzing the human life cycle and individual life histories. Selection operates on body size from conception to maturity, where adequate nutrition and relative absence of infection will allow for optimal growth. However, optimal growth depends on the mix of food resources, exposure to disease, and a host of other variables—environmental, human biological, and cultural. For example, Blanckenhorn [(20), p. 385–6] noted that "It is widely agreed that fecundity selection in females [for optimal fertility] and sexual selection in males [for mate competition] are the major evolutionary forces that select for larger body size in many organisms." For humans, larger women have larger newborn infants and larger infants have a higher survival rate than smaller infants. However, the energetic (or caloric) costs of maintaining a larger female, gestating a larger infant, and breastfeeding this infant for a year or more are substantial and may not be possible in a subsistence society. A case in point is the short-statured KhoeSan peoples of southern Africa. Based on skeletal remains from the Later Stone Age and contemporary body size values, Pfeiffer et al. (93) speculated on selective pressures that acted on these populations from the Later Stone Age up to historic times when Bantu and European intrusions probably modified the ecological and cultural conditions of the KhoeSan peoples. There are advantages to a shortened growth period and smaller size in organisms because the reduced time to sexual maturity allows less time for pre-adult mortality (viability selection) (20). However, there is no evidence for reduced maturation time in KhoeSan populations. Sociocultural factors, including reduced male to male competition, mobility needs, and a dispersed food supply were suggested as selective pressures leading to small body size. Another example of sexual selection playing no role in a short-statured population is for a central African pygmy population (94). Baka pygmy couples were compared with Nzimé Bantu couples, where they were tested on preference for short or tall partners. The authors found that there was positive assortative mating for stature in both groups of couples, but for the Pygmies, the assortative mating actually led to a slight preference for tallness.

An example of food energy availability and births can be given for Turkana pastoralist women, who are lean in physique, but have a moderate-to-high completed fertility (CF = 7 live births). Nevertheless, because of limited food resources unique to their cultural subsistence practices, the women lose body energy stores with subsequent pregnancies placing late parity infants at higher risk than early parity infants (95). Also, breast feeding patterns are linked to maternal size, where larger (taller and more robust) mothers had a greater frequency of breast feeding bouts than thinner mothers (96). The trade-offs occur in women's body size and the ultimate fertility outcome along with infant and child mortality rates. On the other hand, selection for smaller body size in mothers is energetically less costly, but produces smaller newborn infants who are at higher risk of morbidity or mortality due to poorer temperature regulation, less effective protection against dehydration, and greater fragility (97, 98).

Yet in this case, selection for smaller female body size may allow for a higher overall fertility and justify the outcome via higher fitness.

Short-Statured, Pygmy, and Pygmoid Populations

Living populations with individuals of very small body size are rare, and are of particular interest within the framework of life history and evolution. These populations (see **Table 1**) are characterized generally as remnants of hunter-gatherer or foraging populations who are either tropical-island or tropical-forest residents. They are somewhat isolated and often inhabit ecosystems with limited food resources. For Africans with the pygmy phenotype and other "pygmoid" populations, there are several selective pressures that have been hypothesized to explain the short stature of these peoples, that is, relative to the taller stature of a majority of living human populations (99–101).

One hypothesis bears on temperature regulation, in that short stature tends to maximize surface area per body weight relationships and should give pygmies an advantage in hot-humid tropical forests. Pygmy short stature is consistent with Bergmann's rule that a small body with high surface area to volume ratio is effective at dissipating body heat in the tropics, particularly the humid tropics. With elevated environmental humidity, evaporative cooling (sweating) is a less effective way to dissipate body heat, but a higher surface area should provide a slight advantage through passive convective heat loss. Austin and Ghesquiere (102) and Austin and Lansing (103) tested Bergmann's rule with temperature stress tests and modeling on Twa pygmies in the Lake Tumba region of the Democratic Republic of the Congo but with limited results; however, on theoretical grounds a greater surface area to weight ratio should provide a slight selective advantage under hot-wet conditions (see *Biogeographic Rules* below). A second hypothesis suggests that small body size is advantageous in reducing individual and population food energy requirements. Small bodies are metabolically efficient and a response to limited food and protein resources is often an evolutionary reduction in body size. This can be the case with pygmy mammalian species found on island or population enclaves – sometimes referred to as "insular dwarfism" (104). Bailey et al. (105) argued that pygmies have traditionally participated in reciprocal exchanges of food ("symbiotic" relationships) with their food-cultivating neighbors because tropical rainforests have limited energy-rich food resources. However, Bahuchet et al. (106) have largely dispelled this myth by demonstrating that the presence of wild yams and other food plants in tropical forests would have allowed early rainforests to have been exploited by foragers before the onset of food cultivation. A third hypothesis has been suggested based on human mobility and agility, such that dense jungle can be more easily navigated by small-sized individuals (101, 107). Navigating dense undergrowth and accessing resources in which tree climbing is a favored skill might have selected for small body size. These are difficult hypotheses to test and the real answer may be in some combination of or all of the causes.

Studies of pygmy growth and development have uncovered endocrine and genetic causes for their phenotypically short stature. Merimee and Remoin (108) gathered data on insulin-induced human growth hormone (HGH) and arginine-induced human growth hormone and associated hormones from 22 pygmies in the Central African Republic. For both tests they found no differences in HGH levels between the pygmies and a European control group; however, the pygmies' plasma glucose responses to insulin and their plasma insulin responses to arginine were similar to HGH-deficient dwarfs. Further studies by Merimee and Remoin (108) demonstrated that pygmies had peripheral tissue insensitivity to HGH due to a deficiency of somatomedin or insulin-like growth factor I (IGF_I), a hormone which affects skeletal growth. Recent work by Bozzola et al. (109) has supported these early studies where they found a marked reduction in HGH receptor gene expression and that pygmies lack both an adolescent growth spurt and an associated pubescent serum IGF_I surge. Also, Becker et al. (110) found distinct differences in Cameroon Baka pygmies and their neighboring non-pygmy Nzimé populations in growth hormone receptor (GHR) and insulin-like growth factor 1 (IGF1) gene frequencies. Studies of the short-statured Aeta from Luzon in the Philippines were conducted by Bernstein and Dominy (111) to test several bioactive breast milk factors (cytokines) as having potential influence on epigenetic "inflammation memory" (maternal to infant transmission via breast milk) and its possible influence on infant growth. Comparisons with Ilocano Philippine and other populations were inconclusive, but the authors suggested that the Aeta population "…offer promise as a model system for testing epigenetic hypotheses focused on the relationships between adult mortality, age of reproductive maturity, and stature." [(111), p. 244]. Finally, convincing evidence that short pygmy stature is under genetic control was provided by Becker et al. (100) via admixture studies of more than 1,100 pygmy and Bantu central African adults from Cameroon, the Central African Republic (CAR), and Gabon.

The effects of genetic differences on growth processes appear to differ among pygmy populations, particularly between the Western cluster of populations with the pygmy phenotype (Gabon, Cameroon, and CAR) and the Eastern cluster of the Congo basin (112). In Eastern Congo Efe and Ngayu Pygmies, birth weights (2,600 g) and birth lengths (44 cm) were slightly less than their Bantu neighbors (birth weight = 3,000 g, birth length = 47 cm) (113). Hence, Efe and Nagau pigmy infants began life at smaller sizes than Bantu. In a large longitudinal sample of Western pygmies (Baka) studied over the long term by French CNRS researchers, pygmy birth weights were close to French standards but the pygmies fell behind the French throughout infancy with values reaching −2 standard deviations (−2 Z-scores), and pygmies remained at −2 Z-scores until adulthood (112). Differences have also been found in adolescent growth spurts: some pygmy populations showed suppressed adolescent growth (114) while others displayed normal adolescent growth (112).

Despite these differences in growth patterns in Western and Eastern African pygmy clusters leading to phenotypic

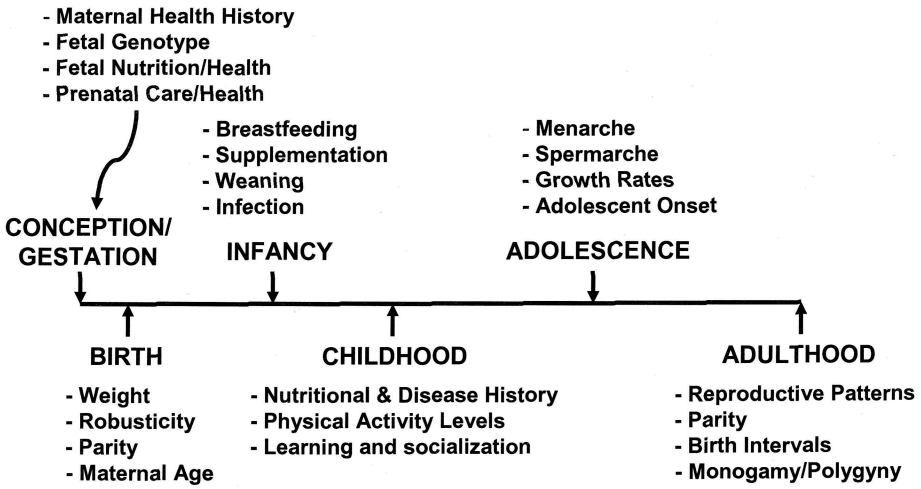

FIGURE 3 | A time line from conception to adulthood of life history, illustrating some of the crucial variables that influence adult size and, potentially, reproduction.

short stature, genetic signatures have recently been identified in both African (Ugandan Batwa and Cameroon Baka) and Asian (Andamanese Onge) that are associated with growth factor binding functions and convergent selection in these tropical rainforest hunter gatherers (115, 116). What is quite clear for these and other studies is that pygmy populations have growth patterns that differ from other populations that lead to short stature, and that these growth patterns have a genetic basis that may have involved convergent evolution between African and Asian short-statured populations.

Returning to the selective pressures hypothesized to have acted to produce short stature, a fourth hypothesis, developed more recently than the other three, has centered on life history processes, mortality, and fertility (41, 52, 117, 118). The hypothesis is associated with a life history trade-off between accelerated growth and early sexual maturation as a compensation for high mortality at relatively young and older (adult) ages and a truncated reproductive life span. This was hypothesized by Migliano (41) and Walker et al. (52) and tested by Migliano et al. (117). Both Walker's and Migliano's research employed comparative data from Asian, African, and South American hunter-gatherer (H-G) populations. Walker et al. [(52), p. 295] suggested it is "...selective pressure for accelerated development in the face of higher mortality..." that has led to the short stature of many H-G peoples. Hence, the argument is that short stature is a by-product of this fertility shift, and there is not direct selection for short stature. Within this theoretical framework, Walker et al. (52) explored growth rates in some detail in 22 small-scale, foraging societies in which height and weight velocities could be compared. They found that faster growth (higher velocities) and an earlier puberty were indeed associated with a higher mortality risk and limited food and resources. These conditions of accelerated but shortened growth, then, produced short stature in these populations. An extension of this work comparing small-scale societies (118) incorporated population density and geographic latitude as variables into the mortality and early maturation model producing short stature. Population density was an important variable suggesting enhanced competition for food resources. Correlation analysis demonstrated that increased population density led to decreased probability of survival to age 15 years, and that probability of survival to age 15 years was positively correlated with body size. In other words, high survivorship was related to larger body size and high mortality was related to small body size. Migliano and Guillon (119) compared life expectancy at birth, survivorship to age 15 years, and life expectancy at 15 years with adult height in 89 small-scale human societies. Using linear regression models, they found that adult height variation is strongly predicted by these measures of mortality (and survivorship), such that an accelerated childhood and adolescence will reduce the chances of death before the ages of reproduction. Hence, an earlier reproductive age will potentially increase the reproductive life span and enhance fertility.

There has been criticism of the mortality/fertility/early maturation trade-off hypothesis. Although they encourage research on life history theory and pygmy stature and identify the work by Migliano (41) and Migliano et al. (117) and Walker et al. (52) as innovative, Becker et al. (120) recognized several problems with the trade-off hypothesis. Two criticisms were based on (1) arbitrary height thresholds to distinguish pygmy from non-pygmy populations and (2) mathematical errors in their models. However, the most significant critique centered on pygmy demographic data, where Becker et al. (120) noted that there is insufficient data on age-specific mortality, fertility,

and life expectancies for African populations with the pygmy phenotype. This is quite true, but an added problem with the hypothesis is that both fertility and mortality are not constant in most populations. These variables fluctuate with sociocultural, socioeconomic, climatic, resource availability, and a whole host of variables. A case in point is the detailed demographic work done by Leslie et al. (121–123) on East African Turkana pastoralists, where seasonal and annual fluctuations in food resources led to more than 2-fold differences in fertility and marked differences in mortality over the short-term and the long term. More recently and returning to pygmies, Ramirez Rozzi (124) found dramatic declines in Baka fertility that were association with acculturation and the introduction of an alcoholic drink that disrupted family relations in this small-scale society. Another counter-argument to the trade-off hypothesis, then, is that mortality at all ages and age-specific fertility rates are temporally fluctuating variables in all societies, and are unlikely to have remained stationary for sufficient numbers of years for selection to have acted on earlier sexual maturity to compensate for higher early adult mortality.

Biogeographic Rules

Walker and Hamilton (118) also found a relationship in a large sample of foraging populations to latitude, which is consistent with other literature that demonstrated a gradient from the equator to high latitudes. Shorter individuals tend to be found in populations from lower (equatorial) latitudes (tropical or warm climates) and taller individuals from populations at higher latitudes (temperate or cold climates). This is consistent with Bergmann's (125) biogeographic rule that states that in related species or populations of homeotherms (endothermic vertebrates), those from warmer climates will have smaller bodies than those from colder climates. The rule derives from the relationship between size in linear dimensions (height in humans), surface area, and weight or volume. As the linear dimension increase by one unit, the surface area increases by the square of that unit, and the volume (weight) increases by the cube of that unit. Hence, the important relationship is the surface area per volume or surface area/ weight (SA/wt), where a high SA/wt ratio (short stature) facilitates heat loss from the surface and a low SA/wt ratio tall stature) reduces heat loss from the surface. These relationships are only for passive heat exchange between the body and the environment. There are many physiological mechanisms that control human temperature regulation, but these passive heat exchange relationships have been shown to operate for humans and to influence body size in population around the world (126, 127).

Roberts (126, 128) early studies demonstrated the strong climatic and latitudinal biogeographic relationships with body size for pre-World War II populations. Katzmarzyk and Leonard (127) then verified these relationships for post-World War II populations. However, they found that the correlations were weakened, perhaps with the post-war worldwide spread of Western culture and technology. Ruff (129, 130) extended these comparative studies to prehistoric human populations from skeletal remains. He found that body breadth (from pelvic dimensions) was an equally important variable in regulating SA/wt ratios [a narrower body allowed a higher SA/wt ratio [heat dissipation] and a broad body allowed a lower SA/wt ratio [heat conservation]]. This result demonstrated the corollary of Bergmann's Rule associated with linearity (131), and enabled Ruff (129, 130) to demonstrate the validity of Bergmann's and Allen's rules for the relationships of body size and proportions from skeletal remains for prehistoric populations.

DISCUSSION

Human body size has shown remarkable variation throughout our evolutionary history. Widespread global distribution has exposed human populations to a variety of environments that have been exploited for food resources in manifold ways. The elaboration of culture in the broad sense and cultures, as successful adaptive entities, has expanded both the environment and the selective pressures to which individuals have been exposed throughout their lives. Human physiological, anatomical, and developmental plasticity contribute substantially to variation in adult body size, that is, body sizes in which some population averages may show statures that are one-and-a -half and body weights that are twice that of other populations. These major differences in average individual sizes, however, have strong genetic components that are expressed through variable nutritional intakes and hormonal regulations, and are manifested by different growth rates and durations.

Darwinian selection has operated in favor of large body size to enhance fertility in women and provide for successful competition for mates in men. But large size in men also is desireable in the context of intra- and inter-population conflicts, which have been common throughout human history (132). Within technologically advanced societies large men and large women have higher fertility than smaller men and women, and taller men tend to be more successful economically and in leadership positions. On the other hand, in traditional or small-scale societies (that have characterized much of our evolutionary history), the energy cost of reproduction and producing large infants, children, and adults is often more than can be sustained by existing resources. In these cases, the selective pressures favoring large body size may be countered by selection for smaller body size and balances are achieved. With Late Paleolithic technology, a large human body size might be less favorable than a smaller body size when hunting for large mammals is conducted over long distances. And among the short-statured Ju/"hoansi, successful hunters tend to have higher fertility than their less-successful cohorts (133).

Life history theory is a productive way to integrate information about these opposing selective pressures to achieve optimal body sizes for individual populations (134). This idea to optimize the adaptive roles of population survival and population persistence through the major variables of individual maintenance, growth, reproduction, and longevity (survival to completed

reproduction and beyond) is an appropriate way to explore these relationships.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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People Are Taller in Countries With Better Environmental Conditions

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Background: Height is considered an indicator of health and well-being of an individual and population. Height variation results from a complex interaction of genetic, environmental, socioeconomic, and cultural influences. In order to understand the contribution of environmental stress associated with the child's growth, we correlated indicators of a stressful environment with adult height.

Methods: We utilized seven equally weighted indicators of a stressful environment: homicide rates, GDP per capita, income inequality (GINI index), corruption perception index (CPI), unemployment rate, urban air pollution, and life expectancy (LE). Data on male and female height by country from 1992 to 1996 were obtained from the NCD Risk Factor Collaboration dataset. We assessed separately data from the 31 member countries of the Organization for Economic Co-operation and Development (OECD). In order to establish whether the indicators reflected a single conceptual dimension, we conducted an exploratory analysis and principal component analysis (PCA) with orthogonal transformation of the original variables. The relationships between male and female heights and the z-transformed principal components: Quality of life (QoL) and the Social factor (SF) that were derived after the PCA was assessed.

Results: Male and female heights strongly correlated ($p < 0.0001$) with each of the seven indicators. In the PCA, the indicators clustered into "Quality of Life" factors (QoL), which comprised the CPI, GDP, air pollution, LE, and "Social factors" (SF), which comprised homicide rate and GINI index. For males and females, the average height by country strongly correlated with QoL ($p < 0.0001$) and SF ($p < 0.0001$). Within OECD countries, male and female height strongly and negatively correlated with the SF, but not with QoL.

Conclusion: Growth attenuation is a tradeoff adaptive response: a calorie used for growth cannot be used for fighting stress. Here we show that: (1) Adult height, when used as a measure of child's growth, is an indicator of a stressful environment in context with the genetic background and spatial factors; (2) Stressful QoL factors and the SF exert a greater effect on men's height than women's height; and (3) The ranking of the indicators of short stature are income inequality > air pollution > GDP > CPI > homicide rate > LE > unemployment.

Keywords: environment, growth, height, stress, inequality, social

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Height variation in the population of different countries and regions and within a specific population is the result of a complex interaction of genetic (1), environmental, socio-economic, and cultural factors (2), including parental education health and literacy (3). Importantly, adults stature is the result of longitudinal growth during childhood. Since height is considered to be an indicator of the health and well-being of an individual and a population, the variation in adult height can be used as an accurate marker of inequalities in human environments.

Millions of children worldwide not only fail to achieve their linear growth potential because of suboptimal health conditions and inadequate nutrition and care; they can also suffer severe irreversible physical and cognitive damage that accompanies stunted growth (4).

Much attention has been devoted to the contribution of nutrition in height and stunting (4). The long-term outcomes of stunting include a pure stature effect, and the effect of lost growth potential encompassing the cognitive impacts of undernutrition [A review of the evidence linking child stunting to economic outcomes (5)].

Stress is defined as a "state in which homeostasis is threatened or perceived to be so (6) and the spectrum of human stressors range from the daily hassles to starvation and bereavement (7)." Before modern times, the greatest stresses were infection, starvation, and malnutrition. These stressors of our predecessors have been replaced by pollution, poverty, gun violence, financial pressure, social and racial discrimination, and economic inequality. These stressors affect entire families, parents and children alike, and their effects depend on the type, intensity, timing, and duration of the exposure to stress.

Macroeconomic indicators of environmental stress include gross domestic product (GDP), income inequality, and unemployment. This economic and social context generates social inequality in access to health resources, social support, and healthy lifestyles. Differences in health outcomes, particularly in children, are the result of social inequality. Income inequality is often associated with increased homicide rates (8, 9). These indicators are social stressors that reduce interpersonal trust and can be associated with variation in levels of health, which includes post-traumatic stress disorder (10).

Another important dimension is the quality of governance effectiveness, and a state's ability to enforce its rules. There is empirical evidence showing that poor governance has a wide range of effects which include difficulties to provide food security and appropriate health services access to the population (11). Countries which score well on the quality of governance also tend to score better than other countries on poverty reduction, health care provision, and subjective well-being (12). A recent study has shown that low government efficiency and corruption have an impact on various indicators of child deprivation which include lack of safe drinking water, malnutrition, lack of access to health care, and lack of access to information (12). The article concluded that low-quality governance explains much of the cross-country variation in child deprivation.

The social stressful conditions, when they are experienced in early life, can profoundly influence child development, growth, and maturation and have long-term consequences on developing biological systems and long-term health (13–15). It was previously reported that children's growth can serve as an indicator of the extent to which social inequality exists in a population, as well as temporal changes in the economic condition of society as a whole and its specific subgroups (16).

There is an emerging notion that a stressful environment changes a child's gene expression and hormonal activity, and contributes to biological changes that may lead to mental and physical disorders (17).

In 2015, Bloomberg ranked the most stressed countries according to their living environments (http://www.bloomberg.com/visual-data/best-and-worst//most-stressed-out-countries). This ranking was based on seven indices, namely homicide rates, GDP per capita, income inequality, corruption perception index (CPI), unemployment rate, urban air pollution, and life expectancy.

Comparing vulnerability to environmental stress across countries can identify those leverage points where vulnerability and, by inference, social and emotional stress can be reduced at least in the short to medium term. Identification of particularly vulnerable nations or regions can act as an entry point for both understanding and addressing the processes that cause and exacerbate vulnerability. Since the impact of the economic and social indicators of stress on child growth and maturation have not been extensively studied, we aimed in this study to understand the impact of these indicators on average male and female height, as a measure of child growth in 71 countries.

METHODS

Data Sources

We used GDP per capita, income inequality, life expectancy, CPI, unemployment rate, homicide rates, and urban air pollution as the indicators of a stressful environment.

For each indicator, we combined the average mean value for women and men by country for the period, 1990–2000.

Data on GDP per capita ($US) were extracted from the national accounts data of the World Bank and the national accounts data files of the Organisation for Economic Co-operation and Development (OECD) and entered into the database.

Income inequality or the GINI index measures the extent to which income distribution (among individuals or households within an economy or, in some cases, consumption expenditure) deviates from a perfectly equal distribution. Thus, a GINI index of 0 represents complete equality, while an index of 100 represents complete inequality. These data were collected from the World Bank dataset and the actual scores were entered into the database.

Life expectancy at birth indicates the number of years a newborn infant would live if prevailing patterns of mortality at the time of birth were to stay the same throughout life. These data were collected from the World Bank's data bank, whose sources are (a) the UN Population Division, World Population Prospects, (b) the United Nations Statistical Division, Population and Vital Statistics Report (various years), (c) census reports, and other statistical publications from national statistical offices, (d)

Eurostat: Demographic Statistics, (e) Secretariat of the Pacific Community: Statistics and Demography Program, and (f) the US Census Bureau: International Database (http://data.worldbank.org/indicator/SP.DYN.LE00.IN) and entered into the database.

The CPI grades countries on the perceived level of public sector corruption by expert assessments and opinion surveys. The scale ranges from 0 to 100, where 0 means that a country is perceived as highly corrupt and 100 means it is perceived as very honest. The actual score was extracted from the website of the international non-governmental organization Transparency International (http://www.transparency.org/research/cpi/overview) and entered into the dataset.

Data on unemployment rate are given as percent of total labor force. It refers to the share of the labor force that is without work and seeking employment. These data were extracted from the World Bank's data bank whose sources were the International Labor Organization's database http://data.worldbank.org/indicator/SL.UEM.TOTL.ZS and entered into the database.

The average data by country from 1990 to 2000 on homicide rates in percent were extracted from the Global Study on Homicide, which was published by the UN Office on Drugs and Crime and based on the intentional homicide count and rate per 100,000 habitants according to country/territory (https://www.unodc.org/documents/congress/backgroundinformation/Crime_Statistics/Global_Study_on_Homicide_2011.pdf) and entered into the database.

Urban air pollution is expressed as the particulate matter concentration micrograms per cubic meter. Fine suspended particles whose diameters are <10 microns (PM10) are capable of penetrating deep into the respiratory tract, where they cause significant health damage. These data were extracted from the database of the Global Model of Ambient Particulates (GMAPS) (18) and entered into the database. Estimates represent the average annual exposure level of an average urban resident to outdoor particulate matter in residential areas of cities with more than 100,000 habitants.

Data on average male and female height by country from 1992 to 1996 were obtained with permission from the NCD Risk Factor Collaboration (NCD-RiSC) dataset (http://www.ncdrisc.org/d-height.html) and entered into the database. This dataset includes sources that were representative of a national, subnational, or community population and had measured height. Self-reported height and data sources on population subgroups whose anthropometric status may differ systematically from that of the general population were not included in the study (19).

We also compared the data on average male and female height as a function of stressful environment indicators from developed and developing countries and data from the 31 member countries of the OECD with those from non-OECD countries. South Korea, Switzerland, New Zealand, and Luxembourg at least one of the indicators of the stressful environment was missing and data from these countries was not included in the analysis.

Statistical Methods

In the analysis, we used information on the average male and female height and the seven indicators of a stressful environment: GDP per capita, income inequality, life expectancy at birth, CPI, unemployment rate, homicide rates and urban air pollution from 71 countries.

All statistical analyses were done using software statistical package (IBM SPSS Statistics 20.0) and statistical significance was set as 5%. The strength of the linear relationship between the average male and female height per country and each indicator of a stressful environment was determined by calculating Pearson's correlation coefficient.

Since the bivariate correlations of the indicators of a stressful environment had a high value, we did an explorative principal component analysis (PCA) in to identify the extent that the indicators of a stressful environment reflect conceptually meaningful separate constructs.

A correlation matrix of orthogonal-transformed data was generated using a PCA (IBM SPSS Statistics 20.0). The procedure uses orthogonal transformation to convert our set of variables into a set of values of linearly uncorrelated variables.

We calculated the Pearson's correlation coefficient between our dependent variable (male and female heights for the71 countries) and the independent scales (QoL and SF). The bivariate correlations were calculated separately for non-OECD and OECD countries using Spearman's correlation coefficient.

RESULTS

When we calculated the bivariate correlations of the individual variables, we found that male and female height was positively correlated with the CPI, life expectancy at birth, and GDP per capita and negatively correlated with homicide rates, income inequality, unemployment rate, and urban air pollution. Men and women were taller in those countries with a low CPI, a high life expectancy at birth, and a high GDP per capita than men and women in those countries with a high CPI, a low life expectancy at birth, and a low GDP per capita (**Table 1**).

The results of the PCA indicated that the individual variables represent two different components according to the Eigenvalue and accounted for 77.6% of the total variance (**Table 2**). The first component, which we called "Quality of Life" (QoL), comprises the CPI, GDP per capita, urban air pollution, and life expectancy at birth, and accounts for 54.1% of the variance. The second component, which we called "Social Factor" reflects social problems conducive to social stress and comprises the homicide rate and the income inequality, and accounts for 23.6% of the variance. The unemployment rate did not fit into any of the other extracted factors because is not an independent dimension. Since the unemployment rate could be included in the QoL and social factor components it was not included in the analysis in order to reduce the risk of multicollinearity with the extracted independent factors. For males and females, the average height by country strongly and positively correlated with QoL ($p < 0.0001$) (**Figure 1**) and strongly and negatively correlated with SF ($p < 0.0001$) (**Figure 2**).

TABLE 1 | The Pearson's correlation coefficients between the seven indicators of environmental stress and male and female heights.

	GDP per capita	Life expectancy	Urban air pollution	Unemployment rate	CPI	Income inequality	Homicide rate
Male height	0.60**	0.62**	−0.51**	−0.30*	0.66**	−0.52**	−0.29*
Female height	0.52**	0.54**	−0.51**	−0.32*	0.61**	−0.52**	−0.26*

*GDP, gross domestic product; CPI, corruption perception index. *p = 0.01, **p < 0.001.*

TABLE 2 | Clustering of the stress determinants by principal component analysis.

Stress indicators	QoL factor	SF factor
CPI	0.903	
GDP per capita	0.895	
Life expectancy	0.818	
Urban air pollution	0.618	
Homicide rate		0.709
Income Inequality		0.696

CPI, corruption perception index; GDP, gross domestic product.

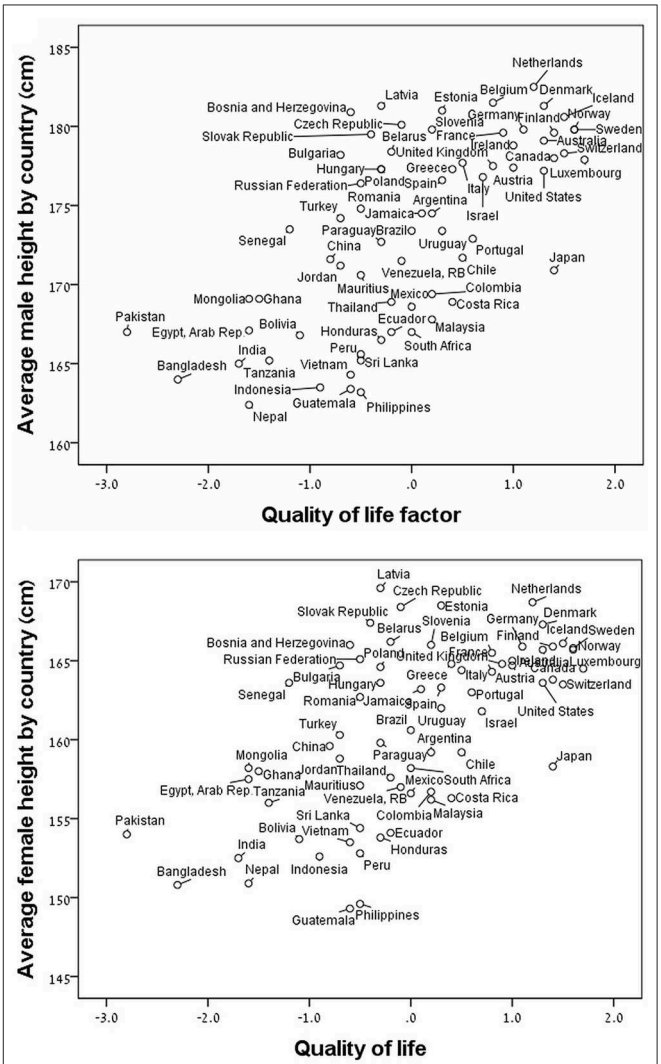

FIGURE 1 | Average height by country as a function of the quality of life factor (Z-score) for males (upper panel; $r = -0.65$, $p < 0.0001$) and for females (lower panel; $r = -0.60$, $p < 0.001$).

