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FIELD GUIDE NO. 03

FOR WOMEN · 35 TO 75+ · EDUCATIONAL REFERENCE

Peri- & Post-Menopause.

An evidence-led reference for understanding the hormonal transition — what the published literature describes about the biology, the symptoms, the labs, and the therapies women and their clinicians consider during peri-menopause and the post-menopausal years.

FOR	USE	FORMAT	AN OPTML FIELD GUIDE
Women 35–75+	Lifetime Reference	Cited Atlas	No. 03

A NOTE BEFORE YOU BEGIN

The most under-explained transition in *women's health.*

Peri-menopause and post-menopause unfold across roughly four decades of a woman's life — and the published medical literature describing them is enormous, fast-moving, and rarely communicated to patients in one place.

This guide is an **educational atlas** — a curated reference of what the peer-reviewed literature reports about the biology, symptom patterns, laboratory measurements, and therapeutic approaches associated with the menopausal transition. Every clinical statement is footnoted to its primary source. The intent is comprehension, not prescription.

The contents are organized to mirror how clinicians think about the transition: the underlying biology first, then the symptoms patients commonly describe, then the laboratory markers used to characterize where in the transition a woman is, then the therapeutic categories that have been studied — and finally the lifestyle levers (training, nutrition, sleep) for which the strongest evidence base exists.

Nothing in this guide is intended as medical advice or treatment recommendation. Read it as a reference. Bring questions to a licensed clinician.

EDUCATION ONLY · NOT MEDICAL ADVICE

This guide presents published research and clinical guidelines for educational purposes. **It does not diagnose, treat, prescribe, or recommend any therapy.** Hormonal therapy and medication decisions involve individual medical history, risk factors, and clinical judgment — those decisions belong with a licensed clinician who has reviewed your personal health record.

CONTENTS

Inside.

What this guide is — *and what it isn't.*

This document is a reference. It collects, organizes, and cites the peer-reviewed literature describing peri-menopause and post-menopause. It is written to help a reader understand what is currently published — not to recommend any particular course of action.

The four things this guide does.

01 **Summarizes the published biology.**
Hormonal changes through the menopausal transition are well-characterized in the literature. This guide presents that biology with citations to the primary references — including the STRAW+10 staging consensus [1], longitudinal cohort studies (SWAN, Melbourne, Penn Ovarian Aging), and the major endocrine society guidelines.

02 **Maps symptoms to mechanisms.**
Each symptom category — vasomotor, cognitive, mood, sleep, urogenital, body composition, bone, cardiovascular — is paired with the mechanism described in the literature and the population-level prevalence data from the major cohort studies.

03 **Reports what studies of therapies have found.**
Where therapies have been studied — hormone therapy, non-hormonal pharmacologic options, lifestyle interventions — this guide summarizes what randomized trials and meta-analyses report. It does not interpret those findings as a recommendation for any individual reader.

04 **Cites every clinical statement.**
Numbered superscript references [2] link each clinical claim to a citation listed in the References chapter at the end. Most citations are peer-reviewed journal articles indexed on PubMed; others are major clinical society position statements.

IMPORTANT — READ BEFORE CONTINUING

Nothing in this guide constitutes medical advice, diagnosis, or treatment. Hormone-related decisions, medication choices, dosing, monitoring, and the assessment of individual risks and benefits require a licensed clinician who has reviewed your personal medical history.

If a section of this guide raises a question about your own health, write the question down and bring it to a clinician. **Do not start, stop, or modify any medication or supplement based on this guide.**

References to specific medications, doses, or laboratory ranges describe what has been published in the medical literature. They are not prescriptions and they are not recommendations.

The menopausal transition is a *staged biological process* — not a single event.

The 2011 Stages of Reproductive Aging Workshop +10 (STRAW+10) consensus is the most widely cited framework for describing where a woman is in the menopausal transition. [1] It divides the reproductive lifespan into ten stages anchored to menstrual-cycle changes and reproductive hormones — most relevantly for this guide, four broad phases: late reproductive, early peri-menopause, late peri-menopause, and post-menopause. [1]

STAGE −3

Late Reproductive

~35–45 yrs

Cycles remain regular. Subtle changes in cycle length and follicle reserve. Anti-Müllerian hormone (AMH) declines. [2]

STAGES −2 / −1

Peri-Menopause

~42–55 yrs

Cycle length variability ≥ 7 days (early); ≥ 60-day amenorrhea (late). FSH rises and fluctuates widely. [1]

STAGE 0

Menopause

~51 yrs (median)

Defined retrospectively as 12 consecutive months without a menstrual period. [3] Median age in U.S. women is ~51. [4]

STAGES +1 / +2

Post-Menopause

~52 yrs onward

Stable low estradiol and elevated FSH. Early post-menopause spans the first ~5–8 years after the final period. [1]

Why the staging matters.

