Evolutionary public health 2

Human reproduction and health: an evolutionary perspective

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According to life history theory, increased investment in reproductive function (physiology and behaviour) at different times throughout the life course affects the risk of many diseases and, ultimately, longevity. Although genetic factors contribute to interindividual and interpopulation variation in reproductive traits, the dominant source of variability is phenotypic plasticity during development and adult life. Reproductive traits in both sexes evolved sensitivity to ecological conditions, as reflected in contemporary associations of hormone concentrations with geographical setting, nutritional status, and physical activity level. Lifetime exposure to increased concentrations of sex hormones is associated with the risk of some cancers, hence decreasing fertility patterns contribute to secular increases in their incidence. Conversely, increased investment in reproductive function might compromise somatic investment in health, such that faster sexual maturation and higher parity increases risk of diabetes and cardiovascular disease. An evolutionary perspective on reproductive biology could improve the efficacy of public health efforts to reduce the risk of hormone-sensitive cancers and other non-communicable diseases.

Introduction

Natural selection favours those characteristics of human physiology and behaviour that increase an individual's chances of passing their genes to the next generation, even though these traits might also reduce the maintenance of health, especially at old age, and ultimately reduce longevity. According to life history theory, this association is due to trade-offs between competing biological functions, as discussed by Wells and colleagues in this Series. On this basis, variability in reproduction must inevitably shape health status, and this might be driven both by genetic differences and by components of phenotypic plasticity at different stages of life.

In this Series paper, we present an evolutionary perspective on the relation between human reproduction and health. We first describe how variability in reproductive function is orchestrated by key hormones that mediate the effect of ecological conditions on sexual maturation patterns and fertility. We then discuss how variability in the production of these sex hormones is associated with energetic traits and with the risk of hormone-sensitive cancers. More broadly, we show that variability in reproductive effort shapes morbidity and longevity in heterogeneous ways, and we discuss potential underlying mechanisms. Differences in the ways that males and females maximise genetic fitness contribute to sex-specific differences in associations between reproductive investment and disease risk or longevity.

Our goal is to illustrate how an evolutionary perspective on human reproduction and its variability can widen the understanding of disease, particularly those that are associated with sex hormones. We also highlight areas that need further research and identify domains in which evolutionary concepts can be useful in informing public health intervention strategies.

Women's reproductive hormones

Reproductive steroid hormones, oestrogens and progesterone, are crucial determinants of fertility because of their regulatory roles in conception, implantation, and pregnancy. They are also necessary for the development and maturation of the normal breast at menarche, pregnancy, and lactation. Conversely, these hormones are also central to the aetiology of ovarian, endometrial, and breast cancer. Findings from studies of populations living in diverse ecologies show that mean concentrations...
of reproductive hormones vary substantially between and within populations (figure 1). For example, average progesterone concentrations in women living in urban parts of the USA, where energy is in surplus, are almost twice as high as in women in the Democratic Republic of the Congo, where energy supply is typically limited.3 Understanding the factors that affect the production of these hormones is therefore crucial for elucidating variation in both fertility and reproductive cancer risk.

Energy availability is a key source of variation in ovarian function.10 Human life history traits (ie, altricial, large brain, neonatal adiposity, slow growth, and late sexual maturation) represent a reproductive strategy that demands substantial energy investment for a protracted

Figure 1: Intrapopulation, intraindividual, and interindividual variation in reproductive hormone concentrations in healthy women of reproductive age

Hormone concentrations were measured in saliva samples collected every day for the entire menstrual cycle and analysed by the same laboratory. (A) Mean differences in progesterone concentrations in women in five populations.3–7 (B) Profiles of oestradiol concentration for 18 days of menstrual cycle aligned on the day of ovulation (day 0) in five Polish women, aged 25–26 years. (C) Profiles of progesterone from four women, aged 25–27 years, from rural Poland, with four consecutive cycles (last 18 days of a cycle) for each woman. All women had regular menstrual cycles, were not using oral contraceptives or other steroid medication, and were not pregnant or lactating for at least 6 months before the beginning of the study.8,9

period of time. Women bear most of the direct costs of reproduction through pregnancy, lactation, and child care, although some costs can be transferred through so-called cooperative breeding. The need to assess and respond to ecological energy availability would therefore have been a strong selective pressure in the evolution of female reproductive physiology. Human ovarian function is responsive to environmental factors that affect the availability of energy for reproduction. Women in populations that experience seasonal or chronic energetic constraints typically show later maturation and lower fecundity than those that have access to constant and plentiful resources.

