Review

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Review

Evolutionary Mismatch in Generation X Women: An Integrated Model of Midlife Hormonal, Metabolic and Cognitive Dysfunction

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Abstract

Chronic stress, circadian disruption, sedentary behavior, industrialized diets and disturbances in the gut microbiome have created an evolutionary mismatch between ancestral physiology and the modern environment. Generation X (Gen X) women (born between 1965–1980) are the first cohort to enter midlife having lived their entire adult lives within these conditions while also carrying distinct cohort-specific factors shaped by major economic and cultural transitions. The interaction of evolutionary mismatch and Gen X pressures destabilizes hormonal regulation, increases allostatic load and impairs mitochondrial function, contributing to fatigue, metabolic inflexibility and cognitive dysfunction during perimenopause and menopause, with implications for postmenopausal health and long-term disease risk. Women with polycystic ovary syndrome have reduced insulin sensitivity and a heightened proinflammatory response that makes them more susceptible to Gen X evolutionary mismatch pressures. This paper synthesizes evidence from evolutionary biology, endocrinology, neuroscience and lifestyle medicine to present an integrated model explaining the mechanisms driving midlife symptomatology in Gen X women. The model places midlife dysfunction within an evolutionary mismatch context, where modern environmental exposures and cohort-specific demands interact with hormonal, immune and metabolic changes to drive convergent pathophysiological mechanisms. A tiered recovery framework is proposed, targeting allostatic load reduction, circadian realignment, restoration of metabolic flexibility, and integration of mitochondrial, musculoskeletal and gut–brain–endocrine signaling systems.

Keywords: evolutionary mismatch; generation X women; Gen X; metabolic dysfunction; metabolic inflexibility; insulin resistance; mitochondrial dysfunction; allostatic load; cognitive dysfunction

1. Introduction

Midlife is increasingly recognized as a critical inflection point for women's long-term metabolic, cognitive and cardiovascular health. Globally, the number of women transitioning through the menopausal transition is substantial and growing, with United Nations World Population data estimating that there are more than 885 million Generation X (Gen X) women aged between 46 and 61 years **[1,2].** These demographic shifts coincide with the rising prevalence of metabolic disease, cognitive disturbance and stress-related morbidity among women in the midlife transition **[3,4].** In Australia, over 80% of women in this age group exhibit elevated metabolic risk based on waist circumference, a key anthropometric marker of central adiposity **[5]**.

While robust birth-cohort comparisons of menopausal symptom severity remain limited, Gen X women are the first generation to navigate unprecedented role complexity and sustained psychosocial strain **[6–8].** This cohort entered adulthood during periods of economic restructuring, rising workforce participation for women, and diminishing structural supports, while

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simultaneously assuming caregiving responsibilities and gendered invisible workloads **[9–11].** These demands are further compounded in women with PCOS who are more vulnerable to converging nutritional, environmental and psychological stressors due to an inherited genetic susceptibility (see Section 8.5) **[12,13]**.

Despite increasing complexity in midlife health presentations, care for perimenopausal and menopausal women remains largely fragmented and symptom focused. Current models frequently center on ovarian hormone deficiency or isolated symptom clusters, such as vasomotor symptoms, mood or sleep disturbance, without accounting for the cumulative biological and psychosocial context in which these symptoms arise **[14–16].** As a result, symptoms are often managed as transient or organ-specific rather than as manifestations of interconnected system-wide dysregulation, with psychological, metabolic and stress-related factors addressed in isolation **[17,18].** This fragmentation may obscure shared upstream mechanisms and contribute to persistent symptoms despite standard interventions. These limitations demonstrate the absence of an integrated framework capable of addressing midlife health as a system-level process shaped by interacting biological, environmental and cohort-specific influences.

Evolutionary medicine provides a unifying framework for understanding the rise of chronic diseases in modern populations despite relatively stable human genetics **[19]**. Central to this approach is the evolutionary mismatch hypothesis, which proposes that physiological systems shaped under ancestral conditions are increasingly misaligned with modern environments characterised by ultra-processed diets, reduced physical activity, chronic psychosocial stress, circadian disruption and ubiquitous chemical exposures **[20,21]**. Traits once adaptive for survival and reproduction, including efficient energy storage, flexible stress responsivity and context-dependent immune activation, may become maladaptive when persistently engaged, contributing to metabolic, inflammatory and neuroendocrine dysregulation in modern societies **[22]**. Importantly, mismatch effects are not uniform across populations but vary by sex, developmental timing and cumulative exposure burden. Midlife, in particular, emerges as a period of heightened biological vulnerability when hormonal transitions converge with long-standing metabolic and stress-related factors **[23,24]**. This perspective is particularly relevant to women, whose reproductive and neuroendocrine systems are highly responsive to metabolic, immune and environmental signals, such that the menopausal transition may unmask or amplify accumulated mismatch-driven dysfunction across the life course **[25,26]**.

While evolutionary mismatch provides a broad explanatory framework for modern chronic disease, it does not adequately account for the heterogeneity in midlife health trajectories observed in women. Existing models, which either generalize across populations or focus narrowly on menopause, remain insufficient to explain the complexity of the midlife Gen X experience **[14,24]**. There is currently no integrative framework that accounts for the interaction of evolutionary mismatch, cumulative exposome burden and midlife hormonal transition in this cohort (Figure 1).

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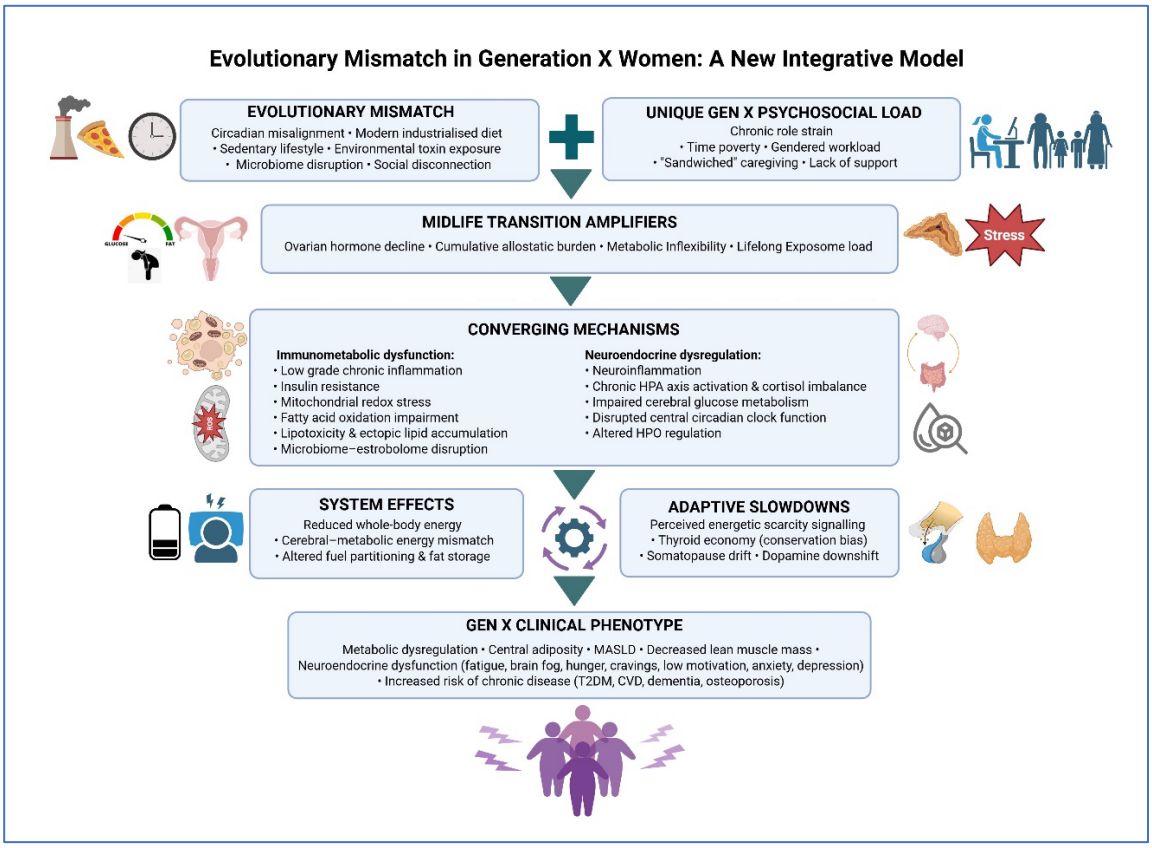

Figure 1. Evolutionary mismatch integrative model of Gen X midlife transition. Abbreviations include Gen X = Generation X; HPA = hypothalamic-pituitary-adrenal axis; MASLD = metabolic-associated steatotic liver disease; T2DM = type 2 diabetes mellitis; CVD = cardiovascular disease.

The model aims to explain the emergence of fatigue, metabolic inflexibility, cognitive dysfunction and increased chronic disease risk during the midlife transition in Gen X women, and to outline clinically relevant pathways aligned with the principles of evolutionary medicine.

2. Evolutionary Mismatch and Female Biology

2.1. The evolutionary Mismatch Hypothesis in Human Health

Human physiology reflects a long history of interactions between our species, our ancestors, and the ecological conditions in which they lived **[27]**. Evolutionary mismatch theory argues that biological traits shaped for ancestral environments can become maladaptive when the surrounding conditions rapidly change, as they have in the Anthropocene **[28]**. Many chronic conditions that were historically uncommon, including obesity, type 2 diabetes mellitis (T2DM), cardiovascular disease (CVD), and polycystic ovary syndrome (PCOS), have increased significantly as modern environments diverge from those in which human physiology evolved **[13]**.

A growing body of epidemiological research shows that contemporary exposures such as circadian disruption, air pollutants, synthetic chemicals, highly processed diets, sedentary lifestyles, psychosocial stress, and cultural pressures, interact with genetic predispositions to destabilize metabolic and endocrine systems **[29–31]**. These mismatch dynamics are especially relevant to women's reproductive health, where strong evolutionary pressures on fertility and the trade-offs between reproduction and survival increase physiological sensitivity to environmental change, with broader systemic effects mediated by sex steroids across metabolic, circadian and neuroendocrine pathways **[32]**.

