A Life Course Approach to Women's Health

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Chapter 10

Endocrine pathways in differential well-being across the life course

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Current challenges in population health require better specification of the pathways to differential health outcomes, and such pathways are often gender specific. In this chapter, considerations of organic design from evolutionary biology are combined with physiological data, to suggest the importance of endocrine pathways in health across the life course.

Endocrine bases of function and health risk are surveyed, and life course action and trajectories for a set of four exemplary endocrine axes (reproductive, adrenal, thyroid, and adipose) are described, to illustrate the role of neuroendocrine-endocrine action in well-being. Reviews of acute and organizational impacts of ecological and behavioral factors on each of these axes demonstrate that hormones translate variation in behavioral, experience, and environmental quality into differential health outcomes over the long- and short-term. This analysis suggests the value to epidemiology of considering endocrine mediation in pathways to health, particularly women's health.

10.1 Introduction

The formidable task of meeting new or, until recently, intractable challenges to human well-being has prompted resurgent evaluation of and debate over the relative roles of population versus individual level interventions in social and public health policy. On the population side, social policy is confronting the need to expand from resource management, to include inequality per se, while public health is evolving toward population health as it strives to incorporate cultural, behavioral, and developmental factors that imply new targets for prevention. Three recent texts share a common theme, namely the absence of well-specified pathways underlying the associations of contexts with health. Biomedical treatments and prophylaxis are challenged by emerging diseases fostered by structural and ecological conditions, and likewise from changing health risk related to demographic aging, and lifestyle changes. Our extensive knowledge of how things work needs to be integrated into design principles that support predictions or hypotheses about life course impact of changing behaviors or circumstances.
10.2 Endocrine architecture of the life course

Contemporary biological views of the life course build on life history theory, which proposes that biological design of the life course for any species is constrained by limited resources. Limited resources include time as well as energy, information, and relationships, and must be apportioned among the crucial enterprises of growth, reproduction, and survival maintenance.10-12 Schedules for deployment of resources among these enterprises with accompanying trade-offs among competing demands (live fast, die young versus live slow, die old; offspring quality versus offspring quantity) form the macroarchitecture of life history. Distinctive features of the human life course include single relatively immature births, prolonged provisioning of young, slow growth with delayed maturation, low mortality, menopause, and long life span. These features apparently co-evolved with a singular cognitive-behavioral complex, including obligate sociality, use of language, pair bonding, and culture.13 Endocranil biology explains sex differences in life history, including biology and behavior, as consequence to their different roles in reproduction.12,13

How the macroarchitecture of life history relates to the microarchitecture of physiology has scarcely interested biologists, but hormones are prime candidates.14 Hormones establish the short- and long-term balance of resource allocations between growth, reproduction, and maintenance. Hormones juggle net energy availability by modulating metabolism and setting internal regulatory parameters, they regulate the rate of growth and the timing of developmental transitions such as puberty, and they dynamically manage the interface between the individual and environment by orchestrating responses to everything from stress to workload. Hormones establish an individual's sex and drive the reproductive life course, including for women the processes of pregnancy, parturition, lactation, and menopause. Endocrine regulation also determines timing of life history events (e.g. puberty, aging), with physiological consequences that shape health risks. A vivid example comes from the concept of fetal programming, which links perinatal and early life events (e.g. birth weight, body proportions, placental size) with risk for adult cardiovascular and metabolic disorders.16-20 Neural
substrates, they proposed, reflect the impact of early environments on fetal development. In turn, set parameters for function and further development over the life course and thereby affect risk for chronic disease. Endocrine factors mediate many of these phenomena.22-30 This burgeoning literature on fetal programming not only has raised the importance of early environments for health risk21-31 (see also special section, International Journal of Epidemiology 30: 13-23, 50-97) and emphasized the importance of maternal conditions in pregnancy for long-term well-being of offspring.4 It has also yielded evidence for impact on life history. Specifically, maternal size and maturity have been linked to age at menarche among females than at birth, those who are long reach menarche six months before those who are short.31 This effect is most pronounced among those with short-average prenatal growth, and potential growth is known to be a sensitive indicator of environmental quality. Incidentally, this literature illustrates the value of specifying proximal causes for epidemiological findings.

Another instance is puberty, in which neuroendocrine mechanisms establish the childhood phase and initiate the process leading to reproductive competence.32-37 Hormones delay maturation and extend the pre-adult period in an event unusual even for primates. Gonadal quiescence, and possibly adrenal androgen damping, are required to establish and maintain immaturity. Although the mechanisms responsible for sustained gonadal quiescence and triggering the onset of puberty remain unknown, they operate via regulatory pathways through the hypothalamus. The brain acts as the mediator for puberty once it commences, and regulates ovarian cyclicity and reproductive aging thereafter. 

Hormones, then, are pivotal for guiding the life course through day-to-day prioritization of resource allocation, as well as the long-term scheduling of growth, reproductive effort, and aging. Fig. 10.1 Knowledge of hormone action explains ongoing function, adaptation, and differential well-being, while consideration of life history offers a view of adaptive goals and trade-offs subserved by hormones.

Fig. 10.1 Overview of exemplar endocrine systems.
10.3 Endocrine trajectories across the life course

We lack an integrated theory of physiological development that proceeds from life history through design to function. Emphasizing the roles hormones play in the physiological architecture of human adaptation and life course requires a rather different view of endocrinology that is prevalent in the endocrine, clinical, and epidemiological literature.