Individual variation in ovarian function has a genetic component, and genotype–environment interactions have been reported for hormone concentrations. Nevertheless, even in natural fertility populations (not practising any form of birth control), genetic factors account for very little variability in human reproductive function, and the main determinants are exposure to ecological factors at different periods through the life course and across generations.

The effects of acute energetic shifts experienced during adult life can be differentiated from the ecological stresses during development. Developmental conditions shape baseline levels of reproductive function by adjusting the speed of growth and maturation in response to ecological factors such as energy supply and infectious disease burden. These adjustments then influence how ovarian function varies in tune with energetic status during adult life, reflecting individuals’ current nutrition, behaviour, and disease ecology.

**Energy metabolism during women’s adult life: physical activity and energy intake**

Women whose energetic status is challenged due to high energy expenditure or low energy intake (eg, professional or recreational athletes, or women with eating disorders or high physical workload) have reduced production of steroid sex hormones. Recreational exercise often reduces hormone levels without changing cycle regularity, although in previously untrained women who begin exercising, an increased energetic demand often does disturb the menstrual cycle. Ovarian hormonal suppression is also observed when dietary energy constraint causes weight loss, even at moderate levels. Large changes in energy availability resulting from eating disorders, such as anorexia nervosa and bulimia nervosa, are often associated with menstrual and hormonal problems.

Ovarian hormonal suppression also occurs in response to physical workloads and seasonal food shortages in more traditional populations. In Polish farming women, progesterone profiles vary with the intensity and duration of their physical workload. Women in the Democratic Republic of the Congo and Nepal show seasonally suppressed levels of ovarian steroids when physical workload is heavy and energy balance is negative.

Increased energy expenditure, either from exercise or occupational work, has a negative effect on ovarian function independent of weight loss. 

Empirical evidence thus indicates that energetic stress, either in the form of increased energy expenditure or negative energy balance, can lead to various degrees of reproductive suppression, which diminishes the chances of successful conception and can even curtail reproductive function temporarily. The resulting lengthened interbirth intervals allow women to improve their own energetic status before engaging in a new pregnancy. Such response to energetic status is considered to be adaptive, and provides a mechanism whereby female physiology can strategically tailor the costly process of reproduction to signals of energy availability. Ultimately, this strategy protects the maternal organism and optimises her lifetime reproductive output.

From an evolutionary perspective, ovarian suppression in response to sub-optimal environmental conditions is a component of healthy reproductive physiology rather than a sign of pathology needing medical intervention. Obesity might appear to be a state of energy surplus, permitting plentiful investment in all biological functions. However, obesity is best considered a disorder of perturbed energy metabolism, and one that compromises many aspects of reproductive endocrinology and reduces fertility.

Although sensitivity of ovarian function to energetic status is considered adaptive in undernourished women, this sensitivity can cause unintended consequences in public health intervention programmes. Wells and colleagues describe how an intervention in Ethiopia to reduce maternal physical workload did not reduce child malnutrition but increased maternal fertility. This was probably mediated by changes in reproductive hormone levels. Similarly, in rural parts of The Gambia, nutritional supplements for undernourished women had relatively modest effects on birthweight and breast-milk composition but reduced the post-partum period of infertility. In Guatemala, women who received high-energy, high-protein supplementation in utero or during early childhood, or both, had shortened median intervals from menarche to first intercourse and from first intercourse to first birth.

These findings highlight the need to address reproductive biology with interventions that consider maternal energy dynamics. Moreover, this scenario has an intergenerational basis: how women’s physiology responds to such ecological factors is strongly affected by their developmental circumstances in early life.

**Developmental plasticity of female reproductive function**

The effects of developmental circumstances on reproductive function have been described in many studies. Evidence derives from observations of selected clinical populations (eg, small-for-gestational age,
intrauterine growth-restricted individuals) and of people who have been exposed to war or famine (appendix). Migrants and adoptees who undergo profound environmental shifts at a specific stage in their life differ in their sexual maturation and in gonadal and ovarian function (panel 1). A different but equally valuable source of evidence stems from reproductive toxicity studies, in which environmental compounds have been found to disrupt reproductive physiology (appendix). Each example involves environmental effects on developmental traits that are relevant to reproduction.