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2.2. Midlife Vulnerability in Women: Ancestral Physiology and Environmental Discordance

Human female physiology evolved under conditions of high physical activity, fluctuating food availability and competing energetic demands operating across survival, body maintenance and reproduction. Within these environments, metabolic and reproductive systems adapted dynamically to resource availability, with reproductive investment modulated in response to energetic conditions **[27,33]**. Women adapted by down-regulating basal metabolic rate and reproductive capacity in times of scarcity.

In contrast, modern environments characterised by reduced physical activity, energy-dense diets, chronic psychosocial stress and delayed reproduction disrupt these evolved regulatory systems **[22]**. Contemporary lifestyles differ markedly from ancestral patterns of movement, diet, circadian rhythm and social structure, creating sustained environmental discordance across multiple physiological domains **[24,32]**.

Midlife represents a period in which the effects of this discordance become increasingly apparent. The menopausal transition, marked by a predictable decline in ovarian steroid hormone production, reflects a normal life-history stage rather than pathological dysfunction **[34,35]**. However, these hormonal changes occur within an environment that differs substantially from the conditions under which female physiology evolved **[36]**.

These interactions position the menopausal transition as a vulnerability window in which accumulated discordance converges with declining physiological reserve, as discussed in Section 4. Rather than representing isolated symptoms, these changes reflect the interaction between endocrine transitions and long-standing environmental mismatch across the life course.

2.3. Evolutionary Mismatch and the Microbiome in Gen X

Humans and their gut microbes have co-evolved for millions of years, and although each person carries hundreds of bacterial species, variation at the strain level is even more extensive. Subtle genetic shifts enable these microbes to respond quickly to selective pressures in ways that far outpace human evolutionary change. A growing body of research shows that bacteria can evolve within a microbiome over periods ranging from days to years, enabling them to establish long-term colonisation of the host **[37]**.

An evolutionary mismatch occurs between the biological systems of Gen X women that are adapted for ancestral conditions and the modern gut microbiome. The modern gut microbiome is characterised by a loss of species diversity and altered composition (dysbiosis) **[38,39]**. Gen X women exhibit elevated metabolic risk based on anthropometric markers and are therefore likely to enter the menopausal transition with dysbiosis **[40]**. Dysbiosis associated with metabolic dysfunction features enhanced energy extraction, production of pro-inflammatory metabolites, and depletion of short-chain fatty acid (SCFA)-producing species **[41,42]**. These changes in the microbiome cause increased gut permeability and the translocation of lipopolysaccharide (LPS) from the gut to the blood stream causing metabolic endotoxemia **[43]**.

3. Generation X as a Distinct Biological and Psychosocial Cohort

3.1. Defining Generation X (1965–1980): Historical, Social and Environmental Context

Born between 1965 and 1980, Gen X women represent a distinct cohort defined by life-course exposure to fully industrialized, digitized and globalized environments, and are among the first generation to reach the menopausal transition after a lifetime within this modern context **[44,45]**. As Gen X women transitioned from childhood into adulthood, they were exposed to sustained macro-level shifts including economic restructuring, rising female workforce participation, rapid technological change and greater labour market volatility relative to the post-war Baby Boomer cohort **[46,47]**. While generational categories are necessarily imperfect and context-dependent, Gen

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X is used here as a pragmatic birth-cohort to examine the timing of environmental and psychosocial exposures relative to the menopausal transition.

3.2. The unique Psychosocial Load of Gen X Women

Gen X women have experienced a distinctive psychosocial load characterised by sustained role strain and time scarcity, which has relevance to stress physiology and allostatic burden **[7,48]**. Expanded workforce participation occurred alongside the rise of post–second-wave feminist ideals, which promoted educational and occupational aspirations for women without equivalent structural change in childcare, domestic labour or workplace flexibility, resulting in prolonged periods of concurrent occupational, familial and emotional demands **[49–51]**. Early exposure to dual-income households and independent caregiving arrangements further normalized high self-reliance and personal responsibility from a young age **[52,53]**.

Relational coordination, anticipatory planning and emotional regulation within families and workplaces have been disproportionately managed by women across adulthood, with particular salience for Gen X women navigating peak career and caregiving demands simultaneously **[9–11]**. These largely unrecognized responsibilities require sustained cognitive and affective effort and contribute to ongoing psychological load independent of acute stressors **[6,54]**. Workforce transitions, extended caregiving and digital substitution for embodied experiences may also alter social connectedness for some women **[55–57]**.

Caregiving pressures are often compounded by delayed childbearing, resulting in overlapping responsibilities for dependent children and ageing parents, a pattern commonly described as the "sandwich generation", with limited opportunity for recovery or reciprocal support **[58–60]**. Patterns of sustained self-reliance established earlier in life may persist into midlife, further increasing cumulative psychosocial demand **[47,61,62]**.

3.3. Why Symptoms Emerge in Midlife and the Menopausal Transition

For many Gen X women, accrued environmental, psychosocial and biological demands were largely accommodated through early and mid-adulthood, supported by substantial adaptive reserve that enabled sustained function despite significant background load **[54,61,62]**. A defining feature of this cohort is not exposure alone, but the duration and developmental timing of that exposure prior to the menopausal transition. As a result, women enter midlife carrying an accumulated biological burden arising from long-term interaction with modern environmental conditions, including chemical, metabolic and circadian challenges **[63–65]**.

Midlife represents a distinct biological phase characterised by reduced physiological reserve and a heightened vulnerability to stresses that were previously well tolerated. In this context, the midlife transition therefore constitutes a vulnerability window in which long-standing exposure and adaptation converge with age-related biological change, unmasking previously compensated dysregulated adaptive physiological and psychological responses **[66,67]**.

4. Midlife Physiological Amplifiers

4.1. The midlife Hormone Transition

The midlife hormonal transition typically unfolds across the mid-40s to the mid-50s, with the average age of natural menopause around 51 years, although timing varies between individuals **[68]**. Perimenopause is characterised by fluctuating E2 levels, early luteal phase changes and declining progesterone levels, alongside age- and stage-related alterations in circadian regulation, including reduced melatonin output, accompanied by increasing hormonal variability **[68,69]**. This period transitions into postmenopause, marked by sustained reductions in ovarian E2 production and age-related declines in androgen levels **[4,70]**. Together, these staged endocrine changes underpin many of the characteristic features of the menopausal transition, including vasomotor symptoms, sleep and

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circadian disruption, mood changes, alterations in body fat distribution, and emerging cognitive symptoms including reduced concentration, impaired attentional focus, and subjective memory difficulties commonly described as "brain fog" **[71,72]**.

4.2. Cumulative Allostatic Burden and Stress System Saturation

Across the life course, Gen X women have adapted to sustained environmental and psychosocial demands through repeated readjustment of neuroendocrine, metabolic, immune and circadian regulatory systems **[62,66]**. The cumulative biological cost of this long-term adaptation is captured by the concept of allostatic load, which refers to the physiological impact of repeated or prolonged activation of stress-responsive systems required to maintain stability in changing conditions **[66,73]**.

While allostatic responses support short-term homeostasis, persistent demand progressively reduces adaptive reserve and narrows functional flexibility across multiple systems **[66]**. By midlife, stress-response and regulatory systems are more likely to approach saturation rather than compensation, such that additional challenges are less effectively buffered **[67,70]**. In this context, the menopausal transition represents a period in which long-standing allostatic burden intersects with age-related biological change, increasing susceptibility to dysregulation as regulatory thresholds are exceeded.

4.3. Lifelong Exposome Load and Biological Accumulation

In parallel with psychosocial and physiological adaptation, Gen X women have experienced sustained exposure to a broad range of non-genetic environmental factors across the life course **[65,74]**. The exposome refers to the totality of environmental exposures encountered throughout life, including industrial pollutants, pesticides, plastics, endocrine-disrupting chemicals (EDC) and other contaminants such as heavy metals **[30,75]**. Gen X women were among the first cohorts to experience continuous, low-dose exposure to many of these agents across critical developmental windows throughout the life course **[74–77]**.

Many components of the modern exposome possess endocrine-disrupting, obesogenic and microbiome-modulating properties, with the capacity to interfere with hormone synthesis, metabolism, mitochondrial function, and receptor signaling **[74,78]**. Accumulated biological exposure over decades is increasingly associated with metabolic dysfunction, immune dysregulation and altered neuroendocrine signaling, with emerging evidence also linking biological accumulation to heightened neurocognitive vulnerability during midlife and later life **[75,79]**.

4.4. Loss of Metabolic Flexibility

Metabolic flexibility refers to the capacity to efficiently switch between fuel sources in response to changes in energy availability, demand and hormonal signalling **[80,81]**. In metabolically flexible systems, glucose and lipid oxidation are dynamically regulated to support cellular energy requirements while minimising metabolic stress **[20,82]**. This flexibility is central to maintaining energy balance, preserving insulin sensitivity and supporting mitochondrial efficiency **[83,84]** .

Repeated exposure to energy surplus, circadian disruption, chronic stress and EDC exposures progressively narrows this adaptive capacity **[20,83]**. By midlife, many Gen X women exhibit reduced ability to transition between fed and fasted states, impaired lipid oxidation, and increased reliance on glucose-dependent metabolism, even in the presence of energy abundance **[83,84]**. Declining E2 further compounds this process by altering substrate partitioning, mitochondrial function and insulin sensitivity **[84–86]**.

4.5. Midlife as a Biological Inflection Point

Taken together, the midlife hormonal transition, cumulative allostatic burden, lifelong exposome accumulation and progressive loss of metabolic flexibility converge to create a distinct biological inflection point in Gen X women. Rather than reflecting a single causal driver or singular

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convergence point, this phase is best understood as one of amplified biological vulnerability, arising from the interaction of multiple long-standing and stage-specific pressures acting across interconnected regulatory systems.

This convergence helps explain why fatigue, metabolic inflexibility, cognitive symptoms and weight redistribution commonly emerge or intensify during midlife, even in women who functioned well across earlier adulthood. Framing midlife as an inflection point rather than a failure provides a coherent foundation for understanding the downstream immunometabolic and neuroendocrine mechanisms described in the following sections, and for identifying opportunities for targeted recovery rather than symptomatic management (see section 9).