For the 40 non-OECD countries, we found that the average male and female heights by country were strongly and positively correlated with the QoL component and strongly and negatively correlated with the Social Factor component (**Table 3**). For the 31 member countries of the OECD, we found that the male and female heights were strongly and negatively correlated with the Social Factor component only (**Table 3**).

We found that between-countries variations are similar to those within countries: for men, the between-countries average height ranges from 158 to 183 cm (Indonesia and Netherlands, respectively), with a standard deviation (SD) of 5.9 cm, as compared to 164–190 cm within the USA (3–97th percentile, SD = 6.5 cm) (20). For women, the between countries average height ranges from 147 to 170 cm (Indonesia and Netherlands, respectively, SD 5.7 cm), as compared to 151–175 cm within the USA (SD = 6.0 cm).

DISCUSSION

This report informs on the results of an investigation on the influence of the environment on a child's growth using average adult male and female heights in 71 countries as the ultimate measure of a child's growth. We found that men and women were taller in those countries with a low CPI, a high life expectancy at birth, and a high GDP per capita than men and women in those countries with a high CPI, a low life expectancy at birth, and a low GDP per capita. Obviously, there is no way to isolate the stressful environmental factors from the genetic background of each country. Scandinavians have both the genetic background of tall stature from their Viking ancestors and have a low corruption rate and high GDP.

Here, we focused on economic and social components of environmental stress, which are both a strengths and a limitation of the current study. We recognize the fact that environmental altitude and humidity may contribute to a child's growth and adult height. In Nepal and Peru, at the bottom of height spectrum, the influence of low oxygen pressure at high altitude has strong effect on growth along with the socio-economic environment (21). The statistical approach for analysis is to analyze all factors one by one. An additional limitation of this

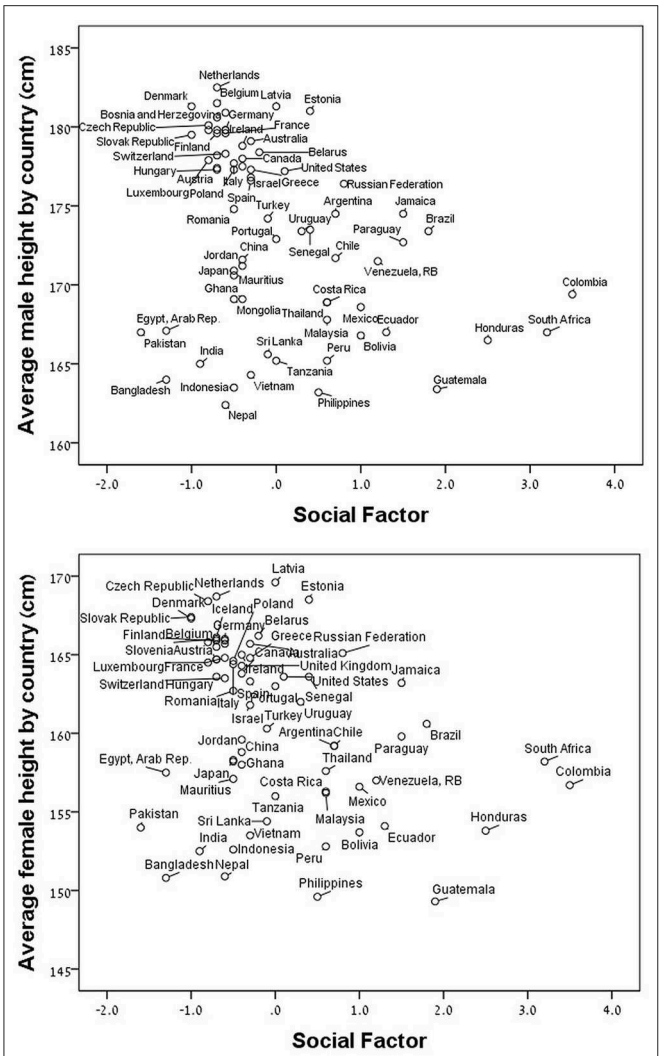

FIGURE 2 | Average height by country as a function of the social factor (Z-score) for males (upper panel: $r = -0.35$, $p < 0.0001$) and for females (lower panel; $r = -0.32$ $p < 0.005$).

TABLE 3 | Pearson's correlation coefficients of male and female height as a function of Quality of Life (QoL) and the social factors for the 31 member countries of the Organization for Economic Co-operation and Development (OECD) and the 40 non-OECD countries.

Correlated variables	OECD countries $N = 31$	Non-OECD countries $N = 40$
Male Height vs. Quality of Life	0.24	0.65**
Female Height vs. Quality of Life	0.05	0.60**
Male Height vs. Social Factor	−0.50**	−0.35**
Female Height vs. Social Factor	−0.48**	−0.32**

**$p < 0.001$.

study is the fact, that we were limited by availability of the data on both growth and the environmental stress indicators; for only 71 countries we had both.

Child health and development are threatened by disasters, political violence, pandemics, and other adversities. Of these adversities, a stressful environment, as defined in this investigation as vulnerability to poverty, homicide, income inequality, corruption, unemployment, and pollution, threatens the health and well-being of many children. Here, we focused on child growth which culminates in the average final adult height at a national level, as a well-established indicator of stress (13, 15, 20, 22).

The results of our cluster analysis of the seven indices of environmental stress revealed that vulnerability is represented by (a) a suite of indices which we called QoL that comprises urban outdoor air pollution, life expectancy at birth, the CPI, and GDP per capita, and (b) a suite of indices which we called Social Factors which comprises homicide rate and economic inequality, as measured by the GINI index. We found that the most vulnerable nations are those of the developing world and those that have recently experienced conflict.

In this investigation, we used national averages in statural height, while recognizing this measure and its range are different in each country. Surprisingly, we found that between-countries variations are similar to those within countries. This comparison suggests that the range of 23–26 cm represents the saturation span for plasticity in height (2,9). We also found that a stressful environment exerts a greater effect on the height of males than that it does on females. Although women experience twice as many stressful events during their lives than men (23), we found that the impact of each and all of the stress indicators on male and female height is similar.

Here we show sexual dimorphism in growth vulnerability to stress even before reproduction. This finding is in line with evidence from humans and experimental animals: stress affects the behavioral, the endocrine, and the molecular responses of stress systems in the hypothalamus. Moreover, this effect presents itself in a clear sexual dimorphic way, with males being more vulnerable in their stress response (24).

The results of this study suggest a strong negative impact on growth of low GDP per capita, CPI, economic inequality, air pollution, and life expectancy, in that order. Milder negative effects on health and growth were found for air pollution, homicide rate, and unemployment. For understanding the mechanism of growth attenuation by stress, we define 'homeostasis' as the steady-state environment of the body that is threatened by stressors, and the "adaptive response" as those mechanisms which are activated to reestablish the steady-state (5). Up to a certain threshold of a stressor's strength and duration, the adaptive response can reestablish homeostasis without any cost to the individual. However, when a stressor cannot be entirely counteracted by the adaptive response and the homeostasis attained is suboptimal, it is associated with harm to the individual. Growth attenuation is a tradeoff adaptive response: a calorie used for growth cannot be used for combatting stress.

In this investigation, we have used national averages in height and environmental stress indicators while recognizing variations within countries. National averages comprise appropriate scales

for information utilized by central governments for determining policies (25). Previous studies of national heights generally used indicators which were chosen subjectively by the authors and based on assumptions about the factors and processes leading to vulnerability, based on literature review, and intuitive understandings of human-environment interaction (26–29). The approach which we used in this study utilized indicators of vulnerability based on a conceptual framework in which risk is defined by established indicators for mortality outcomes (30).

Membership in the OECD reflects a minimum level of QoL. Since the QoL might have a different effect on child growth in developed and developing countries, we investigated the potential differential effect of QoL and social factors on child growth within member countries of the OECD. Although the effect of QoL on child growth was not statistically significant for member countries of the OECD, it is possible that this result is an artifact because of insufficient variation in QoL in developed countries. However, we found that the correlations with child growth were strongly significant when we measured more sensitive and more variable indicators of the social factor. Male and female heights are sensitive to the social factors of national economic inequality and homicide rate in all the countries and, specifically, in OECD countries.

In conclusion, we found that adult height, when used as a measure of a child's growth, is an indicator of a stressful environment in context with the genetic background and spatial factors. We also found that stressful QoL factors and the social factors exert a greater effect on the height of men more than that of women. Specifically, we found that the ranking of the indicators for a short stature are GDP per capita > the CPI > economic inequality > urban air pollution > life expectancy > homicide rate and unemployment.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: http://data.worldbank.org/indicator/SP.DYN.LE0; http://data.worldbank.org/indicator/SL.UEM.TOTL.ZS; http://www.ncdrisc.org/d-height.html. The detailed information about data sources is provided in the Methods section.

AUTHOR CONTRIBUTIONS

AG: co-conceptualized and co-designed the study, reviewed, revised, and approved the manuscript. GM: co-conceptualized and co-designed the study, carried out the PCA statistical analysis, entered the results, reviewed, revised, and approved the study. ZH: conceptualized and designed the study, oversaw it's conduct and drafted the initial manuscript, reviewed, revised, and approved the study.

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Nutrition Justice: Uncovering Invisible Pathways to Malnutrition

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We propose the use of the analytic frame of "nutrition justice" to reconcile the separate imperatives of Global Health for nutritional sufficiency for all, the requirement to eradicate childhood malnutrition, and the need for strategies to check the emerging pandemic of the double burden of malnutrition in the Global South. Malnutrition and its consequences of growth stunting are the result of disruption to the nutritional ecology of childhood from structural violence. This is mediated through loss of food security and perturbation to the cultural status of food, and on the prerequisites for nurture during infancy and early childhood. These socio-political factors obscure the role of biological adaptation to nutritional constraint on growth and hence the causal pathway to the double burden of malnutrition. In this paper we describe how the effects of historical and contemporary structural violence on the nutritional ecology of childhood are mediated using the examples of remote Aboriginal Australia and the Lao PDR. Both populations live by force of circumstance in a "metabolic ghetto" that has disrupted the prerequisites for parental nurturing through loss of food security and of traditional sources of transitional staple foods for weaning. Growth faltering and stunting of stature are markers of adaptation to nutritional constraint yet are also the first steps on the track to the double burden. We discuss the implications of these observations for strategies for global food sufficiency by mean of a thought-experiment of the effect of food and nutrient sufficiency for growth on future health and metabolic adaptation.

Keywords: nutrition, malnutrition, child, adaptation, food security, hunger, justice

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INTRODUCTION

The ability of our speciesto adapt to almost all of Earth's environmental niches is the hallmark of the success of our survival strategies, but contains the seeds of its demise in the face of the inexorable increase in the global population, the persistent wastage of food, and from the impending effects on climate change on water and food security. Climate change is considered to be the greatest global threat to health for the twenty-first century with the poorest nations most at risk adverse effects. The world population is projected to reach 9 billion or more in the next 30 years, with most of the growth occurring in the poorest nations (1, 2). These have the least capacity for either adaptation or mitigation and will suffer most from the complex but fixed relation between future population growth and the adverse effects on health (3).

The key to human adaptation is hidden in the critical period during the transition from the separate endocrine mediators of fetal and postnatal growth. Karlberg's Infancy-Child-Puberty model shows how and when these three phases of growth interact to create the characteristic shape

of the child's growth curve over time (4). A marked delay in the time of transition from the Infancy to the Childhood phase results in a reduction of final stature below the genetic potential of the individual (5–7). However, the deep factors that influence the timing of the transition from the Infancy to the Childhood phase that occurs from 9 months onwards as the fetal influences on growth ebb, and which provide the ability to slow growth in response to nutritional constraint, are typically obscured by the cultural context. This is because the individual child either suffers malnutrition and needs urgent nutritional rehabilitation within the context of humanitarian health intervention, or because the child with growth faltering lives in a community in a subsistence economy and is unremarkable due to the normalization of morbidity. In both situations the complexity of the causal pathway remains obscure to the health professionals involved because they extend beyond social determinants that typically limit the extent of the public health model (8).

We emphasize that this perspective interrogates qualitatively different factors on the causal pathway to childhood undernutrition, growth faltering and stunting, and runs in parallel to, and complements, those that have been systematically documented over the past six decades. These extend from the effect of the allostatic load from the metabolic burden on the immune system from recurrent respiratory and gastrointestinal infection with impaired small bowel absorptive capacity, that is in turn exacerbated by an unhygienic environment; and from barriers to food security (9), within social marginalization, poverty, disempowerment, and structural violence (10).

The ability to respond to the nutritional environment through a change in the tempo of growth in early development offers a literal and metaphorical key to addressing both sides of the coin of the challenge of global food security. For post-industrial high-income nations a shift in food production and use is necessary for ecological reasons; for emerging economies (low-income nations), erasing the double burden of malnutrition is the pressing challenge. The need to encompass a wide-angle view is expressed by the calls for "A new nutrition manifesto for a new nutritional reality"(11) and also "A future direction for tackling malnutrition" (12). The term "nutrition justice" has previously been used by Wells (13), Swinburn et al. (14), and Swinburn (15) and highlights the moral imperative for equity in food security, and hence builds on the origins of the deep causes of the global syndemic of obesity and malnutrition as being within structural inequity (16), as well as food as the commodity that has been at the base of the pyramid of power since before the Neolithic farming revolution (13).

In this paper we argue that these apparently categorically separate problems are inextricably linked when viewed from the perspective of what we call "nutrition justice." Although previous evidence has demonstrated a link between malnutrition and global inequity (17, 18), we use the expression "nutrition justice" to highlight that the prerequisite for global food security goes beyond the humanitarian approach to the child suffering malnutrition as a victim of social marginalization, poverty, and conflict, and that it should include an analysis of how the invisible forces of structural violence operate to embed such disadvantage and prevent equity in access to optimal nutrition.

In this paper we propose that the concept of childhood adaptation to nutritional constraint with a change in the tempo of growth at a critical period, expressed as phenotypic plasticity, could be used as a model beyond the niche of evolutionary developmental biology, and specifically that it could provide an explanatory model for the contemporary challenges of global nutrition. The first of these is the problem of childhood malnutrition, with its consequence of growth faltering and loss of final height potential, which leads to stunting of stature. The second is the imperative for global food security as Earth's population heads toward 10 billion people: a 10-fold increase in 250 years (19).

We argue for the use of the concept of adaptation to achieve an explicit connection between the intractable problem of childhood malnutrition in marginalized communities and the moral challenge for the world as a whole to achieve a sustained level of food production sufficient to ensure global food security. In this context we use adaptation both in its literal sense in respect of the fall in tempo of growth to nutritional constraint, and in its metaphorical sense in terms of the radical changes that are required to achieve global food security.

The expression nutrition justice was coined during discussion between the authors on the paradox of endemic growth faltering from malnutrition in the midst of plenty amongst children in communities in remote Aboriginal Australia (8). These children grow up in a metabolic ghetto within a wealthy nation (13), suffering endemic growth faltering during the first year of life. They go on to carry a high risk of the early-onset of metabolic syndrome with its life-shortening consequences (20, 21). Growth faltering amongst Aboriginal children goes beyond being an irreversible health problem into the moral dimension of children's rights. This intersects with a separate question, which is: How can 10 billion people be provided with sufficient food to allow each child to reach her growth potential?

At present the focus of the EAT-Lancet Commission is on how post-industrial high-income nations should respond with respect to the achievement of the structural changes in the mechanisms of food production and through ecosystem changes (19). This top-down approach detracts attention from the question of how the eradication of childhood malnutrition is to be achieved. If the broad-brush aim of the Commission is that people in the global North should eat less, or less of some food groups, so that more is available to the global South, then it begs the questions of how much more food energy is needed for each child at the microcosm of the village in Nepal, Indonesia, Vanuatu, or Laos, and how will that be achieved at the village, district, and national levels?

Our aim is to close the conceptual space using an evolutionary-developmental approach that starts with a thought experiment: since nutrition justice requires that all babies and children should be fed sufficient food energy for optimal growth, then what are the practical implications for the achievement of the necessary additional food energy and protein intake?

ADAPTATION

The notion that growth faltering represents an adaptive phenomenon with its onset situated at a critical period of somatic development (and seen as a delay in the time of transition from the Infancy to the Childhood phase that results in a reduction of final stature) (5–7), rather than a perturbation of homeostasis that can be normalized with medical intervention, requires a shift toward the interdisciplinary perspective of evolutionary developmental biology.

At the end of the Pleistocene and the beginning of the Holocene, c 12,000 years before present (B.P.) societies shifted from hunter-gatherer toward a mixed food economy in the Near East. The Neolithic farming revolution took place in several separate sites more or less simultaneously (22). With technological changes in food production came changes in social relations. Importantly, food became a resource that could be stored, hoarded, and controlled. Even before the Neolithic Demographic Transition (23, 24), there is the first evidence of food being used to mediate political power (13). Archaeological evidence from the Natufian culture suggests rapid climate change during the Younger Dryas stadial (11,700–10,500 years B.P.) was a critical factor in this radical change. Climate and food production changed faster than evolutionary adaptation in human populations, and this was reflected in the marked fluctuations in population in this era (25, 26). From this perspective, the success of hominins is an outcome of the enhanced evolved capacity for metabolic adaptation within an individual's lifetime or between generations to different ecological zones with an unpredictable food supply (10). There is plausible evidence that this capacity emerged amongst our hominin antecessors in response to rapid changes in the environment from climatic fluctuations during the upper Pleistocene (27).

Wells characterizes as a "metabolic ghetto" the populations of, or within, a nation that demonstrate such phenotypic adaptations (13). These phenotypic adaptations include lower muscle bulk, shorter stature, and a metabolism adapted to parsimony. These characteristics stem from undernourishment in fetal life or early childhood, leading to structural and functional changes in organs responsible for nutrient regulation (e.g., adipose tissue and pancreatic beta cell dysfunction). In conditions of food abundance in post-natal life this may lead to preferential deposition of visceral (central) adipose tissue and insulin resistance and predispose the child to development of obesity and Type II diabetes (28).

At a population level, nutritional constraints over successive generations leads to the selection of phenotypic traits that represent trade-offs between survival and thriving. The double burden of malnutrition with early morbidity from diabetes and cardiovascular disease is the cost of adaptation in previous generations. Laboratory studies provide a glimpse of epigenetics mechanisms which may be relevant in humans (29, 30).

The metabolic ghetto aptly describes the situation in remote Aboriginal Australia. The fine-tuned adaptation to the nutritional environment of pre-contact society was violently disrupted and replaced by a limited range of foods supplied as rations within a clear hierarchy of power (31), which was followed by documented evidence of transgenerational malnutrition (32). It is in this context that the high rate of heart disease and diabetes amongst such populations should be understood. We argue that these are not "lifestyle" diseases as such, but are the result of nutritional constraint over both the long and short term. Since colonialism, the evidence is clear that malnutrition in this case has been closely linked to questions of power and marginalization.

In Australia the double burden affects two distinct population groups, Aboriginal people and South Asian migrants (33, 34). The Aboriginal population in Australia carry a high burden of obesity from late childhood, and a high prevalence of early-onset metabolic syndrome with onset of insulin-insensitive diabetes in adolescence. The high risk of cardiovascular disease in both Aboriginal and South Asian populations is in marked contrast to the rapid rate of decline in mainstream society with the death rate from cardiovascular disease in mainstream Australian population falling by 80% in the past four decades. For example, in the age group 75–79, the rate fell from 125 to 25 per 100,000 per year (35), whereas amongst Aboriginal men aged in the 55–74 age group, nearly half were at high risk for CVD, and 20–26% had known symptomatic heart disease (33).

West-Eberhard provides an evolutionary interpretation to the double burden of malnutrition: childhood malnutrition followed by the early-onset onset of morbidity from obesity and metabolic syndrome (36). In putting forward the "visceral adipose tissue prioritization" hypothesis she argues that "socially subordinate individuals are under selection to adjust to the consequences of limited resources … including alternative traits that salvage elements of their compromised survival and reproduction," and contrasts these effects with the traits selected in the socially higher ranked individuals ("who were more involved in high-stakes social competition and less exposed to hunger and infection") for subcutaneous adipose tissue and stature, amongst other morphological features that signal higher value for reproductive success. She argues that this reflects selection bias from the social stratification that emerged within agricultural societies and that prioritization of deposition of visceral adipose tissues reflects a local response to the metabolic load from immune stimulation from the increased burden of gastrointestinal infection and infestation from poor sanitation in sedentary groups, and its adverse effect on nutritional status.

Strategies to eradicate the double burden of malnutrition require a shift in perspective in order to frame its etiology as the consequence of a metabolic maladaptive response to long-standing population adaptation to nutritional constraint produced by a particular power arrangement. This raises the question of whether it is possible to reconcile the need for the improvement of childhood nutrition in a population in which growth faltering and stunting is endemic when there is strong evidence that the shift to a diet high in refined carbohydrate and fat results in metabolic maladaptation, and is the leading etiological factor to the double burden of malnutrition (37, 38).

STRUCTURAL VIOLENCE

The emergence of the double burden of malnutrition and syndemic of obesity and diabetes highlights the cost of disruption to adaptation of childhood growth to transgenerational nutritional constraint. However, its distribution uncovers evidence for the "known unknown" structural factors that act as barriers to the normalization of homeostasis. From a Western scientist's perspective it is clear that the double burden is emblematic of the transition from a pre-industrial to a post-industrial economy, and the disruption of transgenerational adaptation of fetal and childhood growth amongst those ranked lowly within the global economy. A second-order consequence of this burden of morbidity is on its deleterious effect on the rate of increase of life expectancy over the past decades for those aged over 60 years in low and mid-income countries, which has risen at only half the rate of that in high-income nations (39).

The concept of the metabolic ghetto provides an explanatory model for understanding the transgenerational effects on metabolism: evolving from an adaptation to being trapped by the forces of power in an adverse nutritional environment, to a transition to food security or access to high quality food. The effects of such a situation are best described by the term structural violence. This is violence that is evident on bodies, psyches, social relations, and health not through an overt act of might, but indirectly as an effect of a system of social relations such as political, legal, and economic arrangements. For instance, it is evident in the physical, intergenerational effects of discriminatory legislation. It is evident in the health conditions and social disintegration of marginal populations where social gradients and wealth are steepest, and where racism is ingrained. The term structural violence was coined by the Norwegian peace philosopher Galtung (40), and has since been popularized by the American public health physician Paul Farmer who has emphasized the damaging trans-generational effects of structural violence on both personal agency and on the individual's physical and mental health (41).

The causal pathways of structural violence and its effects are most apparent when examined among a distinct group within a population. Australian Aboriginal people provide a tragic example because they were victims of legal, physical, territorial, and social exclusion from the time of British settlement in the late eighteenth century. This became entrenched through legislation from the 1880s onwards in each jurisdiction. For instance, Aboriginal children were excluded from school, families were excluded from their land which was a source of nutrition; and men were excluded from unions so that they could not get paid work through until the mid-twentieth century (42). For some, as clients of today's byzantine and punitive welfare state, the effects of structural violence can be understood as a colonization of the mind that exerts a profoundly debilitating effect on personal agency (43).

When the colonial frontier zone extended to the tropical savanna region of northern Australia and vast cattle stations took over the country in the late nineteenth century, the population of Aboriginal people collapsed as a consequence of massacres, influenza epidemics, and hunger (44–46). The remnant populations worked on cattle stations as an unpaid workforce under conditions of dire deprivation and hunger (32, 45). The legacy of transgenerational malnutrition is now evident in the endemic rate of non-communicable disease from metabolic syndrome (20, 38). The adverse effect on fetal and early postnatal growth is compounded by a complex mix of cultural factors in regard to the hierarchy of food items and choices (47), and adverse health behaviors, particularly smoking, and alcohol consumption during pregnancy that affect birth weight (48–50). For instance, how food is used within the family is a crucial question for nutrition. This was illustrated by the ethnographic method used in separate studies in Trinidad and Nauru that delineated the depth of inequality from structural violence from historical that accounted for the extent of NCD morbidity (51).

Structural violence is also perpetrated through invisible conflicts between the deep patterns of behavior of mainstream Western society and Aboriginal society. This can be seen in the collision over cultural attitudes and value-beliefs about feeding babies during the critical growth phase of the transition from breast-feeding to a mixed diet, and how it has adverse effects on food energy intake and hence growth faltering. Families two or three generations distant from their pre-modern hunter gatherer ancestors do not share the same belief in the equation that has been internalized over millennia in families of the descendants of Neolithic European farmers and gardeners that food intake is a necessary investment in a child's growth, stature and strength, and hence their future capacity as a farmer or warrior (8). Hunter-gatherers had ample access to food resources, so skill as a hunter, story-teller, and in ritual expertise were valued above brawn. A peripatetic lifestyle meant that mothers carried their babies, so a heavy baby was a disadvantage. Aboriginal grandmothers now do not wish to understand children's nurses and doctors' fixation on weight and growth.

Babies in Aboriginal society were accorded autonomy as a sentient individual (52), and were (and still are) expected to make choices in a way that is in conflict with the pattern of heteronomous parenting in which the parent decides when and how the child should eat, sleep, and wear (8). The result is that babies and toddlers were offered the breast and finger-food, but it was (and is) their decision as to whether they would eat. Anorexia after an illness therefore leads to growth faltering, as shown by figures from the public health Healthy Under-5s Kids program of the Northern Territory where one-fifth of children are under-weight or under–height for age (53).

Yet these factors are often invisible to public health approaches. The Western public health approach takes an immediate approach. It addresses problems as they surface and become apparent in clinics and emergency departments. This obscures the evidence for the effects of entrenched structural inequalities and the transgenerational consequences of morbidity from maladaptation, as well as from the deep cultural factors.

The effects of structural violence are also apparent in Western social democracies. For example in the UK data from the Biobank study shows that inequality is expressed through phenotypic and economic disadvantage. Men of lower social status are shorter, and women are fatter (higher BMI), with BMI having an inverse relation with income (54).

GLOBAL FOOD SECURITY

At present nearly one billion people are hungry, two billion people do not have regular access to sufficient food, and the number of chronically undernourished people increased by 10 million between 2017 and 2019 to 821 million (16). Childhood malnutrition accounts for nearly half of child deaths under the age of 5 years (11). Yet two billion people eat too much and of the wrong food (55). Although the global average daily energy intake has increased over the past three decades to 2,710 Kcal, the poorest nations have seen the smallest increases (+80 Kcal), and the lowest increase in protein (56). The second Sustainable Development Goal is to end hunger, achieve food security and improved nutrition, and promote sustainable agriculture (14, 19). The "EAT-Lancet Commission on health diets from sustainable food systems" advocates global transformation of the food system that would allow food for 10 billion people (19).

For SDG 2 to be met (57) with respect to the eradication of hunger, a reciprocal response from the global North is required. This includes an international commitment to a healthy diet in the global north: reduced meat consumption; an increased intake in legumes, fruit, nuts, and vegetables; the re-orientation of agriculture; sustainable food production; coordination of government of land and oceans; and halving of food waste (55). Since the geopolitical changes of globalization and poverty affect food security, trade policies need to be reformed to facilitate food security, and sustainable food systems (58).

Climate change threatens the conditions for the human needs for food, water, sanitation, and shelter to be met (1) The most severely affected will be the 2.5 billion farmers, herders, forest-dependent, and fishermen who depend on renewable resources (59). The effect of climate change on food production and security in low-income nations has widespread implications with regards to the increase in childhood malnutrition, with adaptation through growth faltering and stunting of stature, followed in adult life by the burden of non-communicable disease. For example in West and Central Africa under-nutrition increased from 33.5% in 1990–92 to 41.3% in 2014–16, and stunting in Africa will increase by 7% by 2030 (1). The OECD predicts that food availability will fall by 2025 by 3.2% due to climate change and worsening morbidity due to infectious disease so that there will then be a food deficit in most low-income countries. Climate change will affect all, but by 2030 the effect of climate change and poverty will severely disrupt the lives of 35–122 million marginalized people (1).

In a global survey of the prevalence of the double burden, when defined using the score for the Global Hunger Index (a combination of three indicators of mortality in early childhood and morbidity from malnutrition) of 20 or greater (60), and the prevalence of obesity, with a BMI of 30 kg/m^3, of 15% or more, Iraq, Guatemala, Namibia, Lesotho, Swaziland, and Botswana were identified (60). This highlights the challenge of human adaptation in its widest sense to the emergence of a global syndemic of obesity, under-nutrition, and climate change (14).

The concept of nutrition justice requires sufficient food available for the world population and that this is contingent on its equitable distribution even without pressure on food systems in relation to the population. The emphasis of the place of children in the ecology of global nutrition and within the current discourse on the future for global nutrition highlights the need to reconcile separate factors that are in evident opposition. The humanitarian approach to intervention for childhood malnutrition in nations in which malnutrition is endemic (61, 62), therefore contains an internal paradox: that if all children were to be provided with sufficient food to achieve their genetic potential for height then there would not be sufficient food available within that nation. This highlights the gap between the clinician's short-term strategy of nutritional rehabilitation and the need to consider the structural and cultural consequences for children in countries (such as Laos which is the focus of the thought experiment that illustrates this point), in which the phenotypic adaptation of short stature allows homeostasis with the available food supply within a self-sufficient subsistence economy (63).