Such literature has focused on the identification, characterization, regulation, and molecular biology of hormones and hormone action, on establishing normative targets for expected levels, and on identifying correlates of risk. Comparative endocrine research has gradually established that, although the endocrine axis and their functional pathways are nearly universal, endocrine function can vary for specific axes and their interrelationships and thus play adaptive roles.

Some of this cross-population variation may be based on genetic diversity, but much of it is influenced by the specific ecologies in which humans grow up and function. The present discussion concerns the endocrine architecture of the life course with respect to differential health outcomes for women. Portions of that architecture are summarized in Fig. 10.1. Subsequent sections provide life course overviews of the following endocrine axes: hypothalamic-pituitary-gonadal (HPG), hypothalamic-pituitary-adrenal (HPA), hypothalamic-pituitary-thyroid (HPT), and weight regulation (lipostasis). For brevity, the somatotropic axis regulating growth, metabolic regulation, and energy partitioning is excluded. Data are drawn mainly from work on North Americans and, where that is unavailable, on Western Europeans, to construct a functional picture for populations with roughly similar (though still diverse) cultural and physical ecologies. Sources have been selected on the basis of order quality and comparability to other sources, of sample sizes, and of appropriateness or representativeness of the sampling strategy. Where possible, 95% confidence intervals are shown.

Understanding endocrine action and regulation entails more than the key peripheral hormones of a given endocrine axis, such as estradiol or cortisol. The biological impact of circulating hormones involves several factors that moderate the relationships of hormones to health outcomes. These include:

1. Regulators of hormone production, such as the pituitary hormones that stimulate target (and activity (e.g., pituitary gonadotropins that control ovulation activity and thus, estradiol levels) or blood sugar levels that drive insulin production. Altered ratios of stimulus to endocrine response indicate developmental transitions (puberty, menopause) or pathologies (diabetes, obesity).

2. Temporal patterns of endocrine release, produced both by endogenous rhythms and by exposure to stimuli. Circadian and pulsatile release patterns often convey information for endocrine action. Disruption of these patterns may contribute to pathogenesis, as in the case of dysregulated gonadotropin pulsatility in anosmics or of trauma-induced changes in circadian HPA activity.

3. Binding proteins and soluble receptors significantly moderate the bioavailability of hormones and thus their biological impact. Although individual differences in carrier protein concentrations have been linked to endocrine phenotypes such as lactation in women, little research has explored the potential contributions of varying concentrations
of binding protein, soluble receptors, or immunoglobulins to individual or population variation in endocrine function and health.

4. Cross-talk among endocrine axes modulates the activity of any one axis in relation to others, and regulates partitioning of the body's resources between competing physiological and adaptive demands: endocrine mediation of short- and long-term trade-offs in the allocation of scarce biological resources represents a rich vein for future research, but lies outside the scope of this survey.

This analysis provides a platform for future research by not only presenting what is known about function and regulation, but also indicating the scope of variation and suggesting its bases in sensitive organizational periods revealed by intervals of change or reorganization. It points, where possible, to potential epigenetic-ecological sources of variation, and draws attention to areas of potential investigation by clarifying the temporal and regulatory dynamics of several hormonal axes.

10.6 Hypothalamo–pituitary–gonadal (HPG) axis

The HPG axis exemplifies centrally regulated endocrine function, controlled via pulsatile secretion by the hypothalamic-pituitary–gonadal axis. The hypothalamus releases gonadotropin-releasing hormone (GnRH) that, in turn, stimulates pulsatile release by the anterior pituitary of the gonadotropins follicle-stimulating hormone (FSH) and luteinizing hormone (LH). The amount and pattern of FSH and LH release drive ovarian activity, including ovarian steroid production, of which the principal form in females is estradiol (E2), along with substantial progesterone (P) output in the latter half (luteal phase) of an ovulatory ovarian cycle. The regulatory loop is closed by feedback effects of circulating ovarian steroids on release of hypothalamic GnRH and anterior pituitary gonadotropins. The axis performs two key tasks: it controls reproductive maturation and closure, and maintains and regulates adult reproductive function. These tasks are central to women's reproductive health, and bear on health through the direct and indirect impact of ovarian steroids on central and peripheral function.

10.6.1 Age-related change

HPG activity in women changes markedly across the life course (Fig. 10.2). In this sequence, a brief postnatal burst of activity, followed by centrally-mediated early gonadal quiescence, a centrally-controlled reactivation at puberty, a period of maturational reproductive function supported by ongoing hypothalamic stimulation (represented here by LH), and monophasic closure of reproductive function following a process of reproductive senescence. A neuroendocrine switch is required to break the HPG-quietness of childhood and initiate puberty, although the precise trigger for this centrally-oscillated mechanism remains unclear.

Furthermore, the axis requires several years to attain mature rates of ovulation and luteinization, a maturational period characterized by menstrual subfertility. At the other end of the reproductive lifespan, menopause is a process comprising several years' altered HPG activity before and after the last menstrual bleed. Reproductive closure occurs mainly through follicle depletion despite accelerated central stimulation compounded by diminishing central sensitivity to ovarian feedback. As described in Chapter 7, menopause occurs on average in the fifth or sixth decade and is generally followed by massive gonadotropin output which gradually declines with age. Life course HPG activity exemplifies the neuroendocrine underpinnings of women’s life history, including a prolonged juvenile period.
of reproductive immaturity, late onset of puberty and first birth, and early reproductive senescence.