The effect of prenatal and postnatal nutritional status on human reproductive traits reveals that nutritional effects during uterine development can act independently or can interact with nutritional effects encountered during early and late postnatal growth. Energetic status during development affects the size and function of reproductive organs and the regulation and sensitivity to energetic stress of the adult gonadal endocrine function. Such effects probably underpin associations between developmental conditions and duration of adolescent subfertility, age at first pregnancy, proportion of ovulatory cycles, and reproductive behaviour, which ultimately underlie the differential parity observed in natural fertility populations. On another level, the duration of a woman’s reproductive period is shaped by developmental conditions because they affect the timing of reproductive maturation, births and reproductive senescence.

Variability in reproductive function and its developmental aetiology has important implications for diverse components of women’s health, including the risk of infertility and susceptibility to many non-communicable diseases. Understanding of the factors that determine the concentrations of individual reproductive hormones might therefore contribute to disease prevention efforts. However, whether investment in reproduction leads to benefits or costs to health depends on the disease outcome, as will be discussed.

**Variation in lifetime steroid hormone exposure and breast cancer**

The health implications of variability in sex hormone production are particularly well studied in relation to cancers of reproductive organs (breast, cervix, endometrium, ovaries). Breast cancer has the highest incidence of these cancers, and the incidence is expected to increase in the next decades. This trend correlates with changes in reproduction-related risk factors observed in many affluent contemporary populations and populations undergoing demographic and economic transition (figure 2). Breast cancer is a multifactorial malignancy in which reproductive hormones, particularly oestrogens, drive a carcinogenic process that is characterised by cross-talk with other signalling pathways associated with energetic status (eg insulin, leptin, growth factors, inflammation).

**Panel 1: Summary of evidence from studies on adoptees and migrants to illustrate developmental effects related to changes in energy availability on reproductive function**

**International adoption from underprivileged to privileged settings**

**Puberty and menarche**

Internationally adopted girls were at 10–20 times increased risk of precocious puberty compared with girls in their country of origin or girls in the adopted country, with highest risk if adopted after 2 years of age. Adopted boys also showed increased risk, although less so than girls.

Adopted children had earlier growth spurt than children in reference populations, and adopted girls had earlier menarche than girls in well nourished populations in both the country of origin and the adopted country. Pubertal growth in adopted children started earlier than in children in reference populations. Girls with the most pronounced stunting and fastest catch-up growth upon migration exhibited the youngest menarchal age. Menarche occurred at similar height and weight in the adopted girls as in girls in an underprivileged reference population in the country of origin, even though the start of puberty was significantly delayed in the latter group.

**Gonadal function**

Adopted girls aged 5–8 years showed signs of increased pituitary and gonadal activity despite prepubertal phenotype in most girls. Adopted girls had higher serum concentrations of follicle-stimulating hormone, luteinising hormone, and oestradiol than controls.

**International migration from impoverished to affluent countries**

**Adrenarche**

First generation migrant girls reached adrenarche earlier than those in their adopted country after adjusting for height and weight.

**Thelarche**

Thelarche occurred earlier in girls from low-income countries of origin living in high-income countries than in girls still living in low-income countries. However, puberty progressed slower with increasing exposure to the high-income country environment.

**Ovarian function**

Women from low-income countries of origin who migrated before puberty and women who were born and grew up in conditions of stable energy intake, low physical activity levels, good sanitation, low immune challenges, and good health care had earlier maturation and higher levels of salivary progesterone than women who grew up in less optimal conditions (low-income countries or first-generation adult migrants). These effects were significantly larger among women who migrated during infancy and pre-menarche. Migrant women had relatively high concentrations of free androgens compared with second-generation women born in affluent conditions.

**Ovarian reserve**

Migrants who moved to comparatively more affluent conditions as children had a significantly larger, age-related ovarian reserve compared with migrants who had moved as adults or who remained in their country of origin.

The reproductive hormone concentrations that are used as reference values in clinical practice are typically derived from women in affluent settings. Interpopulation studies by reproductive ecologists (figure 1) suggest that women in affluent settings have atypically high hormone concentrations and that the low baseline concentration of...
hormones in women from traditional societies are probably closer to the evolutionary norm (panel 2). Moreover, reproductive patterns in many affluent populations are shifting away from the natural fertility norm that prevailed during most of our species’ recent evolutionary history. This ancient pattern, maintained in some contemporary traditional populations, is characterised by comparatively late age at menarche, young age at first birth, high parity, and prolonged periods of breastfeeding. This combination is generally thought to protect against breast cancer, primarily by reducing the number of menstrual cycles during a lifetime. During our evolutionary past, a small number of menstrual cycles and low production of hormones during these cycles would have led to low lifetime exposure to endogenous reproductive steroids. Reproductive risk factors are most relevant for hormone receptor-positive breast tumours, whereas hormone receptor-negative tumours (20–30% of breast cancers), which are associated with poor prognosis, have a different aetiology.