The question is therefore how to reconcile the two conflicting imperatives of optimal health for all with nutritional sufficiency, and yet equitable distribution of food resources. This question is dealt with tangentially by The Lancet Commission (19). This Commission advocates for global food sufficiency for a world population of 10 billion people through a radical alteration of strategies for food production and the type and quality of food raises several questions. Recommendations include obtainment of protein sources primarily from plants, doubling of the consumption of fruits, vegetables, legumes, and nuts; and more than 50% reduction in global consumption of red meat and foods with added sugars.

The first question is how this can be achieved in the face of evidence for an increase in the discrepancy between food production and consumption in several countries in Africa, particularly those in which is there is no evidence of a reduction in the rate of increase in the population.

The second question is whether global food energy sufficiency can be achieved with the recommended strategies and yet be sufficient in protein and micronutrient intake to provide equity of opportunity for every child to achieve their genetic potential in height. This would be contingent on a major shift in food resources in countries, particularly in South and S. East Asia, which are now food sufficient but at the cost of transgenerational metabolic adaptation to a nutritional plane provided by a low-protein rice or vegetarian-based diet.

A THOUGHT EXPERIMENT

Our notion of nutrition justice requires that every child has sufficient food to reach her genetic potential for height. If this were achieved, there would be no difference in mean stature between countries because of nutritional constrain. In this thought experiment we seek to identify the cultural, economic, and logistic barriers to this nutritional utopia using as an example the hill village of Kandon in north-east Laos in which author Holly has conducted ethnographic field studies over many years (63). Our starting point is the question: "if every child in the village aged from 6 to 18 months had one egg per day, and every

child from 18 months to age 5 years had 300–500 Kcal more than she does now, where would the food come from, and what would the effect be at a district level?" The reason for using the addition of a daily egg to the diet is because it is a realistic food source in that village, and because it has been shown that children aged 6–9 months assigned one egg per day for 9 months showed increased height and weight for age, although its benefit was not maintained at 24 months in the absence of that additional source of food energy (64, 65).

In Kandon village there are 1,260 individuals, of whom 13 are children aged 6–18 months. If each were given one egg a day in additional to their usual diet, that would require that the village source nearly 5,000 extra eggs a year. The village currently has 1,007 individual birds. Assuming 15% (151 individual birds) are roosters, and 20% (201 individual birds) are immature, this leaves 655 hens at most. The average hen lays 63–100 eggs a year. So, the village would produce between 41,265 and 65,500 eggs a year. This works out at 33–52 eggs per individual man, woman and child in the village per year. That is, the existing egg production in the village is not sufficient for one egg per person per day if the eggs are spread evenly.

In addition, there are serious questions over whether eggs already produced by village chickens are routinely used for consumption. In observations in the village, eggs from village chickens did not form an important part of the diet in this village and are mainly used for hatching. In an intensive study of the diets of this and other ethnic Katu villages in the same District, a nutritionist made an extensive report of what people ate, and did not mention eggs a single time in her 245-page report (66). It was furthermore my observation, and this was confirmed in interviews, that poultry mortality was high. In at least one case, a mass mortality of poultry in the village was confirmed through laboratory testing as Highly Pathogenic Avian Influenza H5N1 (67). This study suggested that HPA H5N1 spills over from commercial chicken farms abroad and then travels to rural Laos via trade routes, where it infects and kills village chickens before dying out there, only to be reintroduced through the market once again. Studies of village chickens in low income settings have noted that "In situations where mortality rates are high, village poultry eggs are rarely consumed as they are prioritized for hatching" (68, 69).

Giving one extra egg to children aged 6–18 months to consume would represent a major diversion of eggs away from current uses for sustaining the poultry population of the village toward using eggs for consumption. The best means to achieve this would be to introduce vaccinations for common poultry illnesses, especially Newcastle Disease (ND). ND is very common, can be lethal to chickens, and furthermore presents with signs that are indistinguishable from HPA H5N1. A vaccination program would have the dual benefit of reducing the impact of ND and increasing the likelihood and effectiveness of H5N1 reporting, which is currently very rudimentary in Laos (67).

In the absence of such a program, it seems inevitable that if people were incentivized to buy an egg a day for each child, for instance by introducing a subsidy for this purpose, eggs for consumption will be sourced instead from the market. The closest market is 40 min away by motorcycle. However, there is a consumer preference in this village to know where food comes from and avoid market food. The eggs in the market usually come from Thailand and Vietnam, but their exact provenance is unknown and the security of the cold chain is uncertain. It is an unregulated market with regard to how the chickens were fed and how old the eggs are, and the eggs are a known source of Salmonella. Food available for sale in the market is also associated with heavy use of pesticides, insecticides, and various drugs (what is glossed as *khemii* in Lao, meaning simply "chemicals"). People also understand that the market is a source of infection, such as what we know as H5N1. Most people in the village avoid market food on the whole and make do with what they can grow themselves or buy from trusted neighbors. A subsidy for egg consumption, without addressing the existing constraints on local egg production, would encourage industrial poultry farms while at the same time (through introduced diseases) undermining existing local efforts at self-provisioning locally-produced, organic food.

This example illustrates the complexity of barriers to the provision of sufficient transitional weaning food in one village. It shows that the first necessary intervention would be for the health of chickens. This would require a OneHealth long-term strategy aimed at supporting the villagers to sustain their own efforts to grow their own food (70).

When we ask the question for older children then the 125 children in that age bracket would require an additional 37,500–62,500 cal per day. (Note that at present high protein high fat nutritional supplementation is supplied in plastic sachets from an international aid organization). The answer begins with land, the source of food. These villagers were relocated from a remote mountainous area, where they had laid claim to 8,000 hectares, of which 2,000 could be used for cultivation. Crops of manioc and rice were grown in fields rotated on a 15-years fallow, and fruit and vegetable gardens on a five-to-seven-years fallow rotation. Diets were supplemented with gathering, fishing and hunting in the remaining territories, domestic animals, and trade (63, 71).

The village, then numbering about 900 individuals, relocated to a more accessible area in 1996. New Kandon now lays claim to roughly 800 hectares, divided between upland fields, forests for gathering, wet rice fields and gardens. Originally, 1,222 hectares had been promised by the District, but in the years following their resettlement the original occupants of the area objected and were able to retain control of a significant amount of their original territory, to the detriment of the new settlers. On settlement, the village split the land equally among every individual. Since then, the population has grown but land has not been redistributed. Additionally, in 2006, the District authorities granted 84 hectares of food gardens in Kandon to a Vietnamese rubber company. This occurred without the consent of the settlers: they explained that a neighboring village had agreed to the project and it was presented to New Kandon as a *fait accompli*. The village received an electricity connection in return for the land, and some wage work on the plantation, but people said that they would much rather have the land back for growing food on. They also raised concerns about the chemicals used by the plantation, which is very close to village homes and the school, as well as the village water supply.

There are no spare gardens or fields that could be used to feed these children. This would require people to find money

and then access the market to buy food. The food would likely be driven in from elsewhere, and also involve significant carbon in its production. Because people would much rather grow their own food organically, and know where it came from, this monetization and carbonization of their food chain is not a cultural preference. In this index village people are happy to earn cash and enjoy limited consumer goods, they are also keenly interested in the health benefits of growing their own food. This requires access to land so people can grow their own food.

This thought strand leads to a consideration of the implications of the carbon economy with respect to "food miles" (72). If people were incentivized to buy more food from the market then they would be driven further into the cash economy and access food that had been trucked in from elsewhere, and villagers would need to drive to markets to access it.

This vignette from the lived experience of villagers illustrates the close connection and dynamic tension between their biological adaptation to their available food supply, with a final height reduced from its genetic potential, and the coercive force to adapt to a market economy that erodes their access to land, erodes their cultural and nutritional self-sufficiency, and brings with it the inevitable threat of the double burden of malnutrition. Indeed, when people in this village were asked what they saw as the major health problems, they identified, along with TB, rising rates of diabetes and cancer. As one woman said "we never had diabetes in the mountains."

The story of this village demonstrates that food energy sourced from industrial agriculture has multiple ramified effects. The increased calories and narrowed micronutrients conflict with existing biological adaptation to a quite different nutritional profile. Additionally, there are cultural implications, as industrialized agriculture is not only antithetical to people's interest in organic self-sufficiency, it also undermines efforts at continued self-sufficiency by taking the best land and introducing degradations such as chemical pollution and the disease burden from Influenza virus H5N1.

CONCLUSION

The double burden of malnutrition requires a double-duty response (37, 73), but this should extend beyond the factors that comprise the usual frame of reference of public health (e.g., dietary patterns, socio-economic factors, hygiene, and sanitation), and include, for example, an ethnographic approach that identifies the cultural barriers to the provision of sufficient food to babies from 6 months of age (8, 71).

For the double burden of malnutrition to be eradicated the focus should, self-evidently, be on the education, vocational training, and nutrition of adolescent girls in emerging economies so that they have the freedom of choice to delay their first pregnancy until they are socially and physically mature.

The erasure of fetal growth constraint, and post-natal adaptation to an insufficient increase in food energy intake during the transitional period with subsequent growth faltering, is contingent on the multi-level approach. This extends from addressing the politics of structural inequality in societies of increasing wealth disparity to the cultural factors that coerce adolescents into pregnancy, and the washing out of the probable epigenetic factors that requires several generations of optimal nutrition.

However, nutritional justice demands that the well-understood approach to the consequences of metabolic adaptation in the global South are matched by social (group) and structural adaptation in the global North. This requires a planetary health perspective in which group selection of traits that are necessary for adaptation to the known future consequences of climate change, in this case behavioral changes to food sustainability, are at one end of a continuum with at the other end, the structural changes needed to erase the metabolic effects of maladaptation to the rapid shift in diet in an emerging or post-industrial economy.

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All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Timing of the Infancy-Childhood Growth Transition in Rural Gambia

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The Karlberg model of human growth describes the infancy, childhood, and puberty (ICP) stages as continuous and overlapping, and defined by transitions driven by sequential additional effects of several endocrine factors that shape the growth trajectory and resultant adult size. Previous research has suggested that a delayed transition from the infancy to the childhood growth stage contributes to sub-optimal growth outcomes. A new method developed to analyze the structure of centile crossing in early life has emerged as a potential tool for identifying the infancy-childhood transition (ICT), through quantifying patterns of adjacent monthly weight-for-age z-score (WAZ) deviation correlations. Using this method, the infancy-childhood transition was identified as taking place at around 12 months of age in two cohorts of UK infants. Here, we apply this method to data collected as part of a longitudinal growth study in rural Gambia [the Hormonal and Epigenetic Regulators of Growth, or HERO-G study, $N = 212$ ($F = 99$, $M = 113$)], in order to identify the ICT and assess whether timing of this transition differs across groups based on sex or birth seasonality. We calculated Pearson correlation coefficients for adjacent monthly WAZ score deviations. Based on the patterns of change in the correlation structure over time, our results suggest that the infancy-childhood transition occurs at around 9 months of age in rural Gambian infants. This points to an accelerated ICT compared to UK infants, rather than a delayed ICT. A comparatively later transition, seen in UK infants, allows maximal extension of the high rates of growth during the infancy stage; an earlier transition as seen in Gambian infants cuts short this period of rapid growth, potentially impacting on growth outcomes in childhood while diverting energy into other processes critical to responses to acute infectious challenges. Growth in later developmental stages in this population offers an extended window for catch-up.

Keywords: infancy, childhood, growth, infancy-childhood transition, hormonal growth regulation

INTRODUCTION

The human growth trajectory is complex compared to other large-bodied mammals; passing through infancy, childhood, juvenility, and adolescence before reaching adulthood (1) it is relatively prolonged via the extension of the pre-pubertal period (2), and is best described as sinuous and containing periods of both relatively slow growth and accelerated growth. Earlier perspectives held that certain stages of growth are uniquely derived in humans (e.g., childhood), and the insertion of these stages into an ancestral primate growth trajectory are responsible for the prolongation of growth overall in humans—itself hypothesized to permit a longer period of brain development (3), to build metabolic and cognitive capital to use in later life (4), or to increase chances of success in relationship to extrinsic mortality risk both in adulthood and during immaturity (5, 6). More recent analyses have suggested that while the human growth trajectory is indeed extended relative to that of our closest living relatives, those stages previously considered novel are present in other non-human primate species, and relatively accelerated, and/or compressed in their time course of expression (7–12). While differences in the length of each stage and the nature of their transitions can be influenced by evolutionary relationships, how quickly or slowly individuals pass through growth stages can also be attributed to a number of (not mutually exclusive) factors, including nutritional status, morbidity burden, and aspects of the social and physical environment such as dominance rank, mortality risk, and seasonality (13–15). In humans, there is significant inter- and intra-population variation in the timing of maturational events, and rates of growth (16, 17). From an applied standpoint, growth in early life has been linked to developmental and health outcomes across the life course such as childhood obesity (18); childhood adiposity; and age at menarche (19).

The model that has been most frequently used to identify the infancy-childhood growth transition (ICT) is the infancy-childhood-puberty (ICP) growth model of (20), which centered the identification of human growth transitions within the context of the hormonal regulation of growth. The three identified phases of growth are described as overlapping and continuous, in that the physiological regulation of each stage "layers" with time and summarily contribute to the growth patterns seen during each stage as well as the ultimate outcome (adult stature). In this model, the infant stage of growth is described as a decelerating continuation of the fetal growth trajectory, largely under the control of insulin and the insulin-like growth factors as mediators of nutritional status. Karlberg proposed that the childhood transition, where the rapidly decelerating growth of infancy switches over to the steadier state and growth rate plateau of childhood, is initiated by the endogenous regulation of growth hormone (GH), starting toward the end of the first year of life, and signaled by the so-called infancy-childhood spurt (ICS). During the puberty phase of Karlberg's model, the hypothalamic-pituitary-gonadal axis further modifies the pulsatile release of GH, and the pubertal growth spurt brings an individual to their final adult stature.

From a clinical perspective, this model is important because it emphasizes the continuity of the growth process and the multiple physiological inputs in shaping growth patterns over time (although these are necessarily still simplified). Understanding variation in the timing of transitions, and underlying causes, could be of great import if it could be demonstrated that this variation is related to factors that might be modified to positively affect growth, particularly before an individual has found the growth trajectory that they will track, or their growth "canal" (21). In addition, the relationship of the timing of the ICT to the presence or absence of catch-up growth in infancy and childhood could be important for understanding not only growth outcomes but also associated health-related outcomes (18). It has been proposed that individuals who experience adverse conditions in early life have insufficient energetic reserves necessary for the ICS, and so the transition to childhood is delayed [DICT, (22)]. Alternatively, in the context of infancy as a phase of rapid growth where growth rate is dependent on nutritional status, it is possible that a truncated period of infancy and an earlier onset of childhood could represent an adaptive developmental response in the case of nutritional insufficiency, or of frequent morbidities directing the investment of energetic resources away from growth and toward immune function and repair. Although body growth rates are lower during childhood than infancy, metabolic costs associated with brain maturation reach a peak in middle childhood (23); by implementing a low-cost somatic growth strategy during childhood, and/or by cutting short infancy and shifting into childhood earlier in development, an individual may free up more capital to support the expensive development of the brain. In the short-term, this could result in outcomes such as stunting; however, later phases of rapid development (i.e., adolescence) may offer opportunities for catching up before the attainment of final adult height.

The ICP model has been implemented in the majority of ICT studies to date, but this method is not without its drawbacks. Perhaps most importantly, although growth data are modeled using the ICP, the ICT itself is identified through visual inspection of plotted growth curves. While previous studies have reported a high degree of interobserver agreement using this method (24), it remains a subjective approach. Importantly, a short-term acceleration in growth velocity just prior to the onset of childhood is the basis of both the (visual) identification of the transition itself, and the framework for understanding the effects of a DICT. The ICT/ICP method has been used in clinical contexts to understand the relationship of a delay in the transition to growth outcomes. For example, in one study of children with idiopathic short stature (ISS), a DICT of around 4 months corresponded to a significantly reduced growth rate during the first 2 years of life (25). The aim of this particular study was to determine the optimal timing of GH therapy in order to maximize outcomes; however, it should be emphasized that the growth patterns of these children, although not necessarily coupled with hormone dysfunction, cannot be taken as representative of broader growth patterns within the larger population from which they were drawn.

This quasi-pathological perspective is found much of the literature on ICT/DICT, yet it is offered as a metric that might be applied to help understand "…the main mechanism resulting in short stature in children living in poor areas of developing countries (p. 6, 21)." This proposes ICT as plastic and significantly influenced by environment; but, other studies suggest a relatively low contribution of the external environment to the timing of the transition [i.e., 28% total variance explained, (26)], and the importance of genetic factors [i.e., mid-parental height, (24)]. Some of these inconsistencies may result from the conflation of the ICT with the ICS, and the associated attempts to disentangle genetic vs. environmental effects on a developmental event (ICS) vs. a transition phase (ICT). One longitudinal study of the ICS in Dutch infants confirmed a transient growth acceleration at around 9 months of age, although the authors caution that this does not justify the construction or use of the ICP as a reference (27). Additionally, the frequency of anthropometric measurements used in ICT studies to date ranges between eight times within the first year of life (24) to nine times within the first 3 years of life (25); this raises questions regarding the minimum number of measurements needed to confidently identify transient growth accelerations in early life.

In 2016, Cole and colleagues published a study that tracked weight centile crossing in UK infants, using two large longitudinal cohorts [Widdowson and Cambridge Infant Growth Study (CIGS), (28)]. The aim of this study was to better understand how previous weight centile crossing predicts future weight gain, and as part of this aim the investigators characterized the correlation structure of monthly weight for age z-score (WAZ) deviation (i.e., centile crossing) by assessing whether the direction of month-to-month change in WAZ was influenced by the direction of WAZ change in a prior time interval. Through application of this method, they identified two main and sequential patterns of growth feedback in infants in both of the UK cohorts: positive feedback (represented by positive correlations between successive deviations, indicating similar direction of centile crossing in each pairs of months analyzed) during the first few months, followed by negative feedback (indicated by negatively correlated successive deviations, and illustrative of growth moving in different directions across the pairs of months analyzed) in the last half of the first year of life. These complementary modes of feedback (28), propose, work together to canalize growth within a particular range of centiles, and awareness of this underlying structure is important for clinicians who are trying to predict and evaluate growth. Following the period of negative feedback in the latter half of the first year of life, the authors further propose that an additional shift in the correlation structure—when the correlations between adjacent monthly WAZ deviations break free of the negative correlation/negative feedback loop and approaches zero—could represent a shift from the infancy stage of growth to the childhood stage of growth (28). In both UK infant cohorts, correlation coefficients between adjacent monthly WAZ deviations were most strongly positive between 3 and 4 months of age ($R = 0.3$), and then decreased reaching a nadir at around 10–11 months ($R = -0.3$); at around 12 months, correlations were close or projected to be close to zero, and this was suggested by the authors as possibly being indicative of the ICT. Using this method, the ICT is identified as taking place later than previously identified in other cohorts from similar populations, using length and the ICP model (∼12 vs. ∼9 months, reviewed above). The authors note that their findings and implications may not apply in populations with higher frequencies of growth disruption due to chronic infection or malnutrition.

Here, we use the approach described by Cole et al. (28), and summarized above, to identify the ICT in a cohort of Gambian infants based on detailed longitudinal weight growth data. Our aims are to both build context for understanding variation in this transition and to specifically investigate the timing of the transition in relationship to infant sex and birth seasonality. The infants in this study live in the West Kiang region of The Gambia, a rural subsistence farming community of savanna and farmland. The annual wet season, from July to October, is characterized by a decline in food stores, an increase in physical labor associated with farming, and a rise in morbidities such as malaria, bacterial infections, and environmental enteropathy especially affecting children under 3 years of age. The dry season, from November to June, brings an increased food supply, less physical labor, and lower rates of morbidity. These factors contribute to variation in growth patterns and health outcomes in individuals living in this region (29–31). Based on prior ICT studies, we hypothesize that Gambian infants should show a delayed ICT compared to UK infants; because our analysis is limited to the first year of life, we specifically hypothesize that we should not be able to identify an ICT in our sample if it is delayed relative to UK infants (where the ICT was identified at ∼12 months). We further hypothesize a seasonal effect on the timing of the ICT.

MATERIALS AND METHODS

The HERO-G Study

This study uses observational data collected as part of a longitudinal cohort study looking at the Hormonal and Epigenetic Regulators of Growth (HERO-G). The primary focus of HERO-G is infant growth from birth to 2 years of age; data were recorded every other day for the first 12 months and additional measurements were recorded at 18 and 24 months. The full HERO-G protocol is described elsewhere (32). The data included in this analysis are limited to the first year of life because it is focused on monthly deviations. To include the 18 and 24-months data would require interpolation to derive monthly values across the second year of life, and this is not warranted or appropriate for this particular analytical approach. Ethical approval for the study was given by the joint Gambia Government/Medical Research Council (MRC) Unit The Gambia Ethics Committee (SCC 1313v3), with additional approval from the University of Colorado Institutional Research Board (protocol number 13-0441). Prior to the start of the study, community approval was obtained from each participating village, and written, informed consent was obtained from each participating family.

Infant Anthropometry

Following their naming ceremony at 1 week of age, infants were seen every other day in their home village for anthropometric measurements until they reached 1 year of age. At each home visit, field workers measured infant weight according to standard protocols. Infants were undressed and weighed using a Seca 336 digital weighing scale. Weights were recorded to the nearest 10 g. Scales were calibrated each day prior to measurement, and weights were recorded in triplicate.

Data Treatment and Analysis

Our analysis follows that of Cole et al. (28), wherein we examine patterns of monthly WAZ deviation correlations in order to identify shifts in patterns of correlation (i.e., negative and positive feedback) as well as determine at what point these feedback patterns indicate a shift to a new phase of growth (ICT) as correlation coefficients approach zero following the lowest negative correlation value (nadir). We used the average of our triplicate weight measurements collected every other day, after removing within-day and between day outliers. We define within-day outliers as any measurement which is farther than 0.15 kg away from the other two measurements. If no two measurements are within 0.15 kg of each other, we do not use data from that day. We define between day outliers as any day where the average weight is >1 kg different from the average of the weight on the neighboring days. Weights were converted to age- and sex-adjusted z-scores using WHO growth standards and references (33, 34).

After removing outliers, we had data coverage sufficient for this analysis from 212 infants (99 female, 113 male). We utilized the increased measurement frequency of our data by using averages of 7-days windows. Specifically, we filtered the data down to 12 adjacent monthly 7-days windows. The windows were centered at the following ages (in days), 12 + i(30), i = 0,...,11. We then computed the average WAZ (z_i), which were calculated as the average of the z scores in the ith 7-days window for each individual. Next, we computed the deviations (d_i), which are the difference in adjacent z_i and are defined by,

$$d_i = z_i - z_{i-1} \qquad i \in (1, 2, \ldots, 12)$$

Finally, to test the significance of the correlation between adjacent d_i we used the R function cor.test (35). The cor.test function computes the Pearson correlation coefficient using all pairwise complete pairs of the data and then performs a one sample *t*-test to determine whether or not the correlation is significantly different than 0. The Pearson correlation ($r_{i,i-1}$) coefficient between adjacent deviations d_i and d_{i-1} is defined by,

$$r_{i,i-1} = \frac{\sum_{k=1}^{n}\left(d_{i,k} - \overline{d_i}\right)\left(d_{i-1,k} - \overline{d_{i-1}}\right)}{\sqrt{\sum_{k=1}^{n}\left(d_{i,k} - \overline{d_i}\right)^2}\sqrt{\sum_{k=1}^{n}\left(d_{i-1,k} - \overline{d_{i-1}}\right)^2}}$$

The Pearson correlation coefficients $r_{i,i-1}$ and associated *p*-values reported in this paper were all computed using the cor.test function. In all figures the correlations are plotted at the midage of the two periods over which the value is computed. We calculated correlations for (1) all individuals, (2) female and male infants separately, and (3) wet (June through October) and dry (November through May) season births separately.

RESULTS

Summary Statistics

Summary statistics for Gambian monthly WAZ and monthly changes in WAZ are shown in **Table 1**, together with the same data from the UK cohorts (from 26), and patterns of the three groups are illustrated in **Figure 1A**. In Gambian infants, the mean WAZ increases during the first few months of life (albeit a slight increase on a negative WAZ value), at the same time that UK infant WAZ decreases. Similarly, WAZ decreases following ∼4 months of age in Gambian infants while it increases at the same time period in UK infants. When all Gambian subjects are combined across categories of sex and season of birth, the mean WAZ increases from −0.7 in month 1 to −0.6 in months 2 and 3, and −0.5 in month 4. It stays close to this value in months 5 and 6 (−0.6), and then declines starting at 7 months of age, down to −1.0 at 10–12 months of age. The mean change in WAZ was positive for the first month but zero for months 2–4, negative in months 5–10, and back to zero at month 11. The SD for monthly changes in WAZ maintained at 0.3 for most months (0.4 in month 1). In Gambian infants, we see consistent moderate variation across the first year of life, whereas there was more variation in 0–6 months compared to 6–12 months in UK infants. Compared to the Widdowson and CIGS results, the HERO-G WAZ scores are lower, and the WAZ deviations and WAZ deviation SDs are smaller.

Correlation Patterns—Entire Dataset

Figure 1B shows the correlations between pairs of monthly WAZ deviations during the first year in all HERO-G infants together. The correlations are plotted (for all figures) at the middle of the two adjacent periods, meaning the correlation between deviations $d_i = z_{i+1} - z_i$ and $d_{i+1} = z_{i+2} - z_{i+1}$ is plotted at the center of the window over which z_i was calculated. The correlations for adjacent monthly deviations start at 0.37 at 1 month, decrease to 0.27 at 2 months, increase slightly to 0.33 at 3 months, then decrease back to 0.25 at 4 months (**Table 2**). These correlations are all significant ($P < 0.001$). At 5 months, the correlations decrease sharply but then rebound at 6 months to 0.18 ($P < 0.05$). Following this the correlations plummet to the nadir of −0.27 at 7 months ($P < 0.001$). After the nadir, correlations increase to −0.2 at 8 months ($P < 0.05$), and rise to just above zero (0.04, ns) at 9 months, after which they decrease again to −0.09 (ns). The HERO-G deviation correlation pattern differs from that seen in the Widdowson and CIGS cohorts in a few ways. First, the peak correlation coefficient is at the earliest time point (1 month) in Gambian infants, vs. 3 months in UK infants. In relationship to this, there is a clear and consistent pattern of increasing correlations across the first 3 months in UK infants, whereas correlations decrease then increase in Gambian infants across this same time period. Second, while there are clear periods of 'catch-up' (positive feedback—birth to 3 months) and 'catch-down' (negative feedback −4-11 or

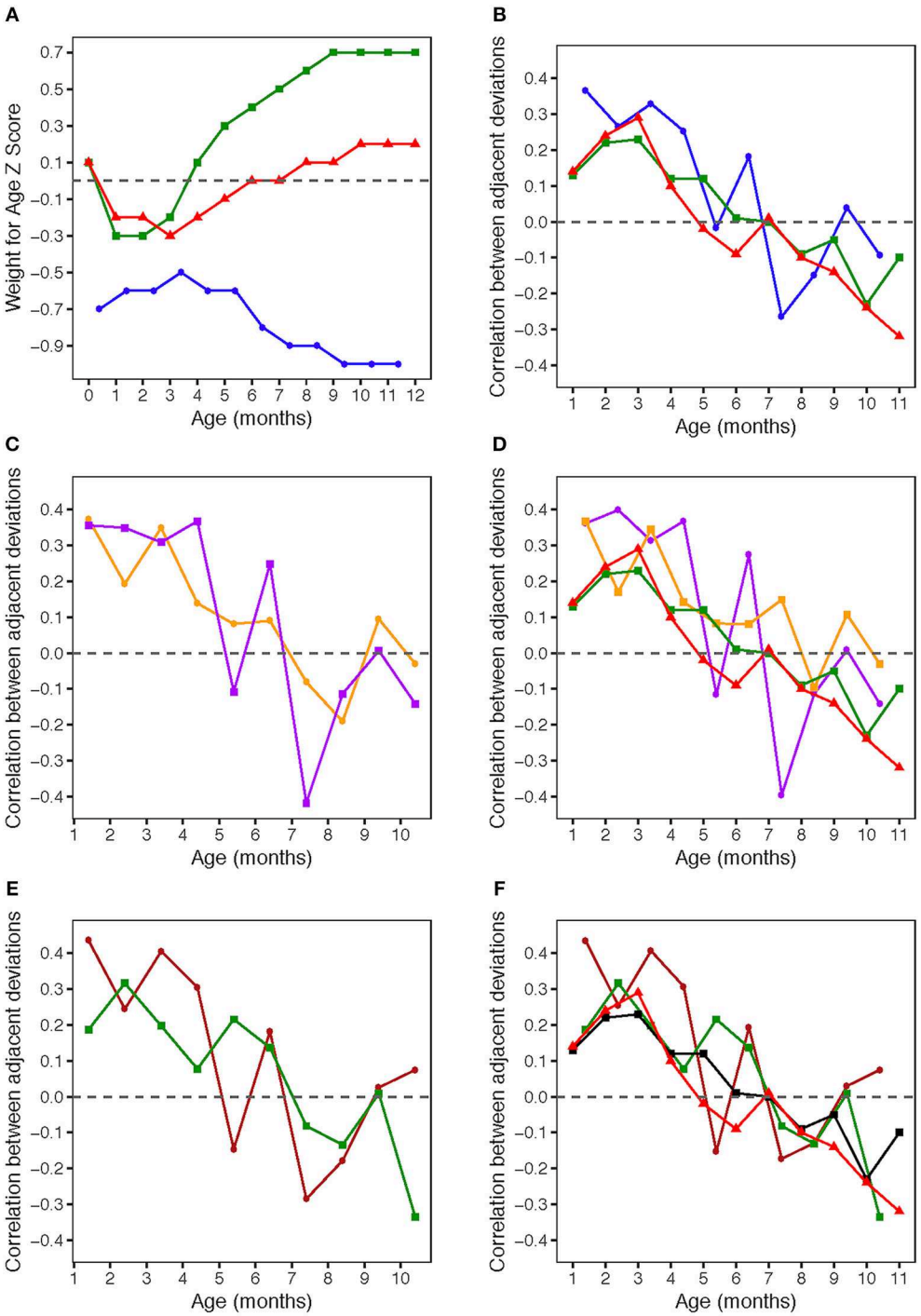

FIGURE 1 | (A) Weight for age z-scores (WAZ) by age. WAZ means and standard deviations given in **Table 1**. Blue circles: HERO-G infants; Green squares: Widdowson cohort; Red triangles: CIGS cohort. Widdowson and CIGS data from Cole et al. (28). **(B)** Correlations by age between adjacent pairs of WAZ deviations. Correlations were computed using data from every available subject. The sample sizes for each correlation are given in **Table 2**. Blue circles: HERO-G infants; Green squares: Widdowson cohort; Red triangles: CIGS cohort. Widdowson and CIGS data from Cole et al. (28). **(C)** Correlations by age between adjacent pairs of WAZ deviations. The sample sizes for each correlation are given in **Table 2**. Orange circles: female HERO-G infants; Purple squares: male HERO-G infants. **(D)** Correlations by age between adjacent pairs of WAZ deviations. Orange circles: female HERO-G infants; Purple squares: male HERO-G infants; Green squares: Widdowson cohort; Red triangles: CIGS cohort. Widdowson and CIGS data from Cole et al. (28). **(E)** Correlations by age between adjacent pairs of WAZ deviations. The sample sizes for each correlation are given in **Table 2**. Brown circles: HERO-G infants born in the dry season; Green circles: HERO-G infants born in the wet season. **(F)** Correlations by age between adjacent pairs of WAZ deviations. Brown circles: HERO-G infants born in the dry season; Green circles: HERO-G infants born in the wet season; Green squares: Widdowson cohort; Red triangles: CIGS cohort. Widdowson and CIGS data from Cole et al. (28).