Studies of hormonal therapy and cardiovascular, cognitive, and skeletal outcomes have reported that the stage at which an intervention is initiated influences the outcomes observed. [5] [6] This "timing hypothesis" — discussed in detail in Chapter 9 — emerged from re-analyses of the Women's Health Initiative [7] and was prospectively examined in the KEEPS [5] and ELITE [6] trials. Knowing which stage describes a given woman is therefore central to interpreting most of the published evidence.

The STRAW+10 framework is also used to define the populations enrolled in clinical trials. When a study reports outcomes "in peri-menopausal women" or "in early post-menopausal women," it is generally referencing the STRAW+10 stage definitions. [1]

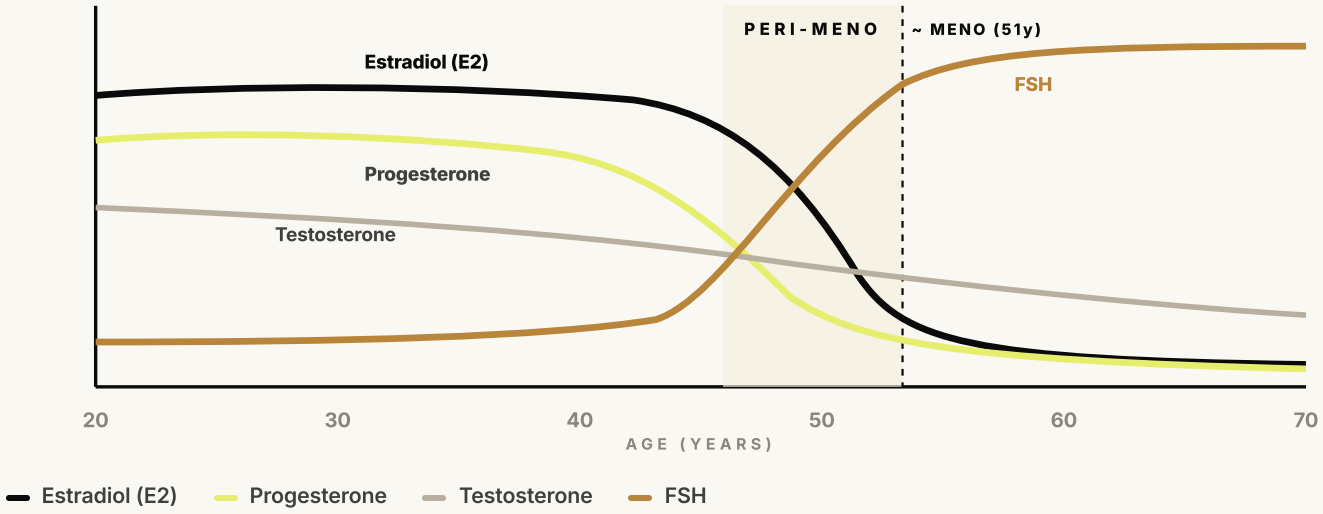
Definitions in this guide. Throughout this document, "peri-menopause" refers to STRAW+10 stages −2 and −1; "menopause" refers to stage 0; "post-menopause" refers to stages +1 and +2 collectively unless specified otherwise.

Hormones across the *female life course.*

Across the female reproductive lifespan, the principal sex steroids — estradiol (E2), progesterone, testosterone — and the pituitary marker follicle-stimulating hormone (FSH) trace characteristic curves that have been measured in multiple longitudinal cohorts. [8] [9]

SCHEMATIC HORMONE LEVELS · AGE 20 → 70

Composite schematic adapted from longitudinal cohort data (SWAN, Melbourne Women's Midlife Health Project, Penn Ovarian Aging Study). [8] [9] [10] Not to scale; depicts directional shape only.



Four observations from the literature deserve emphasis. First, estradiol does not decline gradually across the late reproductive years — it remains relatively stable until late peri-menopause, after which it drops over a comparatively narrow window. [8] Second, progesterone declines earlier and more progressively than estradiol because ovulatory cycles become less frequent during peri-menopause. [10] Third, testosterone declines gradually from approximately the mid-twenties onward; this decline is largely independent of the menopausal transition itself. [11] Fourth, FSH rises markedly during late peri-menopause and remains elevated in post-menopause, which is why a single elevated FSH measurement is sometimes used as supportive — though not diagnostic — evidence of the transition. [1]

Interpretation note. The schematic above depicts mean directional changes reported in cohort studies. Individual women show substantial variability around these means — particularly in the timing and rate of estradiol decline through peri-menopause. [8]

Estrogen is *three molecules*, not one.

The word "estrogen" refers to a family of related steroid hormones. The three principal forms in human physiology are estrone (E1), estradiol (E2), and estriol (E3); each predominates at a different stage of life and binds the estrogen receptors with different affinity. [12]

The three estrogens.