A commonly overlooked mediator of bioavailable estrogen is the blood-borne carrier protein, sex hormone binding globulin (SHBG), which binds circulating estradiol and other steroids. They display a profile of SHBG that is distinct from that of its target hormones (Fig. 10.2). Levels of SHBG in women notably exceed those in men, despite the absolutely greater overall amounts of gonadal output in men that women, pregnancy excepted. This suggests a larger role for SHBG in modulating gonadal steroid action in women than men.
10.4.2 Ecological and behavioural factors

Unlike men, in whom gonadal activity is continuous and high after puberty, women produce varying levels of ovarian hormones depending on follicular activity. Behavioural and ecological factors heavily influence ovarian activity. First, timing of puberty and onset of menstruation varies widely between populations; this variation is partly attributable to genetic effects but principally to environmental conditions such as gestational factors, nutrition, and infection (see Chapter 2). Similarly strong environmental effects on reproductive ageing, or menopause in particular, have not been observed (see Chapter 4). Second, timing of marriage, patterns of sexual activity, and contraceptive practices influence timing and numbers of pregnancies, during which follicular activity is suppressed. Third, intense sustained breastfeeding suppresses ovarian activity, maintaining postpartum amenorrhoea for months and damps ovarian activity once menstruation resumes. Moreover, women's nutritional status and workload are known to affect steroid output over the ovarian cycle, and hence also modulate exposure. Unfavourable energetic status from marginal nutrition, heavy workload, or illness, is accompanied by increased menstrual irregularity, increased menstruation, and reduced ovarian steroid output overall. Other moderators of ovarian steroid levels include smoking, psychological stress, diet composition, and steroid contraceptive use.

Dietary sources of and environmental exposures to oestrogen agonists and antagonists (phytoestrogens, PCBs) have recently been implicated as modulators of steroid exposure that influence both reproductive function and health risk. For instance, the very low prevalence of menopausal symptoms among Japanese has been attributed to habitual phyto-oestrogen consumption, by contrast, decades of high steroid levels may contribute to symptom prevalence and severity at menopause in Western populations.

Social, cultural, and individual factors that affect women's well-being (health, nutritional status, workload, stress) and reproductive life histories also affect amount and degree of ovarian activity across the life course. Such factors, as well as the gene-environment interactions that catalyse, produce inter- and intra-population variation in life course pattern and amount of ovarian activity and degree of ovarian output. For instance, Ellison and colleagues' comparative studies have shown population differences in fetal steroids levels that persist across the reproductive life course and correspond to their degree of sectorial and ecological stress (Fig. 10.3).

10.4.3 Ovarian steroid exposure and risk

Steroids act on target tissues via receptors and other intracellular mechanisms. The nature and intensity of these reactions depend on receptor distribution, type, and density. The nuclear-level role of steroid activation also mediates their carcinogenic effects in target tissues. Considerable evidence links amount of steroid exposure to degree of cancer risk (see Chapter 3), and implicates culturally- and behaviourally-mediated variation of women's reproductive life course, health and nutrition, and workloads in cancer risk by mediating exposure to ovarian steroids. Therefore, with early age at menarche, late age of first birth, few births, little or no breastfeeding, excellent nutrition, low-physical activity, and high ovarian output per cycle, women in Western post-industrial societies experience substantially increased ovarian steroid exposure and hence increased risk of reproductive cancer. Chronic exposure to high levels of ovarian steroids may also exacerbate the risk of adverse
symptoms in menopause: although a minority of western women experience the core symptoms of menopause (hot flashes, night sweats), a much smaller proportion report such symptoms in populations as diverse as Japan or Guatemala. 12,14 Population differences in FPG activity, as illustrated in Fig. 10.3, suggest a possible need for population-adjusted formulations of steroid contraceptives to reduce side effects.27

Ovarian steroid exposure and its moderators influence risk for other morbidities.28 Patterns of exposure in western postindustrial societies, combined with sedentary lifestyles and prolonged life span, contribute to dramatic increases in rates of osteoporosis in these populations (see Chapter 7). Ovarian steroid effects on metabolism promote fat deposition, which results in a visible change in body contours at puberty and contributes to the large sex difference in adult body composition.29 Such energy storing action has adaptive value in settings of uncertain food supply but among overnourished populations, contributes to risk for obesity. Additionally, where lean body mass is valued in women, the adiposity-promoting action of ovarian steroids both sets up women for a conflict between social values and body size and may promote vulnerability to eating disorders that address both problems (body image and ovarian activity) (see Chapter 8).

Where reproductive risk is low, women outline men, which implies the existence of protective factors in women, risk factors in men, or both. Changes in relative risk for diverse chronic diseases (cardiovascular, mood disorders) after menopause imply endocrine involvement (see Chapters 5 and 8).30 Ovarian steroids moderate risk for hypertension and cardiovascular events, through direct action on serum lipid profiles and plaque formation.31 Turning from physical to mental health, ovarian steroids exert multiple effects on the central nervous system (CNS),32 and have been implicated in risk for mood disorders.
specifically for depression (reviewed in Chapter 8). Oestrogens also act as neurogenic agents that promote dendrite and synaptic formation, blunt neurotoxicity from glucocorticoids and free radicals, and acutely enhance mood and cognitive performance, whereas progesterone acts neuroprotectively by reducing secondary neural damage in cerebral trauma or stroke. 67-68

10.5. Hypothalamo-pituitary-adrenal (HPA) axis

The adrenal gland secretes a range of hormones with diverse physiological roles across the life course, but which spread resources among competing physiological demands. Such adaptive adjustments are essential but costly, and carry a cost-benefit trade-off: adrenal hormones mobilize resources to accommodate small and large physiological and psychological challenges, but continual or prolonged activation leads to functional impairment. 69

The adrenal comprises two functionally distinct compartments, cortex and medulla. The former produces mineralocorticoids, glucocorticoids, and adrenal androgens that regulate basic functions, from electrolyte balance to glycogen metabolism and stress response. The medulla acts as a neurotransmitter structure by releasing the adrenergic neurotransmitters epinephrine and norepinephrine into the bloodstream.