5. Converging Immunometabolic Mechanisms

5.1. Overview: Disruption of Integrated Neuroendocrine–Immune–Metabolic Networks

The intersection of lifelong evolutionary mismatch and the midlife hormonal transition, disrupts interdependent regulatory networks that coordinate energy sensing, substrate allocation, inflammatory tone, and stress adaptation (Figure 2). Midlife symptomatology is therefore better understood as network-level failure across neuroendocrine, immune, and metabolic systems, rather than isolated dysfunction within any single axis. Under sustained metabolic stress, circadian disruption, and chronic psychosocial load, systems that evolved for short, intermittent challenge, shift toward persistent activation with reduced resolution **[24,67]**. As adaptive reserve declines, coordination between immune activation, insulin action, mitochondrial energetics, and central neuroendocrine control becomes less flexible, resulting in reduced metabolic efficiency, impaired fuel utilization and persistent low-grade inflammation. The mechanisms underpinning this shift are outlined below, beginning with immunometabolic disruption and extending to central neuroendocrine dysregulation, which together form the core biological hub of the proposed model.

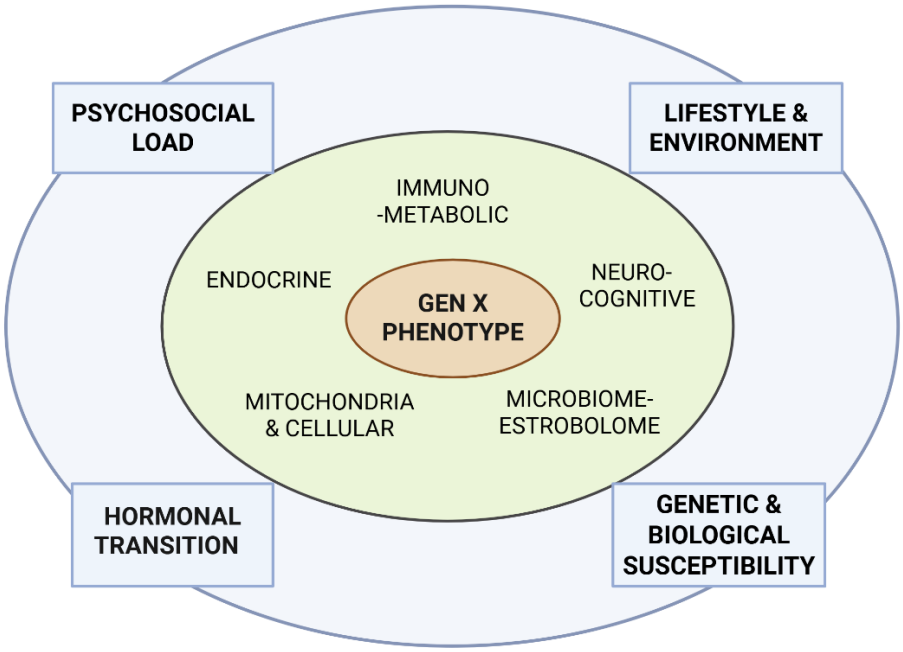

Figure 2. Spheres of Influence Within the Evolutionary Mismatch Model of Gen X Women.

5.2. Chronic Low-Grade Systemic Inflammation and Immune Dysregulation

Chronic systemic inflammation (CSI) reflects sustained, subclinical immune activation arising from repeated exposure to metabolic stressors, environmental inputs and disrupted physiological

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signaling **[87,88]**. Components of the modern exposome, including ultra-processed foods, EDCs and bioaccumulative compounds, can activate innate immune pathways directly or via mitochondrial and oxidative stress signals, contributing to persistent low-grade CSI **[65,74]**. This state is characterised by increased cytokine-mediated crosstalk between immune and metabolic tissues and impaired resolution of inflammatory responses **[89]**. Repeated immune activation without effective resolution contributes to broader immune regulatory fatigue, marked by impaired inflammatory control, altered immune tolerance and reduced adaptive flexibility. Declining E2 and progesterone signaling during the midlife transition further diminishes immune regulation. Estradiol, in particular, exerts well-characterised anti-inflammatory and immunomodulatory effects, with emerging evidence suggesting complementary immunoregulatory actions of progesterone, increasing susceptibility to persistent inflammation and immune-mediated dysfunction in vulnerable individuals **[90–92]**.

5.3. Insulin Resistance (IR) and Impaired Substrate Handling

Insulin resistance reflects disruption of integrated fuel-sensing and metabolic coordination mechanisms that regulate glucose and lipid utilization in liver, skeletal muscle, and adipose tissue, becoming increasingly pronounced during the midlife transition **[93,94]**. As insulin responsiveness declines, compensatory hyperinsulinemia preserves short-term glycemic stability while progressively distorting substrate partitioning and energy distribution between tissues **[95]**. This compensatory state prioritizes storage over oxidation, even in the context of abundant circulating fuels.

Declining E2 availability further alters insulin sensitivity, lipid flux, and mitochondrial substrate preference, reducing the capacity to flexibly oxidize glucose and free fatty acids in accordance with energy demand **[84,96]**. Impaired coordination between insulin action and mitochondrial energy production constrains metabolic adaptability, favoring lipid sequestration and inefficient fuel utilization **[96,97]**. In the modern environment, IR arises as a coordinated cellular response to sustained substrate oversupply, hyperinsulinemia, inflammation, and hormonal effects. This results in attenuated insulin signalling, reduced glucose transporter type 4 (GLUT4) activation, increased diacylglycerol/ceramide accumulation, and other tissue-specific responses that were adaptive in an ancestral environment. This adaptive response becomes maladaptive in the contemporary environment and is exacerbated by midlife declines in E2, progesterone, and growth hormone/insulin-like growth factor-1 (GH/IGF-1) that remove key counter-regulators of mitochondrial biogenesis and lipid oxidation. This amplifies redox stress, impairs mitochondrial coupling efficiency, and progressively constrains systemic bioenergetic capacity **[98]**.

5.4. Mitochondrial Redox Stress and ATP Production Inefficiency

As impaired substrate handling restricts coordinated fuel oxidation across tissues, mitochondrial redox balance becomes increasingly mismatched to nutrient availability **[96,99]**. Under sustained metabolic pressure, excess reducing equivalents (e.g. NADH and $FADH_2$), accumulate within the electron transport chain while oxidative throughput is limited, increasing electron leak and yielding lower mitochondrial adenosine triphosphate (ATP) output alongside amplified oxidative stress **[97,100]**. This reflects a bottleneck in bioenergetic processing rather than primary mitochondrial failure, where impaired nutrient delivery exceeds the capacity for efficient oxidation **[101]**. These intrinsic bioenergetic constraints are further intensified by evolutionary mismatches including circadian disruption, ultra-processed food exposure, EDC and cumulative environmental toxic burden, each of which independently impairs mitochondrial efficiency, redox control, and energy coupling **[102–104]**.

Midlife hormonal shifts further shape this mitochondrial landscape in a sex-specific manner. E2 normally supports mitochondrial adaptability by enhancing fatty acid oxidation capacity, improving electron transport efficiency, and coordinating mitochondrial biogenesis and mitophagy through adenosine monophosphate-activated protein kinase- (AMPK), sirtuin 1- (SIRT1), and peroxisome

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proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α)-linked pathways **[105–108]**. Progesterone has been associated with enhanced mitochondrial ATP synthesis and reduced oxidative stress in experimental models, while chronic glucocorticoid signaling can disrupt mitochondrial function in a tissue- and exposure-dependent manner **[106]**. In combination, ovarian hormone withdrawal and elevated glucocorticoid levels shift mitochondrial metabolism toward lower efficiency and greater redox imbalance, compounding pre-existing metabolic vulnerability during the midlife transition **[109,110]**.

This bioenergetic inefficiency is accompanied by a persistent cellular redox imbalance arising from incomplete oxidative metabolism and increased reliance on glycolytic flux, placing sustained demands on antioxidant systems **[104,111]**. Over time, repeated redox strain and constrained ATP generation reduce the capacity to restore metabolic balance at the cellular and tissue level **[111,112]**. This state contributes to metabolic inflexibility and impairs downstream lipid handling and immune pathways, positioning mitochondrial redox stress as a central mechanism within the broader immunometabolic cascade.

5.5. Lipotoxicity and Ectopic Lipid Accumulation

When free fatty acid (FFA) delivery exceeds oxidative and storage capacity, surplus lipids accumulate within non-adipose tissues, giving rise to ectopic lipid deposition and lipotoxic stress **[84,96]**. Impaired fatty acid oxidation, coupled with altered lipid trafficking and reduced mitochondrial processing capacity, promotes intracellular accumulation of lipid intermediates rather than inert triglyceride storage molecules **[96,100]**. These intermediates, including diacylglycerols, ceramides and acylcarnitine's, disrupt cellular signaling, membrane integrity and organelle function in multiple tissues **[113]**. Lipotoxic intermediates interfere with mitochondrial respiration, induce oxidative and endoplasmic reticulum stress, and impair insulin-responsive pathways, reinforcing metabolic inflexibility **[114,115]**. During the midlife transition, declining E2-mediated regulation of glucose and lipid metabolism and decreased mitochondrial efficiency further constrains adaptive substrate handling, increasing susceptibility to ectopic lipid accumulation and amplifying downstream immunometabolic dysfunction **[96,116]**.

5.6. Microbiome–Estrobolome Disruption

Disruption of the gut microbiome during the midlife transition alters not only metabolic and immune signaling but also the regulation of sex steroid bioavailability through the estrobolome **[117]**. Menopause-associated reductions in E2 are accompanied by shifts in microbial composition, functional capacity, and estrobolome activity, resulting in diminished enterohepatic E2 recirculation and altered systemic hormone dynamics **[117,118]**. Large-scale metagenomic analyses demonstrate that postmenopausal women exhibit reduced microbial diversity, depletion of key estrobolome-associated microbes, and lower abundance of β-glucuronidase producing species capable of deconjugating E2—changes that correlate with adverse cardiometabolic profiles **[94,119]**. Concurrent impairment of gut barrier integrity and SCFA production further amplifies immune activation and metabolic stress, reinforcing bidirectional dysregulation between host metabolism, inflammation, and hormonal signaling **[120,121]**. Within the Gen X cohort, lifelong microbiome disruption imposed by dietary, environmental, and pharmaceutical exposures impact microbiome composition, diversity and the microbiome–estrobolome axis, which are particularly vulnerable during midlife, exacerbating this bidirectional relationship **[39,117]**.