E2 · ESTRADIOL

The dominant estrogen in the reproductive years. Synthesized primarily by ovarian granulosa cells. Binds both estrogen receptor alpha (ERα) and beta (ERβ) with high affinity. [12] Serum concentrations fluctuate cyclically in premenopausal women and decline substantially after the final menstrual period. [9]

E1 · ESTRONE

The predominant estrogen after menopause. Derived mainly from peripheral aromatization of androstenedione in adipose tissue and other peripheral sites. [13] Weaker biological activity at ERα than estradiol; post-menopausal E1:E2 ratios are typically reversed compared with the reproductive years. [13]

E3 · ESTRIOL

The dominant estrogen in pregnancy. Produced in large quantities by the placenta. Outside of pregnancy, serum levels are low. E3 has weaker affinity for ERα than E2 but is sometimes used in topical compounded preparations. [14]

A NOTE ON TERMINOLOGY

"Estrogen" in the medical literature most often refers to estradiol (E2) unless specified. Clinical assays measuring "estrogen" typically measure E2 specifically. The interchangeable use of the words in non-clinical writing can blur which molecule is actually being described.

The two main estrogen receptors.

Estrogen receptors are nuclear hormone receptors expressed throughout the body. Two principal subtypes have been characterized: ERα and ERβ, encoded by different genes (ESR1 and ESR2 respectively). [15] Their tissue distribution differs in ways that help explain the wide range of tissues affected by estrogen status. [16]

- **ERα** — high expression in the uterus, mammary gland, ovarian theca cells, bone, vascular endothelium, and liver. Pharmacologic estrogen effects on bone density and on hepatic protein synthesis are predominantly mediated by ERα. [15]
- **ERβ** — high expression in the ovary (granulosa cells), prostate, lung, gastrointestinal tract, and central nervous system. The relative balance of ERα/ERβ signaling appears to modulate cellular responses to estrogen in several tissues. [16]
- **Membrane-bound estrogen signaling** — in addition to classical nuclear receptors, estrogens act through membrane-associated receptors (including GPER), producing rapid non-genomic effects on vascular tone and other tissues. [17]

Why this matters for later chapters. The tissue distribution of ERα and ERβ underlies several themes that recur throughout this guide: why estrogen status influences bone density, vascular health, cognition, urogenital tissues, and mood; and why different routes of estrogen administration produce different patterns of effect. [15] [16]

Progesterone: the *second luteal hormone.*

Progesterone is a steroid hormone produced primarily by the corpus luteum following ovulation, and by the placenta during pregnancy. Outside of pregnancy, serum progesterone is elevated only during the luteal phase of an ovulatory cycle; in anovulatory cycles or in post-menopause, luteal-phase progesterone is absent. [18]

Endogenous progesterone vs. progestins.

The medical literature distinguishes **progesterone** — the endogenous hormone, also available pharmaceutically as micronized progesterone — from **progestins**, a broader class of synthetic compounds (e.g. medroxyprogesterone acetate, norethindrone) that bind the progesterone receptor with varying selectivity and also bind other steroid receptors to varying degrees. [19] Clinical trial outcomes attributed to "progesterone" in older literature were often obtained with synthetic progestins; this distinction is now considered important when interpreting older trials, including the Women's Health Initiative. [20]

Why progesterone is added when estrogen is administered.

In women with an intact uterus, unopposed exogenous estrogen administration is associated with increased risk of endometrial hyperplasia and endometrial cancer. [21] Adding a progestogen (progesterone or a progestin) opposes the proliferative effect of estrogen on the endometrium; this combination is the basis for the standard estrogen-plus-progestogen regimens described in clinical guidelines for women with a uterus. [22] Women who have undergone hysterectomy generally do not require progestogen for endometrial protection. [22]

Non-endometrial effects reported in the literature.

Beyond the endometrium, the literature describes progesterone effects on the central nervous system (via GABA-A receptor modulation by the metabolite allopregnanolone, with reported effects on sleep architecture and anxiety), [23] breast tissue, and the cardiovascular system. Comparative studies between micronized progesterone and synthetic progestins (notably medroxyprogesterone acetate) have reported different metabolic and breast-tissue profiles, although head-to-head trials with long-term clinical endpoints remain limited. [24]

> **What this guide will and will not say about progestogens.** Where the literature reports differences between micronized progesterone and specific synthetic progestins, this guide will summarize those findings with citations. It will not recommend any particular agent — individual choice involves clinical history and considerations outside the scope of an educational reference.

Testosterone in women: *biology and trajectory.*

Although often discussed primarily in the context of male physiology, testosterone is also produced by the ovaries and adrenal glands in women and circulates at concentrations roughly one-tenth those of men. [11] The literature describes a gradual decline in circulating testosterone beginning in approximately the mid-twenties, which is largely independent of the menopausal transition itself. [25]

Sources and metabolism.

In premenopausal women, approximately 25% of circulating testosterone is secreted directly by the ovary, 25% by the adrenal cortex, and the remaining ~50% is generated by peripheral conversion of pre-cursor androgens — particularly androstenedione and DHEA. [26] Following natural menopause, ovarian stromal cells continue to produce some androgens; following bilateral oophorectomy, total testosterone levels fall more sharply. [27]

Free vs. total testosterone — and SHBG.