TABLE 1 | Average weight z score (WAZ) and average WAZ deviations by months, comparison between HERO-G and Widdowson and CIGS cohort data, reproduced from [a]Cole et al. (28).

HERO-G data				Widdowson data[a]			CIGS data[a]	
Age months	***n***	**Weight *z* score**	**Weight *z* score deviation**	***n***	**Weight *z* score**	**Weight *z* score deviation**	***n***	**Weight *z* score**	**Weight *z* score deviation**
1	194	−0.7 ± 0.9	0.1 ± 0.4	1,040	0.1 ± 1.1	−0.4 ± 0.6	253	0.1 ± 1.0	−0.3 ± 0.6
2	198	−0.6 ± 0.9	0.0 ± 0.3	1,080	−0.3 ± 0.9	0.0 ± 0.4	254	−0.2 ± 0.9	−0.1 ± 0.4
3	201	−0.6 ± 1.0	0.0 ± 0.3	1,079	−0.3 ± 1.0	0.2 ± 0.4	255	−0.2 ± 0.9	0.0 ± 0.3
4	192	−0.5 ± 1.0	0.0 ± 0.3	1,072	−0.2 ± 0.9	0.2 ± 0.3	253	−0.3 ± 0.9	0.1 ± 0.3
5	193	−0.6 ± 1.0	−0.1 ± 0.3	1,071	0.1 ± 0.9	0.2 ± 0.3	251	−0.2 ± 0.9	0.1 ± 0.3
6	197	−0.6 ± 1.0	−0.1 ± 0.3	1,065	0.3 ± 0.9	0.1 ± 0.2	251	−0.1 ± 0.9	0.1 ± 0.2
7	194	−0.8 ± 1.0	−0.1 ± 0.3	1,054	0.4 ± 0.9	0.1 ± 0.2	247	0.0 ± 0.9	0.0 ± 0.2
8	192	−0.9 ± 1.0	−0.1 ± 0.3	1,043	0.5 ± 0.9	0.1 ± 0.2	251	0.0 ± 0.9	0.1 ± 0.2
9	186	−0.9 ± 1.0	−0.1 ± 0.3	1,009	0.6 ± 0.9	0.1 ± 0.2	250	0.1 ± 0.9	0.0 ± 0.2
10	182	−1.0 ± 1.0	−0.1 ± 0.3	969	0.7 ± 0.9	0.0 ± 0.2	247	0.1 ± 0.9	0.1 ± 0.2
11	187	−1.0 ± 0.9	0.0 ± 0.3	913	0.7 ± 0.9	0.0 ± 0.2	245	0.2 ± 0.9	0.0 ± 0.2
12	187	−1.0 ± 0.9	NA	852	0.7 ± 0.9	0.0 ± 0.2	247	0.2 ± 0.9	0.0 ± 0.2

12 months) in the UK infants, as defined by Cole et al. (28), there are no such clear corresponding phases in the Gambian infant pattern. Instead, there are several shorter-term shifts from positive to negative feedback, although the overall direction of the correlations (moving from positive to negative values over time), and the range of correlation coefficients themselves is similar. Third, the correlation coefficient approaches zero at different ages; based on the full Gambian dataset, this takes place around 9 months of age, and in the Widdowson cohort this takes place closer to 11 months. This shift is not yet seen in infants in the CIGS cohort although (28) estimate that this would occur around 12 months of age.

Correlation Patterns—Infant Sex

When separated by infant sex (female $n = 99$, male $n = 113$), different patterns of WAZ deviation correlations in female and male infants become apparent (**Figure 1C**). Female infant WAZ deviation correlations shift during the first few months of life, from a peak zenith of 0.37 at 1 month, to 0.2 at 2 months, to 0.35 at 3 months. At 4 months, the deviation correlation drops to 0.15, and stays around 0.1 through months 5 and 6 before dropping below zero at 7 and 8 months. The nadir for female correlations is −0.2 at 8 months, and increases to 0.1 at 9 months, finally dropping down again to just below zero at 10 months. Only months 1 and 3 of the female deviation correlations are significant ($P \leq 0.001$). The male pattern differs from the female pattern in a few respects. Deviation correlations remain near constant during the first 4 months (0.36, 0.35, 031, 0.37, all significant at $P \leq 0.001$), reaching a zenith at 4 months. Across this same time period, female deviation correlations shift several times (**Figure 1C**). Male deviation correlations drop precipitously at 5 months to −0.11, and rebound to 0.25 at 6 months ($P < 0.05$). Female values remain fairly constant during the same time period. The male nadir (−0.42) is reached at 7 months ($P < 0.001$), and correlations move in a positive direction in months 8 (−0.11) and 9 (0.01), where it approaches zero (0.01) before dropping down to −0.14 at 10 months. The female nadir (−0.19) is reached shortly after 8 months, and then the correlation pattern tracks that of males in months 9–10. Overlaying male and female Gambian infant patterns on those of UK infants (28) illustrates that while the overall direction of deviation correlations over time is similar across all groups, the female HERO-G infant pattern and range of correlation coefficients is more similar to those of UK infants than the male HERO-G infant pattern (**Figure 1D**), especially between months 4–7.

Correlation Patterns—Infant Season of Birth

Deviation correlations computed separately for infants born during the dry season ($n = 138$) and the wet season ($n = 74$) are plotted in **Figure 1D**. Several differences are apparent in the pattern of correlations between birth seasons. From 1 to 2 months, infants born in the wet season initially catch up (0.19 to 0.32), while infants born in the dry season initially catch down (0.44 to 0.24), then both shift in opposite directions from 2 to 3 months, with infants born in the dry season catching up (0.24 to 0.41), and those born in the wet season catching down (0.32 to 0.20). All of these correlations between adjacent deviations are significant for infants born in the dry season ($P < 0.01$), while only the correlation illustrating catch-up between months 1 and 2 for infants born in the wet season is significant ($P < 0.01$). Deviation correlations decrease from months 3 to 4 in infants born in both seasons (dry season: 0.41 to 0.30; wet season: 0.2 to 0.08). At 5 months patterns diverge again, with a positive shift for infants born in the wet season (0.22) and a steep drop in infants born in the dry season (−0.15). At 6 months, deviation correlations are very similar for both groups (dry season: 0.18; wet season: 0.14), and both drop below zero at 7 months (dry season nadir: −0.29; wet season: −0.08). Between 8 and 9 months, infants born in both seasons move in a positive direction again (dry season: −0.18 to 0.03; wet season −0.13 to 0.01); at 9 months the deviation correlation for both groups is

TABLE 2 | Correlations by age between adjacent pairs of weight z score deviations measured over 30 days and associated *p*-values for the full HERO-G dataset analyzed and for each subset of the data considered.

	All ($n = 212$)		Female ($n = 99$)		Male ($n = 113$)		Born in dry season ($n = 138$)		Born in wet season ($n = 74$)	
Age (months)	**Corr**	***p*-value**	**Corr**	***p*-value**	**Corr**	***p*-value**	**Corr**	***p*-value**	**Corr**	***p*-value**
1	0.37	0.0000	0.37	0.000	0.36	0.000	0.44	0.00000	0.19	0.133
2	0.27	0.0002	0.19	0.067	0.35	0.000	0.24	0.00599	0.32	0.009
3	0.33	0.0000	0.35	0.001	0.31	0.001	0.41	0.00000	0.20	0.118
4	0.25	0.0004	0.14	0.205	0.37	0.000	0.30	0.00055	0.08	0.543
5	−0.02	0.8132	0.08	0.460	−0.11	0.276	−0.15	0.10052	0.22	0.092
6	0.18	0.0119	0.09	0.399	0.25	0.012	0.18	0.03886	0.14	0.290
7	−0.27	0.0002	−0.08	0.446	−0.42	0.000	−0.29	0.00109	−0.08	0.532
8	−0.15	0.0472	−0.19	0.084	−0.11	0.269	−0.18	0.04822	−0.13	0.324
9	0.04	0.5981	0.09	0.394	0.01	0.949	0.03	0.78016	0.01	0.949
10	−0.09	0.2212	−0.03	0.791	−0.14	0.174	0.07	0.42418	−0.34	0.010

close to zero. At 10 months, the patterns diverge once again, as deviation correlations for infants born in the dry season increases slightly (0.07), and that for infants born in the wet season drops and reaches its minimum (−0.34). The deviation correlation pattern of HERO-G infants born in the wet season is more similar to that of the Widdowson and CIGS cohorts than HERO-G infants born in the dry season (**Figure 1E**); patterns of the three groups are almost identical across the first 4 months. The pattern of HERO-G infants born in the wet season diverges between 4 and 6 months, suggestive of positive feedback and catch-up growth, while the CIGS and Widdowson infants continue to catch down during this time. The patterns of all four groups are most similar between 7 and 9 months (**Figure 1F**). HERO-G infants born during the dry season show a pattern of increasing deviation correlations toward the end of the first year, similar to what is seen in the Widdowson cohort; the deviation correlations in HERO-G infants born in the wet season, like infants in the CIGS cohort, do not increase past the nadir that falls on the last time point.

DISCUSSION

We analyzed monthly WAZ deviation correlations across the first year of life, applying the method of Cole et al. (28), in order to identify the infancy-childhood transition in rural Gambian infants. Cole et al. (28) identified two 'phases' of deviation correlations within the first year of infant life: (1) positive feedback during the first few months, and (2) negative feedback from 6 to 10/11 months. These feedback phases were proposed as the mechanism by which an individual finds and tracks their growth canal. Further, Cole et al. (28) proposed that the point after the nadir of the negative feedback phase at which the correlations approach zero could represent a 'release' from the negative feedback prior to that point, and a shift into a new phase of growth (i.e., childhood via the ICT).

We hypothesized, based on prior work on the ICT using the ICP model, that (1) the ICT in Gambian infants as a group would be delayed compared to the two UK infant cohorts analyzed by Cole et al. (28), and (2) the ICT in Gambian infants born in the wet season would be delayed (DICT) relative to the ICT in infants born in the dry season. The results of our analysis did not support the first hypothesis; based on the ages at which adjacent monthly deviation correlations approached zero following a nadir, the HERO-G infants go through an ICT earlier than either the Widdowson or CIGS cohorts (∼9 months of infant age compared to ∼12 months).

The pattern of deviation correlations in infants born in the wet season was such that the nadir of the correlations fell on our last calculable correlation (10 months of infant age), so we were unable to determine whether and when after that point deviation correlations might have approached zero.

However, the deviation correlations were close to zero at 9 months of age, the time point prior to the wet season birth nadir, at the same time as they were close to zero in infants born in the dry season. Our next measurement following 12 months of age in the HERO-G infants was 18 months, and interpolation would be required to derive monthly WAZ scores, and calculate deviation correlations; interpolation of monthly values from biannual known data points is not appropriate in this case, and therefore we are unable to further test this hypothesis with data from this cohort. Like infants born in the wet season, the CIGS cohort infants (28) did not show an increase in WAZ deviation correlations following the nadir, although based on later measurements it was concluded that the transition would have likely followed the nadir at around 12 months. It may also be the case that multiple rounds of growth faltering and catch-up in infants born in the wet season would complicate or obscure patterns of deviation correlations calculated with this method. We also did not find any effect of sex on the timing of the ICT, although our patterns of deviation correlations suggest that males have an earlier correlation nadir than females, and take 2 months following the nadir to approach a zero correlation (females take one). The overall pattern of deviation correlations in HERO-G females was more similar to that of UK infants compared to HERO-G males. Only two of the ten female correlations were significant, while six of ten were significant for males; in general, correlations were also higher in males compared to females.

That Gambian infants transition to childhood earlier than UK infants, rather than being delayed, runs counter to previous ICT analyses that use the ICP model to identify the ICT. There are a couple of potential methodological reasons why this might be so. First, we used weight and adjacent monthly deviation correlations of WAZ to identify the ICT, instead of length measurements as used by the ICP model. It is probable that shifts in weight precede shifts in length and as such appear at earlier chronological ages. Cameron (36) notes that weight is a more "eco-sensitive" characteristic than length, since it can change rapidly over short periods of time based on various acute stressors. The linkages between short-term episodes of wasting, and longer-term stunting outcomes were examined in a large (n > 5,000 individuals) data set derived from regular growth monitoring of Gambian children (37). Results demonstrated that episodes of wasting were predictive of stunting, and suggest that the outcome of stunting is an adaptive phenotype in the context of episodes of wasting in the first year of life. However, even if a weight-based ICT can be conceived to causally precede a length-based ICT, this would still imply that a length-based ICT in Gambian infants would be proportionally advanced relative to a length-based ICT in UK infants. Second, the diagnostic indicator of an ICT using the ICP model is a transient acceleration in length velocity, identified through visual inspection of individual growth curves. The basis for using the ICS as a marker for the ICT is the proposal that an infant must have a certain amount of energetic reserve to transition into childhood from infancy, and without it the infancy-childhood spurt is not possible, causing the transition to be delayed. Using this method, studies have identified an ICS and the ICT in infants who have had as few as four measurements taken during the first year of life; this raises questions about whether the ICS is a real biological phenomenon or an artifact of the ICP model parameters. This possibility notwithstanding, it is interesting to note that in the full HERO-G dataset, as well as that calculated separately for males and infants born in the dry season, WAZ deviation correlations show a brief rebound pulse at 6 months of age, crossing from a negative to positive correlation before shifting negatively again. This might represent a transient acceleration in weight, potentially preceding a transient acceleration in length.

More generally, acceleration in developmental timing is just as plausible a response to adverse environmental conditions as a delay; developmental rate and mortality risk interact and form the basis for individual trade-offs between survival, immune function, physiological efficiency, and so on, as individuals navigate their course to maturity (38). Life history theory enumerates the many potential contributors to shaping an individual's life course, including the rate of development and timing of developmental events. Growth rate and growth duration are linked to age at first reproduction. Growing for a longer period of time and ending up as a larger-bodied adult with a later age at reproductive maturation, is one way to achieve higher fertility and decreased mortality of offspring for populations with low sources of extrinsic mortality. Ceasing growth early, and initiating reproduction at a smaller adult size, offers an advantage for high-mortality environments in that it provides a better chance at reproducing prior to death. Therefore, population- and species-level differences in growth patterns and resulting terminal size are shaped by past and current environments, with both earlier- and later-maturing pathways having their respective costs and benefits. A large body of literature discusses accelerated development as an adaptive response to indicators of a high-mortality risk environment. This has been shown in animals ranging from insects (39) to primates (40). In humans, a short stature phenotype seen in several populations globally (e.g., the Aeta, Agta, Batek, Biata) has been proposed to result from a shortened growth period of slower growth, facilitating earlier reproductive maturation in high mortality-risk environments (41). Conversely, previous research in The Gambia has demonstrated that taller mothers—indicative of a longer period of growth—have lower offspring mortality (42). Other authors have suggested that the tempo of maturation is shaped by two key transitions: the ICT, which sets the pace for height, and the childhood-juvenility transition (the ICP model subsumes juvenility within childhood), which offers another opportunity for individuals to recalibrate their tempo based on environmental influences during that time (43). Taken together, this body of work suggests that it is possible that in populations that have experienced challenging environments/stressors in early life for generations, accelerating the age at onset of childhood is an adaptive tradeoff that effectively allows an individual to conserve resources to be channeled to brain development during this critical phase of development, while somatic growth deficits can be caught up later in growth. Recent analysis of the full course of development in The Gambia has demonstrated catch-up growth during an extended adolescence can ameliorate much of the deficit incurred via growth stunting by 2 years of age, especially in girls (44).

In summary, using a method to identify the ICT based on WAZ deviation correlations within the first year of life, we have identified this transition to take place at around 9 months of age in the HERO-G cohort of rural Gambian infants. This is approximately 3 months earlier than the ICT was suggested to take place in two cohorts of UK infants, based on the same method. This suggests that the ICT in Gambian infants is accelerated, instead of delayed as would be predicted based on previous analysis of the ICT using the ICP model (20). Further, we found different patterns of age-related correlations across groups split by sex and season of birth, suggesting that this approach might be used in other populations to better understand how different intrinsic and extrinsic factors shape the pattern of correlations across the first year of life. Ultimately, a truncated infancy growth period and an associated accelerated timing of the ICT may be linked to a trade-off for Gambian infants, whereby cutting short the high growth-rate, high-cost infancy stage, and transitioning to childhood earlier permits allocation of resources to brain development without simultaneous drain of these resources by rapid body growth.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article are stored on the Open Science Framework (OSF),

doi: 10.17605/OSF.IO/5ND3Y, and at the time of article submission are available on request and subject to review. These data will be made publicly available no later than July 1, 2021. Requests to access the datasets should be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the joint Gambia Government/MRC Unit The Gambia Ethics Committee (Project number SCC1313v3) University of Colorado Boulder Institutional Review Board (protocol number 13-0441). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

RB, NA, DD, KO, AP, and SM conceived of and designed the HERO-G study. SD supervised and coordinated field staff. AF organized and maintained the study database. FS supervised ultrasonography and midwifery. GO and EV performed the statistical analysis. RB wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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REVIEW
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Life History Transitions at the Origins of Agriculture: A Model for Understanding How Niche Construction Impacts Human Growth, Demography and Health

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Over recent millennia, human populations have regularly reconstructed their subsistence niches, changing both how they obtain food and the conditions in which they live. For example, over the last 12,000 years the vast majority of human populations shifted from foraging to practicing different forms of agriculture. The shift to farming is widely understood to have impacted several aspects of human demography and biology, including mortality risk, population growth, adult body size, and physical markers of health. However, these trends have not been integrated within an over-arching conceptual framework, and there is poor understanding of why populations tended to increase in population size during periods when markers of health deteriorated. Here, we offer a novel conceptual approach based on evolutionary life history theory. This theory assumes that energy availability is finite and must be allocated in competition between the functions of maintenance, growth, reproduction, and defence. In any given environment, and at any given stage during the life-course, natural selection favours energy allocation strategies that maximise fitness. We argue that the origins of agriculture involved profound transformations in human life history strategies, impacting both the availability of energy and the way that it was allocated between life history functions in the body. Although overall energy supply increased, the diet composition changed, while sedentary populations were challenged by new infectious burdens. We propose that this composite new ecological niche favoured increased energy allocation to defence (immune function) and reproduction, thus reducing the allocation to growth and maintenance. We review evidence in support of this hypothesis and highlight how further work could address both heterogeneity and specific aspects of the origins of agriculture in more detail. Our approach can be applied to many other transformations of the human subsistence niche, and can shed new light on the way that health, height, life expectancy, and fertility patterns are changing in association with globalization and nutrition transition.

Keywords: life history theory, origins of agriculture, population growth, niche construction, nutrition transition, diet, infectious disease, trade-off

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INTRODUCTION

Over recent millennia, human populations have regularly reconstructed their own subsistence niches, a practice known as "niche construction" (1). Arguably the most important such transformation occurred with the origins of agriculture. From around 20,000 years ago in the Levant, for example, populations began to aggregate in long-term settlements, and to systematically exploit wild grain (2) and produce new staple foods such as bread (3), which led to widespread domestication of plants and animals throughout the Near East (4). Over the past 10,000 years, the domestication of numerous species of plants and animals has occurred independently and in different ways in different parts of the world (5, 6), though a small proportion of humanity continues to practice hunting and gathering. Such domestication events also led to increased use of secondary animal products such as milk, which further led to the independent evolution of lactase persistence in some human populations (7). However, the adoption of agriculture is only one such example of niche construction. We can use the same conceptual approach to consider more recent societal transformations, such as industrialisation, or globalization and the ongoing nutrition transition. These transformations of the human niche are widely understood to generate both benefits and costs for human health.

Many of these transitions have been sufficiently rapid that the biological consequences cannot be attributed only, or even primarily, to genetic change. Rather, physiological and behavioural plasticity are also implicated. Various mechanisms of developmental plasticity are now understood to contribute to substantial variability in phenotype and health outcomes through the life-course. For example, variability in nutrition, growth rates, and exposure to infections in early life shapes many traits at later ages, including body size and composition, reproductive scheduling, and the risk of various diseases (8). The transitions associated with the origins of agriculture, and the domestication of animals and use of secondary animal products, were both transitions in the energetics of the human diet, where dietary shifts were characterized by more energetically-rich but less diverse sources of food and increased risk of famine. However, these subsistence shifts also involved more fundamental transformation of the human niche, for example by changing patterns of physical activity and reshaping exposure to predators and pathogens and social inequality (9).

Today, we face a paradox that apparent improvements in human living conditions, including economic growth and nutrition transition, are strongly associated with emerging epidemics of chronic non-communicable disease, such as obesity and cardiovascular disease (10). Moreover, while the burden of infection appeared to decline over the twentieth century (11) through the development of diverse forms of prevention and medical treatment, many pathogens are evolving resistance to drug therapies while new diseases can evolve (12, 13). The burden of infection faced by future human populations may therefore be more threatening, and there is an urgent need to understand how alterations to human subsistence niches impact our biology and health.

Here, we develop a conceptual framework based on evolutionary life history theory (14), and apply it to improve understanding of how human biology changed in ancestral populations in association with the origins of agriculture. In this article, we use this term to refer to the suite of domestication events of plants and animals that is highly variable temporally and geographically, but which fundamentally changed the human subsistence niche wherever it occurred. By focusing on patterns of change that occurred in a major past transformation of our subsistence niche, we may gain valuable new insight into what is happening in contemporary populations. The patterns of change that we describe are largely regulated by hormonal mechanisms and many occur during development, hence our framework offers a new perspective on the role of endocrinology, in particular pediatric endocrinology, in the evolutionary trajectory of our species.

It has long been recognised that the emergence of agriculture had profound effects on human biology, at the level of both populations and individuals. For example, the shift from foraging to farming was associated with major increases in population size in some places, demonstrated by the emergence of villages and urban settlements from 12,000 to 5,000 years before present (BP) in the Levant, China, India, and West Africa (5). Population growth in the pre-agricultural Palaeolithic is likely to have occurred at a very slow overall rate, subject to local boom-bust dynamics (15). In contrast, the transition to agriculture was associated with more systematic population growth (16, 17).

Exactly what stimulated the adoption of agriculture is controversial. Boserup (18) and Cohen (19) suggested that larger populations stimulated a need for agricultural production to meet food requirements. The main demographic change was not a reduction of mortality, but rather a decrease in the average inter-birth interval, so that any increases in mortality were over-compensated by rising fertility (16). However, a classic review of the literature by Cohen and Armelagos found many indications that health deteriorated in the early agricultural era (20). This perspective—that human populations expanded in size, despite living conditions actually worsening (20)—has become the dominant paradigm, however little attention has been directed to whether these parallel trends might have some deeper biological link.

In this review, we develop a new hypothesis to explain these trends: that the correlated changes in phenotype and population size reflect a reorganization of human life history strategy, to accommodate the composite change in ecological conditions provoked by niche construction (10). Changes in each of food supply and environmental risk are expected to impact life history strategy, especially when both factors change simultaneously. We first describe life history theory and summarise evidence for trade-offs between individual life history traits obtained from studies of contemporary human populations. We then consider how the onset of agriculture altered the human niche, impacting a series of selective pressures including energy supply, dietary diversity, and pathogen burden. We review evidence for life history trade-offs in the archaeological record, noting that these shifts are likely to have been variable and distributed over a range of timescales, depending on how the transition to agriculture

played out locally. Finally, we discuss how, if our hypothesis is correct, it may apply to other systematic shifts in living conditions that had an impact on human energetic ecology, such as industrialisation.

LIFE HISTORY THEORY AND PHENOTYPIC CHANGE

Life history theory offers unique opportunities for biologists to investigate phenotypic change in populations over time (14). The value of this theory is 2-fold—first, it models variability in phenotype in general, rather than individual traits, and second, it can address phenotypic variability or change that arises both through genetic adaptation, and also through mechanisms of plasticity, whether physiological, developmental, or behavioural (21).

Life history theory considers how organisms maximise their genetic fitness through harvesting resources from the environment, and investing them in a suite of biological functions throughout the life-course (14, 22). In theory, multiple currencies of resource allocation may be important, such as different nutrients (23), but in practice the theory gives priority to "energy" and "time" as the most important resources, and assumes that organisms making the best use of energy over their lifespan will receive the highest fitness payoffs (24).

The theory assumes that for any individual organism, the supply of energy is finite, and that allocating more energy to one function precludes its allocation to other functions (22). Traditionally, life history theorists focused on three competing functions, namely maintenance (M), growth (G), and reproduction (R) (22). Maintenance refers to keeping the body in good condition through diverse homeostatic process, thereby promoting longevity and maximising the future opportunities for reproduction. Growth refers to the process of development and maturation, and typically occurs prior to reproduction in most mammals. Reproduction refers to all processes involved in finding a mate, producing offspring and investing in them, and essentially allocates energy to the next generation. From an inclusive fitness perspective, investment in "reproduction" may incorporate patterns of social behaviour that benefit kin who share genes (25).

The principle of competition between these functions results in energy-allocation trade-offs between them at any given stage of life. Natural selection then favours the emergence of life history traits, and broader developmental or life-course strategies, that are shaped by such trade-offs. Each organism's life history can be summarized as a cumulative series of energy-allocation decisions, represented by a suite of developmental and reproductive traits. These include how fast and large to grow, how to address risks and defend against threats, and how to schedule reproductive effort (14).

In practice, however, we have argued that it is more appropriate that four life history functions be differentiated (21). Whilst "defence" (D) against pathogens and predators was initially considered to come under the general umbrella of maintenance (22), it is increasingly recognised that defence is subject to overt trade-offs against each of maintenance, growth, and reproduction (10). Both immune function and activating the "fight-or-flight" response to avoid predation reduce the availability of resources for other life history functions. In **Box 1** and **Figure 1**, we review the implications for life history theory of treating defence as a separate life history function, increasing the number of binary trade-offs that can be tested in empirical work.

Initially, life history theory was primarily used to explore phenotypic differences between species (30). The diverse selective pressures associated with any given ecological niche favour the emergence of broad species-specific energy allocation strategies, underpinned by genetic adaptation. Life history variability is assessed by considering a set of demographic and physical traits that can be readily assessed in any organism. For mammals, these traits include size at birth, time taken to reach maturity, the frequency of reproducing, the number of offspring produced per reproductive event, and the total lifespan (30).

The two main ecological factors driving life history trade-offs across species are the supply of resources (effectively, energy), and the risk of mortality (33). First, organisms subject to high mortality risk are unlikely to maximise fitness if they prolong the period of growth, instead selection favours earlier reproduction. Moreover, because of the high risk of mortality for each individual offspring, organisms in such environments should produce large numbers of offspring but allocate little parental investment to each. In this way, mortality risk inherently shapes life history traits such as physical growth, maturation rate, and reproductive scheduling (30, 32). Second, all other things being equal, a greater supply of energy allows individual organisms to grow bigger, or the number of offspring produced to be greater, or the investment per offspring to be increased, promoting offspring fitness. Again, therefore, local ecological productivity shapes life history traits.

Within species, genetic variability may also contribute to life history variability among individuals. For example, most life history traits in humans have been shown to have a component of genetic variability, demonstrated at the broader level by calculations of heritability and at more specific levels by the findings of genome-wide association studies (**Table 1**) (53).

In non-human animals, experimental support for the notion that natural selection shapes life history traits has been provided by elegant studies of small freshwater fish called guppies, living in the mountain streams of Trinidad (54). These studies clearly illustrate the influence of mortality risk on life history strategy. Typically, the streams have waterfalls that restrict predators to the lower reaches. Guppies living downstream, with a high risk of predation, grow faster, and start to breed earlier than those living upstream. Transplanting downstream guppies into the upstream environment resulted in a slower life history emerging across generations—the onset of reproduction was later, and fewer but larger offspring were produced. In contrast, introducing the predators upstream elicited a faster guppy life history strategy, indicated by earlier onset of reproduction. Further studies have shown that this variability is in part genetic, supporting the hypothesis that different life history strategies can evolve through genetic change in different environments (54).