Taken together, these findings suggest that the gut microbiome, already compromised by evolutionary mismatch, becomes uniquely vulnerable during the menopausal transition due to declining E2, chronically low dietary fibre intake, dysbiosis, and lower β-glucuronidase–mediated E2 recycling. As a result, altered microbiome function amplifies metabolic and hormonal dysfunction and represents a potentially modifiable component of the Gen X phenotype within a broader, staged recovery framework discussed in section 9.

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5.7. Neuroendocrine Dysregulation

5.7.1. Neuroinflammation and Disruption of Hypothalamic Regulation of Whole-Body Energy Homeostasis

From an evolutionary perspective the hypothalamus functions as a central regulatory hub that integrates metabolic, endocrine, immune, neural, and environmental signals to assess whole-body energy metabolism and coordinate adaptive physiological responses **[13,122]**. Under conditions of perceived energy scarcity, hypothalamic signalling prioritises survival by downregulating energetically costly processes, including reproduction, tissue repair, and anabolic metabolism **[12,123]**.

In contemporary midlife women, IR and CSI act as convergent upstream drivers that disrupt this regulatory architecture **[124,125]**. Insulin receptors are expressed across key hypothalamic neuronal populations involved in energy sensing and neuroendocrine coordination **[12,126]**. In insulin-sensitive states, central insulin signalling supports appropriate integration of metabolic and hormonal inputs. However, IR impairs hypothalamic insulin signalling, altering neuronal responsiveness and disrupting feedback integration across multiple endocrine axes **[12,125]**.

Chronic systemic inflammation further amplifies this disruption. Circulating pro-inflammatory cytokines, FFAs, and related metabolic stress factors, relay signals to hypothalamic nuclei, activating local neuroimmune pathways and inducing microglial and astrocyte inflammatory responses **[126–128]**. In ageing and altered metabolic states, hypothalamic inflammatory signalling—including interleukin-1β (IL-1β), tumour necrosis factor-α (TNF-α) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation—is upregulated in the mediobasal hypothalamus **[128–130]**. This neuroinflammatory state interferes with neuronal insulin signalling, mitochondrial function, and synaptic communication, and impairs hypothalamic energy sensing **[131,132]**.

During the menopausal transition, progressive follicular depletion is accompanied by declining ovarian steroid output, rising follicle stimulating hormone (FSH) and luteinizing hormone (LH), and reduced inhibin signaling, creating a hypothalamic microenvironment that is increasingly permissive to innate immune activation, including inflammasome-linked neuroinflammatory processes **[88]**. This shift is associated with reduced neuroimmune and metabolic regulatory capacity and heightened hypothalamic vulnerability to inflammatory and insulin-resistant states, consistent with evidence that the menopausal transition is accompanied by altered neuroimmune signaling and stress responsivity **[133]**.

Experimental evidence supports a role for E2-deficiency in hypothalamic neuroinflammatory-mediated disruption of energy regulation. In an ovariectomized mouse model of menopause, Yang et al. demonstrate that E2-deficiency induces microglial activation and increased expression of pro-inflammatory genes within hypothalamic nuclei. This results in increased inflammatory cytokine production (TNF-α, IL1β) and prostaglandin synthesis that disrupt hypothalamic neuronal circuits involved in whole-body energy homeostasis and contributes to the development of visceral obesity **[124].**

This pattern of hypothalamic dysregulation may contribute to the persistence of maladaptive neuroendocrine response patterns, with downstream effects across gonadal, adrenal, thyroid, and somatotrophic axes **[133]**. In metabolically and hormonally susceptible states, such changes provide a mechanistic basis for considering how chronic stress and HPA axis activation may further potentiate hypothalamic neuroinflammatory tone and neuroendocrine dysregulation **[124,133]**.

5.7.2. Chronic HPA Axis Activation and Cortisol Dysregulation

The HPA axis is an evolutionarily conserved system that coordinates metabolic, immune, and behavioural responses to environmental challenge by mobilising energy substrates and prioritising short-term survival **[134,135]**. The HPA axis is part of a co-operative network of feedback mechanisms involving the central nervous system (CNS), autonomic nervous system (ANS), and immune system, that co-ordinate the systemic inflammatory response (Figure 3) **[130]**. While acute activation is

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adaptive, persistent engagement of this system becomes maladaptive, particularly under conditions of chronic psychosocial stress, CSI and metabolic dysfunction.

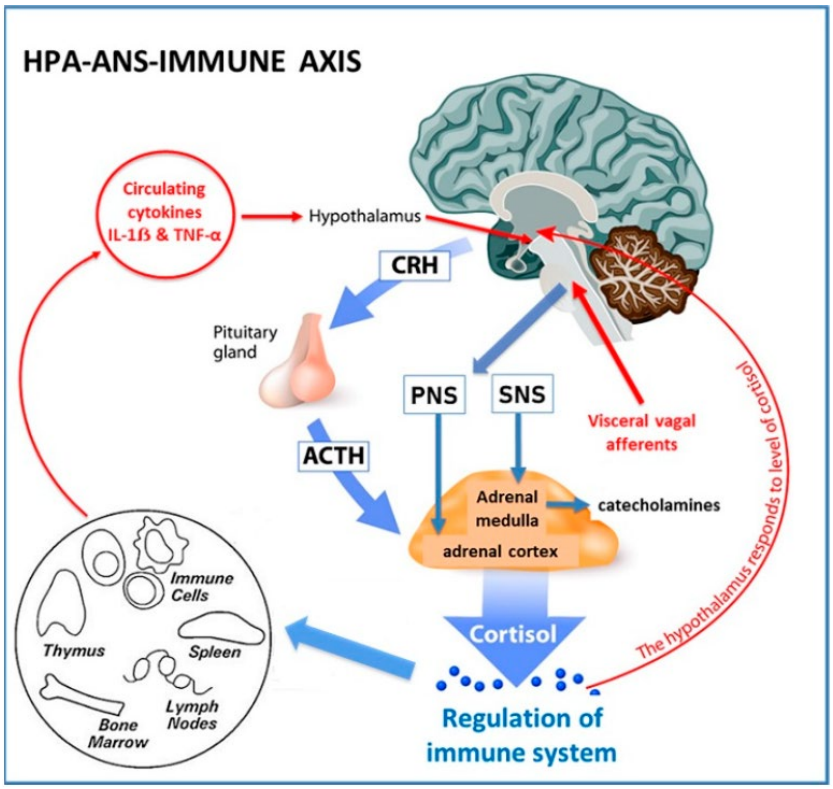

Figure 3. Hypothalamic-Pituitary-Adrenal-Immune Axis (HPA). The hypothalamus releases corticotropin releasing hormone that stimulates production of adrenocorticotropic hormone (ACTH) from the anterior pituitary. ACTH stimulates the synthesis of immunosuppressive glucocorticoids (cortisol) from the adrenal cortex. Pro-inflammatory cytokines and neural inputs activate the HPA-axis to release ACTH, and the HPA-axis is subject to a classic negative feedback loop by cortisol that inhibits both corticotropin releasing hormone and ACTH. Sympathetic neural activation of chromaffin cells in the adrenal medulla leads to an increased release of catecholamines into the circulation. Sympathetic innervation of cortical cells leads to the release of glucocorticoids. CNS-controlled SNS output is, therefore, converted to hormonal immunoregulation in peripheral tissues. ANS, Autonomic Nervous System; Parasympathetic Nervous System (PNS); Sympathetic Nervous System (SNS); CRH, Corticotropin Releasing Hormone; Adrenocorticotropic Hormone (ACTH); IL-1SS, interleukin-1SS; TNF-α, tumour necrosis factor-α. Reprinted with permission from Parker et al 2025 **[130]** © Designua|Dreamstime.com.

In Gen X women, midlife coincides with multiple convergent drivers of sustained HPA axis activation, including chronic stress exposure, IR, inflammatory signalling, and the menopausal transition itself **[88,136]**. These conditions are associated with altered cortisol dynamics, including elevated basal levels, flattened diurnal rhythms, impaired cortisol awakening responses, and reduced glucocorticoid receptor sensitivity, reflecting stress-system dysregulation rather than isolated hypercortisolaemia **[134,135]**. Metabolically, chronic glucocorticoid signalling promotes IR, visceral adiposity, and impaired substrate handling, while CSI further stimulates HPA axis activity, reinforcing a self-perpetuating neuroendocrine–metabolic loop **[134,137]**.

Beyond metabolic effects, sustained HPA axis activation has direct implications for cognitive function. Cortisol receptors are densely expressed in the hippocampus and prefrontal cortex, regions critical for memory, executive function, and stress regulation **[135,138]**. Under conditions of chronic stress, impaired glucocorticoid negative feedback permits prolonged CRH–ACTH–cortisol signalling, while circulating pro-inflammatory cytokines further activate hypothalamic stress response pathways (Figure 3) **[130]**. Prolonged glucocorticoid exposure under these conditions is

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associated with impaired synaptic plasticity, reduced neurogenesis, dendritic remodelling, and altered neurotransmission, changes that align with cognitive inefficiency, reduced attentional capacity, and diminished stress tolerance reported during midlife **[135,138]**.

The menopausal transition further increases vulnerability to cortisol-mediated neural effects. Loss of the modulatory influence of E2 is associated with heightened HPA axis reactivity, increased neuroimmune activation, and reduced mitochondrial and metabolic resilience within the brain **[88,139]**. In this context, sustained stress signalling may bias central immune surveillance toward a pro-inflammatory state. As a result, glucocorticoid exposure interacts with E2 withdrawal to amplify cytokine-driven modulation of synaptic plasticity and stress-sensitive neural circuits in females **[133]**.

5.7.3. Impaired Cerebral Glucose Metabolism and Reduced Brain Energy Availability

During midlife, female brain energy metabolism undergoes a coordinated shift characterised by reductions in cerebral glucose uptake, altered substrate utilisation, and declining metabolic efficiency, particularly during the menopausal transition **[140–142]**. Longitudinal and cross-sectional FDG-PET neuroimaging studies demonstrate that women show region-specific reductions in cerebral glucose metabolism during midlife that are temporally aligned with endocrinological changes rather than chronological aging alone **[140]**. This metabolic transition occurs despite normal peripheral glucose availability, indicating an impairment in cerebral glucose handling rather than simple systemic hypoglycaemia **[141]**.