Both compartments operate synergistically to promote short- to long-term adjustments to physiological and environmental load (Fig. 10.7, left). The sympatho-adrenal-medullary (SAM) axis organizes swift (to milliseconds) endocrine responses that rapidly initiate physiological (e.g., heart rate) and cognitive (e.g., heightened arousal, vigilance) adjustments and, in turn, facilitate behavioral reactions. This axis has been implicated in the etiology of hypertension under conditions of damped stress or arousal. A rather slower (15-30 minutes to peak response) HPA cascade involves corticotropin releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol, and mediates adjustments in physiological priorities from long-term (e.g., growth, reproduction, digestion) to short-term (vigorous activity, alleen) functions.

Two kinds of adrenocortical hormones, the glucocorticoid cortisol and the adrenal androgen dehydroepiandrosterone-sulfate (DHEAS), are discussed below. The contrast in functional roles illustrates two aspects of endocrine action, for cortisol mediates acute, rapid responses to arousal or stress, whereas the adrenal androgen DHEAS shows little episodic or diurnal variability, but undergoes distinctive patterned changes across the life course that reflect paedomakers of life history.

10.5.1 Cortisol

This portion of the HPA axis is regulated by episodic and circadian hypothalamic output of CRH, that consequently stimulates the anterior pituitary to release ACTH. In turn, ACTH stimulates adrenocortical release of cortisol. Commonly viewed as a stress hormone, cortisol may be better imagined as an activational hormone that facilitates or mobilizes responses to psychosocial load. 68-70 Release is pulsatile and episodic, exhibits strong diurnal variation, and responds acutely to psychosocial conditions including sleep-wake patterns, eating, vigorous physical activity, and psychological challenge (worry, excitement, performance, anxiety, new situations). 71-72 Hence, at any given moment, circulating levels reflect impact of experience and behavior within the last hour, although physiological and affective load drive cortisol release by different pathways. 73-74 HPA
reactivity—threshold, latency, magnitude, and duration of cortisol release—has been identified as a factor in well-being, including cardiovascular, infection, and psychobiology.

Cortisol acts to promote immediate survival needs at the expense of long-term processes by stimulating anabolic and inhibiting catabolic pathways. It increases blood glucose, vigilance, and attention focusing, reduces food intake, HP3 activity, gut motility, growth, and memory formation, and alters immune activity. Cortisol exerts non-linear (inverted-U-shaped effects on memory, arousal, stress integration, and emotion regulation, due to the concentration dependent differential activation of two glucocorticoid receptors.

10.5.1 Age-related change

The adrenal gland undergoes a brief period of postnatal reorganisation and achieves adult periodicity by 6 months of age. Thereafter, age-related change occurs until a trend of gradually increasing-cortisol emerges from the third decade (Fig. 10.4). No early sex differences in circulating cortisol have been reported but sex differences in HP3 regulation appear from birth, whereby a lower level of extracellular cortisol accompanies a given level of the trophic hormone, ACTH, in males than females. ACTH exhibits both.

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Fig. 10.4: Pituitary-adrenal activity over the life course. Left panel: Plasma cortisol binding globulin (CBG) concentrations (left axis; solid circle, solid line) by age and mean 24-hour serum ACTH values in children (mean age 7.2 years; hatched bar) and adults (mean age 25 years) of both sexes (mean ± 95% confidence interval; X, dashed line). Slope by age for CBG, significant and age-specific variation is large. Note apparent large drop in advanced age, possibly involving inactivation of ASMA, eosinophilic AASUI and chronic stress. Right panel: Mean cortisol concentrations (right axis; solid circle) and 95% confidence interval (X, dashed line) shown for all age groups, except infants, shown separately because their HRAs are undergoing substantial reorganisation in the first six months. Median 24-hour cortisol by age, both sexes with 95% confidence intervals. Lines represent slopes by age (solid for male, dotted for female) applied to this value range. Age trend significant in both sexes, infants under 6 months show different—4 cortisol output that indicates a developmental period. CBG, ACTH, 17, 37, 204, 215, Cortisol 25, 263.
lower levels and lack of sex differences in childhood, and sex differences in adulthood with
small or absent cortisol differences. Both age and sex discrepancies suggest differences in
ACTH delivery to the adrenal, or in adrenocortical sensitivity or responsiveness to ACTH
stimulation.

Indeed, sex differences in responsivity of the HPA axis emerge with age.9 In a psychosocial
challenge test, young men were both more likely to have raised cortisol levels (75%, 6 times
more than women), and showed larger cortisol increments than younger responders (no sex
difference in non-responders). Conversely, cortisol responses in older female responders
were greatly reduced in male responders aged or young.10,11 Age-related shifts in sex differ-
ences in HPA response to such challenge may reflect sex differences in vulnerability to
psychosomatic stressors over the life course. Concurrently declining cortisol-binding
protein (CBP) leaves more free, bioavailable cortisol and magnifies such differences.
Age-related enzymatic shifts in adrenal function may contribute to changing neuroendocrine
rhythms: increased ratios of cortisol to adrenal androgens have been observed in the
controspinal fluid of children (aged 3–8 years) and elderly (>60 years), who may be
more vulnerable to psychosomatic effects of stress.12 Greater increases in ratios of plasma-corti-
col to adrenal androgens in women may compound neuroendocrine risk.13 Finally, circadian
cortisol variation increases markedly with age in women (Fig. 10.5), such that the
early adult sex difference (greater variation in men) reverses with aging.