BOX 1 | Incorporating defence as a separate function into life history theory.

Early work on life history theory considered that there were three competing functions (maintenance, growth, and reproduction) giving rise to three potential binary trade-offs (14, 22), as illustrated In **Figure 1A**. Particular attention was directed to the trade-off between reproduction and survival, whereby producing more offspring was assumed to reduce investment in homeostatic maintenance (e.g., through mechanisms such as oxidative stress), thereby accelerating ageing and shortening parental lifespan (26). For example, experimental studies in animals tested the effect of imposing a greater reproductive burden (e.g., augmenting brood size in birds) on parental lifespan (27), while observational analyses in humans tested for inverse correlations between fertility and lifespan (28, 29).

We propose that defence can be differentiated conceptually from maintenance as involving metabolic responses that respond to the activities of external organisms that threaten survival or fitness through predation or infection/parasitism. On this basis, defence manifests specifically as short-term responses to combat these external threats, and to repair any immediate damage to organs and tissue, with these responses necessarily precluding optimal investment in other life history functions. In contrast, the routine allocation of resources to preserving organs, tissues and immune function in good operating condition, in the absence of specific activities by predators, pathogens, or parasites, can be considered homeostatic maintenance.

Treating defence as a discrete life history function increases the number of binary trade-offs in the model from three to six, as illustrated in **Figure 1B.** This approach offers a richer conceptual framework for investigating adaptation to ecological conditions or change (note that the number of binary trade-offs can be further expanded by considering those across generations, as illustrated in **Figure 4**). We suggest that the value of this framework may be further enhanced by paying particular attention to trade-offs that manifest during development, as well as those occurring during adult life. For example, many of the most salient markers of growth (e.g., limb lengths) reach their final value at the start of adult life, meaning that the most important trade-offs involving these outcomes must have occurred during earlier stages of development. It has already been recognised that the effect of mortality risk on life history trade-offs varies according to the age of the organism (30), and we suggest that the same issue is relevant for growth, which for example has relatively high costs in infancy and adolescence but reduced costs during childhood and much lower costs during adult life (31).

In conventional life history theory, much attention has been directed to "extrinsic mortality risk" as a key factor shaping the likelihood of survival and lifespan. For example, the "disposable soma" theory assumes that the higher the risk of mortality, the lower the optimal level of investment in maintenance as the pay-offs are unlikely to be recouped (32). This approach expects an inverse association between mortality risk and lifespan. However, by differentiating defence as a discrete function, we can see that threats to survival and fitness can be countered by mounting specific responses to reduce the risk of mortality, but at a cost to the ability to invest in other functions. Not all infections directly threaten survival, but they can still demand expensive immune responses. Paradoxically, this scenario results in the potential to observe positive correlations between lifespan and markers of ill-health, as individuals manage to survive for longer, but in sub-optimal condition.

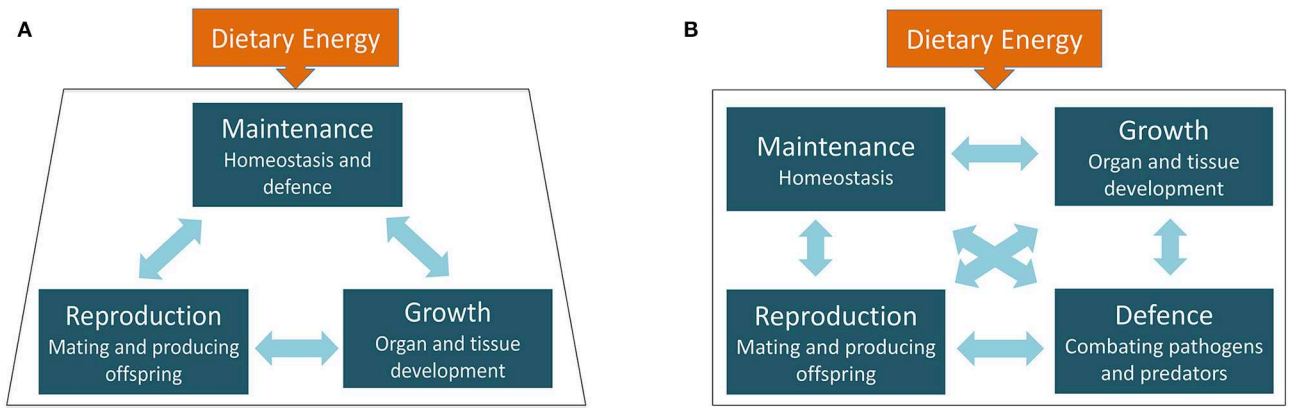

FIGURE 1 | The principle of life history theory, showing **(A)** the traditional 3-function model and **(B)** our expanded 4-function model. The arrows represent the binary trade-offs, between maintenance, growth and reproduction in the traditional model, and between maintenance, growth, reproduction, and defence in the expanded model.

Similar to work on other species, much research on human life history strategy has analysed the same set of demographic traits, i.e., size at birth, growth and maturation rates, adult size, reproductive scheduling, and lifespan (55–57). However, a range of somatic traits can also be considered from the same perspective. The "embodied capital" conceptual model of Kaplan and colleagues considers the body in terms of a range of traits that reflect somatic investment (58). This investment may be considered in physical terms, expressed through the characteristics of individual tissues and organs, or in functional terms, expressed through a range of capabilities. Of particular relevance for studying past human populations, this conceptual approach allows the life history framework to be applied to many aspects of human anatomy, physiology, and morphology.

For example, adult stature is a marker of investment in overall growth, adipose tissue is a marker of investment in reproduction for females (59), and in defence (for funding immune function) for both sexes (60), while organ mass and quality are markers of investment in maintenance (61). This means that variability across different morphological traits can be used to index life history trade-offs, offering a new perspective on the archaeological skeletal record.

In stochastic environments, however, there are benefits to withholding a portion of energy from immediate investment, to

TABLE 1 | Evidence for heritability of life history traits and examples of individual genetic determinants.

Trait	Population	Heritability	GWA evidence	References
Birth weight	UK twins	44%		(34)
	Norwegian families	31%		(35)
	Swedish twin pairs	25–40%		(36)
	Meta-analysis of 69,308 Europeans from 43 studies		7 alleles associated with birth weight variability	(37)
Age at Menarche	Australian sister-pairs	69%		(38)
	Dutch families	70%		(39)
	US families (Fels study)	49%		(40)
	Meta-analysis of 182,416 women of European descent from 57 studies		106 alleles associated with variability in age at menarche	(41)
Adult height	Gambian families	60%		(42)
	Indian families	74%		(43)
	European twins	81%		(44)
	∼450,000 UK Biobank participants of European ancestry		3,290 near-independent SNPs associated with variability in height	(45)
Body mass index	Finnish twins	80%		(46)
	Nigerian families	46%		(47)
	Chinese twins	61%		(48)
	∼450,000 UK Biobank participants of European ancestry		716 near-independent SNPs associated with BMI	(45)
Age at menopause	US families (Framingham)	52%		(49)
	Dutch mother-daughter pairs	44%		(50)
	Dutch twins	71%		(51)
	17,438 women from two US cohorts		13 SNPs associated with variability in age at menopause	(52)

be able to draw on it at some future time when new stresses or opportunities emerge. Several different strategies are available whereby organisms may store energy in generalised forms, so that it can be allocated to any life history function when needed (62). The origins of agriculture led to food surpluses and storage (63), while the origins of dairying involved the use of secondary animal products that provide a constant source of energy rich food, as grazing animals process grasses that humans cannot eat into milk and its by-products. Beyond the physical storage of foodstuffs, there are other social and biological means of storing energy. Mutually supportive social relationships are one such method, for example humans are "cooperative breeders," whereby kin provide support to mothers during reproduction and mitigate some of the energetic costs (62). A second method is the storage of energy as lipid in adipose tissue. Should dietary energy intake decrease unexpectedly, or infection elicit an immune response, energy needs can be met by oxidising lipid stores (62). Similarly, humans are "capital breeders," whereby females tend to store energy prior to pregnancy so that reproduction is viable regardless of external ecological conditions (64). As a fundamentally social species that also has greater levels of body fat than most other primates, humans have evolved the capacity to store energy in several different forms, indicating that our life history strategy was strongly shaped by stochastic environments (65).

So far, we have considered how human life history traits in general may have emerged through genetic adaptation in response to variable ecological conditions. However, the same traits also show substantial plasticity, indicating that such responses may also occur over faster timeframes. Here, selection has favoured the evolution of reaction norms that allow fitness-maximizing traits to emerge in response to stimuli and stresses encountered within the life-course. Reaction norms refer to the spectrum of phenotypes produced by a genotype across a range of environmental conditions (14). To highlight this plasticity, **Table 2** summarises secular trends in human life history traits, indicating their capacity to respond to changing ecological conditions and generate new trade-offs.

Beyond any genetic determinants, therefore, life history strategies may vary through mechanisms of developmental plasticity, through which phenotype may be adjusted in association with recent or prevailing conditions. Such phenotypic adjustments can then be considered to have adaptive benefits, promoting survival and fitness. For example, secular declines in mortality risk are associated with secular increases in adult height

TABLE 2 | Evidence for plasticity in life history traits, demonstrated by secular trends.

Trait (units)	Population	Rate in units per decade	Decade per SD change	References
Birth weight (g)	Canada (1985–1998)	27.7	18.1	(66)
	Norway (1967–1998)	36.8	13.6	(67)
	India (1963–1986)	32.2	15.5	(68)
	Papua New Guinea (1969–1996)	70.4	7.1	(69)
	Vietnam (rural) (1999–2010)	95.0	5.3	(70)
Age at menarche (y)	Spain (1925–1962)	0.26	3.8	(71)
	South Africa (black) (1956–2004)	0.50	2.0	(72)
	India (1979–2003)*	0.20	4.9	(73)
	Korea (1920–1986)	−0.64	1.6	(74)
	Colombia (1944–1984)	−0.55	1.8	(75)
Height (cm)	Czech (f) (1935–1955)$*	1.1	5.4	(76)
	Indian (f) (1979–2003)*	2.2	2.1	(73)
	Portugal (m) (1904–1996)	1.0	6.1	(77)
	Poland (1965–1995)	2.1	2.9	(78)
	Belgium (1830–1980)$	1.0	6.0	(78)
Adult BMI (kg/m^2)	Sweden (f) (1985–2002)	1.2	2.5	(79)
	Greece (m) (1990–2006)	0.6	5.3	(80)
	United States (m) (1980–1987)	0.8	3.7	(81)
	China (1991–2011)	1.2	3.0	(82)
	Brazil (f) (1975–2003)	1.1	2.7	(83)
Age at menopause (y)	Spain (1883–1941)$	0.34	11.7	(84)
	Sweden (1908–1930)$	1.00	4.0	(85)
	United States (1912–1969)$	0.59	6.8	(86)
	Iran (1930–1960)$	0.70	5.7	(87)
	Korea (1927–1947)$	1.7	2.3	(88)

BMI, Body mass index; m, male; f, female.

**Based on mothers being on average 24 years older than daughters, and assuming that the data were collected the year prior to publication.*

$*Period over which trend assessed based on age at birth.*

(89), indicating that in benign environments, energy can be re-allocated from defence to growth. Similarly, patterns of growth in early life predict the timing of pubertal maturation, though in different ways depending on the quality of the environment (33).

Overall, life history strategies can change over time through both genetic and plastic responses, and both mechanisms may be relevant to phenotypic change associated with the origins of agriculture. Regardless of mechanism, such changes in trade-offs are assumed to be fitness-enhancing. Moreover, this theory predicts fundamental connections between changes in different biological traits. We emphasise that both natural selection, and ecological stresses within the life-course, do not act on individual traits, rather they act on strategies (90), which can be readily conceptualised as trade-offs. For example, we should focus not on height as a discrete outcome, nor even on the *strategy* of growing, but rather on the *trade-off* between allocating resources to growth vs. other life history functions. Our argument is that the origins of agriculture provoked trends in many components of biology, such as body size, fertility, and health status, through shifting these trade-offs to new niche-specific optima. To provide empirical support for this theoretical framework, we now review evidence for life history trade-offs in contemporary human populations, focusing primarily on plastic responses.

EVIDENCE FOR LIFE-HISTORY TRADE-OFFS IN HUMANS

Many studies illustrate trade-offs between life history functions, though the findings are often not presented within this conceptual framework. Trade-offs might be driven by variability either in energy supply, or in the energy demanded by particular biological functions. In each case, the optimal allocation of energy between competing functions may change. For example, **Figure 2** illustrates how an infection may elicit increased energy allocation to immune function, at a cost to all three other functions. In practice, most studies enable only two-function (binary) trade-offs to be considered. Between the four life history functions that we propose, a total of six binary trade-offs can be assessed. Evidence for each of these is now briefly reviewed, addressing where possible both short-term trade-offs that may be reversible (evident for example in adults) and also developmental trade-offs in early life that may be less reversible. Specific examples are also summarised in **Table 3**.

Maintenance-Growth (M-G)

By strict definition, a trade-off between maintenance and growth can only occur during development, as growth in its normal

sense ceases with the realisation of adult size. However, a looser definition of growth, which extends to tissue deposition and renewal processes, allows adult phenotype to be addressed. For example, bone maintenance continues through adult life and may be adversely affected by dietary or infectious stresses, as well as by reproduction in women (110). Similarly, adult weight gain, which comprises both fat and lean tissue, is associated with faster telomere attrition, a marker of cellular aging (94).

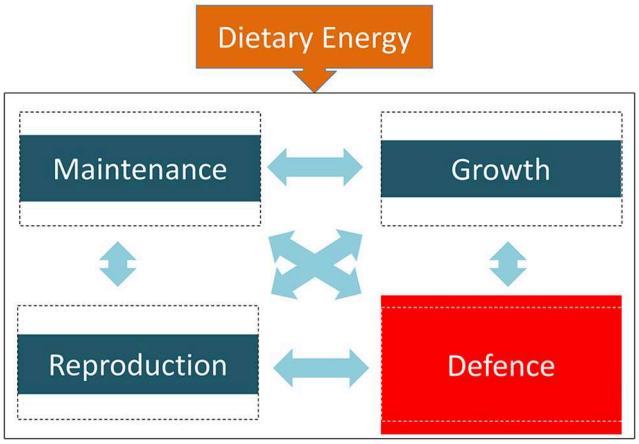

FIGURE 2 | A life history trade-off, whereby allocating more energy to defence (e.g., from fighting an infection) results in less energy being available for maintenance, growth, and reproduction. The dotted line boxes indicate "equal" levels of investment across the four functions, and the coloured boxes indicate the actual magnitude of investment.

During development, reduced energy supply affects tissues to different degrees, as recognised by the thrifty phenotype hypothesis (111). Essential organs such as the brain and lungs are protected, at a cost to other organs (112, 113). In particular, the brain has an obligatory demand for energy, and meeting this demand can directly impact on the growth of competing tissues, such as the liver, pancreas, and muscle mass, which contribute to metabolic homeostasis (114). In turn, the preservation of homeostatic capacity slows the rate of ageing and promotes longevity.

In a study comparing lowland and highland children from Peru, for example, highland children exposed to high composite levels of ecological stress (poverty, under-nutrition, hypoxia, infections) protected growth of the brain and torso, at a cost to limb lengths, in particular the length of the tibia (112). Similarly, survivors of severe-acute malnutrition in Malawi protected both their brain and their lung function (essential for supplying the brain with oxygen) in mid-childhood, at a cost to leg length and muscle function (113). In turn, leg length is a strong predictor of metabolic health in adult life (115, 116). Thus, when energy

TABLE 3 | Evidence for life history trade-offs in humans between maintenance (M), growth (G), reproduction (R), and Defence (D).

Trade-off	Population	Life-history trait	Exposure	Outcome	References
M-G	UK	Longevity	Rapid infant growth	Arterial stiffness	(91)
	UK	Longevity	Post-natal growth	High blood pressure	(92)
	India	Cellular health	Adult weight gain	Telomere attrition	(93)
	US	Cellular health	Adult weight gain	Telomere attrition	(94)
M-R	Global data	Maternal longevity	Reproductive effort	Shorter lifespan	(95)
	UK	Maternal longevity	Reproductive effort	Shorter lifespan	(29)
	Finland	Maternal longevity	Bearing twins	Shorter lifespan	(96)
	UK	Bone health	Early menarche	Reduced bone strength	(97)
M-D	Europe	Longevity	Infant disease load	Shorter adult lifespan	(89)
	Ethiopia	Mental health	Fetal fat deposition	Poorer mental health	(98)
	Meta-analysis	Metabolic homeostasis	Hepatitis C infection	Increased risk of type 2 diabetes	(99)
	Meta-analysis	Metabolic homeostasis	Periodontal disease	Increased risk of cardiovascular disease	(100)
G-R	SS Africa	Child growth	Number of siblings	Growth declines w. sibling no.	(101)
	UK	Child growth	Earlier reproduction	Low birth weight	(102)
	UK	Bone health	Early menarche	Reduced bone size	(97)
	India	Adult height	Early menarche	Short adult stature	(103)
G-D	SS Africa	Child growth	Maternal malaria	Low birth weight offspring	(104)
	Guatemala	Child growth	Diarrhoeal disease	Reduced growth	(105)
	Ecuador	Child growth	Immune activity	Reduced growth	(106)
	Europe	Adult height	Infant mortality rate	Mortality declines predict taller height	(89)
R-D	Senegal	Maternal mortality	Malaria	Reproduction increases infection risk	(107)
	UK athletes	Reproductive investment	Endurance exercise	Decline in testosterone	(108)
	UK athletes	Immune function	Endurance exercise	Increase in immune markers	(108)
	Malaysia	Reproductive investment	Reduced maternal stress	Increased breast-milk transfer	(109)

SS Africa, sub-Saharan Africa.

supply is restricted, protecting brain growth comes at a direct cost of a reduced capacity for maintenance, which may contribute to an increased risk of chronic diseases at later ages (111, 117).

Although maintenance is usually measured at the level of physiological homeostasis, physical activity level can also be considered as a broader marker, though it is also relevant to other life history functions. At a behavioural level, activity is a key aspect of subsistence effort (118) but it also contributes to cellular homeostasis, promoting antioxidant enzymes that scavenge free radicals and prevent telomere attrition (119–121). Among a rural population of Yucatan Maya, where children used to provide significant levels of domestic and subsistence labour to the household economy, a longitudinal analysis showed that those demonstrating greater allocation of energy to physical activity were shorter and lighter than their less active peers (122). However, as we discuss below, physical activity also plays a unique role in life history trade-offs, as cooperative behaviour and "labour subsidies" allow the maintenance needs of some individuals to be met by the physical activity patterns of others (118).

Maintenance-Reproduction (M-R)

A trade-off between maintenance and reproduction could be shown by testing for elevated mortality risk following the production of offspring. For example, early studies suggested that producing offspring is correlated with reduced lifespan among parents of both sexes (28, 29), though in general the strongest evidence is for mothers. However, several studies have failed to demonstrate negative associations between reproduction and lifespan (123, 124), and the evidence that greater reproductive effort promotes faster ageing through oxidative damage is inconsistent (26). We suggest that a wider range of metabolic traits relative to fitness merit consideration.

Reproduction is a challenging period for maternal metabolism, temporarily depleting the mother of energy, micronutrients, and mineral. For example, higher parity, short inter-birth interval, and earlier age at first birth were associated with reduced bone quality among Tsimané forager-farmer women after adjusting for potential confounders (125). These findings are especially relevant to our hypothesis, as bone mineral density can potentially be examined in the archaeological skeletal record. However, studies from high-income countries indicate that the net loss of bone during lactation may be resolved after weaning (126). Moreover, other studies of the Tsimané found that despite their high fertility rates, markers of cardio-metabolic disease are amongst the lowest reported in human populations (127, 128). The costs of reproduction may therefore be both "condition dependent," i.e., varying in association with broader ecological conditions, and also outcome-dependent, i.e., varying across different markers of maintenance (26). In addition, they may also be shaped by experience in early life. For example, the effect of activity level on reproductive function in rural Polish women was found to be mediated by size at birth (129).

Parent-offspring conflict theory assumes that offspring are selected to demand more resources than their parents are selected to provide (130). During pregnancy, this results in a "metabolic battle" over maternal circulating nutrients. The fetus and placenta (which share a common genotype) secrete hormones that increase maternal glucose levels and blood pressure, which act to force more nutrients across the placenta. The mother responds by counter-effects, reducing the pool of nutrients (131). The metabolic strain of pregnancy makes mothers vulnerable to conditions that impair maintenance, such as gestational hypertension and diabetes. Whilst these metabolic conditions are strongly associated with obesity in contemporary populations, there are indications that they also affected past populations, perhaps through the adoption of diets that exposed metabolism to unprecedented levels of refined carbohydrate (132). Any metabolic costs of particular diets to the mother are expected to have been exacerbated by the effects of maternal-offspring conflict.

For cardio-metabolic outcomes, therefore, reproduction appears to increase the risk of chronic diseases in women, indicating that it imposes costs on homeostasis. However, these costs may to some extent be mitigated by breast-feeding (133), moreover reproduction is protective against diseases associated with excess fuel availability, in particular cancers (134). Therefore, trade-offs between reproduction and maintenance vary in association with the underling metabolic pathways to disease. Intriguingly, both short and long inter-birth intervals have been associated with elevated maternal mortality risk (135).

Some costs of reproduction can potentially be offset by greater kin support, as expressed in the concepts of cooperative breeding (136) and pooled energy budgets (118). In this context, sedentary farmers might be able to draw on a larger pool of relatives than foragers, while also benefitting from new cereal-based weaning foods (137) that could promote such kin-cooperation. Conversely, the costs of reproduction could also be elevated by shorter inter-birth intervals, hence markers of health and longevity must be assessed to test whether the transition to agriculture was beneficial or detrimental to "maintenance" in women.

Maintenance-Defence (M-D)

Defence typically requires that baseline homeostatic processes be curtailed in favour of more aggressive metabolic activities, that either protect the body from external threats (predators), supply damaged tissue with resources, or neutralise pathogens and parasites.

The generic costs of immunity have been elegantly revealed through studies of non-human animals, that for ethical reasons are not appropriate in humans. For example, a study of bumblebees showed that, after imposing starvation to ensure limited energy availability, simply activating the bee's immune system in the absence of actual exposure to pathogens reduced survival of the bees by 50–70% (138). Immune function can therefore be regarded as a high-benefit, high-cost trait, that is potentially life-saving but metabolically expensive to run (139). Similarly, many experimental studies have shown that injecting animals with foreign antibodies generates an elevation in metabolic rate, which clearly reduces the availability of energy to other functions (140, 141).

In young men, observational studies showed that even mild respiratory infection increases resting metabolic rate (142). In children, likewise, each degree of temperature rise associated with fever increases metabolic rate by ∼11% (143). A recent study

of Shuar forager-horticulturalist children of Amazonian Ecuador found resting energy expenditure to be increased by ∼20% relative to children from industrialized settings, due to persistent immune activation (144). At the level of cellular metabolism, injury or infection elicits a state of inflammation, disrupting homeostatic processes such as the maintenance of core body temperature, appetite and sleep patterns (139). These responses impair components of cellular homeostasis such as DNA repair and telomere maintenance (145, 146).

The costs of defence relate not only to immune function itself. Many pathogens may not necessarily threaten survival, but nonetheless rely on their hosts for nutrition, shelter, warmth, and a "home base" for reproduction. Until cleared from the body, all their metabolic requirements are necessarily met by the host organism (147). Given the high costs of prolonged immune response, the optimal trade-off may be to tolerate some parasites or pathogens (148, 149). The lower the level of energy supply, the higher may be the resulting tolerated pathogen burden. This issue is particularly relevant to early agricultural communities, as they experienced unprecedented exposure to pathogens and parasites compared to ancestral foragers.

From a behavioural perspective, the stress response plays a key role in enabling escape from predators, but again at a cost to normal homeostatic function (150, 151). The hormone cortisol plays a key role in allocating energy between different physiological systems. High cortisol levels maintain alertness and the capacity to respond to stresses, but at a cost to cardio-metabolic health (152–154).

The study of Mayan children discussed above showed that children with higher levels of physical activity not only demonstrated poorer growth, but also had reduced subcutaneous adiposity, indicating that working harder on subsistence tasks reduced allocation to immune function (122). In extreme conditions, however, physical activity could itself be considered an investment in defence. One such example comprises fleeing from predators, however farmers may also need to work especially hard in some seasons to reduce the risk of famine (155), or protect crops from insect pest invasions. In contrast to moderate activity levels, intense levels can cause weight loss (156, 157), and can result in the net production of free radicals, causing oxidative damage (158).

Beyond direct energetic costs, greater investment in immunity may also compromise other nutrient-dependent forms of maintenance. For example, among Tsimané forager-horticulturalists in Bolivia, markers of elevated immune activation were associated with estimates of lower trabecular bone density, a risk factor for fragility fractures at older age (159). Although exposure to pathogens in early life may also contribute, the markers of immune activation in this study were measured during adult life, and indicate continued deficits in bone maintenance generated by the burden of infections.

Growth-Reproduction (G-R)

At the simplest level, reproduction broadly occurs only when growth has ceased, meaning that the starkest trade-offs are driven by a time-shift in allocating energy between these functions. However, considered in more detail, there are more subtle trade-offs between these functions.

First, there may be a genetic basis to a trade-off between maturation rate and adult size. Both stature and age at menarche demonstrate heritability (see **Table 1**), and short stature has been correlated with earlier menarche (160, 161). This suggests that some populations might have adapted to high-risk environments by shifting the G-R trade-off systematically in favour of earlier reproduction (33). Within populations, genetic variability in these traits indicates a range of variability in this trade-off (162). However, the same trade-offs can also emerge through plastic mechanisms.

First, early reproduction appears to curtail maternal physical growth. Several studies have shown that adolescent childbearing is associated with a reduced rate of linear growth, indicating that the energy costs of reproduction reduce the allocation of energy to maternal growth (163). Second, several studies have shown a trade-off between weight gain and height gain. For example, age at menarche is positively correlated with adult height (161, 164), but negatively correlated with adiposity through adult life (165). This indicates that the developmental pathway to earlier reproduction favours the allocation of energy to somatic stores, at a cost to linear growth. Whereas stature and lean mass are markers of growth, gluteo-femoral adipose tissue can be considered an investment by females in reproduction, providing energy stores to fund lactation (59, 166).

Catch-up growth allows the body to respond to early under-nutrition, should more resources become available. However, studies show that rapid catch-up growth may promote adiposity over linear growth. For example, studies of Indian girls who were adopted by Swedish families in early life showed that in the improved nutritional environment, they underwent very early puberty and remained short as adults (103, 167). Again, this highlights the diversion of resources from growth and maintenance toward earlier reproduction.

Growth-Defence (G-D)

Numerous studies in children show that infections reduce linear growth rate, examples including helicobacter pylori infection and diarrhoea (105, 106, 168). Among Shuar forager-horticulturalist children in Amazonian Ecuador, even mildly elevated immune activity reduced growth rate by half (106). In the reverse direction, childhood immunisation programmes are beneficial for child growth, through reducing the allocation of energy to fighting infections (169). Aside from linear growth, infections can also reduce tissue masses. In acute illness, for example, in the absence of adequate dietary supply, lean tissue may be broken down to release acute-phase proteins. Similarly, populations occupying environments with higher infectious burdens show lower levels of truncal subcutaneous fat (170), a depot closely associated with immune function (60, 171).

From an inter-generational perspective, maternal infections during pregnancy also reduce the energy available for fetal growth (172). Numerous studies have linked maternal pregnancy infection with lower birth weight (173, 174), and these associations persist into post-natal life. For example, infants exposed to maternal HIV, but themselves uninfected, show poor

growth during early infancy, the period of exclusive breastfeeding (175). Placental malaria likewise constrains infant catch-up growth (176).

These trade-offs may generate correlations between the burden of infectious disease encountered in early life, and subsequent adult height. Many studies have assessed childhood infection burden through the proxy of infant mortality rate, on the assumption that higher infant mortality indicates exposure to a higher disease load amongst those who survived. Over the twentieth century, declines in infant mortality rate within countries correlate strongly with increases in adult stature 20 years later (89). While these studies are observational and cannot prove causation, they support the hypothesis that linear growth benefits from less energy being allocated to immune function, consistent with the mechanistic studies reviewed above.

When dietary quality improves in the absence of increased infection burden, more energy can be allocated to growth. For example, among moderately malnourished young children in Burkina Faso, providing high-energy ready-to-use therapeutic foods along with medical care resulted in 93% of weight gain comprising lean tissue, indicating prioritised allocation of energy to growth (177, 178).

Reproduction-Defence (R-D)

Immediate trade-offs between reproduction and defence are illustrated by the greater susceptibility to infections among women during pregnancy and lactation. For example, the energy demands of lactation make mothers more susceptible to malaria infection during the early post-partum period (104).

As with growth, greater exposure to infections in early life can slow the rate of maturation and hence potentially delay reproduction. For example, Ellison reviewed data on infant mortality rate in the 1940s, and mean age at menarche in the 1960s—1970s, in populations from low- and middle-income countries (179). Among populations where mortality was generically low, there was no association between infant mortality and age at menarche. Above a certain threshold of infant mortality, however, there was a dose-response linear correlation between the two parameters. This implies that in populations suffering a high disease burden, expending more energy fighting infections slows the rate of maturation.

However, growth-defence trade-offs can also lead to *earlier* menarche, which may in turn result in shorter adult height. As discussed above, maternal infections during pregnancy may reduce fetal growth, propagating to shorter adult height of the offspring. Catch-up growth may exacerbate this effect, by accelerating pubertal development but thereby shortening the duration of growth (164). Both of these R-D trade-offs could have operated in populations undergoing the transition to agriculture.