Most circulating testosterone is bound to sex hormone-binding globulin (SHBG) and to albumin. The biologically active fraction is sometimes characterized as "free" or "bioavailable" testosterone. [28] Because SHBG concentrations are influenced by several factors — including oral estrogen administration, insulin resistance, thyroid status, and liver function — total testosterone alone may not reflect tissue exposure. [29] Measurement methodology matters: liquid chromatography-tandem mass spectrometry (LC-MS/MS) has been recommended over older immunoassays for measuring testosterone at the lower concentrations seen in women. [30]

Reported roles and the state of the evidence.

Randomized trial evidence is most established for the effect of testosterone therapy on hypoactive sexual desire in post-menopausal women, where multiple controlled trials have reported improvements in measures of sexual function. [31] The 2019 Global Consensus Position Statement on the Use of Testosterone Therapy for Women concluded that the only evidence-based indication for which testosterone therapy could be considered in post-menopausal women is hypoactive sexual desire disorder; for other potential indications (mood, cognition, bone, body composition), the available evidence was judged insufficient to support a clinical recommendation as of that statement. [31]

Note on availability. No testosterone product is currently FDA-approved for use in women in the United States; in clinical practice testosterone is sometimes prescribed off-label, with the literature on dosing, monitoring, and safety summarized in Chapter 11 of this guide. [31]

DHEA, FSH, LH, AMH, SHBG: the *supporting cast.*

Beyond estrogen, progesterone, and testosterone, several additional hormones are routinely measured or referenced in the context of the menopausal transition. Each conveys different information about ovarian function, pituitary signaling, or hormone bioavailability. [32]

DHEA & DHEA-S

Dehydroepiandrosterone and its sulfate. The most abundant circulating steroids in human plasma. Produced primarily by the adrenal cortex (zona reticularis). Serve as precursors to both androgens and estrogens. Concentrations peak in early adulthood and decline progressively with age — a pattern sometimes termed "adrenopause." [33]

FSH · FOLLICLE-STIMULATING HORMONE

Pituitary glycoprotein. Stimulates ovarian follicle development. Rises sharply in late peri-menopause as ovarian feedback declines, and remains elevated in post-menopause. [9] Single FSH measurements are highly variable during peri-menopause and are not generally considered diagnostic in isolation. [1]

LH · LUTEINIZING HORMONE

Pituitary glycoprotein. Triggers ovulation in the reproductive years. Also rises in peri- and post-menopause, though with less consistent diagnostic utility than FSH at the population level. [9]

AMH · ANTI-MÜLLERIAN HORMONE

Produced by ovarian granulosa cells. Reflects the size of the growing follicle pool and therefore correlates with ovarian reserve. [2] Declines steadily with age. Low or undetectable AMH has been studied as a marker of late reproductive stage and approaching menopause. [34]

SHBG · SEX HORMONE-BINDING GLOBULIN

Liver-synthesized glycoprotein. Binds estradiol and testosterone in circulation. Concentrations are increased by oral estrogen, thyroid hormone, and pregnancy; decreased by insulin resistance, obesity, and androgens. [29] Influences the "free" fraction of sex steroids.

INHIBIN B

Produced by growing follicles. Provides feedback inhibition of pituitary FSH secretion. Declines earlier than estradiol during late reproductive aging, contributing to the rise in FSH that characterizes late peri-menopause. [35]

How these markers interact.

The hypothalamic-pituitary-ovarian axis operates as a feedback loop. As the ovarian follicle pool diminishes through the late reproductive years, inhibin B declines first, releasing FSH from feedback suppression. Estradiol fluctuations during peri-menopause partly reflect this loss of inhibin-B feedback combined with episodes of accelerated follicular development. [35] AMH — produced by smaller pre-antral follicles — provides a complementary measure of follicle reserve that is relatively independent of cycle day, making it a useful marker in the late reproductive and early peri-menopausal stages. [2]

Interpreting hormone panels. A single hormone measurement during peri-menopause has limited diagnostic value because of the wide cycle-to-cycle variability described in cohort studies. [9] Patterns over time, considered alongside menstrual cycle history, are generally more informative — a point revisited in Chapter 8.

Peri-menopause is a *multi-year hormonal volatility window*, not a steady decline.

Among the more durable findings of the longitudinal cohort studies of the menopausal transition is that peri-menopause is characterized by hormonal volatility rather than a smooth monotonic decline. [9] Estradiol in particular shows wide cycle-to-cycle and week-to-week variability during late peri-menopause, sometimes reaching reproductive-range concentrations and sometimes falling to post-menopausal levels within the same calendar quarter. [9]

The two peri-menopausal sub-stages.