10.5.1.2 Ecological and behavioural factors
Since cortisol operates through its responsivity to ecological and behavioral conditions,
virtually all literature on cortisol could be relevant. Initially, cortisol was viewed as strictly
derived by 'stress', and either summed or modulated; hence, increasing cortisol must
reflect exogenous stimuli, and previous activity of the axis should not affect its current

Fig. 10.5 Sex differences in aging of HPA axis, circadian patterns. 24-hour continuously monitored
plasma cortisol, by sex and age. Left panel: women 20–29 years (dashed line) versus 50–75
years (solid line). Right panel: men 21–29 (dashed line) versus 50–83 years (solid line). Women
show greater circadian and phase shift with age than do men. Data source: 12.
activity. Later, a body of animal literature has established the importance of experience and begun to unpack the epigenetic bases of variation in HPA function.89-92 This and human clinical work has shown that HPA function is affected by genetic conditions, postnatal care, and other early experiences, acute stress, and chronic depression.17,41,83

Cortisol exhibits wide individual variation that can persist over time and represent stable individual characteristics.93 For instance, a large cross-sectional study of Canadian cortisol levels in Swedish children showed over five-fold variation in individual mean diurnal values.94 Diurnal measures repeated over 0.5 to 8 years on a subset of pubertal children, showed high longitudinal stability of cortisol output. The broad stable individual variation in cortisol was not associated with anthropometric correlates, which suggests little effect on lipolytic and glucose homeostasis, although cortisol is related to their regulation. Such findings may be due to differences in target tissue sensitivity, but they may also be due to organizational effects on metabolic regulation. Reports of a U-shaped relationship between birthweight and glucocorticoid secretion in childhood,95 as well as of persistently higher adrenocortical activity in those exposed to postnatal stress,96 support the latter possibility.

10.5.1.3 Cortisol and health risk

As a component of stress response, cortisol has been implicated in an extensive range of health risks, including cardiovascular, metabolic, gastrointestinal, reproductive, immunological, neurological, and related cognitive and psychiatric disorders.97-104 Target tissue variation in sensitivity to glucocorticoids contributes to individual differences in cortisol effects.98 Glucocorticoids have been found to impede memory formation and mediate autonomic reactivity in the brain.98,105 Socioeconomically mediated gender differences in experience to and coping with stressors may thereby contribute to differential health risk. Additionally, increased stress reactivity and central resistance to glucocorticoid feedback is thought to exacerbate risk for depression in women, and contribute to the paradox that adult women have greater rates of physical morbidity than men but lower risk of mortality.130

10.5.2 Adrenal androgens

The role of the adrenal androgens in life history merits attention, for humans and for other primates poses qualitative and quantitatively distinctive adrenal activity patterns. Adrenal androgens—androsterones, dehydroepiandrosterone (DHEA) and its sulfate (DHEAS)—are weak androgens produced by the zona reticularis of the adrenal cortex in abundance quantities that, from puberty, exceed those of all other steroids. Circulating adrenal androgens exhibit progressive changes across the life course101,112 that are most evident for DHEAS, the quantitatively predominant adrenal hormone. (Fig. 10.6). Changes in adrenal androgen output after both, at adrenarche and puberty, and with aging reflect adrenal reorganizations that dismantle or elaborate some having enzyme activity favoring their production.113 Although adrenal androgens as well understood, regulation of adrenal androgen production is not: ACTH stimulates episodic, pulsatile and circadian DHEA release in parallel with cortisol (DHEA does not), but these hormones run counter under other circumstances. Under stress or physical trauma, cortisol may be elevated or flat while adrenal androgens are reduced. Moreover, ACTH does not account for the lifetime pattern of change. Alternatively, insulin-like growth factors (IGFs) stimulate adrenal androgens...
production, and insulin-like growth factor-I (IGF-I) correlates with DHEAS production from adolescents into old age.104

Functions of adrenal androgens remain perplexing, for their massive production helps in explanation.104 DHEAS provides substrates for substantial peripheral testosterone reduction of androgens and androgens that exert significant steroid target tissues bioactivity.104 Where synthesized in brain, they exhibit neurotransmitter activity with mood, sleep, and memory-enhancing effects. Multiple suggested cerebroprotective, immunomodulating, neurotrophic, anti-inflammatory, and angiogenic effects strongly explain the neural DHEAS production of humans.104

10.5.2.1 Age-related change

Circulating concentrations of DHEAS (Fig. 10.14) are high at birth, decline rapidly over the first year of life to the low and slightly rising levels in early childhood, and show an increase in slope between six and eight years of age. This shift, adrenarche, occurs somewhat earlier in girls than boys. In contrast, adrenal androgen output in mid-childhood is probably unrelated to timing of puberty; adrenarche occurs at similar ages in very lean as in early maturing populations.105,106 At puberty, adrenal androgen output increases sharply and almost steadily to reach peak values in the early mid-20s, and thereafter declines with age.107 These age-related changes in DHEAS may either have functional implications on their own, related to direct effects of DHEAS, or they may indirectly influence aging processes reflected in DHEAS. Otherwise, DHEAS may serve a background or buffering role that moderates the impact of variation in other steroid hormones, such as glucocorticoids. Marked sex differences in adrenal androgen emergence with adrenarche and puberty: androgens generate the great preponderance of DHEAS and peaks a minor fraction, yet circulating levels in men exceed those in women.108 Consequently, divergent age-related changes, the ratio of cortisol to DHEAS follows a U-shaped curve with age109 that is particularly pronounced for women in whom age and body mass index (BMI)-adjusted cortisol in 20% higher and DHEAS 40% lower than in men.109
3.2.2 Ecological and behavioural factors