Neuroimaging evidence further indicates that these metabolic changes are not uniformly distributed across the brain. Sex-specific analyses reveal that women exhibit greater vulnerability to reductions in glucose metabolism within the prefrontal cortex, posterior cingulate cortex, temporal lobes, and hippocampal regions, all of which are critical for executive function, memory consolidation, and attentional control **[143,144]**. Structural–metabolic coupling studies demonstrate that reduced glucose metabolism is associated with alterations in cortical thickness and white matter integrity, suggesting that impaired energy availability may contribute to downstream changes in neuronal maintenance, synaptic function, and network efficiency during healthy aging in women **[144,145]**.

Declining E2 signalling appears to play a central role in this bioenergetic shift. Estrogen receptors are densely expressed in brain regions involved in glucose transport, mitochondrial function, and synaptic plasticity. In vivo imaging studies demonstrate progressive reductions in brain E2-receptor density during the menopausal transition **[108,146]**. Loss of oestrogenic support is associated with reduced glucose transporter expression, diminished mitochondrial oxidative capacity, and compensatory reliance on alternative substrates, reflecting a state of relative cerebral energy insufficiency during the menopausal transition **[140–142]**. Collectively, these changes provide a mechanistic framework linking midlife hormonal transition to impaired cerebral glucose metabolism and reduced brain energy availability, with implications for emerging cognitive inefficiency and increased vulnerability to later-life neurodegenerative risk in Gen X women **[141,146]**.

5.7.4. Disruption of Central Neuromodulatory and Circadian Signalling During Midlife

During the menopause transition, fluctuating and subsequently low E2, disrupts cerebral neuromodulatory balance, and increases vulnerability to mood and cognitive symptoms **[147,148]**. Neuroendocrine models of perimenopausal change describe coordinated involvement of monoaminergic systems (e.g., serotonin, dopamine and noradrenaline), alongside gamma-aminobutyric acid (GABA)-modulating neurosteroids (e.g., allopregnanolone), and hypothalamic neuropeptides (e.g., kisspeptin and neurokinin B) **[147]**. Across this network, E2 functions as a key upstream regulator of pathway coupling, synthesis, and receptor dynamics, positioning hormonal withdrawal as a central driver of neuromodulatory instability during midlife **[147,149]**.

Within this neuromodulatory framework, reduced dopaminergic tone represents a plausible contributor to the symptoms reported by many midlife women, including reduced focus, decreased reward sensitivity, drive and goal-directed behaviour. Dopamine circuits play a central role in

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motivation, effort allocation and executive control, and experimental and human evidence indicates that E2 modulates dopaminergic signalling and dopamine metabolism **[147,150]**. Postmenopausal studies examining proxies of prefrontal dopamine regulation, including catechol-O-methyltransferase (COMT) genotype and circulating E2, further support menopause-related effects on working memory circuitry **[151]**.

Midlife endocrine change also intersects with circadian regulation via the suprachiasmatic nucleus (SCN), the central pacemaker coordinating sleep–wake timing and peripheral clock entrainment **[152,153]**. E2 contributes to sleep–wake regulation through hypothalamic and SCN-linked pathways, and the menopausal transition is associated with increased sleep disturbance, reduced melatonin secretion and greater circadian vulnerability, particularly in the presence of vasomotor symptoms and stress-system activation **[152,154]**. At the molecular level, menopause-related E2 depletion has been linked to altered expression of circadian clock gene markers, including reduced *Per2* gene expression, in studies designed to distinguish menopause-dependent effects from ageing per se **[155]**.

More broadly, effective communication between central and peripheral circadian clocks is integral to metabolic and neuroendocrine homeostasis, and disruption of this coordination is increasingly recognised as a contributor to age-related physiological dysregulation **[156]**. Across mammalian systems, ageing is associated with dampened circadian amplitude and increased circadian misalignment, which are linked to metabolic and cardiovascular risk, while interventions that strengthen circadian organisation are positioned as potential levers for improving healthspan **[157]**. In midlife women, the convergence of neuromodulatory disruption with circadian misalignment provides a mechanistic bridge between mood and cognitive changes, and metabolic vulnerability during the menopause transition **[147,154]**.

6. Systemic-wIde Effects of Convergent Mechanisms

6.1. Reduced Whole-Body Energy Throughput

The converging immunometabolic and neuroendocrine disruptions described above reduce the body's capacity to generate and distribute usable metabolic energy across tissues, creating a biologically constrained total energy budget. Whole-body energy throughput refers to the system-level capacity to produce ATP, allocate substrates, and sustain parallel physiological processes under everyday demand **[122,158]**. Human energy expenditure is not indefinitely expandable; experimental and ecological evidence demonstrates that total daily energy expenditure operates within constrained limits, with compensatory reductions occurring when demands rise rather than linear additive scaling **[159,160]**. Under conditions of increased chronic metabolic and endocrine demand, this energetic margin narrows further.

Within this limited energetic margin, physiological trade-offs intensify. Immune activation, stress mobilization, tissue repair, cognitive processing, thermogenesis, and reproductive signalling compete within a compressed energy envelope. Impaired metabolic flexibility and reduced mitochondrial reserve capacity limit the efficiency with which fuels are oxidised and ATP production is upregulated in response to demand **[160,161]**. The result is not merely altered biomarkers but diminished functional capacity at the whole-body level.

This reduced energy throughput represents the systemic consequence of multisystem dysfunction. As the effective energy budget contracts, discretionary outputs such as spontaneous movement, thermogenesis, and behavioural drive diminish, while effort cost rises and recovery slows **[159,162]**. This constrained energy landscape establishes the context within which cerebral metabolic mismatch and altered fuel partitioning develop, as explored in the following sections.

6.2. Cerebral–Metabolic Energy Mismatch

Reduced whole-body energy has disproportionate consequences for the central nervous system, whose metabolic demands remain high and relatively inflexible. The brain depends on continuous

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oxidative metabolism to sustain synaptic signalling, network integration, and regulatory control **[146]**. When systemic metabolic flexibility narrows and substrate utilisation becomes constrained—due to IR, CSI, and excessive allostatic load—a relative cerebral energy shortfall can emerge even without overt hypoglycaemia. In this state, neural demand remains constant while the efficiency of glucose delivery, transport, and oxidation becomes compromised, creating a mismatch between energy supply and functional demand **[142,143]**.

Rather than reflecting primary structural degeneration, this pattern is increasingly understood as a bioenergetic phenomenon in which impaired peripheral metabolic regulation interacts with central fuel handling. Systemic IR, glycaemic variability, and altered endocrine signalling influence central glucose sensing and regulatory feedback loops between brain and periphery, reinforcing bidirectional metabolic strain **[163,164]**. Under these conditions, reduced whole-body level metabolic flexibility constrains the brain's ability to adjust substrate use dynamically, limiting compensatory responses during periods of stress or fluctuating fuel availability.

Within an energy allocation framework, cerebral metabolic energy mismatch represents a predictable systems-level consequence of a limited total energy budget. When system energy margins narrow, high-cost neural processes become especially sensitive to reductions in substrate efficiency. The result is not necessarily neuronal loss, but altered energy dynamics at the network level, linking peripheral metabolic dysfunction to central functional vulnerability **[164,165]**.

6.3. Altered Fuel Partitioning and Fat Storage Bias

Under conditions of chronic metabolic stress, CSI, IR, hyperinsulinemic signalling, and limits to subcutaneous adipose tissue expandability, energy allocation becomes redistributed rather than simply increased overall. Altered fuel partitioning results in a shift in substrate distribution whereby incoming nutrients are preferentially directed toward storage depots, particularly visceral and ectopic sites, rather than being oxidised within lean tissues for immediate metabolic work **[166,167]**. This redistribution can occur even when total caloric intake remains relatively stable, reflecting changes in hormonal and cellular signalling that influence how fuels are handled rather than how much is consumed **[166]**. Clinically, this process can contribute to weight-loss resistance despite reduced calorie intake during changes to dietary intake.

Insulin plays a central role in this process as a nutrient-partitioning hormone. Chronic elevations in circulating insulin, whether primary or secondary, promote lipogenesis and suppress lipolysis within adipose tissue while simultaneously influencing hepatic and skeletal muscle substrate handling. When subcutaneous adipose tissue approaches its capacity to safely expand, lipid redistribution to the liver, pancreas, and skeletal muscle increases, leading to ectopic triglyceride accumulation and intracellular diacylglycerol signalling that impairs insulin action at the tissue level **[168,169]**. In this context, selective IR may develop as a protective adaptation against further nutrient overload yet paradoxically reinforces continued storage in visceral and hepatic depots **[170]**. Postmenopausal hormonal shifts further modify this partitioning pattern, favouring central adiposity and altered lipid oxidation dynamics **[96,166]**.

The systemic consequence of this altered fuel partitioning is a phenotype characterised by central fat accumulation, increased visceral and hepatic lipid deposition, dyslipidemic patterns, and reduced oxidative capacity of skeletal muscle. Impaired mitochondrial adaptability and reduced oxidative responsiveness in muscle limit effective substrate switching, further biasing fuel substrates toward storage rather than utilization **[171,172].** Over time, this creates a dual vulnerability: expansion of metabolically active adipose depots alongside diminished lean muscle tissue resilience **[173]**. These shifts in whole-body energy dynamics are not random but reflect coordinated prioritisation across tissues in response to sustained metabolic pressure, setting the stage for the adaptive neuroendocrine recalibrations.

7. Metabolic and Neuroendocrine Adaptations

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7.1. Evolutionary Logic of Energy Conservation Under Perceived Scarcity

Building on the system-level constraints outlined in Section 6, we propose that the Gen X midlife phenotype is shaped not by absolute energy intake, but by the central interpretation of effective energy availability. In evolutionary terms, the brain does not directly "respond" to calories per se, but to integrated signals of long-term energy sufficiency and safety—signaled through leptin and insulin, stress-axis feedback, and circadian stability **[174–177]**. When these signals indicate uncertainty or reduced energy reliability, hypothalamic control systems shift toward a survival-orientated state **[175,178]**.