Defence may also relate to psychosocial factors associated with the stress response. Activating the "flight-or-fight" response reduces energy availability for other functions. Studies have associated maternal stress during pregnancy with lower birth weight (180). A recent randomised trial showed that reducing anxiety among healthy first-time mothers was associated with increased breast-milk transfer, and with greater weight gain in the infant (109).

Composite Trade-Offs and Inter-Generational Effects

So far, we have considered evidence for binary trade-offs between life history functions. Few studies have considered how ecological factors shape "bundles" of trade-offs more comprehensively, however we review several examples highlighting the relevance of life history trade-offs for understanding the potential consequences of variability in ecological conditions. None of these studies explicitly examines the consequences of change in human subsistence mode, but each shows how variability in ecological conditions is associated not simply with variability in a specific trait, but rather in composite life history strategies that respond through genetic change or reaction norms to maximise fitness. Our emphasis here is that coherent trade-offs, in response to particular selective pressures, are expected to result in multiple traits clustering within individual organisms.

One such example has been observed in non-human animals, and relates to the emergence of distinct "animal personalities." This has been attributed to the action of selection on traits that coordinate risk-taking behaviour (181). A similar scenario may relate to suites of life history traits in human populations.

A second example goes beyond the traditional focus on energy allocation, to consider dietary macronutrient composition. The framework of "nutritional geometry" assumes that animals satisfy competing appetites for different macronutrients in ways that maximise fitness (182). In Drosophila, diets that maximised longevity had different composition to those that maximised fecundity. When offered a choice of complementary foods, flies regulated their food intake to maximize lifetime egg production (183). Similar experimental work on mice has likewise shown that dietary macronutrient composition effects both health and longevity (184). Changes in the diet therefore appear to drive composite changes in life-history trade-offs in non-human animals.

A third example comprises a study of 22 small-scale human societies by Walker et al. (33). This study showed that variation in both the supply of energy, and mortality risk, is associated with varying patterns of growth, indicating that environmental conditions drive trade-offs across populations. The authors identified one subset of societies, occupying more favourable conditions, which demonstrated faster growth and earlier puberty. These populations attained adulthood faster because of greater energy availability, proxied by larger adult size. However, the authors also identified another subset of populations that experienced low sub-adult survival rates. In this subset, earlier maturation and reproduction is again favoured to counter mortality risk, but at a cost to adult body size. The authors concluded that both genetic adaptation and life-course plasticity might contribute to these contrasting strategies. Individual studies have elucidated in more detail several relevant trade-offs. For example, among Pume foragers in Venezuela, early female reproduction is favoured by a rapid growth spurt prior to the adolescent onset of reproduction, and the provision of food by kin (energy-pooling) to meet the metabolic costs of this fast life history strategy, which collectively maximises female fitness (185–187).

A fourth example illustrates how these trade-offs may emerge through the life course, in response to variable investment in early life. In a longitudinal cohort study from Brazil (188), lower levels of maternal investment were associated with developmental trade-offs that favoured immediate survival and early reproduction at a cost to growth and maintenance (**Figure 3**). Maternal capital was assessed by scoring "penalties" in each of maternal height, nutritional status, family income, and education level. A composite score of these penalties enabled mothers to be ranked in terms of overall capital level, assumed to equate to variable capacity for maternal investment.

Lower-capital mothers produced daughters with smaller size at birth, who continued to show poor linear growth during infancy. Compared to daughters of high-capital mothers, the low capital daughters did not experience earlier menarche, but nevertheless were more likely to have produced offspring by 18 years, while being both shorter and more centrally adipose in early adulthood. This study highlights a life-course developmental trajectory of growth being curtailed from fetal life onwards, and energy instead being allocated to body fat to fund reproduction (peripheral fat) and immune function (central fat). Overall, low maternal investment drove trade-offs that promoted reproduction and defence at the expense of markers of maintenance and growth.

This study illustrates how reproduction brings the life history strategies of two generations together. The mother's allocation of energy to reproduction is shaped by her own life history trade-offs, while the magnitude and developmental timing of this investment shapes the cumulative emergence of trade-offs in the offspring (**Figure 4**). In that sense, the daughters' trade-offs are responses to trade-offs occurring during maternal development.

Having demonstrated comprehensive evidence in support of binary, composite and inter-generational trade-offs in contemporary human populations, we now turn to the origins of agriculture to consider whether there is also evidence for such trade-offs in association with major changes in human diets and living conditions.

THE ORIGINS OF AGRICULTURE

It is now generally recognized that the transition to agriculture involved a long-term co-evolutionary relationship that increased the population size and density of both humans and their domesticated plant and animal species over thousands of years. This process, where it occurred, involved the replacement of foraged and hunted foods with domesticated varieties and animal by-products, and involved the gradual selection for larger grain size indices representing greater agricultural productivity (189). However, it is also important to note that a proportion of human populations never adopted any form of agriculture, others did so only transiently, and still others practised mixed foraging and farming (190, 191). Where agriculture did emerge, it did so in a wide variety of ways and on different timescales, and can therefore be assumed to have impacted human biology in heterogeneous manner. Wherever it occurred, the association between niche construction and human biology is likely to have involved positive feedback, so that farming stimulated new life history trade-offs that may then have shaped the subsequent trajectory of agricultural development.

Domestication involved "a continuum of human, plant, and animal relationships … and was driven by a mix of ecological, biological, and human cultural factors" (6). Its timing varied substantially across different geographical regions, and whereas in some (e.g., the New World) crop domestication preceded that of animals by several millennia, in others (e.g., Africa, Arabia, India) the converse occurred (6). The role of active human selection for specific traits also varied, and some traits that were beneficial for humans likely emerged as a by-product of cultivation/husbandry practices (6). Given this heterogeneity, we should expect human life history traits to have shifted, by genetic or plastic mechanisms, whenever the changes to the socio-ecological niche were of sufficient magnitude to favour such responses. Which periods generated the greatest selective pressures, opportunities, or stresses, and hence drove the most marked life history shifts, is an important topic for further work.

With richer and more stable resources and larger social groups aggregating at specific settlements, storage of food surpluses, new forms of cooperative behaviour, and the exploitation of renewable dairy animal by-products, the transition to agriculture dramatically shifted the energetic ecology of the human dietary niche. The human gut is small in size with a limited transit time, thus constraining the volume of food that can be ingested and, through digestion, converted to metabolisable energy. By consuming foods that are energy-rich and extra-somatically processed (e.g., ground grain/carbohydrate and milk), dietary energy supply can be increased despite our biological constraints.

However, beyond dietary shifts *per se*, any observed changes in human biology that occurred in association with the transition to agriculture should be considered in the context of changes in the entire ecosystem. Human life history transformations occurred alongside similar changes in a variety of the organisms that were farmed. Through the process of domestication, humans actively or passively selected for and against many of the traits that represent life history adaptations of crop and animal species.

For example, human activities changed the morphology of plants in favour of increased grain sizes and non-shattering spikelet scars of wheat, barley, and rice (189). This had the effect of producing larger, more energy-rich grains that were less likely to be lost in harvesting, but often required further processing before consumption. Moreover, by selecting against components of plant and animal "defence," humans had to invest more time and effort in defending their new resources against the pathogens and predators that target these species. Over thousands of years, early farmers were therefore drawn into a new "labour trap," and exposed to new stresses associated with enhanced seasonality of the food supply (192).

In these respects, domestic plant and animal species showed their own life history shifts whereby investment in defence was suppressed, while investment in the traits that from a human perspective drive agricultural yield increased (**Figure 5**). In crops, this is reflected by larger grain size, whereas the size of animals often decreased initially (193) while their fertility increased (192). In each case, these trends indicate greater

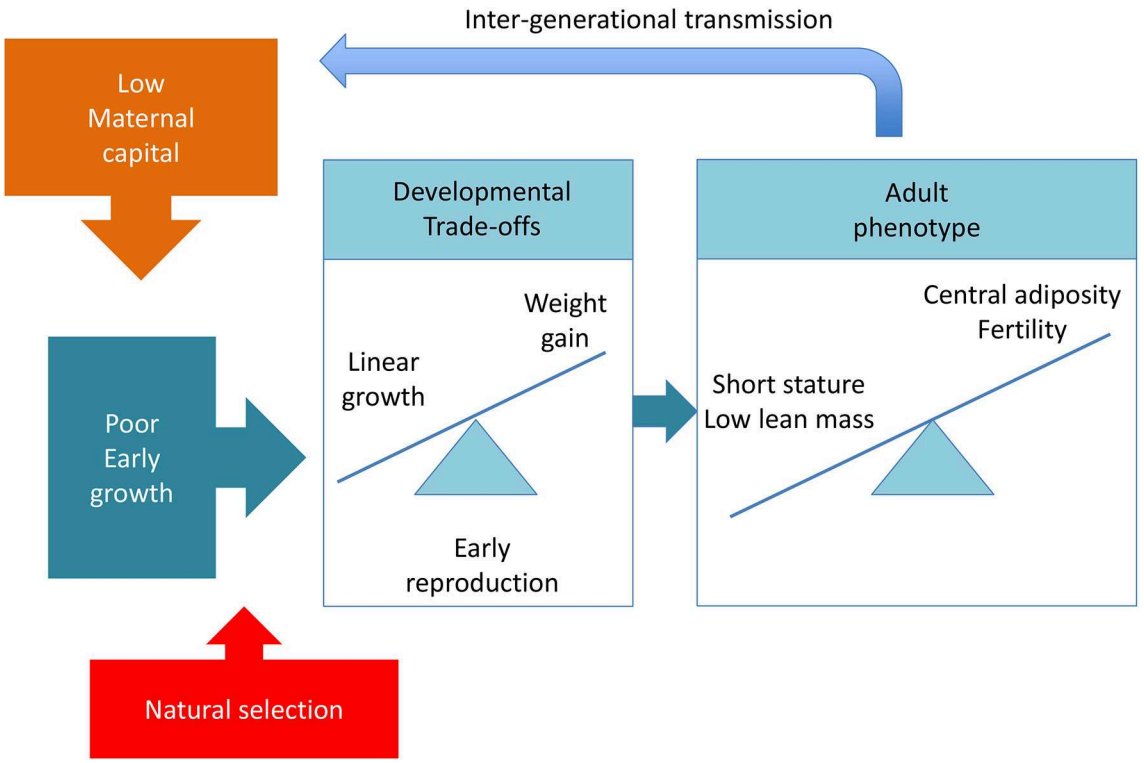

FIGURE 3 | Summary of findings from the Pelotas 1993 birth cohort study, where low maternal capital was associated with developmental trade-offs in the daughter between linear growth and weight gain. At 18 years, daughters showed preferential energy allocation to reproduction and defence, at a cost to growth and maintenance. Based on data from Wells et al. (188).

investment in reproduction, and hence greater potential harvests for humans. This evidence indicates that humans may have changed through similar correlated shifts in life history trade-offs, allowing adaptation to the new agricultural niches.

Foragers diversify their efforts across multiple food webs, and are protected against shocks in any one of them (194). In contrast, farmers increasingly invest in a single food web, and become more susceptible to any ecological stress that reduces its productivity (192). Agricultural settlements are often near natural watercourses, which allowed for the development and intensification of irrigation to maintain crop yields, which created more larval habitats for vector-borne diseases (195). These concentrated communities may then have seen a further intensification of the infectious burden, radically transforming the risks of morbidity and mortality.

Composite Stress Imposed by Agriculture

The adoption of agriculture transformed the entire human subsistence niche, changing both the human diet and many other aspects of the local ecology, which we argue may have led to a cascade of coordinated life history trade-offs. However, these changes must have played out in varying ways according to the historical period, the local ecology, and the type of agriculture that developed. As all of these factors would have been under the influence of longer-term climatic trends, the selective pressures must therefore have varied accordingly. We briefly summarise some of the key stresses and some of the trends that might have shaped them.

Compared to forager diets, those of early farmers tended to incorporate higher levels of carbohydrate from grains, but lower levels of fibre, micronutrients, and protein (9, 20, 196). These changes would have altered the macronutrient substrates available for metabolic processing, with implications for life history trade-offs as highlighted above regarding experimental work on non-human species (183, 184). In humans, for example, low levels of dietary protein are associated with slower childhood growth (197, 198) and with higher levels of fat storage (182, 199). In this context, the implications of dairying are of especial interest. Following the emergence of a specialised dairying economy in the European Steppe by 7000BP, single nucleotide polymorphisms (SNPs) associated with lactase persistence appear to have evolved by ∼5600BP (200). In particular, the adoption and spread of intensive dairying may have buffered the difficulty of agricultural subsistence in Northern Europe and led to the modern north-south gradient of body size in Europe, an interpretation supported by the detection of selection for reduced height in the Iberian Neolithic but increased height in the Neolithic populations of the steppe (201).

Agriculture also exposed human populations to greater seasonality in food supply, exacerbated by the risk of famine through harvest failure. Other seasonal stresses that could

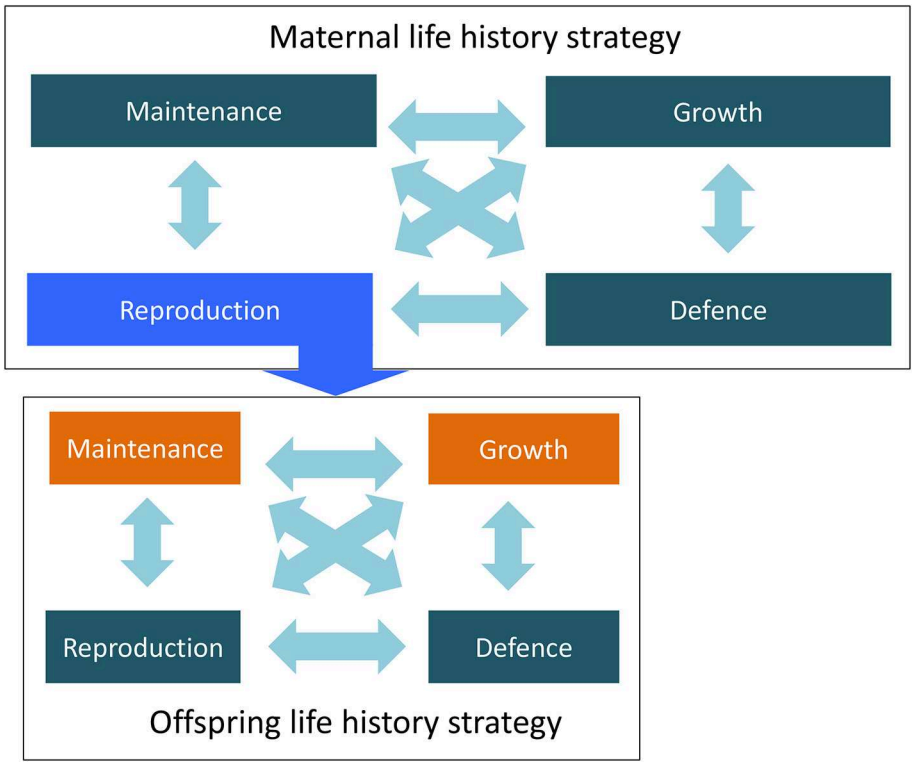

FIGURE 4 | Life history trade-offs across two generations, showing how the relative allocation of energy by the mother to reproduction shapes the energy available for allocation between all four functions in early life in the offspring.

dramatically reduce annual yields include floods, or spikes in agricultural pests.

A second key stress experienced by growing sedentary populations comprised exposure to a range of pathogens (195), driven by several related factors. First, higher population densities inherently favoured greater opportunities for infection. This scenario was then exacerbated by greater exposure to pathogens associated with human/animal faeces and contaminated water sources, and by the proximity to domesticated animals, some of which transmitted novel diseases to humans. Indeed, the longer the history of domestication of a species, the more common infectious diseases they share with human populations (202), indicating a long history of exposure to zoonotic disease following domestication. However, although early farming populations are widely assumed to have acquired an elevated burden of pathogens from their newly domesticated animals, emerging evidence suggests they may also have passed pathogens adapted to humans back to their stock animals, one example being the transfer of salmonella to pigs (203). Human populations also became susceptible to new "crowd" infections that, since they infect people only briefly before they recover or die, require a relatively large population size for their persistence (204), and against which foragers had been protected through their nomadic lifestyle and small population size. This enhanced overall disease load had two key effects on life history strategy—first, it increased the energy demand for immune function, and second it increased extrinsic mortality risk, which would then favour earlier reproduction (either achieved through maturing earlier, or through ceasing growth at smaller size). Each of these effects would inherently reduce the energy available for growth and maintenance.

Over the longer-term, climate change altered seasonal patterns and extended the dry season, leading to agricultural intensification and the adoption of practices such as mass irrigation (205). These more concentrated communities may then have experienced greater susceptibility to the stresses highlighted above.

Finally, there is growing evidence that the ecological stresses associated with the transition to agriculture may have intensified under the influence of early states, and that their political institutions may have influenced the crops grown, the diet consumed, the extent of crop irrigation, and the risk of disease and subsistence crises (192). Furthermore, states presupposed growing levels of social inequality, and state control over resources.

Since farming can increase dietary energy supply relative to foraging, one could question whether the transition to agriculture must inevitably have driven life history trade-offs. Could not the additional energy costs of immune function have been met simply by consuming more calories? Alternatively, farmers could have demonstrated lower physical activity levels, thus reducing their energy demands, for example by benefitting

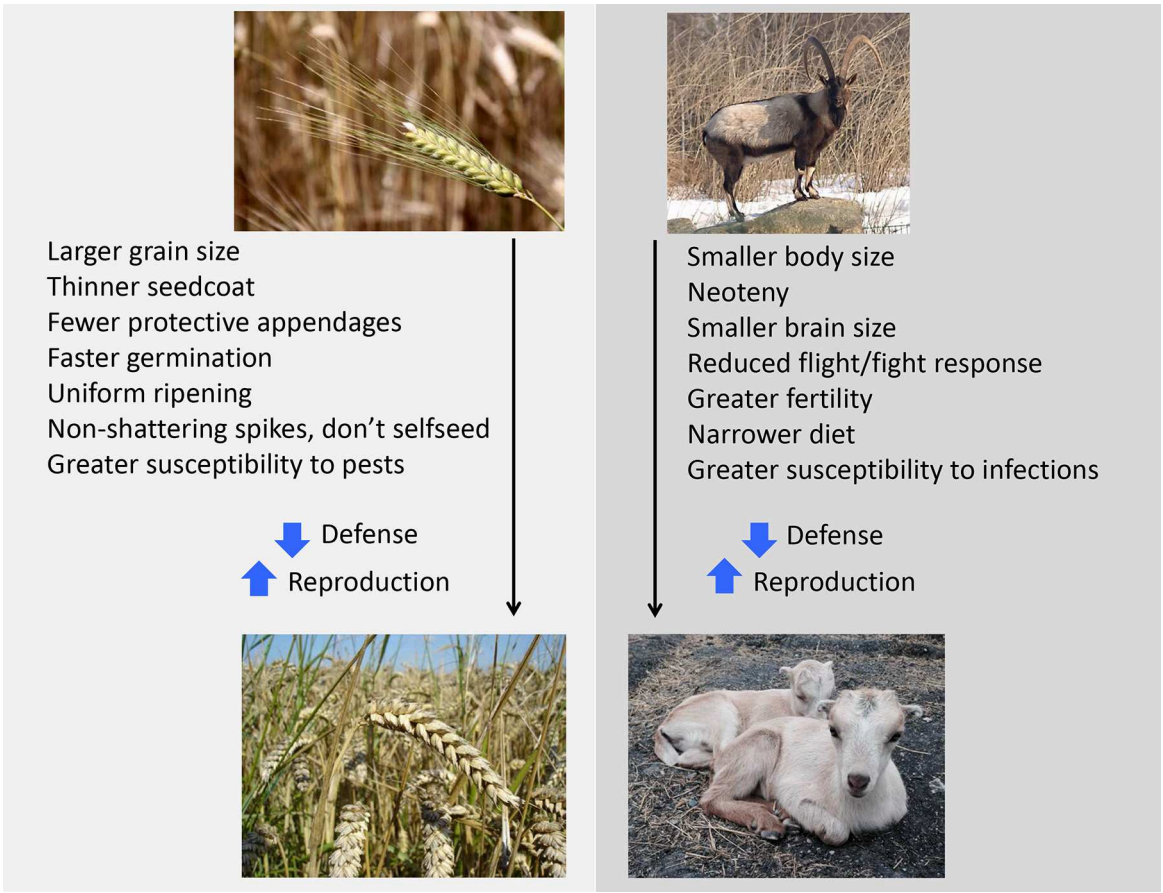

FIGURE 5 | Trade-offs between traits in crop and domesticated animal species, reflecting artificial selection by humans during the early agricultural period (192, 193). Photo credits (**Top left**) LepoRello (https://commons.wikimedia.org/wiki/File:Triticum_boeoticum_Bajuwarenhof_Kirchheim_2012-08-05.jpg), "Triticum boeoticum Bajuwarenhof Kirchheim 2012-08-05," https://creativecommons.org/licenses/by-sa/3.0/legalcode (**Botttom left**) User:Bluemoose (https://commons.wikimedia.org/wiki/File:Wheat_close-up.JPG), "Wheat close-up," https://creativecommons.org/licenses/by-sa/3.0/legalcode (**Top right**) F. Spangenberg (Der Irbis, own photo) (https://commons.wikimedia.org/wiki/File:Bezoarziege.jpg), "Bezoarziege," https://creativecommons.org/licenses/by-sa/3.0/legalcode (**Bottom right**) Cleur Monie (https://commons.wikimedia.org/wiki/File:Lamancha_mix_goat_kids.jpg), https://creativecommons.org/licenses/by-sa/4.0/legalcode.

from new "economies of cooperation" that are less amenable to exploitation by individual foragers (9). However, a review of energy expenditure in contemporary subsistence farmers suggest that levels of energy expenditure are moderate to high (206), while a study of Hadza foragers found that their energy expenditures were lower than expected (207), despite high levels of physical activity. Food production generates new demands for "food processing," meaning that farmers may have to work harder to produce the same amount of dietary energy as foragers. Contemporary subsistence farmers also demonstrate prevalences of child malnutrition that are amongst the highest of all human populations (208), indicating that the composite stresses of food insecurity and infections is detrimental to growth. This is an important point, as many ecological stresses relevant to the transition to agriculture may have acted most strongly during early development, rather than during adult life. Finally, trade-offs could have occurred in response to changes in dietary macronutrient composition, as well as in the overall energy budget. For all of these reasons, we therefore consider that phenotypic shifts mediated by trade-offs were likely inevitable in early farmers. The mechanisms could have allowed phenotypic responses favouring growth and maintenance during better ecological conditions, and the reverse pattern during more stressful periods.

Overall, we can assume the emergence of agriculture changed the human diet while provoking profound life history trade-offs that increased the allocation of energy to reproduction and defence, at a cost to growth and maintenance, as illustrated in **Figure 6**. We now review evidence in favour of each of these trends.

Reduced Allocation to Growth

There is relatively consistent evidence for a decline in adult body sizes associated with the transition to agriculture (209–214). A recent systematic review found evidence of declining stature in 14 different analyses among populations from Europe, Africa, the Middle East, Asia, Central and South America, and North America (215). While the trend toward decreasing stature is

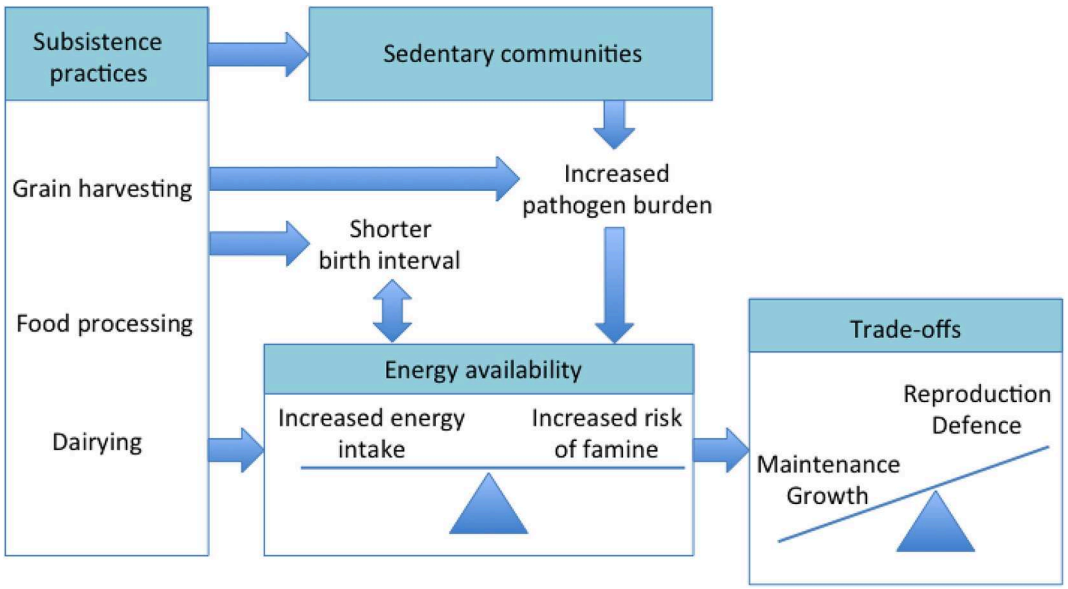

FIGURE 6 | Summary of how the combination of changes in subsistence practices may have increased energy availability, but also changed the ecological stresses in early agricultural populations. These composite changes may have elicited life history trade-offs favouring reproduction and defence, over maintenance and growth, as described in detail in the text.

commonly associated with the transition to agriculture, there is some evidence for temporal and regional variation. In some cases the initial transition to agriculture was associated with an early small increment in stature, followed by later, long-term systematic decline (9); or more subtle patterns of decline that varied between men and women (216). In other regions stature remained relatively consistent across the transition or even increased (217). Some of the cases where more complex patterns are observed involved the transition to wet-rice agriculture that may have had different energetic consequences, both in terms of the high energetic demand of paddy field farming, but also higher yields and lower amylose content (218, 219), while others may have reflected broader socio-economic changes in the Holocene.

More recent studies have analysed long diachronic samples. One such study shows that within the central European steppe, there was a significant decline in stature between the Mesolithic and Neolithic (220) that persisted among both men and women through the bronze and iron ages before a recovery in the Medieval period. Similarly, height declined sharply in association with the adoption of agriculture in India, and has remained low subsequently (221). Another recent study reported a similar decline in stature among the earliest farmers in the Nile Valley, followed by a subsequent increase in stature with the rise of the Egyptian Empire (222), trends that are matched by evidence for periods of childhood stress (223).

These bulk of studies typically document a decline in stature that is either immediately associated with the agricultural transition or occurs with agricultural intensification. This trend appears to persist in many contexts for thousands of years before an eventual increase. In each case, the initial size reduction demonstrates decreased energetic investment in somatic growth, which suggests a shift in life history strategy following the transition to domesticated plant and animal resources. Overall, therefore, the available evidence suggests that in most regions the allocation of energy to somatic growth initially declined in association with the transition to agriculture, but was followed by increases associated with subsequent shifts in energetic ecology.

Since height in many populations has recently increased, it is not clear whether the declines associated with adopting agriculture involved genetic adaptation, although there is some evidence for a general correspondence between stature estimates and polygenic risk scores for genes associated with stature (224). Intriguing evidence comes from inter-ethnic studies of birth weight, where the ethnicity of each parent can be considered separately by comparing offspring with parents of contrasting ethnicity. In this study, infants with European mother and south Asian father weighed less than infants with two European parents, suggesting that in the Indian population, genes expressing the paternal growth drive may have been selected to demand a lower nutritional transfer from the mother during fetal life (225). This may relate to the challenges of developing agriculture in an environment with high ecological volatility associated with the monsoon. Further studies are needed to test this hypothesis more robustly.

Increased Allocation to Reproduction

It has long been considered that there is a causal relationship between subsistence strategies, as the basis for the mode of production, and demographic change, with agricultural subsistence directly leading to more permanent settlement and hence the demographic expansion of populations (16, 226). However, prehistoric demography is challenging to interpret,

as it is dependent on proxy data. Many early estimates of exponential growth in human populations were based on evidence from rapid increases in settlement sizes, but recent use of radiocarbon dates as proxies for demography highlight more subtle fluctuations of population in some regions throughout the Holocene (227).

The strongest evidence for population growth in the Holocene comes from direct analysis of human remains and modern human genetic diversity. In the most systematic study of Neolithic demography, for example, Bocquet-Appel compared palaeodemographic data from 200 cemeteries (228). The results suggest there was a relatively abrupt increase in fertility following the transition to agriculture in the Northern Hemisphere. In the Levant, this is estimated to represent an increase in total fertility from 4.5 to 10 throughout the reproductive lifespan (228). The notions that fertility increased and inter-birth intervals decreased are supported by ethnographic studies of demography among recent or contemporary foragers and transitional-farmers (229), and by comparisons across subsistence mode that control for phylogenetic relationships (230).

Recent evidence for an agricultural demographic transition also comes from genetic estimates of population sizes. For example, Gignoux and colleagues investigated mitochondrial DNA diversity and revealed strong evidence for demographic expansions in the past 10,000 years in Europe, south east Asia, and sub-Saharan Africa (231). In all cases, coalescence times linked these demographic expansions closely with the adoption of agricultural subsistence.

Evidence regarding the effect of the transition to agriculture on mortality patterns is less consistent. Comparing palaeodemographic life tables of hunter-gatherers, horticulturalists, and agriculturalists, mean life expectancy was 21.6, 21.2, and 24.9 years, respectively, with none of the differences being statistically different (232). However, we should also note that mortality rates before and after the transition to agriculture might not necessarily be the same as those during the transition, and there are many uncertainties that are difficult to resolve when estimating past mortality rates (232). Moreover, the implications of transitioning to agriculture may not necessarily have been equal for the two sexes. In a study of age at death in the Levant, for example, life expectancy of Neolithic populations appeared to be slightly greater than that of the earlier Natufian hunter-gatherers. However, relative to males, female longevity appeared to decline, suggesting an elevated burden of maternal mortality in the Neolithic (233).