High parity exerts a protective effect against breast cancer, but this protection is limited to women who start reproduction at an early age; for those who begin childbearing at an age of 30 years or more, parity is linked to an increase in lifetime breast cancer risk, possibly due to the transient, hormonally-induced proliferation of pre-existing tumour cells. Women with a longer reproductive lifespan have increased breast cancer risk, independent of childbearing history. Moreover, women who reach menarche early have, in addition to a long exposure to reproductive steroids, an increased risk of breast cancer associated with their high baseline levels of oestrogen during regular menstrual cycles.

Breastfeeding is another modifiable behaviour that can affect the incidence of breast cancer. Extended breastfeeding has the potential to reduce the risk, and mimicking the cancer-protective molecular mechanisms of breastfeeding has been proposed as a potential preventive approach. Collectively, these data indicate that reproductive scheduling is an important component of breast cancer risk.

Given the sensitivity of reproductive hormone production to ecological energy availability, it is unsurprising that the incidence of breast cancer is also associated with secular trends in two markers of energy availability, namely body-mass index (BMI) and physical activity level. Obesity and sedentary behaviour now account for a high proportion of breast cancer risk. Fortunately, these risk factors are also the most amenable to modification. Healthy weight and physical activity during childhood might protect against breast cancer in adulthood by delaying the onset of puberty, whereas weight control and physical exercise in adult women favourably changes reproductive hormone profiles and other biomarkers for breast cancer diagnosis and mortality (eg, adiposity, insulin resistance, growth factors, and chronic low-grade inflammation).

Prevention efforts against breast cancer have primarily focused on modifiable risk factors that operate during a woman’s adult reproductive span. However, prenatal and early postnatal developmental factors might also affect breast cancer risk in adults. Specifically, good energetic status during uterine growth (increased birthweight...
and length and rapid growth during childhood and adolescence) predispose individuals to this malignancy.79 Moreover, maternal lifestyle exposures have been shown to directly affect the progeny’s risk.79

Epigenetic processes could explain the links between developmental conditions, energetic status, reproductive function, and breast cancer susceptibility. Maternal micronutrient status and BMI at the time of conception predict tissue-wide DNA methylation patterns in the offspring,77 although how these factors contribute to breast cancer aetiology remains unclear.72 An alternative modulating factor might be the resident gut microbiota,73 which can affect the metabolism and secretion of systemic non-ovarian oestrogens.72 The relation between the human so-called estrobolome and reproductive physiology are yet to be explored but might have important implications for prevention and treatment of reproductive cancers.

Given the life-course nature of breast cancer development (ie, the accumulation of genomic and epigenetic abnormalities in breast epithelial cells during the entire life course75), prevention strategies that target early-life exposures hold promise. Some public health interventions, however, might also have unintended negative consequences. For example, interventions to increase birthweight through maternal nutritional supplementation70 or to improve childhood nutrition and growth21 might also result in direct epigenetic changes that ultimately increase breast cancer risk.99

An improved understanding of how factors operating at different life stages alter the sensitivity of ovarian function to acute, short-term energetic constraints is needed to maximise the benefits of interventions targeting adult energy metabolism and, consequently, disease risk. For example, women who were relatively fat at birth (based on ponderal index at birth) need more physical activity than women who were lean at birth to achieve a similar decrease in ovarian hormone production.4 Consequently, women who were fat at birth are predicted to need high levels of physical activity to achieve similar reductions in breast cancer risk; hence intervention strategies might need to be tailored accordingly.

**Costs of reproduction and women’s health**

For many other diseases, enhanced reproductive effort might generate health costs rather than protective effects. Life history theory predicts trade-offs between reproduction and other functions such as maintenance, growth, and immune defence.1 Markers of lifetime reproductive investment (eg, number of pregnancies and surviving offspring, duration of interbirth intervals, and breastfeeding duration and other forms of parental care) are therefore expected to predict disease risk and longevity.