This defensive recalibration activates conserved programs with two coupled outputs. First, an energy conservation bias suppresses discretionary expenditure and anabolic investment—including thermogenesis and trophic drive—to safeguard immediate viability **[179,180]**. Second, an acquisition bias amplifies hunger salience and food-seeking behavior while reducing competing motivational outputs, increasing the likelihood of restoring perceived energy security **[174,181]**. In modern environments, IR, CSI, stress and circadian disturbances can chronically distort these sufficiency cues, sustaining scarcity-like signaling despite adequate calorie availability **[174,182]**. The result is a persistent scarcity-adapted neuroendocrine state, where energy expenditure is down-regulated and food-directed motivation is enhanced, creating a self-reinforcing metabolic–behavioural loop (see Figure 4).

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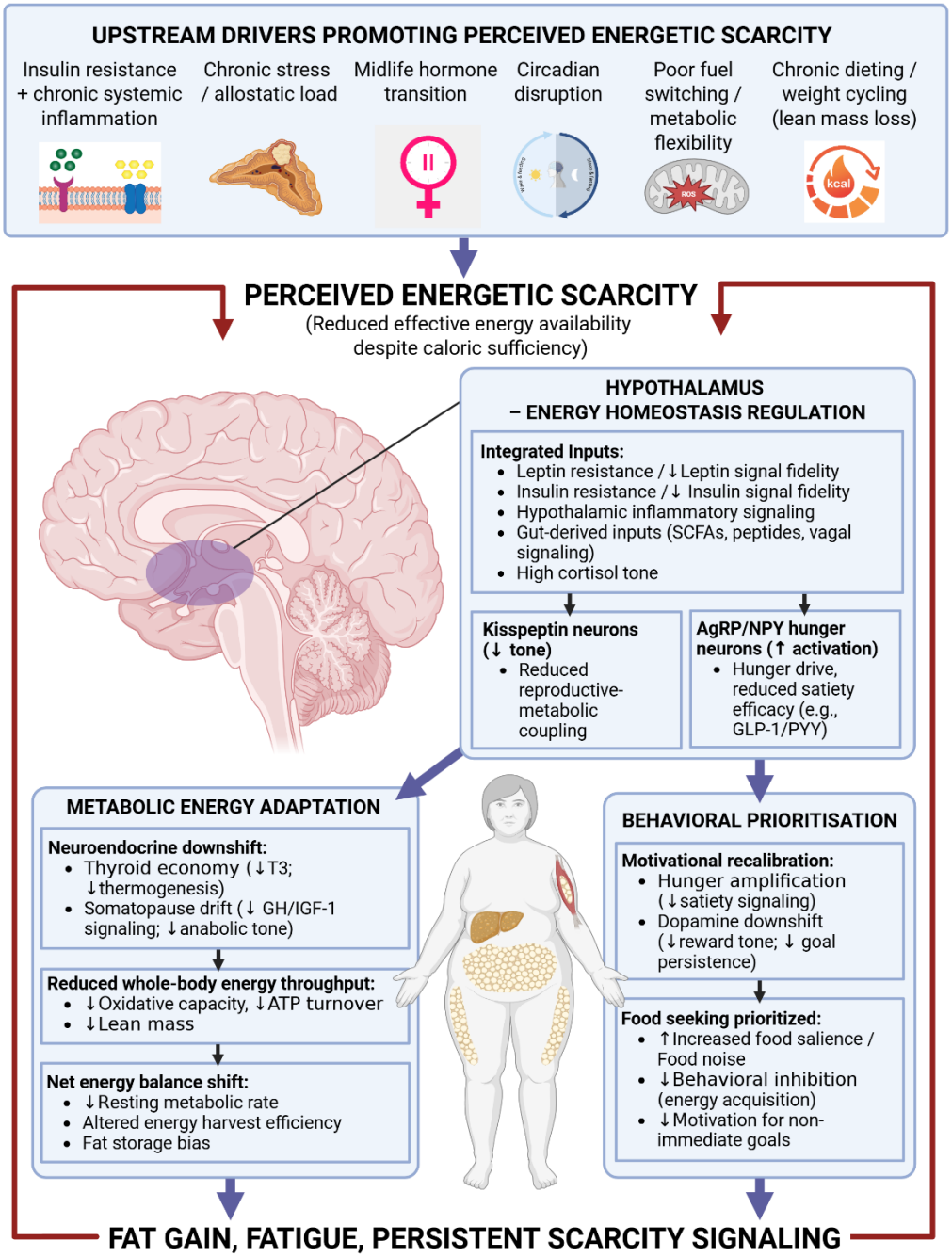

Figure 4. Adaptive Metabolic and Behavioural Responses to Perceived Energetic Scarcity. This schematic illustrates a self-reinforcing metabolic–behavioural loop arising from perceived energetic scarcity within an evolutionary mismatch context. Upstream midlife drivers, including insulin resistance with chronic low-grade inflammation, chronic stress and allostatic load, hormonal transition, circadian disruption, impaired fuel switching, and weight cycling with lean mass loss, contribute to reduced effective energy availability despite caloric sufficiency. These pressures distort hypothalamic energy homeostasis regulation through integrated inputs comprising leptin and insulin resistance with reduced signal fidelity, hypothalamic inflammatory signaling, gut-derived inputs including short-chain fatty acids (SCFAs), enteroendocrine peptides such as GLP-1 and PYY, vagal pathways, and elevated cortisol tone. Recalibration is characterised by reduced kisspeptin tone and increased AgRP/NPY activation, promoting hunger drive and reduced satiety efficacy. Downstream effects diverge into metabolic and behavioural arms. The metabolic energy adaptation arm involves neuroendocrine downshift, including thyroid economy and somatopause drift with reduced growth hormone (GH) and insulin-like growth factor-1 (IGF-1) signaling, leading to reduced whole-body energy throughput marked by lower oxidative capacity, reduced adenosine triphosphate (ATP) turnover and diminished lean mass. This contributes

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to a net energy balance shift with reduced resting metabolic rate, altered energy harvest efficiency, and a bias toward fat storage. In parallel, behavioural prioritization reflects motivational recalibration combining hunger amplification with dopaminergic downshift, resulting in increased food salience and food noise, reduced inhibitory control over energy acquisition, and diminished motivation for non-immediate goals. Together, these adaptations promote fat gain, fatigue and persistent reductions in effective energy availability, reinforcing a scarcity-adapted set point under conditions of abundance. Abbreviations: AgRP, agouti-related peptide; ATP, adenosine triphosphate; GH, growth hormone; GLP-1, glucagon-like peptide-1; IGF-1, insulin-like growth factor-1; NPY, neuropeptide Y; PYY, peptide YY; SCFAs, short-chain fatty acids; T3, triiodothyronine.

7.2. Central Energy Recalibration Under Chronic Stress, Inflammation and Metabolic Dysfunction

Building on the neuroinflammatory disruption outlined in Section 5.7.1, chronic metabolic stress biases hypothalamic integration of adiposity-related cues **[174,183]**. In physiologically stable states, leptin and insulin signal energy sufficiency and nutrient availability, enabling hypothalamic nuclei to calibrate feeding, energy expenditure and reproduction **[122,184]**. In states of chronic metabolic stress, low-grade inflammation in the mediobasal hypothalamus induces central leptin and insulin resistance, degrading these signals in arcuate and ventromedial neurons **[129,175]**. Downstream effects are mediated through conserved nutrient- and energy-sensing pathways, including AMPK-linked nodes **[122,175]**. Elevated glucocorticoid output from chronic stress and allostatic load further shifts hypothalamic set-points toward defensive recalibration **[185–187]**. The net effect is not simply hyperphagia or weight gain, but a central recalibration of long-term energy security despite caloric abundance.

One consequence of this altered regulatory landscape is reduced reproductive–metabolic coupling mediated through kisspeptin neurons. Kisspeptin populations in the arcuate and anteroventral periventricular nuclei integrate metabolic, stress and sex steroid inputs to coordinate gonadotropin-releasing hormone (GnRH) pulsatility with energy sufficiency **[188–190]**. Chronic cortisol exposure, inflammation and impaired leptin signaling each suppress kisspeptin activity, uncoupling reproduction from metabolism **[191–193]**. In females, these circuits are tightly linked to reproductive and metabolic status, reflecting sex-specific evolutionary pressures on reproduction **[189,194]**. In midlife women, declining E2 further amplifies this suppression, potentially favoring energy conservation over anabolic and reproductive investment **[195]**.

With reduced kisspeptin output, arcuate agouti-related peptide/neuropeptide Y (AgRP/NPY) neurons become relatively disinhibited **[196]**. These neurons encode a potent hunger signal and are activated not only by acute caloric deficit but also by diminished effective leptin and insulin input **[197,198]**. Sustained activation of AgRP/NPY circuits heightens food-directed motivation, suppresses competing drives, and makes satiety functionally less effective than hunger **[199,200]**. Feeding behavior is thus biased toward restoring perceived energy security **[196,200]**. In the broader mismatch context, this hypothalamic recalibration establishes a famine-alarm state in which defensive conservation and acquisition programs are co-activated despite environmental energy abundance.

7.3. Behavioural Prioritization Through Gut–Brain Signaling and Reward Recalibration

Adaptive energy conservation in midlife extends beyond hypothalamic recalibration to include gut–brain signaling and reward pathways. Menopausal shifts in E2 and estrobolome activity drive reductions in microbial diversity and gut-ecosystem stability, reflecting lifelong environmental exposures **[78,117]**. These shifts occur within an integrated gut–brain axis that continuously informs central appetite networks about nutrient status and energy availability **[201,202]**. Microbial ecology therefore becomes functionally relevant to hunger salience and feeding behavior rather than a passive background variable.