Importantly, however, our conceptual framework is relatively robust to this uncertainty. As discussed above (**Box 1**), we do not need to assume a simple linear correlation between health and lifespan. Rather, rising rates of markers of disease in bone among early agricultural populations could simply reflect that people typically lived in poorer states of health. Since early farmers do not appear to have lived significantly longer than their hunter-gatherer predecessors, elevated frequencies of pathological indicators are unlikely to be an artefact of a new reservoir of older individuals, in whom such deterioration would be expected regardless of their subsistence niche, but rather indicate higher levels of morbidity throughout a similar lifespan.

Collectively, therefore, there is strong evidence for a major demographic shift associated with the origins of agriculture, driven primarily by rising fertility rates. While it is expected that higher resolution data will reveal subtle and minor regional variations to this trend that are dependent on local circumstances, there is no doubt that the transition to agriculture was accompanied by a significant demographic shift that stimulated the population growth of the last 10,000 years.

Increased Allocation to Defence

There is a significant body of evidence that many of the most significant infectious diseases that afflict human societies originated in other species, were propagated by the process of domestication, or found enhanced environments for vector-borne transmission following the transition to agriculture (234, 235). There is also a demonstrable link between agricultural land use and infectious disease risk today (236).

The impact of these diseases on human populations is demonstrated by genetic evidence, which suggests that pathogens have been the main selective pressure in recent human populations (237, 238). Palaeopathological evidence from prehistoric archaeological sites is consistent with the hypothesis of increased exposure to pathogens among early farmers. An early, and now classic, synthesis of research in this area identified widespread increases in markers of disease associated with the transition to agriculture in different regions (20). While some of the assumptions of this interpretation have been challenged (239), the general observations have been repeated in other regions and very large datasets (240) suggesting that the relationship between the agricultural transition and exposure to infectious disease is widespread and consistent.

More recent comparisons of hunter-gatherer and Neolithic skeletons spanning the earliest origins of agriculture in the Levant have demonstrated an increase in pathological conditions causing inflammatory lesions among the earliest farmers, and this has been interpreted as evidence for heightened immune function in response to pathogen exposure (241). The most significant recent review of palaeopathological evidence for infectious disease following the transition to agriculture demonstrates increases in the prevalence of four infectious diseases that are slow to progress and leave signatures on the skeleton: treponematosis, tuberculosis, dental caries, and periodontal disease (242). These infectious diseases generally represent chronic conditions that cause consistent, long-term effects on human health, and therefore represent markers of elevated morbidity rather than overt mortality risk and shorter lifespans (as discussed above). Their slow progression in part explains the fact that they are manifest in skeletal lesions, as the skeleton is slow to remodel and only reflects conditions over a long period of time. Such diseases would have necessitated heightened and sustained immune response, which as discussed above would be energetically costly.

The long-term energetic costs of pathogen response could be exacerbated by the evolution of pathogens themselves. Pathogens may become more or less virulent through time, depending on mechanisms of transmission, morbidity, mortality, and the frequency of epidemic waves. If an infection immunizes those

who survive, and returns at a relatively short interval of 5–10 years, then it will automatically become a childhood disease. One consequence of this, observed both in mathematical models and in recent demographic datasets, is that adult life expectancy may increase even as life expectancy at birth declines (243). Using average lifespan as a marker of investment in defence is therefore of limited value, and markers of skeletal health in different age groups merit more attention. This underscores the importance of demography to our interpretation of palaeopathological data in the archaeological record (244).

An increased parasite burden would also place energetic demands on the host. Recent evidence demonstrates for example the presence of whipworm at the early farming community of Çatalhöyük in modern Turkey (245). In sum, the prehistoric impact of pathogens on human populations seems clear, both in the increased burden of infectious disease, and the energetic consequences of the immune response.

Reduced Allocation to Maintenance

In contrast to the three life history functions considered above, it is more challenging to interpret changes in energy allocation to maintenance in the past, as the only remaining biological tissues are typically bone and teeth. One possible approach is to consider markers of bone maintenance. Recent evidence documents a general decline in the mechanical competence of the skeleton associated with the transition to agriculture, both in cortical (222, 246) and trabecular (247) bone. While this is perhaps best interpreted in relation to decreasing mechanical loading of the skeleton and dietary shifts, it also reflects a decreased investment in skeletal tissue remodelling throughout the adult lifespan, and thus decreased investment in skeletal maintenance.

While it is difficult to identify other specific markers of cell maintenance in the past, we can draw on physiological studies in living humans to interpret archaeological evidence. One measure of maintenance is antioxidant capacity, which fights the accumulation of free-radicals that are associated with multiple diseases. While antioxidant profiles have not been sufficiently compared between hunter-gatherers and agricultural populations, there is evidence that more homogenized diets with lower diversity of plant foods lead to lower antioxidant levels (248), and that antioxidant levels are inversely proportionate to cancers (249). Likewise, higher antioxidant levels appear to prevent low-density lipoprotein oxidation, which delays the onset of atherogenesis and progression of atherosclerosis (250). This evidence is suggestive of an association between dietary shifts and a decrease in measures of somatic maintenance.

One line of evidence that can illuminate this issue comes from the analysis of mummified human remains. A recent study of 137 mummified humans from recent ancient populations from Egypt and Peru, and recent ancestral populations in southwest America and the Aleutian Islands, demonstrated the presence of atherosclerosis in 34% of all individuals, with a prevalence ranging from 25 to 60% within populations (251). This study found high frequencies of atherosclerosis among several agricultural populations. While the Aleutian Islanders included in this study practiced a hunter-gatherer subsistence strategy, their diet was also very high in animal protein and fat as is typical of arctic foragers. At this stage, there is no similar prehistoric evidence from terrestrial or marine foragers at lower latitudes, however living Tsimané forager-horticulturalists from Bolivia show low levels of coronary atherosclerosis (128). How the transition to agriculture affected cardiovascular health therefore remains unclear, and might demonstrate heterogeneous effects.

More broadly, further work is required to clarify trends in the allocation of energy to maintenance. However, under the logic of the capacity-load model (252), reduced linear growth can also be considered a marker of depletion of maintenance in the long-term. Growth is most sensitive to insults in early life, and this is a key period for the development of the metabolic capacity for homeostasis (252). During development, growth is associated with organ size (253), and in adulthood, shorter adults have smaller organs and poorer capacity for metabolic homeostasis (117, 254). Thus, the declines in growth described above provide indirect evidence for reduced energy allocation to maintenance.

Of relevance here, the allocation of energy to maintenance also involved new forms of pooled energy budgets (118), where both adults and children could undertake specific subsistence tasks. On the one hand, parental subsistence activities may have increased the supply of energy to meet the maintenance costs of children, for example by developing food stores that could feed entire households during "hungry seasons." On the other hand, farming also provided new opportunities for children to contribute to subsistence effort, for example by shepherding domesticated animals, or by gleaning crops at harvest time. The energetic consequences of variation in habitual activity, as a component of both intra-and inter-individual life-history trade-offs, is an area that requires further research.

In summary, the preponderance of evidence suggests that there were general and coordinated life history shifts associated with the transition to agriculture, supporting the overall trends illustrated in **Figure 6**. Agricultural subsistence generated more energetically-rich food through the processing of grain and through secondary animal by-products like milk. The energetic and mechanical properties of this diet, in combination with the storage of surpluses, ensured the perpetual availability of weaning foods, and led to shorter inter-birth intervals. Agricultural communities were also typically sedentary which, in combination with living in close proximity to domestic animals, increased the pathogen burden. The general features of agricultural societies led to increased energetic availability in general, but also an increased risk of famine, and overall characteristics of the environment that lead to life-history trade-offs. From the review above, we note that the transition to agriculture appears to be typically associated with reduced energetic investment in maintenance and growth, and increased investment in reproduction and defence.

Our review has assumed that these life history transitions were primarily driven by plastic responses, and we have drawn on similar evidence from contemporary humans to provide mechanistic support. However, early agriculturalists may have replaced foragers in any given niche, as well as exposing themselves to new selective pressures, hence genetic factors undoubtedly merit further research. The population growth that followed the transition to agriculture increased the opportunity

for new mutations to manifest (255), while niche construction is likely to have intensified selection on certain genes (9, 256). In **Table 4**, we provide examples of genetic change in traits relevant to all four life history functions, likely to have occurred in response to selective pressures provoked by the transition to agriculture.

While these trade-offs seem to generally hold for most of the available evidence, we may expect variations in some populations dependent upon a variety of ecological factors including the nutritional composition of crops and the local infectious disease burden. In that sense, we suggest that "the exceptions prove the rule," in that it is also possible for the adoption of agriculture to elicit different life history strategies through the same plastic mechanisms. For example, should farm yields and ecological conditions permit, greater energy might be allocated to growth. More broadly, our framework can also be applied to populations that did not adopt agriculture, including contemporary foraging societies, or those currently transitioning, as discussed in **Box 2**.

The Central Role of Women and Inter-Generational Effects

While life history trade-offs could have emerged both through genetic adaptation, and life-course plasticity, it is worth focusing briefly on inter-generational trade-offs. The transition to agriculture had major impact on women, for several reasons. First, as highlighted above, increases in fertility inherently place unique energetic stresses on women, through the processes of pregnancy and lactation. While agriculture made possible new cereal-based complementary foods, allowing populations to wean their offspring earlier than typical of foragers (272), the changes may also have accelerated the rate at which successive offspring were produced. Second, women's subsistence tasks also changed. There is strong evidence that women performed a high proportion of repetitive subsistence-related labour, following the adoption of agriculture in central Europe. In particular, habitual loading of the upper limbs due to repetitive use of the saddle quern to process grain, led women to have greater mechanical loading than contemporary athletes (273). This labour may have simultaneously raised their energy needs, whilst also increasing their exposure to pathogens. While much of the evidence suggests a decrease in terrestrial mobility associated with the transition to agriculture in most but not all contexts (222, 246, 274, 275), this may have been counterbalanced by an increase in manual labour among both sexes (273, 276), so specific aspects of behavioural shifts associated with the transition to agriculture are expected to be spatially and temporally variable (277).

The notion that energetic stresses experienced by women propagate metabolic penalties to the next generation is supported by data on contemporary human populations. For example, across 96 countries, an index of societal gender inequality (indicating women's low status in society relative to men, mediated by a lack of access to resources and opportunities that promote health, education, and autonomy) was associated with three markers of child under-nutrition (low birth weight, and child stunting and wasting) as well as the risk of child mortality in the first 5 years of life (**Figure 7**) (278). In contemporary populations, women continue to be allocated both subsistence tasks as well as the primary responsibility for looking after infants and young children.

However, many studies have shown that male offspring are more susceptible to malnutrition in early life (279), most likely because their faster growth rate makes them more sensitive to any constraints on energy supply. Of interest here, there is evidence for more significant body size shifts among men than women (220), which suggests that male offspring disproportionately picked up the signal of energetic stresses affecting adult women.

Unanswered Questions

While we have found supportive evidence for our primary hypothesis, that the adoption of agriculture profoundly changed human biology through re-organising life history trade-offs, many more specific questions remain. Given the considerable spatial, temporal, ecological, and cultural variation in the transition to agriculture globally, one would not predict a uniform response in different regions. Our key aim at this stage has been to provide a broad and solid conceptual framework that may inform and guide such future research questions. A series of issues meriting further work, regarding the timing of change, the environmental factors responsible, and the biological mechanisms involved, are listed in **Table 5**.

Progress in investigating these questions requires more integrative approaches to the bioarchaeology of past populations. Research programmes in this field are often determined by focus and methodology, investigating variation in prehistoric human health, diet, or activity in isolation. Studies that are beginning to combine relevant datasets in the study of prehistoric dietary transitions, incorporating for example the study of body size, activity patterns, and diet (280), provide a model of such fruitful integration. Major global comparisons of prehistoric health, such as those conducted in the "Global History of Human Health" project (240, 281, 282), provide useful integration of relevant palaeopathological and growth data, but would benefit from broader integration and theoretical context to begin to investigate past life history transitions.

A key challenge for bioarchaeologists is the interpretation of detailed demographic and life history data from skeletal assemblages. There are many approaches to palaeodemographic interpretation of factors relevant to the interpretation of life history traits, such as population structure, mortality, and migration (283), the challenges of which have been discussed at length (284). New osteological approaches have also been developed for the interpretation of fertility (285) and the timing of puberty (286) that deserve greater attention. Future research could address many of the questions posed above through systematic comparison of skeletal assemblages and the integration of bioarchaeological studies of prehistoric growth, activity, diet, and pathology with skeletal estimates of life history parameters including fertility, birth weight, age at menarche, and age at death and mortality profiles. There are also opportunities to apply modelling approaches. For example, both human biology and agriculture can be approached through the lens of "risk management" (287, 288).

TABLE 4 | Hypothesised selective pressures and genetic change impacting life history functions associated with the transition to agriculture.

Inferred selective pressure	Change in alleles	Life history functions affected	References
Increased burden of infectious disease	Most adaptations targeting coding variation related to human innate immune function have occurred in the last 6,000–13,000 years	Defence	(257)
Rising population density and pools of standing water favour mosquito-borne diseases	Selection for various forms of haemoglobinopathy in last 5,000 years, providing protection against malaria	Defence	(258)
Changes in the physical properties of food	Quantitative genetic models show directional changes in skull morphology indicating trend toward lower masticatory demands	Growth	(259)
Domestication of plants	Modifications to Cytochrome P450 and NAT2 genes promote detoxification of plant secondary compounds	Defence	(256)
Introduction of dairying	Independent emergence of alleles for lactase persistence emerged in several different global regions in association with dairying	Growth	(260)
Increased consumption of starch from new crops	Genetic variants of TCF7L2 associated with improved blood sugar regulation evolved in three global regions at the same time as agricultural transition	Maintenance	(261)
Consumption of new fermented products that contain alcohol	Selection on alcohol dehydrogenase alleles resulting in more efficient ethanol metabolism	Maintenance	(262)
Increased risk of famine associated with crop failure	Derived GIP-1920A haplotype could have maintained higher maternal blood sugar levels during famines, favouring fetal survival and growth	Reproduction	(263)

BOX 2 | Populations that did not adopt agriculture.

While our focus has been on the transition to agriculture, much may be gained from extending the investigation of trends in life history trade-offs to populations that did not adopt any kind of farming, or who made only transient shifts toward agricultural subsistence, or who are only just starting to make this transition.

In the long-term past, populations that continued to forage provide a key reference against which to compare early farmers. Prehistoric foragers did not necessarily inhabit stable ecological environments, and may for example have had to adapt to major climatic change, as highlighted by research on the Natufians in the Levant (2, 264). Moreover, populations that persisted in foraging may have been exposed to the impact of neighbouring farmers on the local ecology (9), and over longer time periods foragers were increasingly pushed toward more marginal habitats (191).

Similarly, it is possible to study more recent "transitions to agriculture," where foraging is only recently or currently being abandoned. Examples include the Toba and Wichí of the Argentine Gran Chaco (265), the Tsimane in Bolivia (266), the Pume in Venezuela (267), the Ache in Paraguay (268), and the Hadza in Tanzania (269). Other researchers have addressed this opportunity by studying groups of farmers and foragers that are closely related, such as the Bofi of the Central African Republic (270).

Such research can provide unique insight into the shifting trade-offs that we consider fundamental to the transition in the past. For example, a study of the Agta, a foraging population from the Philippines, found that more sedentary groups engaging in horticulture demonstrated increased levels of viral and helminthic infections but also higher fertility levels compared to those still foraging, thus supporting the notion that the shift toward sedentary life diverts energy toward defence and reproduction (271).

For those addressing genetic adaptations, a current limitation is the bias of genome-wide association (GWA) studies toward individuals of European ancestry. For example, a summary of GWA studies reported up to 2019 found that 78.4% of individuals included in such studies were of European ancestry, and just 10.2, 2.0, and 1.3% of Asian, African or Hispanic/Latin American ancestry, respectively (289). Further work could provide a more comprehensive perspective on genetic change associated with the transition to agriculture.

While our main aim is to encourage application of the life history theoretical framework to the archaeological record, it may also be used to shed light on life history traits in contemporary farmers, especially where they have practiced a specific form of agriculture for many centuries (**Box 3**). One intriguing issue relates to human—plant—parasite interactions. Although cultivated crops most obviously supply human energy needs, they may also supply specific nutrients that promote immune defence against local pathogens (299). For example, the cultivation of fava beans is common among circum-Mediterranean populations, and dates back to ∼8,500 years in the Levant. These populations also demonstrate high levels of deficiency in the enzyme glucose-6-phosphate dehydrogenase (G6PD), and both G6PD deficiency and fava beans increase risk of "favism," a form of acute haemolytic anaemia. However, G6PD deficiency also confers protection against malaria, and this protection is enhanced by consumption of fava beans (299). This and other examples indicate that the type of crops cultivated could alter the impact of pathogens on human biology, with potential implications for life history trade-offs.

Overall, we hope that our conceptual approach will stimulate more work on the transition to agriculture, and indeed it could also be applied to other transformations of the human subsistence niche, as briefly reviewed next.

BEYOND AGRICULTURE

The life history transitions that we have focused on around the origins of agriculture are by no means unique. Our over-arching

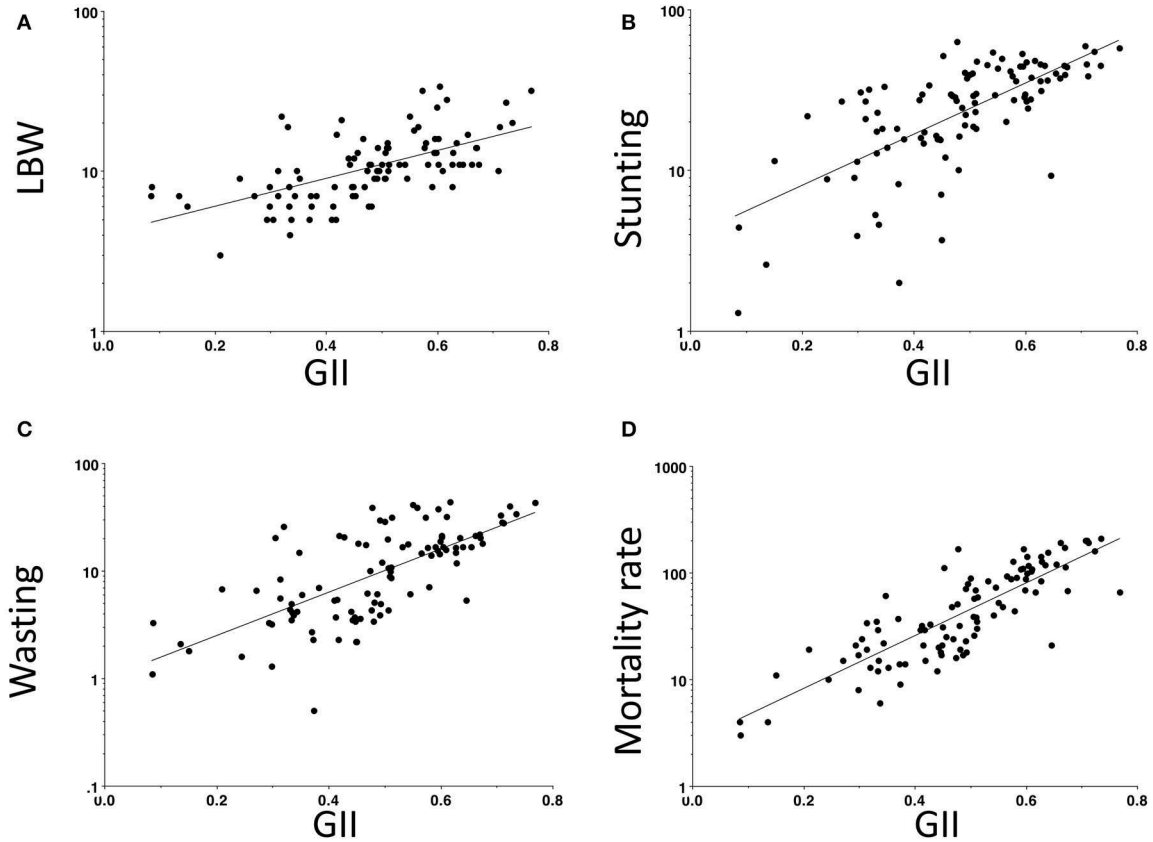

FIGURE 7 | Associations of the Gender Inequality Index (GII), a marker of societal gender inequality, with the prevalence of **(A)** low birth weight, **(B)** child stunting, **(C)** child wasting, and **(D)** the risk of child mortality in the first 5 years of life, across 96 countries. Reproduced with permission from Marphatia et al. (278).

TABLE 5 | Issues that merit investigation in future work.

Timing
Which periods generated the greatest selective pressures, opportunities or stresses, and drove the most marked life history shifts?
How correlated were life history trade-offs temporally?
What were the implications for human life-history trade-offs of first domesticating crops vs. animals?
Were there periods that favoured increased energy allocation to growth and maintenance?
How did past disease epidemics emerge, and in which periods did mortality risk peak?
Environment
How did human life-history trade-offs vary in association with different types of agriculture?
How did trade-offs vary in association with different ecological conditions?
To what extent did "labour traps" associated with dietary and cultural transitions determine energetic allocation toward activity?
How did changing activity patterns shift energy allocation through the lifespan?
Mechanism
To what extent were genetic vs. plastic responses involved?
Beyond energy supply, what other "nutritional currencies"—e.g., macronutrients/micronutrients—drove trade-offs?
What was the shape of life history trade-offs (linear, non-linear)?
Were trade-offs conditional on phenotype, or on developmental experience?

hypothesis is that much adaptive change in humans may be underpinned by such life history transitions. There is evidence that the trends we discussed above were already operating at slower paces during the palaeolithic, and we can project them back into the deeper past. Indeed, contrasting with the current focus on skeletal traits such as the form of bipedalism and the size of the adult brain, the entire evolutionary history of hominins can be portrayed as the evolution of different life history strategies, as explored in another paper in this collection (300). The same approach can also be used to reconstruct the evolution of human childhood and "emerging adulthood" (301, 302).

Similar trade-offs are expected to have occurred since the origins of agriculture. **Figure 8** summarises a series of events in recent human history where combined changes in mortality risk and subsistence niche can be expected to have elicited the reorganisation of human life history strategy. Some of these have already been supported by evidence. For example, Stock and Migliano linked a reduction in stature among Great Andamanese Islanders with increased mortality associated with exposure to British colonial rule (303). We briefly consider in more detail two recent examples.

Onset of Industrialisation

The early industrial revolution was another period in which, paradoxically, substantial population growth occurred in the UK while markers of health and, in some populations, life expectancy declined. These correlated trends were highlighted in the nineteenth century by pioneering political economists, who understood very well that while the overall supply of food was

BOX 3 | Life history adaptations evident in contemporary farmers.

One example of how a particular form of agriculture has left a signal in contemporary life history trade-offs is given by the Sardinian population, a genetic isolate occupying an island off the Italian mainland. Their subsistence mode was historically based on sheep farming and cultivating cereals and legumes, under the notable ecological stress of endemic malaria. Until recently, the typical phenotype of Sardinians included short stature (290) but also longevity, indicated by a high prevalence of centenarians (291), as well as lactose intolerance (292). The population also shows a very high prevalence of G6DP deficiency, which can be attributed to the selective pressure of malaria. Co-adaptation of the microbiota also appears to contribute to longevity (291), whereas gene polymorphisms of cytokines playing a major regulatory role in the inflammatory response are not associated with life expectancy (293). The microbiome can impact many metabolic traits in the host, for example by varying in its species diversity, the presence of species that aid the digestion of particular diets, and its inflammatory profile (294–296). This suggests that, aside from any selective pressures acting directly on human genetic determinants of lifespan, the transition to agriculture might also have elicited life history trade-offs through changes in the genetic profile of the microbiome.

In recent decades, the eradication of malaria, nutrition transition, and dietary change has elicited a rapid secular trend in height in Sardinia, greater than elsewhere in Italy (290), but also increased rates of auto-immune diseases such as coeliac disease and type 1 diabetes (292, 297, 298). The high levels of these diseases may reflect the overloading of homeostatic traits that evolved to optimise fitness in pre-modern conditions.

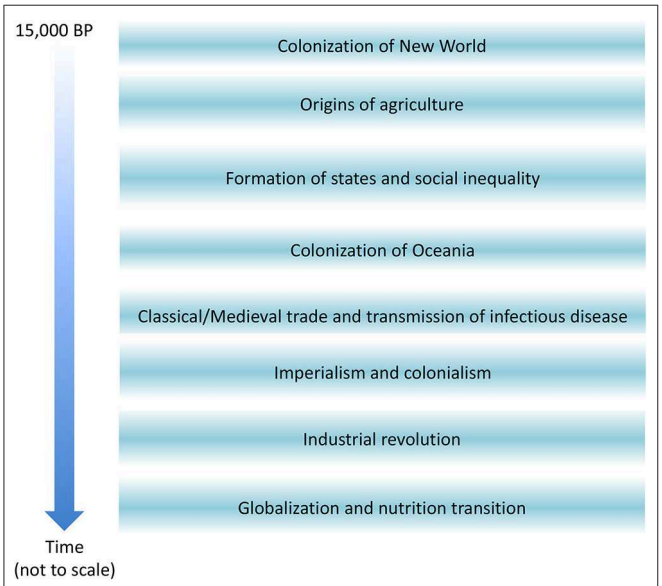

FIGURE 8 | Potential events in human evolutionary and recent history, where changes in mortality risk and dietary subsistence may have elicited the reorganisation of human life history strategy.

increasing, many of the new factory workers were exposed to appalling living conditions and suffered high rates of infant, child, and adult morbidity and mortality (304).

Data on soldiers born in the southern part of the UK indicate a broad decline in adult height from the mid eighteenth to the mid- nineteenth century, reaching a nadir around 1,855 (305). At the same time, the rapidly growing industrial cities were characterised by worsening air pollution and exposure to infectious disease (304). Adults also demonstrated high levels of degenerative diseases, which were directly linked with poor living conditions (306). Nonetheless, the nineteenth century also saw substantial population growth in the UK, from around 11 million in 1,801 to 37 million by 1,901 (307).

These trends match closely with those we have described for agriculture, and indicate the diversion of energy to immune function and reproduction, at the expense of growth and maintenance. Another similarity is that these life history transitions occurred under the influence of dietary change, as new industrial foodstuffs (bread, jam) and imported foods from overseas colonies were used to reduce the costs of expanding the new urban proletariat (308).

Nutrition Transition

The latest life history transition could be said to be taking place through globalisation and the nutrition transition. In high-income countries, the long-term transitions have been favourable to health, indicating the benefits of better food supplies and public health efforts to combat infectious disease (89). Industrialised countries have seen secular increases in height as well as steady improvements in life expectancy, and both of these have been directly associated with declines in infant mortality rate, indicating a lower allocation of energy to immune defence in early life (89). The twentieth century has also seen major demographic changes, encompassing both later onset of reproduction and reduced family size. These demographic changes have been in large part achieved by the uptake of various forms of contraception. Thus, in high-income countries, life history transitions have seen a re-allocation of energy to growth and maintenance, over reproduction, and defence.

In low- and middle-income countries, however, the trends are more complex. Secular increases in height have been relatively modest, especially in south Asia and sub-Saharan Africa (309), whereas increases in obesity have been much more noticeable (310). Improvements in life expectancy have been variable, and epidemics such as HIV briefly reduced it in some countries. Moreover, within recent decades, around 80% of the global burden of chronic non-communicable disease is now occurring in low- and middle-income countries (311).

Why are these trends different from those in high-income countries? A key factor is likely to be the persisting high burden of infectious disease, which is detrimental both to child growth and health (maintenance) (89), as well as other social and environmental stresses (312). Given higher extrinsic mortality risk, it is arguably unsurprising that energy allocation to growth and maintenance is constrained in favour of greater allocation to reproduction and defence. Contrasting with the modest secular increase in height, many populations are showing substantial increases in central abdominal fat, as well as secular declines in the average age at menarche (313). These trends may be exacerbated by the fact that nutrition transition is not only

increasing energy availability, but also changing the composition of the diet, making it more obesogenic (314).

CONCLUSIONS

In summary, we have used life history theory to consider how rapid environmental shifts may have impacted human growth and development by orchestrating coordinated and synchronic life-history trade-offs in human populations. The primary change appears to have been a systematic shift toward allocating energy to reproduction and defence, indicated by population growth and both direct and indirect indications of higher infectious disease load. This shift reduced the energy available for growth and maintenance, indicated by declines in stature and an increase in markers of degenerative bone disease. Where populations did not follow this general pattern, we can still use life history theory to understand how different life history transitions emerged.

The conceptual model that we developed may help understand other major transitions such as industrialisation and rapid nutrition transition. Over the last 150 years in high-income countries, public health efforts have simultaneously improved diet and reduced infection risk, thus reversing the life history transitions that were provoked by adopting agriculture (8). In contemporary low and middle income countries, conversely, where infectious disease burdens remain high for both infants/children and adults, and agricultural yields have been poor for decades, the subsistence niche has changed substantially less over centuries (though this is also related to historical trends such as colonialism) (8). As rapid nutrition transition occurs, the change in energy availability is not accompanied by equally rapid changes in broader living conditions, providing us with new insight into why the primary secular trends relate more to adiposity than to adult height.

We thus link the construction of novel niches with life history responses, including evolutionary strategies for body size. This approach may ultimately help understand how developmental plasticity mediates links between changes in our subsistence niche and human health outcomes.

AUTHOR CONTRIBUTIONS

JW conceived the original idea (10). JW and JS developed the idea in detail and co-wrote the manuscript.

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Sexual Dimorphism of Size Ontogeny and Life History

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Background: Ecological and physiological factors and social and economic constraints affect sex-specific body size. Here, we used the male/female (M/F) height ratio as an indicator of the combined effect of genetic and sex characteristics. We hypothesized that (1) sexual dimorphism in body size will be established during infancy and adolescence when growth velocity is maximal, (2) living standards and health are important factors which can affect sexual dimorphism in body size, (3) variations in sexual dimorphism in body size are due to the differential response of boys and girls to environmental cues, and (4) sexual dimorphism in body size will be more pronounced in those populations whose average height and weight are the greatest.