Reproduction necessitates additional energy and nutrients, and physiological and metabolic adjustments of pregnancy can cause permanent changes in the mother, especially when parity is high. Plausible biological mechanisms that are implicated in the trade-offs between reproduction and longevity include increased production of pro-inflammatory cytokines, insulin resistance, increased production of triglycerides and LDL cholesterol, and increased oxidative stress.77 Some of these changes have life-long consequences. In the USA, for example, self-reported health status, a reliable predictor of mortality, was lower in women with at least three pregnancies than in women who had fewer pregnancies.78

In high-income countries, parity is positively correlated to the risk of obesity,73 diabetes, and cardiovascular disease. Outcomes of the Framingham Heart Study and the National Health and Nutrition Examination Survey showed a positive association between the number of pregnancies and the subsequent development of cardiovascular disease.80 In British women, each additional child increased the risk of coronary heart disease by 30%.81 Six pregnancies or more increased a woman’s risk of all types of stroke by 70%.82 Among Australian women living in rural areas, those with five children or more were at 35% higher risk of diabetes than women with one or two children.83 In Finland, parity of five children or more was related to more than 40% higher risk of diabetes compared with the average risk for Finnish women.84 In low-income countries, high parity is also associated with an increased risk of maternal mortality, in part by reducing resistance to infectious diseases.85

Although high reproductive investment often correlates with increased risk of disease, its association with mortality is not uniform.86 In historical Swedish87 and Polish88 populations, the number of offspring was inversely associated with maternal longevity, whereas a U-shaped relationship between these traits has been
described in other studies. In historical Germany, the number of offspring was inversely associated with maternal longevity among poor women who did not own land (a marker of low socioeconomic status), whereas a positive association was observed among women of high economic status. Trade-offs between costs of reproduction and longevity probably apply mostly to women for whom such costs are a substantial part of their overall energy budget.

The evidence for trade-offs between reproductive effort and longevity in women is heterogeneous. At the genetic level, reproductive performance and lifespan both show heritability, but genetic linkage between the two has not been described in detail and the outcomes are inconsistent. A series of specific genes related to diseases in women (eg, BRCA1-2, APOE, ESR1, and genes involved in the hypothalamic-pituitary-ovarian axis) have also been examined for their relation with fertility, but with mixed results.

The available data suggest complex interactions between reproduction and mortality, and they highlight the importance of socioeconomic indicators and related variables such as nutritional status. Although much work remains to be done to understand these trade-offs, life history theory provides a valuable framework for investigating how other context-specific variables such as disease burden, health-care practices, and individual lifestyle might modify reproductive costs. This approach might ultimately make public health programmes more effective while reducing their unintended adverse consequences.

Other health outcomes in women
In addition to overt disease, current knowledge of the factors that affect natural variation in endogenous reproductive hormones prompts reconsideration of the pharmacodynamics of exogenous hormones, such as in contraceptives or hormone replacement therapies. This reconsideration has important implications for establishing effective doses and tolerability of these exogenous hormones and for assessing associated disease risks. Specifically, the tolerance and associated health risks of hormonal treatments that were developed and tested in affluent populations might not necessarily be appropriate for more traditional populations with lower baseline physiological hormone production or for individuals with acute or prolonged energy deficits due to dieting or illness. As yet, however, this issue has received little attention.

Variability in reproductive physiology can also help explain reported variability in how women from different ecological and biocultural backgrounds experience the menopausal transition. The variation in severity of perimenopausal symptoms between different populations could relate to population differences in lifetime production of reproductive hormones. The incidence and experience of menopausal symptoms might be more pronounced in women for whom menopause is associated with a large reduction in ovarian steroid production from regular menstrual cycles to a hypo-oestrogenic status. Again, however, evidence to substantiate this hypothesis is pending.

Men’s reproductive hormones
Men’s biology has likewise been shaped by selective pressures that promote reproduction, but targeting behaviours and physiology that increase the likelihood of mating rather than energetic investment in offspring. Accordingly, men have trade-offs between reproductive effort and health outcomes that often contrast with women’s. As in women, male reproductive biology is sensitive to harsh environments and energy constraints from nutritional deficits, high workloads, or immunological challenges. This sensitivity has been observed in spermatogenesis and other physiological functions that promote reproduction, including upper-body muscle mass growth and reproductive behaviour.

Testosterone has a key role in male reproductive endocrinology. In well nourished, healthy men, testosterone promotes lean tissue growth. Low testosterone concentrations have been associated with increased morbidity and mortality, although population variability remains poorly described. Nevertheless, high testosterone can also invoke health costs in men who are nutritionally or immunologically compromised, although the magnitude of the effect varies in association with ecological conditions. For example, testosterone concentrations tend to be higher in men living in affluent settings than in men living in less affluent regions of the world with limited energy availability. Low testosterone in men living in nutritionally stressed populations seems to be an adaptive response, attenuating the energetic costs of testosterone-supported anabolism and elevated metabolism and the metabolic costs of chronic infection.