Mechanistically, the gastrointestinal tract communicates nutrient availability via enteroendocrine peptides including glucagon-like peptide-1 (GLP-1), peptide YY, cholecystokinin and ghrelin, together with vagal afferents projecting to the nucleus tractus solitarius and

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hypothalamic appetite circuits **[184,203]**. Microbiota-derived metabolites add a further regulatory layer. SCFA's produced by microbial fermentation of dietary fibre, modulate enteroendocrine release and vagal signaling, and may also act centrally via the circulation **[184,204]**. Experimental evidence indicates that acetate and related SCFAs can alter arcuate nucleus neuropeptide expression, enhancing anorexigenic pro-opiomelanocortin tone and suppressing AgRP activity under defined conditions **[201,205]**. Dysbiosis may alter SCFA production profiles, gut hormone dynamics, vagal tone and inflammatory signaling, collectively reducing satiety fidelity and biasing output toward orexigenic drive **[206–208]**. Within the broader mismatch framework, the microbiome acts as an amplifier of hunger-related inputs under conditions of metabolic and neuroendocrine imbalance.

Beyond homeostatic appetite control, midlife also involves recalibration of mesolimbic circuitry. E2 modulates dopaminergic tone within prefrontal and striatal pathways governing motivation, effort and reward valuation **[147,150]**. Reduced E2 signaling is associated with altered dopaminergic efficiency, receptor dynamics and reward responsivity **[150,209]**. Lower dopamine tone can reduce baseline motivation and goal-directed behavior while heightening the impact of immediately rewarding stimuli **[204,210]**. When coupled with hypothalamic famine-alarm activation (see Section 7.2) and microbiome-modulated hunger cues, dopaminergic downregulation may intensify attention to palatable foods, increase "food noise," and weaken behavioural resistance to energy acquisition **[211,212]**.

Collectively, these processes extend the adaptive conservation model into behavior. Distorted integration of chronic energy availability cues, gut-derived signals and reduced dopaminergic tone may converge to prioritize acquisition behaviours while dampening effortful, non-immediate goals. In calorically abundant environments, this conserved bias toward energy procurement may reinforce persistent intake and reduced discretionary activity, strengthening the metabolic–behavioural feedback loop depicted in Figure 4.

7.4. Thyroid Economy and Reduced Metabolic Rate

Chronic disruption of central leptin and insulin signaling, inflammation and glucocorticoid excess extend beyond appetite circuits to reshape downstream neuroendocrine outputs governing metabolic rate **[129,213]**. This includes altered hypothalamic–pituitary–thyroid dynamics and shifts in peripheral thyroid hormone activation **[213–215]**. In this context, thyroid economy denotes a coordinated reduction in effective thyroid action that lowers metabolic rate and thermogenic output, to create a "thrifty" metabolic state that lowers the caloric cost of maintaining body weight **[216,217]**. Although often described during caloric restriction, this response reflects a broader conserved energy-preservation strategy **[181,218]**, whereby metabolic rate is downregulated beyond that predicted by changes in body mass alone **[181]**.

Mechanistically, adaptive thermogenesis is consistently associated with reduced effective triiodothyronine (T3) availability and attenuated thyroid-driven metabolic gene expression, often accompanied by increases in reverse T3 and deiodinase shifts that collectively reduce intracellular T3 action **[219–221]**. While some studies report higher circulating free T3 in advanced obesity, this does not preclude reduced thyroid signaling at the tissue level **[218,222]**. Attenuated thyroid activity suppresses mitochondrial biogenesis, lowers ATP turnover, and constrains oxidative phosphorylation capacity, alongside reduced uncoupling protein 1-linked thermogenesis in brown and beige adipose tissue **[218,220]**.

Functionally, this reduction in thyroid-mediated energy throughput limits lipid oxidation and heat production, reducing total energy expenditure in ways that materially alter day-to-day energy requirements **[181,223]**. Within this framework, thyroid economy represents recalibrated tissue-level thyroid activity that lowers metabolic drive and total energy throughput, conserving energy under conditions of chronic metabolic stress.

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7.5. Reinforcement of the Maladaptive Energy Conservation Cycle

These adaptations stabilize a self-reinforcing metabolic–behavioural state. Hypothalamic recalibration drives simultaneous acquisition and conservation. Behavioural reprioritization increases food salience and reduces resistance to reward, and thyroid economy lowers thermogenesis and overall energy throughput. Together, these shifts favor fat storage and reduced discretionary activity despite caloric sufficiency.

Within this reinforcing architecture, age-related attenuation of the somatotropic axis further slows metabolism. Somatopause—characterised by declining pulsatile GH secretion and lower IGF-1—reduces anabolic capacity, promotes sarcopenia, weakens metabolic buffering and accelerates brain ageing **[224–226]**. Because skeletal muscle is a principal determinant of resting energy expenditure and insulin-mediated glucose disposal, loss of lean mass lowers total energy turnover and reduces metabolic flexibility **[80,227]**. In metabolically dysregulated midlife women, mismatch-related factors—including visceral adiposity, IR, CSI, sleep and circadian disruption, repeated weight cycling, and declining E2—may further blunt GH pulsatility or impair GH/IGF-1 signaling, amplifying loss of muscle mass, strength, and metabolic capacity **[228–232]**.

Menopausal declines in microbial diversity may promote adiposity by promoting host energy-harvest efficiency **[41,233,234]**. Obesity-associated microbiomes appear enriched in functions that ferment otherwise indigestible substrates into absorbable metabolites, potentially increasing net caloric availability **[42,203]**. Even modest gains in effective energy extraction, when combined with heightened hunger signals and reduced metabolic throughput, may favor positive energy balance and weight gain.

This creates a cycle of reinforcement: adiposity and IR further impair hypothalamic integration of adipose tissue cues; CSI and stress-related inputs sustain defensive recalibration; and reduced lean mass lowers metabolic throughput and energetic flexibility. In Gen X midlife women navigating hormonal transition in environments of abundance, this conserved energy-conservation bias may stabilize a scarcity-adapted set point that is biologically coherent yet clinically maladaptive. In summary, the body behaves as if it must conserve energy, even though food is plentiful, leading to persistent weight gain, reduced activity, and difficulty reversing this adaptation pattern.

8. The Generation X Clinical Phenotype

8.1. Metabolic Dysregulation and Central Adiposity (Visceral Fat Accumulation)

A central feature of the Gen X clinical phenotype is metabolic disturbance accompanied by visceral and ectopic fat deposition and central adiposity **[84,95]**. Visceral adipose tissue is metabolically active and strongly associated with IR, CSI, and impaired metabolic flexibility **[25,93]**. These alterations contribute to dysregulated glucose and lipid metabolism and may occur even when BMI is normal **[235,236]**.

8.2. Decreased Lean Muscle Mass and Functional Decline

Gen X women also have progressive loss of lean skeletal muscle mass, or sarcopenia. Declining hormone levels, together with IR and CSI, may impair muscle protein synthesis and promote gradual loss of metabolically active tissue **[237,238]**. Reductions in lean muscle mass contributes to reduced physical capacity and metabolic dysfunction **[227,228]**. These changes can occur gradually and may be overlooked during midlife, yet they have important implications for long-term health, physical independence, and quality of life **[239]**.

8.3. Neuroendocrine Symptom Cluster

In addition to measurable changes in body composition and metabolic function, many Gen X women experience a constellation of symptoms reflecting disruption of neuroendocrine and energy-regulation systems. This cluster commonly includes persistent fatigue, cognitive impairment often

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described as "brain fog", dysregulated appetite and cravings, and changes in mood and motivation **[26,67]**.

These symptoms reflect the convergent effects of the neuroendocrine–metabolic disturbances described in preceding sections. Fatigue is associated with impaired mitochondrial function, reduced metabolic flexibility and disrupted circadian regulation (Sections 4.4, 5.4, 5.7.2); cognitive changes with altered cerebral energy metabolism and neuroinflammatory signalling (Sections 5.7.1–5.7.3); dysregulated appetite with disruption of hypothalamic energy sensing and reward pathways in the context of IR and modern food environments (Sections 7.1–7.3); and mood and motivational changes with altered neuromodulatory tone and stress-axis dysregulation (Sections 5.7.2, 5.7.4).

Collectively, these symptoms are best understood as clinical expressions of integrated system-level dysfunction rather than isolated hormonal effects, reflecting the cumulative impact of evolutionary mismatch across metabolic, neuroendocrine and behavioural domains.

8.4. Increased Long-Term Chronic Disease Risk

The metabolic, endocrine, and neurophysiological changes described above may have important implications for long-term health. The convergence of central adiposity, IR, declining muscle mass, and neuroendocrine dysregulation during midlife may create an environment that increases susceptibility to several chronic diseases later in life. These include T2DM **[240]**, CVD **[241]**, osteoporosis **[242]** and dementia **[142,243]**.

From an evolutionary perspective, women have historically demonstrated a longevity advantage relative to men, a pattern observed across many populations and attributed in part to biological, behavioural, and reproductive factors. However, the convergence of metabolic, endocrine, and environmental pressures described in this review raises the possibility that the health trajectories of Gen X women may be increasingly shaped by conditions that were largely absent during earlier periods of human evolutionary history. Whether these interacting influences may alter the long-standing female longevity advantage in future generations remains an important area for further investigation.

8.5. Gen X Phenotype and Polycystic Ovary Syndrome (PCOS)

PCOS may represent an early-life expression of the same evolutionary mismatch processes that underpin the Gen X midlife phenotype. Although typically diagnosed during reproductive years, PCOS is characterised by IR, CSI and hormonal imbalance that persist across the lifespan **[244,245]**. Women with PCOS exhibit many of the typical features of the Gen X phenotype described above (Sections 4-7) but have a lower threshold for the development of IR and CSI. Pooled data from 25 euglycemic–hyperinsulinemic clamp studies indicate that women with PCOS have a 27% reduction in insulin sensitivity compared to controls **[246]**. The authors concluded that PCOS is underpinned by intrinsic IR, independent of BMI, age, ethnicity, and diagnostic criteria **[246,247]**.

Pooled analysis of data from 63 studies revealed a 26% higher CRP in women with PCOS versus controls **[248]**. Sensitivity analysis of 35 high-quality studies showed an 80% higher CRP in PCOS versus controls that was independent of obesity and associated with low-grade CSI. A recent more nuanced analysis of inflammation in PCOS, suggests that PCOS is characterized by tissue-specific immune mechanisms, with distinct inflammatory signatures that vary across different organs and tissues **[249]**. These data suggest that women with PCOS have a proinflammatory design characterised by increased systemic and/or tissue-specific immune activation that is intrinsic to the condition **[250]**.