Methods: To study the ontogeny of sexual dimorphism from birth until the age of 18 years, we used the 2000 CDC growth data. Data on height by country, life expectancy, and gross domestic product (GDP) per capita based on purchasing power parity were extracted from the national accounts data of NCD Risk Factor Collaboration, the World Bank, Eurostat: Demographic Statistics, Secretariat of the Pacific Community: Statistics and Demography Program, and the US Census Bureau.

Results: We found that sexual dimorphism in body size starts at age 1 month, peaks at age 3 months, and diminishes by age 24 months. During childhood, there is no sexual difference in body size, and it is gradually established when the boys enter puberty. The M/F height ratio correlates positively with the average male and female height and weight by country.

Conclusion: Sexual dimorphism in body size occurs when (a) the growth velocity is maximal during infancy and adolescence, (b) living standards are high, and health correlate positively with male/female height ratio. Anthropological studies and our results emphasize mostly the female resiliency hypothesis: shorter male heights in times of environmental stress lead to smaller sexual dimorphism in body size.

Keywords: sexual size dimorphism, male/female height ratio, hypoallometry, hyperallometry, environmental stress, subsistence-based societies, GDP per capita, life expectancy

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For some animal species, sexual, survival, and fecundity selection can influence the degree of sexual dimorphism in body size (1, 2). In humans, ecological and physiological factors and social and economic constraints may also affect sex-specific body size (3, 4) The relationship between male and female body size is hyperallometric in those taxa where males are larger and hypoallometric in those taxa where females are larger (5). In humans, different hypotheses have been proposed to explain the variation of

sexual dimorphism in height, but no consensus has emerged. It has been proposed that the extent of sexual dimorphism in human populations results from a trade-off between size-related mortality and size-related obstetric complications and fertility (2). A study of dental data for great apes and ten hominid samples reported a decline in sexual dimorphism in body size during the last three million years (6). There is a contrasting report that contemporary agriculturalists exhibit a greater degree of sexual dimorphism in stature than present-day hunter-gatherers (7). Sociologists argue that sex differences in stature between societies can be influenced by female discrimination, female labor participation, and relative mobility and the effects of famine and crisis periods (3, 4).

Sexual dimorphism in body size may serve strategic evolutionary fitness goals, which are also the outcome of the different responses of boys and girls to environmental cues. Stature variation among populations results from a complex interaction of genetic and environmental influences. Two genotypes that can produce the same adult height under optimal environmental circumstances can also produce different heights under circumstances of deprivation (3). Thus, children who are tall in a wealthy community might be short when the economic conditions are poor. Height is generally believed to be mostly influenced by the quality and quantity of nutrition and the disease environment, to the extent that some economic historians have used height as a measure of a population's living standards (8–10). The male/female (M/F) height ratio can serve as an indicator of the combined effect of genetic and sex characteristics and the social and economic environment. Since stature is most vulnerable in youth, especially during the first year of life (11), analyzing adult heights can indicate the susceptibility of children to their environment.

Against this background, we hypothesized that (1) sexual dimorphism in body size will be established during infancy and adolescence when growth velocity is maximal, (2) living standards and health are important factors which can affect sexual dimorphism in body size, (3) variations sexual dimorphism in body size are due to the differential response of boys and girls to environmental cues, and (4) sexual dimorphism in body size will be more pronounced in those populations whose average height and weight are the greatest.

In order to understand the impact of living standard and health on sexual dimorphism in body size, we correlated the gross domestic product (GDP) per capita based on purchasing power parity and life expectancy (survival selection) with the sexual dimorphism in body size in both 161 modern countries and subsistence-based preindustrial societies. We considered a country and a society to be a population of people that is related by geographical context and by descent, but also by its physical cultural and economic environment. A population so understood is a temporally continuous, spatially scattered entity that changes over time (12). We used the average male and female height and weight by country from 1992 to 1996 as obtained from the NCD Risk Factor Collaboration (NCD-RisC) dataset of average country heights from 1896 to the present day (http://www.ncdrisc.org/d-height.html) and a database of 34 preindustrial societies.

METHODS

Data Sources

To study the ontogeny of sexual dimorphism on male and female height from birth until the age of 18 years, we used the 2000 CDC growth data http://www.cdc.gov/growthcharts/.

GDP per capita is an economic snapshot of a country and was used to estimate the country's economic health. Data on GDP per capita ($US) based on purchasing power parity were extracted from the national accounts data of the World Bank (http://data.worldbank.org/indicator/NY.GDP.PCAP.CD) and entered into the database.

Life expectancy at birth indicates the number of years a newborn infant would live if prevailing patterns of mortality at the time of birth were to stay the same throughout life and was used as a measure of health. There are great variations in life expectancy between different parts of the world, and these differences are mostly caused by differences in public health, medical care, and diet. The data on life expectancy at birth were collected from the World Bank's data bank, whose sources are (a) the United Nations (UN) Population Division, World Population Prospects, (b) the United Nations Statistical Division, Population and Vital Statistics Report (various years), (c) census reports, and other statistical publications from national statistical offices, (d) Eurostat: Demographic Statistics, (e) Secretariat of the Pacific Community: Statistics and Demography Program, and (f) the US Census Bureau: International Database (http://data.worldbank.org/indicator/SP.DYN.LE00.IN) and entered into the database.

To determine whether sexual dimorphism in body size will be greater in countries whose population's average height and weight are greater than those in countries whose population's average height and weight are smaller, we used data on average male and female height by country in 161 countries from 1992 to 1996. These data were obtained with permission from the NCD Risk Factor Collaboration (NCD-RiSC) dataset (http://www.ncdrisc.org/d-height.html) and entered into the database. This dataset includes sources that were representative of a national, subnational, or community population and had measured height. Self-reported height and data sources on population subgroups whose anthropometric status may differ systematically from that of the general population were not included in the study. Size dimorphism is defined as the ratio between male and female height.

Data on 34 subsistence-based societies was obtained from Robert Walker's unpublished open source field notes (http://anthropology.missouri.edu/people/walker.html) and his published reports (13). The data on population density, which in subsistence-based society represents the economic wealth in a positive correlation, the average male and female height, body weight, life expectancy at birth, and at the age of 15 years was entered into the dataset. At the time of data collection on the subsistence-based societies, ethical approval was not required, and the authors had no access to any individual's data.

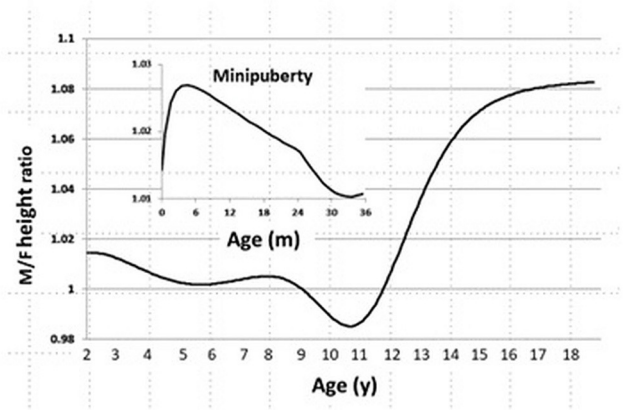

FIGURE 1 | Sexual dimorphism in body size from age 0 to 20 years in the CDC 2000 database. Male/Female height ratio as a function of age. Minipuberty occurs mainly in the first 3–6 months of life in both sexes when there is transient activation of the hypothalamic-pituitary-gonadal axis during the neonatal period and results in high serum gonadotropin and sex steroid hormone levels.

Statistical Analysis

All statistical analyses were done using a software statistical package (IBM SPSS Statistics 20.0) and statistical significance was set as 5%. The M/F height ratio as a function of age was calculated using growth data from birth until age 18 years. The Pearson's correlation coefficient was used to calculate the strength and direction of association of the linear relationship between the M/F height ratio by country and the average anthropometric parameters of males and females from 161 countries, GDP, and life expectancy. The Spearman's correlation coefficient was used as a nonparametric measure of the strength and direction of association between the M/F height ratio and the average anthropometric parameters of males and females, life expectancy, population density in preindustrial societies.

RESULTS

In the CDC 2000 growth database, we found that sexual dimorphism in body size starts at age 1 month, peaks at age 3 months, and declines by age 24 months. During childhood, we also found no sexual difference in body size, and it is gradually established when the boys enter puberty (**Figure 1**).

We found that the M/F height ratio correlates positively and strongly with the average male height by country ($r = 0.519$, $p < 0.0001$). The correlation between the M/F height ratio and the average female height by country was also positive, but not as strong as that for the average male height by country ($r = 0.18$, $p = 0.019$, **Figure 2A**). The correlation between the M/F height ratio and male weight ($r = 0.54$, $p < 0.0001$) was also positive and stronger than that between the M/F height ratio and female weight ($r = 0.29$, $p < 0.0001$, **Figure 2B**).

We found that life expectancy at birth and GDP strongly and positively correlate with the M/F height ratio in modern countries ($r = 0.57$, $p < 0001$; $r = 0.40$, $p < 0001$, respectively, **Figure 3**). The ratio is greater in countries with high life expectancy at birth (healthy countries) and in countries with a high GDP (wealthy countries).

In subsistence-based preindustrial societies, we also found that some allometry occurs. Specifically, we found that the M/F height ratio correlated positively and strongly with the male and female weight ($r = 0.57$, $p < 0.0001$; $r = 0.43$, $p < 0.001$, respectively) and with male height only ($r = 0.41$, $p < 0.001$), (**Figures 4A,B**). The correlations with weight were stronger than that for height. These results found in preindustrial societies are similar to those found in modern countries, the correlation between male/female height ratio with male size was greater than with the female size (**Tables 1**, **2**). In preindustrial societies, male and female height and weight correlated strongly and significantly with life expectancy at birth and at age 15 years (**Table 3**).

DISCUSSION

In *Homo* species and the great apes, males have greater body size and are more muscular and stronger than females (3, 14). As well as these biological differences between males and females, other determinants, such as nutrition, health care, and disease, might play an important role in determining height differences between males and females. Here, we report that the ontogeny of size dimorphism is related to sex hormones; it is evident during minipuberty, and it is established during puberty. It is greater in tall populations living in good economical and health circumstances than in short populations living in poor and stressful conditions.

Gray and Wolf and others found that dietary factors can influence the degree of sexual dimorphism in size resulting in a decrease in male-female height differences under conditions of nutritional stress and an increase the M/F height ratio with improved diet (15–18).

We found a positive correlation between the M/F height ratio and health, as indicated by life expectancy. It seems that women are more resilient during environmental stress (19). This summary of a sex difference in mortality included the probability of survival to age 70 by county in the United States, the Human Mortality Database data for 18 high-income countries since 1900, and mortality data within and across developing countries over time periods for which reasonably reliable data are available. These data reveal that in each period of economic development after the onset of demographic and epidemiologic transition, cross-sectional variation in sex differences exhibits a consistent pattern of female resilience to mortality under adversity.

Current theory on the sexual dimorphism of the stress response posits that females exhibit an affiliative behavior (a "tend and befriend" response) whereas males exhibit more of a fight or flight response to stress (20). Oxytocin is thought to be important in female affiliative behavior whereas testosterone or vasopressin might be more important for male social behaviors (21). In a US national sample of 432 female and 1,200 male Vietnam veterans, for both genders direct links

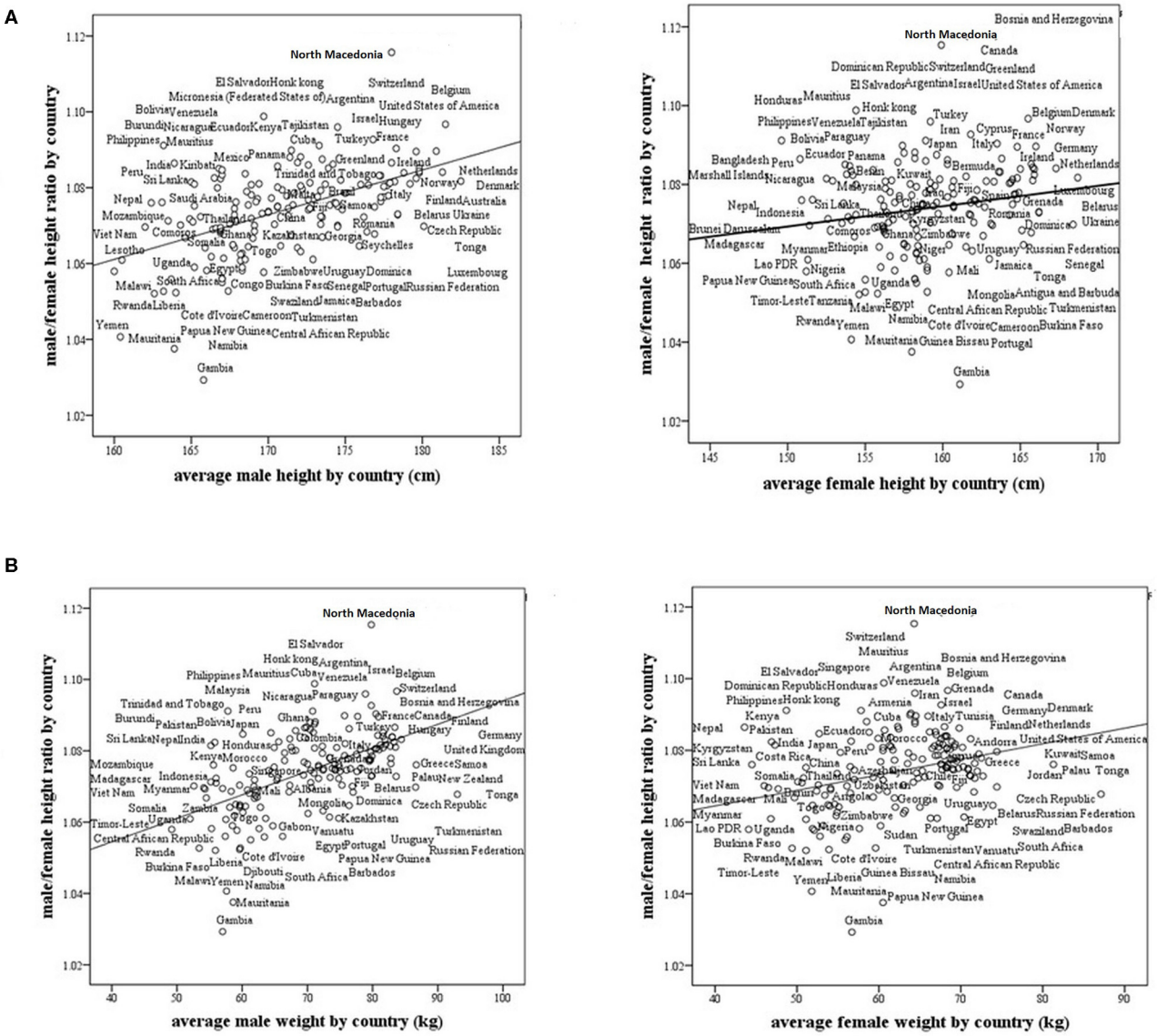

FIGURE 2 | Male/female height ratio as a function of the average male and female size in 161 modern countries. **(A)** Male/female height ratio as a function of the average male and female height by country. For males, $R = 0.519$, $p < 0.0001$, and for females, $R = 0.18$, $p = 0.019$. **(B)** Male/female height ratio as a function of the average male and female weight by country. For males, $R = 0.54$, $p < 0.0001$ and for females, $R = 0.29$, $p < 0.0001$. R-Pearson's correlation coefficient.

to post-traumatic stress disorder PTSD from war-zone, war-zone stressors appeared preeminent for PTSD in men, while post-trauma resilience recovery variables were more salient for women (22). This sexual dimorphism in the stress response is supported by experimental work with rodents. In a study of prenatal restraint (PS) stress on anxiety- and depression-related behavior in both male and female adult Sprague-Dawley rats, PS significantly increased anxiety-related behavior in male, but not in female offspring. Likewise, depression-related behavior increased in male PS rats only. Further, male PS offspring showed increased basal plasma corticosterone levels in adulthood (23). Further, the data indicated that epigenetic regulation is affected differentially in male and female PS offspring. These sex-specific alterations may, at least in part, explain the female resilience hypothesis. The Chinese Center for Disease Control and Prevention published an analysis of coronavirus cases. Although men and women have been infected in roughly equal numbers, the death rate among men was 2.8 percent, compared with 1.7 percent among women. Men also were disproportionately affected during the SARS and MERS outbreaks (24). One hypothesis is that women's stronger immune systems confer a survival advantage to their offspring, who imbibe antibodies from mothers' breast milk that help ward off disease, while the infants' immune systems are still developing (24). It was suggested that

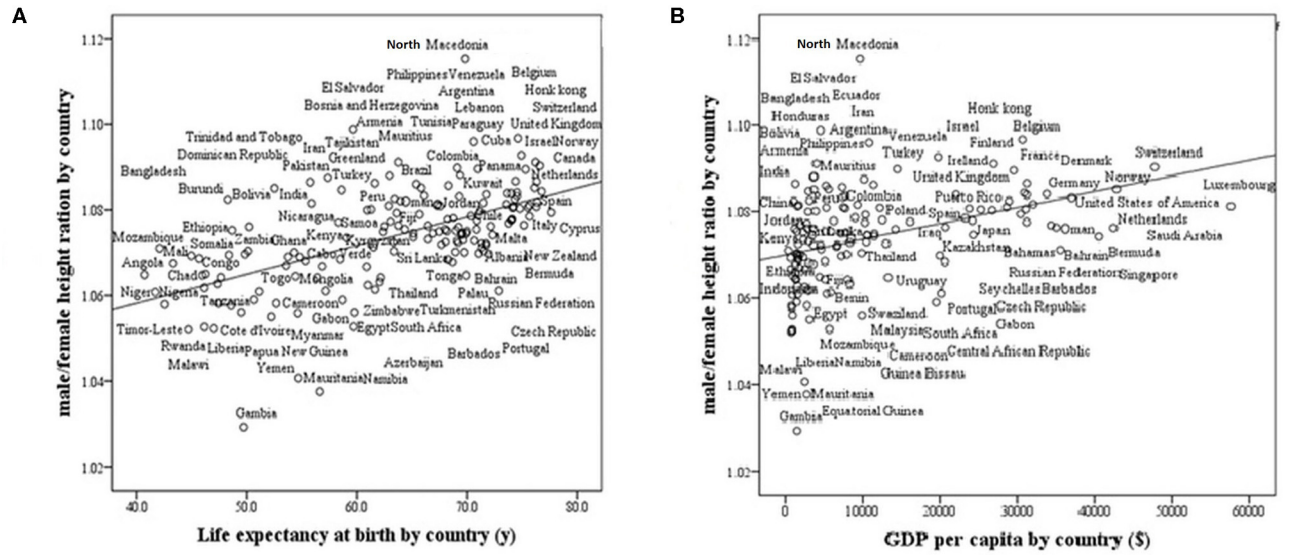

FIGURE 3 | Male/female height ratio as a function of life expectancy at birth and GDP per capita in 161 modern countries. R-Pearson's correlation coefficient. **(A)** Life Expectancy at birth by country. $R = 0.57$, $p < 0.0001$. **(B)** GDP (Gross domestic product based on purchasing power parity) per country. $R = 0.40$, $p < 0001$.

estradiol also contributes to cognitive stress resilience in females (25). The contribution of this mechanism, combined with intra-hippocampal synthesis of estradiol, contributes to mediating cognitive resilience to chronic stress demonstrated by females, but not males.

Moreover, males are more susceptible to fluctuations in nutritional quality; for example, the impairment in long bone growth is greater in males than females under the same food deficits (14). However, food consumption behavior cannot be neglected at higher income levels; for example, teenage girls in wealthy societies in the twenty-first century might consume less food in order to be slim for cultural and fashion reasons. Before the industrial revolution, food, and health resources were scarce, and there were gender-related conflicts about its distribution. A long-term nutritional shortage and poor health during childhood can result in a reduced adult height in both sexes with greater impact on men's height than that of women.

In this investigation, we defined sexual dimorphism in body size as the ratio between male and female height. This definition differs from that of some biologists and anthropologists who used the difference between the mean heights of males and females to define sexual dimorphism in body size. We also used national averages in height and weight, while recognizing variations within countries. We previously found that between-countries variations are somewhat smaller than within countries: for men, the between-countries average height ranges from 158 to 183 cm (Indonesia and Netherlands, respectively), with a standard deviation (*SD*) of 5.9 cm, as compared to 164–190 cm with an *SD* of 6.5 cm within the USA (CDC 2000; 3–97th percentile).

Gray and Wolfe (16) compared the mean heights of men and women in various societies from Africa, the Mediterranean region, Eastern Eurasia, and North and South America. The results of our study confirm their results of increasing sexual dimorphism in body size with increasing height of the population. Baten and Murray performed a time-series analysis by birth cohort of average heights of men and women who were imprisoned in nineteenth century in Bavaria (26) They showed that final adult height of women responded much more systematically than did men's heights to differences in economic, nutritional and disease conditions in infancy. Female height, but not male height, was reduced by the 1840 potato crisis, tuberculosis prevalence, and illegitimate birth. Finally, a study of the Indian population between the 1930s and 1970s reported that the mean height of both females and males increased when the food supply increases in a similar manner. However, they also reported an increase in sexual dimorphism in body size that occurred during a food crisis in the states of Kerala and Orissa when a clear decline in height of both men and women was evidenced, pointing in their view to a rise in female discrimination during poor times when care and investment in girls is reduced disproportionately (27).

Gustafsson and Lindenfors investigated whether there was an allometric relationship between male and female stature in humans in 124 populations who lived in the latter part of the twentieth century. They found that sexual dimorphism in body size did not correlate with height (28). Here, we describe a strong hyperallometry when the M/F height ratio is correlated with male, but not female, body size. Hence, we posit that sexual dimorphism in body size can be attributed to a male's negative response to a stressful environment.

Holden and Mace investigated the connection between sexual dimorphism in body size and the division of labor in worldwide

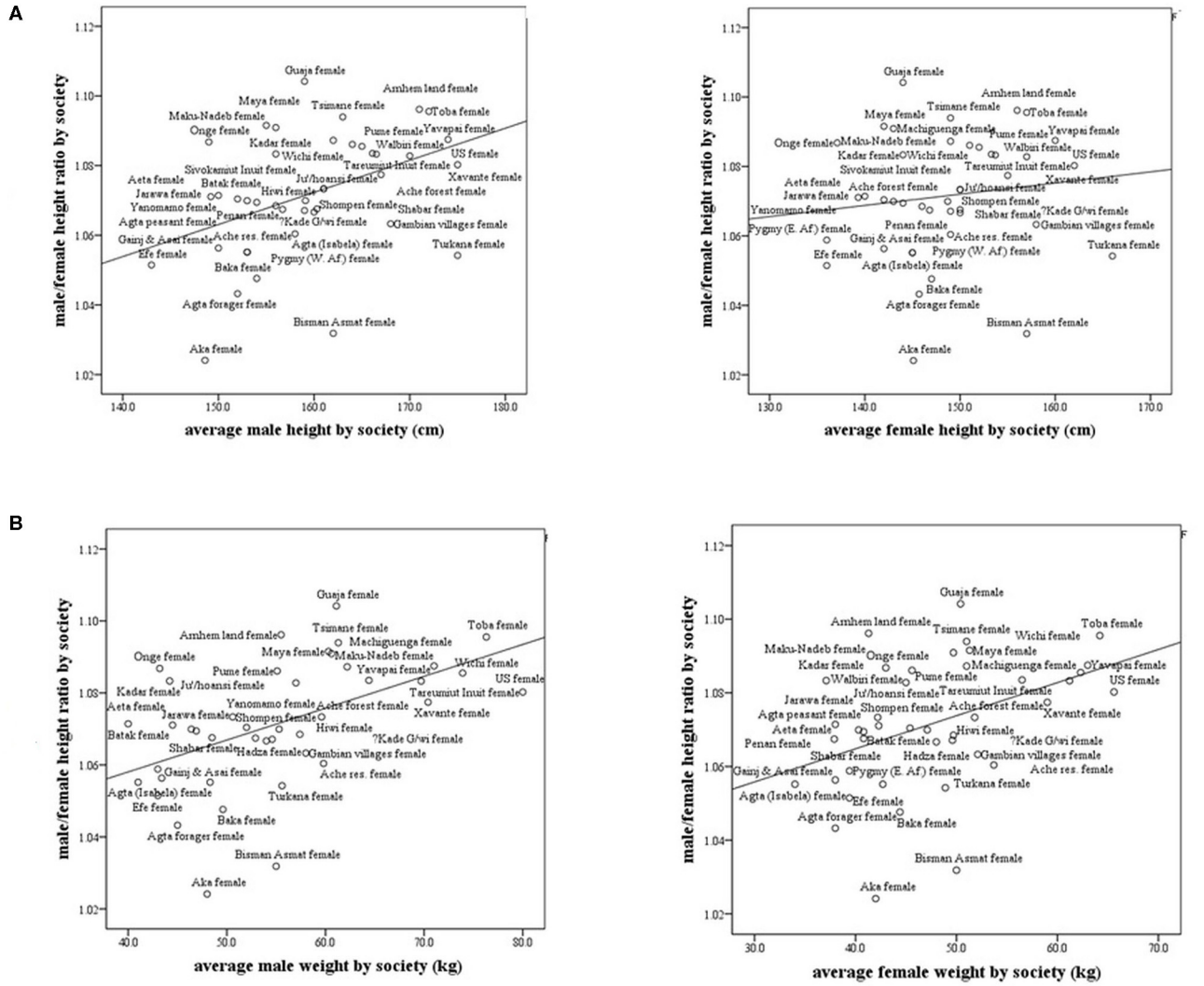

FIGURE 4 | Male/female height ratio as a function of the average male and female height and weight in subsistence-based preindustrial societies. R-Spearman's correlation coefficient. **(A)** Male/female height ratio as a function of the average male and female height in subsistence-based preindustrial society. For males, $R = 0.41$, $p < 0.007$ and for females, $R = 0.15$, $p = 0.33$. **(B)** Male/female height ratio as a function of the average male and female weight by society. For males, $R = 0.57$, $p = 0.0001$ and for females, $R = 0.43$, $p = 0.005$.

TABLE 1 | Analysis of allometry for 161 modern countries.

	Male	Female
Male/Female height ratio correlated with height per country *(R)*	0.52***	0.18**
Male/Female height ratio correlated with weight per country *(R)*	0.54***	0.29***

Sexual dimorphism in body size as a function of the average male and female height and weight.
R-Pearson's correlation coefficient.
***p < 0.001, ***p < 0.0001.*

TABLE 2 | Analysis of allometry for 38 subsistence-based preindustrial societies.

	Male	Female
Male/Female height ratio correlated with height *(R)*	0.41**	0.15^{NS}
Male/Female height ratio correlated with weight *(R)*	0.57***	0.43**

Sexual dimorphism in body size as a function of the average male and female height and weight.
*R-Spearman's correlation coefficient, **p < 0.001, ***p < 0.0001.*
NS, not significant.

sample of 76 nonindustrial populations (29). They used data on sexual division of labor for five subsistence activities, namely hunting, gathering, fishing, pastoralism, and agriculture, from an "Ethnographic Atlas" by Murdock 1967, data on stature were taken from a variety of published sources. They concluded that sexual dimorphism in stature is negatively correlated with the extent of women's participation in the labor force and a sex-biased parental investment. They also found that women were

TABLE 3 | Male and female height and weight correlated with life expectancy at birth and at age 15 y and population density in subsistence-based preindustrial societies.

	Life expectancy at birth (R)	Life expectancy at age 15 y (R)	Density population, (R)
Average male height	0.69**	0.61**	NS
Average female height	0.72**	0.70**	NS
Average male weight	0.8**	0.68**	−0.45*
Average female weight	0.71**	0.67**	−0.48**

R-Spearman's correlation coefficient.
*$p < 0.01$. **$p < 0.001$.*

taller than men in those societies, that the women's contribution to food production was greater than that of the men resulting in improvement of females' nutritional status in these societies.

Other factors which have been reported to influence the M/F height ratio in preindustrial societies are probably the male and female division in agricultural tasks (30). The women in these societies usually were engaged in cattle farming and garden work, thereby increasing their "advantage of proximity" to milk and vegetables. In contrast, grain cultivation which was usually done by men requires more upper-body strength than herding cattle; hence a grain-oriented society might distribute more nutritional and health resources to male offspring (3). When agricultural patterns changed, for example from cattle farming to grain-based agriculture, women's height, and health might have declined (31).

Finally, the calculation of target height and the prediction of adult height are influenced by the sexual difference in height in various countries. The method of calculating the mid-parental target height was developed in the nineteenth century in the United Kingdom: the mean sex height difference was typically 13 cm; and we therefore used the formula: (father's height + mother's height + 13 cm)/2 for boys and (father's height + mother's height −13 cm)/2 for girls. We now show that the average male/female height ratio and also the mean sex difference in height are dissimilar in different countries (**Figures 2**, **3**). In the calculation of mid-parental height and target height the male-female difference for each country needs to be adjusted to a country's sexual dimorphic size ratio.

The utilization of anthropometric data by country bears a certain limitation. The population of some countries descent from many different immigrations arrived in different moments at the same country. Averaging gives extra weight to that majority ethnic group of a country.

We conclude that sexual dimorphism in body size occurs when (a) the growth velocity is maximal during infancy and adolescence, (b) living standards are high, and health correlate positively with male/female height ratio. Anthropological studies and our results emphasize mostly the female resiliency hypothesis: shorter male heights in times of environmental stress lead to smaller sexual dimorphism in body size.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article.

AUTHOR CONTRIBUTIONS

AG co-conceptualized and co-designed the study, carried out the statistical analysis and interpreted the results, and reviewed, revised and approved the study. ZH conceptualized and designed the study, oversaw it's conduct and drafted the initial manuscript, and reviewed, revised, and approved the study. Both authors contributed to the article and approved the submitted version.

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