The STRAW+10 framework subdivides peri-menopause into an early stage (cycle length variability ≥ 7 days from prior regular cycles) and a late stage (≥ 60 consecutive days of amenorrhea), with characteristic hormonal patterns assigned to each. [1]

EARLY PERI-MENOPAUSE · STAGE −2

Cycle-length variability of 7 or more days from prior regular pattern. Cycles may still be ovulatory. FSH levels become more variable; some cycles show elevated early-follicular FSH (>25 IU/L) while others remain in the reproductive range. [1] Estradiol levels in this stage are generally not consistently low and may actually be transiently elevated relative to the reproductive years in some women. [36]

LATE PERI-MENOPAUSE · STAGE −1

≥ 60 days of amenorrhea. FSH is more consistently elevated. Estradiol fluctuates more widely and trends downward overall. Anovulatory cycles predominate; luteal-phase progesterone is therefore commonly absent for extended intervals. [1] This is the stage in which vasomotor symptoms become most prevalent in cohort data. [37]

Duration of peri-menopause.

The duration of peri-menopause varies substantially. In the Study of Women's Health Across the Nation (SWAN) cohort, the median duration from the onset of cycle irregularity to the final menstrual period was approximately 4 years, with a wide inter-individual range. [38] Earlier onset of cycle changes did not strictly predict an earlier final menstrual period; rather, both the duration and the timing showed substantial variability across women. [38]

Factors associated with earlier age at the final menstrual period in cohort studies include current smoking, lower socioeconomic status, certain genetic variants, and prior chemotherapy or pelvic radiotherapy. [4] The age at natural menopause for an individual is partially heritable, with twin and family studies estimating heritability in the 30–85% range depending on the population studied. [4]

> **Why the volatility matters.** The wide fluctuations in estradiol described above contribute to one of the practical difficulties in interpreting peri-menopausal symptoms: a woman may experience symptoms consistent with both estrogen excess (e.g., heavier bleeding, breast tenderness) and estrogen deficiency (e.g., hot flashes, sleep disruption) within the same calendar period. [9]

What the cohort studies actually show.

Three large prospective cohort studies have characterized hormone trajectories across the menopausal transition in detail: the Study of Women's Health Across the Nation (SWAN), the Melbourne Women's Midlife Health Project, and the Penn Ovarian Aging Study. [8] [9] [10] Their findings — broadly consistent across populations — are summarized below.

SWAN: trajectories anchored to the final menstrual period.

In SWAN, hormone profiles were aligned to each woman's eventual final menstrual period (FMP) rather than to calendar age, allowing the hormonal trajectory to be characterized relative to a biological anchor. [9] The principal SWAN findings include:

- **Estradiol** begins a steeper decline approximately 2 years before the FMP and reaches a relatively stable post-menopausal nadir approximately 2 years after the FMP — a roughly 4-year window of substantial change. [9]
- **FSH** rises more gradually beginning approximately 5–7 years before the FMP, accelerates in the 2 years before the FMP, and reaches a plateau approximately 2 years after the FMP. [9]
- **Inhibin B** declines earlier than estradiol, supporting the model in which loss of inhibin feedback drives the early FSH rise. [35]
- **Total testosterone** shows minimal change directly attributable to the menopausal transition itself; the age-related decline is gradual and largely linear. [11]
- **SHBG** tends to decline through the transition, which can result in stable or modestly increased free testosterone even as total testosterone declines slowly. [29]

Variability around the means.

Published SWAN analyses emphasize that the population-level trajectories described above conceal substantial inter-individual variability. [39] Cluster analyses of SWAN data have identified multiple distinct hormone-trajectory subgroups — for example, women with markedly elevated estradiol peaks during late peri-menopause versus those whose estradiol declines monotonically — which appear to correspond to different symptom patterns and to different timing of the FMP itself. [39]

> **Practical implication.** Cohort-level descriptions of "the" menopausal transition smooth over substantial individual variation. Interpreting a particular woman's hormone profile generally requires multiple measurements over time alongside her menstrual cycle history — a point developed in Chapter 8. [9]

Reading note. Throughout this guide, references to "early peri-menopause" and "late peri-menopause" correspond to STRAW+10 stages −2 and −1 respectively. References to "the transition" refer to the broader window from the onset of cycle changes through the early post-menopausal years. [1]

When the transition happens *earlier than expected.*

A subset of women experience the menopausal transition substantially earlier than the population median of approximately 51 years. The literature distinguishes several scenarios, each with its own definitions, mechanisms, and reported outcomes. [40]

The four scenarios in the literature.

01 **Early menopause (age 40–45).**
A natural menopause occurring between ages 40 and 45 is sometimes termed "early menopause" in the literature. [40] Estimated to occur in approximately 5% of women. [4] Cohort studies have associated early menopause with modestly increased long-term risks for cardiovascular disease and osteoporosis compared with menopause at the typical age. [41]

02 **Premature ovarian insufficiency (POI, before age 40).**
Defined by amenorrhea before age 40 with elevated FSH on two separate occasions. Affects approximately 1% of women. Causes include genetic, autoimmune, iatrogenic (chemotherapy, radiation), and idiopathic categories. [42] Clinical guidelines recommend hormone therapy until at least the average age of natural menopause to mitigate associated long-term skeletal and cardiovascular risk, in the absence of contraindications. [42]