Because interest in life course patterns of adrenal androgens has been so recent, and largely focused on ageing data concerning their sensitivity to ecological and developmental factors, studies remain scanty. Initial reports document large population differences in DHEAS output across the life course that track maturational turning and show that western populations have chronically elevated values from puberty onwards. Reduced DHEAS and hence reduction of its anti-inflammatory, chemoprotective, and endocrinological buffering activities may reflect action of life history trade-offs to prioritize immediate needs over long-term maintenance in populations confronting lower environmental quality and greater health risks. More usually, DHEAS is reduced by severe illness or chronic stress. Furthermore, by contrast with cortisol, DHEAS is reduced in depression.111

10.2.3 DHEAS and health risk

DHEAS may offer sex-differentiated protective effects against cardiovascular disease (CVD), cancer, immune-based diseases, mood and memory disorders, and ageing.108,112,115 Lower DHEAS characterizes Alzheimer’s disease and diabetes, and is associated with reduced bone density in middle-aged women (not men), depressed mood in older women (not men), and prospectively with risk for prostatic and breast cancer and for CVD mortality in elderly men (not women).111,112,115 A direct etiological role is difficult to infer even from prospective studies, because DHEAS may simply reflect differential ageing and its associated abnormalities or index other physiological processes that influence health status. Relationships of adrenal androgens to life expectancy remain complex. Follow-up of populations showing short-term associations of DHEAS with cardiovascular mortality risk has diminished the estimate of their effect on survival risk for men, and shown no effect on women.116-117 Nevertheless, enthusiasm for DHEA replacement therapy focuses on its putative role in ageing116-118 and possible direct protective actions including buffering neurotoxic effects of glucocorticoids.119

10.3 Thyrotropic axis and central metabolic regulation

The hypothalamic-pituitary-thyroid (HPT) axis comprises a primary endocrine pathway regulating energy homeostasis. Central regulation originates in the hypothalamus, proceeds through secretion of thyrotropin-releasing hormone (TRH) to stimulate anterior pituitary release of thyroid stimulating hormone (TSH), and hence prompt thyroid hormone (thyroxine (T4) and triiodothyronine (T3)) production. Thyroid activity responds to energy expenditure, increases metabolic rate, and hence serves an important adaptive function.120

16.1 Age-related change

The formulation of reference ranges for normal thyroid (thyroid) functioning are of considerable public health importance in determining the widespread risk for and functional impact of hypothyroidism.121 Yet reference values remain elusive for lack of a definitive marker of euthyroid status.122,123 The primary hormone, TSH, represents actual thyroid function indirectly, while 92-96% of the principal thyroid hormone, thyroxine (T4), is tied up in circulating binding proteins that themselves undergo developmental change.120,122 As the biologically free T4 is considered an optimal marker of thyroid activity, T4 exhibits a
complex pattern of age-related change over a narrow range of variation across the lifespan (Fig. 10.7) that is thought to indicate maturation-related pituitary and thyroid regulation. However, following a normative TSH and T4 surge, little or no age-related change in T4 has been observed, although TSH declines through childhood and adolescence. Sex differences have not been seen systematically at any age. Reports of elevated TSH with age are based on populations unscreened for health status. Studies of well-screened healthy aged populations, by contrast, indicate that TSH levels decline steadily from late infancy throughout adulthood, reflecting diminishing pituitary response to hypothalamic releasing hormones.

### 10.6 Ecological and behavioural factors

Of the endocrine axes discussed here, the HPT is most overtly influenced by ecology and behaviour. Thyroid dysfunction arises principally from iodine deficiency or overexposure; iodine bioavailability depends on diet, soil and water content, and is antagonized by goitrogens. Overall, one billion people are considered at risk for iodine-deficient disorders (IDD). Consequently, most post-industrial countries have national neonatal screening programs to detect congenital hypothyroidism, and national salt iodization campaigns in the last decade have decreased IDD rates. Iodine deficiency is often essential for thyroid action (selenium, zinc, copper, etc.) also compromised HPT function.

### 10.6.3 Thyroid function and health risk

Thyroid dysfunction related to iodine malnutrition is readily prevented by iodine prophylaxis that persists widely, even in Europe, despite massive international campaigns. Neonate hypothyroidism congenital, or iodine deficient, characterized by elevated TSH, above 10 IU/ml, generates concern because it impacts brain development and is the main
preventable cause of mental retardation. If congenital or severe and chronic, hypothyroidism results in cretinism or goitre, respectively. Within a broad zone of subclinical hypothyroidism, inadequate thyroid function at any age associates with poor cognitive function and motor performance (learning, memory, attention, reaction time), and depression. Distractability, insomnia, anxiety, and emotional instability accompany hypothyroidism. But the most significant long-term consequence of mild-to-moderate iodine insufficiency is hypothyroidism in ageing, associated with osteoporosis, muscle atrophy, and cardiac dysfunction. Conversely, high iodine intake increases risk of autoimmune hypothyroidism, which increases consistently with age. Indeed, iodine supplementation must be monitored and moderated to maintain intakes within a range that avoids hypo- and hyperthyroidism.