Evolutionary theories for the pathogenesis of PCOS propose that inherited gene variants provided a survival advantage in an ancestral environment but became maladaptive in the modern world **[13,251]**. In addition, women with PCOS have an increased risk of pregnancy complications **[252]** and cardiometabolic disease **[245]** that impact long-term health and may have implications for transgenerational disease transmission **[253]**. Gen X women with PCOS therefore represent a high-

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risk subgroup that require increased screening and surveillance for metabolic, immune and reproductive disorders.

Beyond reproductive years, the metabolic and inflammatory features of PCOS persist and may become more clinically significant during the midlife transition. As women enter perimenopause and menopause, the loss of estrogen-mediated metabolic protection, combined with age-related changes in body composition and insulin sensitivity, may unmask or exacerbate underlying IR, CSI and cardiometabolic risk **[84,96]**. This transition may contribute to a more pronounced expression of the Gen X phenotype, including central adiposity, metabolic inflexibility, fatigue and increased risk of chronic disease **[244,245]**. Women with a history of PCOS may therefore experience an accelerated or amplified trajectory of midlife metabolic and neuroendocrine dysfunction.

9. Clinical Translation and Recovery Pathways

The mechanisms described in preceding sections indicate that evolutionary mismatch influences metabolic, endocrine and neurological health through disruption of core regulatory systems, including circadian rhythms, energy metabolism, stress physiology and microbial signaling **[27]**.

Translating this model into clinical practice requires interventions that target upstream regulatory processes rather than isolated symptoms, with a focus on restoring alignment between biological systems and modern environmental inputs. Such approaches prioritize metabolic flexibility, circadian synchronization, neuroendocrine stability and tissue function, as summarized in Table 1.

Table 1. Evolutionary Recovery Framework for Generation X Women: Intervention Domains and Physiological Targets.

Intervention Domain	Key Interventions	Primary Physiological Targets
Circadian realignment	Consistent sleep–wake timing, morning light exposure, reduction of evening light exposure, alignment of feeding and activity with circadian rhythms	SCN circadian entrainment, hypothalamic–pituitary rhythm regulation, cortisol–melatonin cycling, metabolic timing
Fuel utilization and metabolic flexibility	Structured meal timing, fibre-rich low-glycaemic dietary patterns to promote metabolic balance and support substrate switching, gentle early time-restricted eating where appropriate	Glucose–fat oxidation balance, insulin sensitivity and IR, hepatic fuel processing, cellular metabolic flexibility
Allostatic load and stress regulation	Stabilization of behavioural rhythms, stress modulation strategies, reduction of environmental stressors and toxic exposures, psychosocial support	HPA axis regulation, ANS balance, inflammatory signalling and CSI, neuroendocrine stability
Central energy regulation and neuroprotection	Stabilization of energy availability, dietary patterns associated with reduced neuroinflammation, strategies supporting hypothalamic energy sensing	Hypothalamic regulation of total body energy balance, cerebral energy metabolism, neuroinflammation, dopaminergic signalling, appetite and energy perception pathways

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	and neuroendocrine signalling	
Muscle mass and mitochondrial function	Progressive resistance training, physical activity promoting mitochondrial biogenesis, adequate protein and micronutrient intake	Skeletal muscle mass, mitochondrial function, thermogenesis, serum glucose disposal
Gut–hormone–microbiome integration	Plant-diverse, fibre-rich dietary patterns, phytoestrogen exposure, reduction of dietary and environmental disruptors of microbial ecosystems	Microbial diversity, estrobolome activity, gut barrier function, gut enteroendocrine cell function, gut–brain–endocrine signalling

Abbreviations: SCN = suprachiasmatic nucleus; IR = insulin resistance; HPA = hypothalamic-pituitary-adrenal; ANS = autonomic nervous system; CSI = chronic systemic inflammation.

This framework is not intended as a prescriptive protocol but as a systems-based model linking therapeutic strategies to underlying physiological targets, supporting the gradual restoration of metabolic and hormonal homeostasis **[156,254]**.

9.1. Circadian Realignment

Clinical strategies therefore prioritize restoration of circadian alignment through consistent sleep–wake timing, exposure to daytime light, reduction of evening light exposure, and synchronization of feeding and physical activity, using chronomedicine strategies that favor earlier daytime energy intake and align with circadian physiology **[254–257]**.

9.2. Fuel Hierarchy Restoration

Recovery strategies focus on stabilizing glycaemic control and insulin sensitivity, improving hepatic fuel processing, and gradually restoring the capacity to transition between glucose and lipid oxidation **[257,258]**. Dietary patterns emphasizing fibre-rich whole foods that support metabolic stability and substrate utilization may further facilitate these processes **[259,260]**. Where appropriate, gentle forms of early time-restricted eating may support metabolic flexibility and improve fuel utilization efficiency, consistent with emerging evidence linking fasting patterns to improved metabolic outcomes **[261,262]**.

9.3. Allostatic Load Reduction

Interventions aim to reduce cumulative allostatic burden by addressing both chronic psychosocial stress and ongoing environmental exposures, including EDCs and other toxic exposures, while strengthening physiological resilience. Strategies include stabilization of behavioural rhythms, targeted stress reduction and support for psychosocial security **[263,264]**.

9.4. Brain Energy and Neuroprotection

Clinical strategies focus on stabilizing cerebral energy availability, reducing neuroinflammatory processes, and supporting hypothalamic signaling and neurotransmitter systems involved in energy perception, cognition and motivation. Where appropriate, hormonal support strategies, including plant-rich dietary patterns high in phytoestrogens and polyphenols, may further support cognitive

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function and neuroendocrine regulation during the menopausal transition, and may contribute to reducing long-term neurocognitive vulnerability **[265–267]**.

9.5. Muscle and Mitochondrial Rehabilitation

Interventions focus on restoring muscle mass and mitochondrial function to support whole-body energy metabolism and metabolic flexibility. Resistance-based exercise and regular physical activity that stimulate mitochondrial biogenesis are central to improving glucose disposal, thermogenesis and overall metabolic capacity. These strategies should be supported by adequate dietary protein intake and sufficient micronutrient availability to optimize muscle maintenance and cellular energy production **[268–270]**.

9.6. Gut–Hormone–Microbiome Repair

Interventions aim to restore gut–microbiome-hormone integration by supporting microbial diversity, metabolic and gut–brain–endocrine signaling. Core strategies include plant-diverse, fibre-rich, whole-food dietary patterns that promote microbial diversity, short-chain fatty acid production and estrobolome activity, alongside intake of polyphenol- and phytoestrogen-rich foods. These approaches should be combined with reduction of factors that disrupt microbial ecosystems, including ultra-processed foods, excessive alcohol and environmental exposures such as EDCs. Collectively, these strategies support gut barrier function, estrobolome-mediated hormone metabolism and downstream metabolic and neuroendocrine regulation **[38,271–274]**.

9.7. Clinical Implications for Practitioners and Health Systems

Implementation of these strategies may benefit from multidisciplinary care models integrating clinical medicine, nutrition, lifestyle interventions, and psychosocial support **[275]**. Recognizing midlife as a critical window for metabolic and neuroendocrine intervention may allow earlier identification of risk and more targeted prevention strategies **[276]**.

At a health systems level, approaches that address lifestyle, environmental exposures, and behavioural health may contribute to reducing the long-term burden of chronic disease and improving population-level metabolic health outcomes **[277]**.

10. Conclusion

This paper presents an integrated evolutionary model to explain the emergence of metabolic, neuroendocrine, and cognitive dysfunction in Gen X women during the midlife transition. Gen X women have experienced sustained exposure to environmental conditions during their whole adult lives, that diverge from those in which human physiology evolved. Within this context, evolutionary mismatch provides a unifying framework linking circadian disruption, metabolic dysfunction, chronic stress, and altered microbial signaling to impaired metabolic flexibility, increased inflammatory tone, disrupted hypothalamic energy regulation, and reduced mitochondrial efficiency. These changes are best understood as a system-level response to cumulative regulatory disruption rather than because of E2 deficiency alone.

The inclusion of PCOS within this framework highlights how early-life phenotypes characterised by IR, CSI and hormonal imbalance may influence midlife trajectories, identifying a subgroup of women with increased susceptibility to mismatch-related dysfunction. Clinically, this model supports a shift toward integrated, evolution-informed and root-cause based strategies targeting upstream regulatory systems, with the aim of restoring metabolic flexibility, cognitive function, and the female healthspan and longevity advantage. Midlife therefore represents a critical window for intervention, with implications for prevention, clinical management, and public health. Future research should focus on validating this life-course model and refining targeted interventions that address both environmental exposures and biological adaptation across the female lifespan.

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Abbreviations

ACTH	Adrenocorticotropic Hormone
AgRP	Agouti-related peptide
AMPK	Adenosine Monophosphate-Activated Protein Kinase
ANS	Autonomic Nervous System
ATP	Adenosine Triphosphate
COMT	Catechol-O-methyltransferase
CSI	Chronic Systemic Inflammation
CRH	Corticotropin Releasing Hormone
CVD	Cardiovascular Disease
CNS	Central Nervous System
E2	17β-estradiol
$FADH_2$	Flavin Adenine Dinucleotide
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
FFA	Free Fatty Acid
FSH	Follicle Stimulating Hormone
GABA	Gamma-Aminobutyric Acid
Gen X	Generation X
GH	Growth Hormone
GLP-1	Glucagon-like peptide-1
GLUT4	Glucose Transporter Type 4
GnRH	Gonadotropin-releasing hormone
HPA	Hypothalamic-Pituitary-Adrenal
IGF-1	Insulin-like Growth Factor-1
IL	Interleukin
IR	Insulin Resistance
LH	Luteinizing Hormone
LPS	Lipopolysaccharide
MASLD	Metabolic-Associated Steatotic Liver Disease
NADH	Nicotinamide Adenine Dinucleotide
NF-κB	Nuclear Factor Kappa B
NPY	Neuropeptide Y
PCOS	Polycystic Ovary Syndrome
PGC1α	Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha
SCFA	Short Chain Fatty Acid
SIRT1	Sirtuin1
T2DM	Type 2 Diabetes Mellitis
TNF-α	Tumour Necrosis Factor-Alpha

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