03 **Surgical menopause (bilateral oophorectomy).**
Removal of both ovaries causes an abrupt decline in estradiol, progesterone, and a substantial fraction of total testosterone. The abrupt hormonal shift is associated with more pronounced vasomotor and other symptoms in observational cohorts than gradual natural menopause. [27] Long-term cohort studies have examined associations between surgical menopause before the typical age and cardiovascular, cognitive, and skeletal outcomes. [43]

04 **Iatrogenic menopause (chemotherapy/radiation).**
Several chemotherapy regimens — particularly alkylating agents — and pelvic radiation can cause partial or complete ovarian failure. The probability and reversibility depend on the agent, dose, and the patient's age and ovarian reserve at the time of treatment. [44]

> **Why these scenarios are categorized separately.** Major clinical guidelines — including the Endocrine Society, NAMS (now The Menopause Society), and ESHRE — treat POI and surgical menopause as distinct clinical entities with different recommendations regarding hormone therapy, monitoring, and long-term risk management. [42] [22]

Post-menopause is the *new steady state* — and it lasts decades.

By definition, post-menopause begins after 12 consecutive months without a menstrual period. [3] Given a typical age at menopause of approximately 51 and a U.S. female life expectancy in the early 80s, [45] the post-menopausal phase comprises roughly one-third of the average woman's life — a longer interval than either childhood or the reproductive years.

Hormonal state in established post-menopause.

In established post-menopause (STRAW+10 stage +2 and beyond), the hormonal milieu is comparatively stable. The principal features described in the literature include: [9] [13]

- **Estradiol (E2)** is consistently low — typically below 30 pg/mL, and frequently below the limit of quantification of older immunoassays. [9]
- **Estrone (E1)** replaces E2 as the predominant circulating estrogen, derived primarily from peripheral aromatization of androstenedione in adipose tissue. [13] The E1:E2 ratio is reversed relative to the reproductive years.
- **FSH** remains markedly elevated (commonly > 30 IU/L) and relatively stable. [9]
- **Progesterone** remains low; luteal-phase progesterone elevations are absent because ovulation has ceased. [18]
- **Total and free testosterone** continue their gradual age-related decline; the post-menopausal ovary retains some androgen-producing stromal tissue, so total testosterone does not drop as sharply at menopause as estradiol does (except after bilateral oophorectomy). [26] [27]
- **DHEA and DHEA-S** continue their adrenal age-related decline, which is independent of the ovarian transition itself. [33]

Two post-menopausal substages.

STAGE +1 · EARLY POST-MENOPAUSE (~5–8 YEARS)

Continued shifts in FSH and estradiol toward steady-state values. Vasomotor symptoms typically persist in this window in a substantial fraction of women. [37] The reported window during which hormonal therapy effects on cardiovascular outcomes appear most favorable — the "timing hypothesis" — corresponds approximately to early post-menopause. [5] [6]

STAGE +2 · LATE POST-MENOPAUSE

Hormonal stability with continued age-related changes in other systems — bone density, body composition, cardiovascular markers. Many of the long-term changes associated with the post-menopausal hormonal milieu manifest cumulatively over this longer interval. [46]

What the next chapters cover. Chapter 5 maps symptoms reported during the transition and post-menopause. Chapters 6 and 7 address body composition, bone, and cardiovascular changes that accumulate across the post-menopausal years. Chapters 8 through 12 address laboratory characterization and the hormone therapy literature.

The post-menopausal years are *not biologically silent.*

A common framing of menopause is that "the transition" ends with the final menstrual period and the post-menopausal years are biologically settled. The cohort literature describes a more nuanced picture: multiple symptom categories — and the underlying biology driving them — extend well into the post-menopausal years for a substantial fraction of women. [37]

Reported duration of vasomotor symptoms.

In the SWAN cohort, the median total duration of frequent vasomotor symptoms — hot flashes and night sweats occurring on six or more days in a two-week period — was approximately 7.4 years, with a median post-final-menstrual-period duration of approximately 4.5 years. [37] Notably, approximately one-quarter of women in the cohort reported persistent frequent vasomotor symptoms a decade or more past the final menstrual period. [37]

Within SWAN, four trajectory subgroups of vasomotor symptom timing were identified: women whose symptoms began early relative to the FMP and persisted; women with later onset closer to the FMP; women with consistently low symptom burden; and women whose symptoms peaked sharply around the FMP and declined more rapidly. [47] Race/ethnicity, body mass index, smoking status, and educational attainment were among the demographic correlates of trajectory subgroup membership reported in those analyses. [47]

Genitourinary changes have a different trajectory.

In contrast to vasomotor symptoms, which often diminish over time, the genitourinary syndrome of menopause (GSM) — encompassing vaginal dryness, dyspareunia, urinary urgency, and recurrent urinary tract infection — tends to progress rather than resolve in the absence of intervention. [48] The biological basis is direct loss of estrogen signaling in vulvar, vaginal, and lower urinary tract tissues, which are densely populated with estrogen receptors. [48] GSM prevalence increases with time since the FMP in cohort studies. [49]

Skeletal and cardiovascular changes accumulate.