HPT function particularly affects women’s health: women experience much more thyroid disorder than men, having 5-6, 2-5, and 2-5 times the population prevalence of hypothyroidism, hyperthyroidism, and thyroid autoimmunity than men, respectively. The gender disparity increases with ageing. Autoimmune hypothyroidism disrupts reproductive health, associating with ovarian dysfunction and infertility, increased pregnancy failure, and autoimmune postpartum rebound from immunosuppression of pregnancy. Increased risk for goitre in women has been attributed to gestogenic effects of pregnancy; thyroid volume increases with parity, so that adequate iodine supply is crucial to avert even moderate iodine deficiency. Hypothyroidism further contributes to risk for chronic depression, more prevalent in women. Hence, much of the burden of dietary and autoimmune thyroid disease is borne by women, and the gender disparity of that burden increases with age.

10.7 Leptin and distributed metabolic regulation
Although it had long been thought that the brain must monitor energy status (energy stores minus expenditure) in order to regulate physiological and behavioral determinants of such status, the basis for signaling energy (net from energy intake and expenditure) remained uncertain until leptin was reported in late 1994. Subsequent research has expanded the view of its role as “lipostat” in weight regulation, to include an array of central and peripheral actions in metabolic, reproductive, affective, and even hematopoietic activity. It has also widened our views of rodent circadian oscillations. Leptin is a cytokine-related hormone produced principally by white adipocytes and shows pulsatility as well as diurnal rhythmicity (nadir [range] - 1030 h [1000-1740 h]; peak [range] - 0210 h [2200-0300 h];). Receptors for leptin are not only found in fat, muscle, pancreas, and liver, but also widely represented in the CNS, particularly at its principal site of action in the ventral, energy-regulating, the hypothalamus. A host of neuropeptides (most importantly neuropeptide Y, proopiomelanocortin, and agouti-Related peptide; peptide) moderate or transduce the central actions of leptin on thermogenesis, energy metabolism, and food intake, as well as hypothalamically-mediated impact on other axes, including the gonadal, adrenal, and thyroid. The soluble form of its receptor circulates as a carrier protein for leptin, regulates its bioavailability, and increases markedly at puberty.

Circulating levels of leptin acts as a trait (energy stores, weight maintenance, long-term energy balance) and a state (acute energy imbalance) marker. Leptin correlates exponentially with body fat stores and provides a metabolic signal to the hypothalamus regions regulating satiety, energy expenditure, and multiple related endocrine axes. But it also prospectively
signal: acute energy imbalance by shifting during weight loss or gain, such that fasting decreases and overfeeding induces leptins, even though meal ingestion has no acute effect. The modulatory impact of leptins on other endocrine systems contributes to its actions over different time horizons: from acute effects on food intake, to effects over hours on glucose metabolism, to changes in CNS gene expression over days, to impacts on weight and body composition over days or weeks, and permissive effects on puberty onset and reproductive function over years.

Body composition, specifically percent body fat versus lean body mass, is the most sexually dimorphic feature in humans, whereby we can body fat in young women a nearly 50% greater than in young men. Accordingly, shortly after birth onwards, leptin concentrations in females exceed those in males of the same body weight among as well as obese individuals. Figure 9.8. Reasons for this difference include effects of sex hormones, the difference in body composition itself, and greater output of leptin by adipocytes in women from early puberty. The strong negative relationship of leptins to adipose tissue mass in men and the less robust positive one to osteodensity in females has been observed in studies of endocrine change in puberty. Grounds for many of these differences not only in body composition but also in eating disorders and overall weight regulations have been sought in such distinctive leptin patterns, but actions of leptin are not so direct. Given the importance of energy status to reproduction, particularly the high energy costs required of women for pregnancy and lactation, relationships of leptin and reproductive function are necessarily complex. Coadjusted steroids may alter sensitivity of the CNS to leptin-mediated signals; reciprocally, leptin output is altered by direct and indirect effects of gonadal steroids, and leptin permissively influences FSH function.

![Figure 10.8](image)

Figure 10.8: Relationship of gender and BMI to leptin levels. The left panel shows leptin concentrations over the first six months. Left panel: Sex differences in leptin levels, closed circle, solid line: men; open triangle, dotted line: 10% fat baseline. Becoming pronounced at puberty and remaining so in adulthood. Right panel: Relationship between leptin and BMI. Shown mediated by fat mass. Mean ± 95% confidence interval for women with BMI <30 solid circle, solid line, hatch area versus those with BMI >30 solid triangle, solid line, dot-dashed area.
10.7.1 Age-related change

Age-related changes in leptin are difficult to disentangle from changes in body composition due to developmental (growth, puberty) or behavioural (activity) factors. As noted above, girls have higher leptin than boys before, during, and after puberty even discounting girls' greater adiposity, though not all reports confirm this pattern (Fig. 10.8). Because it signals energy stores, leptin was also expected to play a permissive role in puberty onset. Consistent with this expectation, leptin increases markedly at puberty, but animal data do not support a causal role. During the years of ovarian cycling, leptin varies with the ovarian cycle in conjunction with progesterone and peaks in the luteal phase. Leptin increases in pregnancy and declines sharply postpartum, which changes correspond to those in essential and human chorionic gonadotropin (hCG). Therefore, BMI-adjusted levels decline progressively with age, including after menopause. In contrast to the relationship of estradiol and leptin over the ovarian cycle, such decline appears independent of diminishing estradiol and other endocrine changes, although they make some contribution.