Changes in testosterone production with age also vary substantially between populations. Men living in developing countries have a low baseline production of testosterone but show muted or no decrease in testosterone with age, whereas age-dependent decrease in testosterone production is pronounced in men living in the USA and other well nourished urban populations.

Men’s reproductive steroid hormones and health
Prostate cancer risk is the most important health issue indicative of trade-offs associated with testosterone. Despite the clear inhibitory effects of androgen deprivation therapy on prostate cancer cell growth, little evidence supports a link between individual testosterone concentrations and prostate cancer risk. Yet men in urbanised areas of developed countries tend to have high testosterone production and a high risk of prostate cancer. The effects of androgens on prostate function and cancer risk are probably cumulative,
rendering point measurements of testosterone at any given age of little diagnostic or predictive value. Thus awareness of lifetime exposure to endogenous androgens between various populations provides some clinical and epidemiological insight into disparities in prostate cancer risk.

Androgen levels might also shape the risk of other diseases, as shown by the effect of increasing testosterone supplementation. Testosterone supplementation is common in contemporary medical practice, often to men who do not exhibit any clinical signs of hypogonadism or androgen deficiency, and health costs are now becoming evident. For example, older men taking testosterone supplements are at greater risk of myocardial infarction than men who do not receive supplements. Testosterone can also compromise immune function and lead to other health disorders, especially in elderly men or men who have other health issues or poor nutrition. By contrast, men who have acute reduction in testosterone due to malaria infection have been found to rebound to preinfection testosterone concentrations after completion of anti-malaria treatment. The deployment of testosterone supplementation clearly needs to take into account these potential unintended effects.

Conclusions
Natural selection has favoured traits that increase reproductive success even if such traits are costly in terms of health, especially at old age when selective pressures are weak. Although the specific mechanisms are still being elucidated, the trade-offs between human reproduction and health probably vary in relation to both environmental conditions and specific disease outcomes. Ongoing demographic transitions are therefore expected to have profound effects, both positive and negative, on the profile of human health and disease.

In nutritional energy-rich environments, increased production of ovarian steroids in women throughout their menstrual cycles and of testosterone in men improve their potential for reproduction. However, the family sizes are decreasing in these populations, and lifetime exposure to high hormone concentrations predisposes these women and men to increased risk of breast and prostate cancers, affecting longevity. Conversely, given the metabolic costs of reproduction, enhanced reproductive investment might increase vulnerability to diseases such as osteoporosis, diabetes, and cardiovascular disease. Such opposing effects illustrate the difficulty of demonstrating trade-offs between reproduction and longevity using epidemiological and demographical data.

The differences in reproductive strategy result in contrasting associations between reproduction and health or longevity in men and women. Some of these differences emerge directly from contrasting production of reproductive hormones, whereas other differences might be mediated by their effects on physiological risk markers such as physical activity level or the amount and distribution of fat and lean tissue. The scenario might be complicated by sexual antagonism, whereby selected alleles increase the fitness of one sex but decrease that of the other, as shown for height, weight, blood pressure, glucose and cholesterol concentrations, and age at first birth in human beings. These differences could explain why women have greater average longevity but worse outcomes for some diseases than men do.

Trade-offs between physiological functions make interventions to reduce disease risk challenging. For instance, the promotion of physical activity to decrease steroid hormone production and reduce reproductive cancer risk needs to be balanced against the effect of suppressed ovarian function on other aspects of health, since endogenous sex steroids are beneficial for reproductive, cardiovascular, bone, and mental health (figure 2).

Interdisciplinary research is needed to investigate these trade-offs in greater detail, especially for women with high fertility in economically developing populations, where decreasing fertility has beneficial effects on child and maternal health but is also contributing to increased breast cancer incidence. An improved understanding of the interactive effects of trade-offs at different stages of life could lead to optimised and integrated public health interventions aimed at pregnancy, infancy, childhood, and adulthood. For instance, the identification of the periods during development during which reproductive function is established and the associated compromises with other vital functions are set is crucial for designing timely prevention programmes. Similarly, a strengthened appreciation of the ways in which fetal development affects reproductive traits (eg, age at menarche) and subsequent health risks in adulthood is invaluable when designing interventions aimed at disrupting inter-generational cycles of vulnerability and disease. It is by improving our understanding of a constantly changing balance between health benefits and reproduction costs that an evolutionary perspective can make an important contribution to public health, particularly through tailoring interventions to contrasting ecological settings.