Bone mineral density (BMD) declines most rapidly in the first 1–3 years after the FMP and continues at a slower rate thereafter; the cumulative effect across two to three post-menopausal decades is substantial. [50] Cardiovascular risk factors — including LDL cholesterol, blood pressure, and visceral adiposity — also shift in characteristic patterns after the FMP, contributing to the well-documented increase in cardiovascular event rates in post-menopausal compared with pre-menopausal women. [51] These trajectories are discussed in Chapters 6 and 7.

> **The reading frame for what follows.** The post-menopausal phase is biologically active. The symptom and physiological changes described above unfold over years to decades, and they form the empirical basis for much of the clinical research summarized in Chapters 5 through 15 of this guide.

What the cohort literature reports about *symptom prevalence and timing.*

The symptoms attributed to the menopausal transition span multiple organ systems. Several large prospective cohort studies — SWAN in the United States, the Massachusetts Women's Health Study, the Melbourne Women's Midlife Health Project in Australia, and the Penn Ovarian Aging Study — have characterized the prevalence, timing, and trajectory of these symptoms. [37] [52] This chapter summarizes their principal findings, organized by symptom category.

Mapping symptoms to mechanism.

Symptoms reported during the menopausal transition fall broadly into categories tied to estrogen receptor distribution in target tissues — vasomotor (hypothalamic thermoregulation), cognitive (cortical and hippocampal estrogen signaling), mood (limbic and prefrontal estrogen and progesterone signaling), sleep (multi-mechanism), genitourinary (direct local tissue effects), and sexual function (multi-mechanism). [53]

SYMPTOM CATEGORY	REPORTED PREVALENCE	TYPICAL TIMING (RELATIVE TO FMP)
Vasomotor (hot flashes, night sweats)	**~70–80% of women report some symptoms** [37]	Peak: late peri-menopause through early post-menopause. Median total duration ~7.4 yrs in SWAN. [37]
Sleep disturbance	**~40–60% in cohort studies** [54]	Increases through peri-menopause; often persists post-FMP. Partly mediated by vasomotor symptoms. [54]
Mood symptoms (depression, anxiety)	**Risk of new-onset depression ~2× elevated during peri-menopause** [55]	Peri-menopause is the window of highest reported risk for new-onset depressive symptoms. [55]
Cognitive symptoms ("brain fog," memory)	**~40–60% report subjective cognitive changes** [56]	Most commonly reported in peri-menopause; objective testing shows small, often reversible decrements in some domains. [56]
Genitourinary syndrome of menopause (GSM)	**~50% by 3 yrs post-FMP, increasing thereafter** [49]	Typically progressive without intervention; unlike vasomotor symptoms, does not tend to resolve. [48]
Sexual function changes (desire, arousal, pain)	**~30–50% in various cohorts** [57]	Multi-factorial; partly secondary to GSM, sleep, mood; partly direct hormonal. [57]
Joint and muscle pain	**~50–60% report new or worsened symptoms** [58]	Onset peri-menopause; persistence variable. Mechanism incompletely characterized. [58]
Skin and hair changes	**Common but heterogeneous in reporting**	Reflect declining collagen synthesis and estrogen effects on skin. [59]

Reading note. Prevalence estimates above reflect women who reported the symptom at any point during a defined observation window in the cited cohort studies. The fraction of women who experience clinically significant or function-impairing symptoms is smaller than the totals above in most categories. Individual experience is highly variable. [37]

Hot flashes and night sweats: *the most-studied symptom.*

Vasomotor symptoms (VMS) — hot flashes during the day and night sweats during sleep — are the most extensively characterized symptom of the menopausal transition. Approximately 70–80% of women in the SWAN cohort reported VMS during the transition, and a substantial fraction reported symptoms severe enough to interfere with daily activities or sleep. [37]

The proposed mechanism.

The current mechanistic model centers on a population of hypothalamic neurons that co-express kisspeptin, neurokinin B, and dynorphin — the "KNDy" neurons. [60] Declining estrogen exposure during the menopausal transition is associated with hypertrophy of these neurons and altered signaling through the neurokinin 3 receptor (NK3R), which in turn influences the activity of nearby thermoregulatory neurons in the medial preoptic area. [60] This model is the basis for the development of NK3R antagonists, a class of non-hormonal agents discussed in Chapter 13. [61]

Prevalence, duration, and trajectory.

In the SWAN cohort, the median total duration of frequent vasomotor symptoms was approximately 7.4 years, with substantial inter-individual variation. [37] Race/ethnicity was associated with reported duration: Black women in SWAN reported a median total duration of approximately 10.1 years, compared with approximately 6.5 years among White women and shorter durations among Asian American women. [37] Higher body mass index, lower educational attainment, current smoking, and depressive symptoms were among the additional factors associated with longer duration. [37]

Among SWAN participants, four distinct vasomotor trajectories were identified: an "early onset" group whose symptoms began before the FMP and persisted; a "late onset" group whose symptoms began closer to or after the FMP; a "high-throughout" group with elevated symptoms across the entire observation window; and a "low" group with consistently minimal symptoms. [47] Approximately one-quarter of women in SWAN reported persistent frequent symptoms a decade or more past the FMP. [37]

Reported associations with longer-term outcomes.