10.7.2 Ecological and behavioural factors

Adjustments in leptin production and regulation could provide powerful means for facultative adjustment of energy management. For instance, early energy restriction might influence the organisation of metabolic regulation reflected in alterations of leptin output by adipocytes. Autonomic regulation of fat cells, or of hypothalamus and thus behavioural responses to leptin signals, is relevant to dietary restriction, but support for use such effects comes from a report that lower BMI or infant weight is associated with greater adult leptin, controlling for adult weight. A small literature on specific ethnicities or non-Western populations is complicated by complexities of controlling for body fat and does not support generalities; thus, it indicates potential population variation in compliance of leptin.

10.7.3 Leptin and health risk

Initially, it was hoped that leptin might provide a pharmacological or even genetic 'magic bullet' for weight regulation, particularly prevention and treatment of obesity and eating disorders, through effects on eating behaviour, on metabolism, or both. That hope has so far failed. Hopefully further research will be able to address worldwide patterns of both undernutrition and pandemic overnutrition and its attendant disorders (obesity, CVD, hypercholesterolaemia). For instance, leptin apparently plays a key role in adaptation to sustained nutritional deprivation by maintaining elevated cortisol and GH to ensure fat mobilisation. These effects, with concurrent suppression of NPY-1, divert energy from growth to metabolic demands. Genetic defects account for a minor fraction of obesity cases; obesity is usually accompanied by leptin resistance and receptor and post-receptor mechanisms for such resistance are under scrutiny. The roles of adrenal and less so of gonadal, steroids in modulating leptin regulation and action may be particularly pertinent to unravelling the physiological, psychobehavioural, and ecological basis of increased vulnerability of women for eating disorders and obesity. Additionally, patterns of leptin production (Fig. 10.8) emphasize that the biology of women reflects adaptation to the heavy energetic demands of...
10.8 Pathways to women's health

Historically, attribution of women's health issues to women's biology or behaviour led to targeting women themselves for prevention and treatment. Recognition that such issues are the life course product of women's specific needs and capacities, with the context in which they develop, function, and age, points to societal-structural targets for health promotion. This survey has integrated the epidemiological and biomedical literatures concerning women's health by drawing pathways to differential well-being from micro-architectural (life history) through microbiochemical (endocrinology) levels. Figure 10.8 outlines a framework for pathway analysis. The upper tier depicts an evolutionary view of life history and its endocrine architecture in relation to life course analysis on the level of the individual. It shows relationships of life history parameters (life history box at top) to...
individuality and function, focusing on mediating endocrine factors, that determine adult outcomes in health, survival, and competence (of organism level 'genotype' and 'outcomes' boxes, upper right), as well as fitness (on the evolutionary level; top right) and gene frequencies. The lower tier concerns relationships of individual life course processes ('life course box' at center) to population-level epidemiology (phenotypes and outcome boxes, lower right), focusing on interactions of social conditions with organism design features to determine population-level outcomes, including quality of life, productivity, and demographics, as well as individual life courses ('biography', center right).

This framework relates design features from evolutionary processes to the population outcomes that concern epidemiologists, through the individual level of the organism. Phenotype emerges from the individualized intersection of evolutionary history with human ecology (political economy; economics, culture) that through time, makes the life course. In aggregate, on the population level, the combined probabilities for exposure and vulnerability established by population ecology and biology produce the array of phenotypes counted in demography as morbidity, mortality, and fertility, and in epidemiology as developmental outcomes. We use breast cancer risk in contemporary postindustrial societies as an example. Changes in practice (decreased breastfeeding); life course construction (delayed reproduction); and values (reduced fertility goals; education and employment for women) increase lifetime exposure to estro-ids (exposed in the phenotype). Concurrent changes in practices (child care, public sanitation; vaccination); values (gender equality); and life course construction (education rather than labor for children) result both in increased life expectancy, and in biological changes (accelerated maturation, upregulated ovarian activity) mediated by estrogen-progesterone feedback associated with life history trade-offs. Together, increased life expectancy and increased steroid exposure converge at the individual level with constitutional-genetic conditions and epigenetic processes (modulators of steroid action [receptors, enzymes, endogenous steroids]); of breast tissue development; and of immune function (stress, exposure) that determine probability of carcinogenesis and progression.

Tracing pathways to health risk (and prevention) brings epidemiology to life, because proximal pathways effect life span development and function, and hence the health of all members of society. Pathway analysis integrates existing epidemiological with biomedical-physiological data in both explicit recognized trends (increased breast cancer) and suggest new hypotheses concerning cause (e.g. compromised immune function) or intervention (e.g. increase breastfeeding). Identification of mediating pathways facilitates recognition of trade-offs such as those between lifestyle choice and health, of early versus later patterns of morbidity, or among diverse dimensions of well-being. Individual processes emerge as central, highlighting the value of rich individual level data for epidemiology.

A life course approach constrains health research to follow the problem rather than vice versa, mandates pursuit of the problem through multiple levels and time frames, suggests routes for intervention, and predicts consequences of social change and lifestyle variation. This is particularly true for certain areas such as women’s health. Social change or structural reforms can cause broad spectrum improvements in well-being, but need to be accompanied by processes at the individual level that operate synergistically to produce specific health trade-offs. The pathways approach should help all concerned with the present complex challenges to health, to meet those challenges through new ideas, research, and policy.