Beyond their direct effect on quality of life, persistent VMS have been examined in cohort studies for associations with longer-term health outcomes. Several analyses have reported associations between persistent or severe VMS and subclinical markers of cardiovascular risk, including carotid intima-media thickness, endothelial dysfunction, and incident cardiovascular events; the magnitude and clinical significance of these associations remain under active investigation. [62] Associations with measures of bone density and cognitive performance have also been reported and remain areas of active research. [63]

Therapeutic literature. Hormone therapy is the most extensively studied intervention for VMS, with consistent reductions reported in randomized trials of estrogen-based regimens versus placebo. [22] Non-hormonal options — SSRIs/SNRIs, gabapentin, oxybutynin, clonidine, and the NK3R antagonist fezolinetant — are reviewed in Chapter 13. [61]

"Brain fog": *what the studies have measured.*

Subjective cognitive complaints during the menopausal transition — most commonly involving memory, attention, and word-finding — are reported by approximately 40–60% of women in cohort studies. [56] Objective neuropsychological testing has documented small, generally reversible decrements in specific cognitive domains during the transition itself, with most measures returning toward baseline in the post-menopausal years. [64]

SWAN cognitive aging findings.

The Study of Women's Health Across the Nation included a structured cognitive aging substudy that administered standardized tests (East Boston Memory Test, Symbol Digit Modalities Test, Digit Span Backward) at multiple time points across the transition. [64] Principal findings included: (1) small decrements in measures of processing speed and verbal episodic memory during peri-menopause; (2) recovery of these measures toward baseline in early post-menopause; and (3) substantial inter-individual variability in trajectory. [64] Importantly, the average magnitude of measured change was small and did not approach the threshold of clinically meaningful cognitive impairment. [64]

Proposed mechanisms.

Estrogen receptors are densely expressed in the hippocampus and prefrontal cortex — regions involved in memory consolidation and executive function. [65] Preclinical work has characterized estrogen effects on synaptic plasticity, cerebral glucose metabolism, and neurogenesis. [65] Clinical findings consistent with these mechanisms include reduced cerebral glucose metabolism in post-menopausal women in some PET imaging studies and changes in white matter microstructure during the transition. [66]

Symptoms attributed to "brain fog" are also influenced by sleep disruption, vasomotor symptoms, mood symptoms, and ordinary aging — all of which co-occur during the menopausal years. [56] Disentangling the relative contribution of each is methodologically difficult.

Dementia risk: a separate question.

The question of whether menopause-related hormonal changes or hormone therapy alter long-term dementia risk is distinct from the question of transition-period cognitive complaints. The available evidence on dementia risk from cohort studies and from hormone therapy trial follow-ups is mixed and has been the subject of considerable debate. [67] The KEEPS-Cognitive Affective substudy [68] and the WHIMS substudy of the Women's Health Initiative [69] reported different findings on cognitive outcomes — partly reflecting differences in the age at initiation of hormone therapy. This evidence is discussed in greater detail in Chapter 9.

> **What this section does and does not establish.** The literature establishes that subjective cognitive complaints during peri-menopause are common, that small objective decrements have been measured, and that most measures return toward baseline in early post-menopause. It does not establish that the menopausal transition itself causes long-term cognitive decline in the typical woman, nor does it support a single intervention recommendation for cognitive symptoms. [64]

Peri-menopause: a *window of elevated risk* for new-onset depression.

Multiple prospective studies have reported that peri-menopause is associated with approximately a two-fold increased risk of new-onset depressive symptoms or major depressive episodes compared with the late reproductive years, with risk returning toward baseline in early post-menopause. [55] [70]

The principal findings from prospective cohorts.

The Harvard Study of Moods and Cycles, the Penn Ovarian Aging Study, and SWAN have each examined depressive symptoms across the menopausal transition. [55] [70] Consistent findings across these studies include: (1) elevated risk of significant depressive symptoms during peri-menopause compared with pre-menopause; (2) higher absolute risk among women with a prior history of depression, including post-partum depression and premenstrual dysphoric disorder; and (3) partial — though not complete — mediation by sleep disruption and vasomotor symptoms. [55]

Estradiol variability rather than absolute level.

One of the more notable findings from this literature is that estradiol *variability* — large fluctuations from week to week — was a stronger predictor of depressive symptoms during peri-menopause than the absolute estradiol level. [70] Women in the Penn Ovarian Aging Study with the greatest within-individual variability in estradiol concentrations across the transition had higher incidence of depressive symptoms, after adjustment for other factors. [70] This pattern is consistent with the broader framing of peri-menopause as a hormonal-volatility window described in Chapter 3.

Anxiety and irritability.

Beyond depressive symptoms, cohort studies have reported elevated rates of new-onset anxiety symptoms and irritability during peri-menopause. [71] The proposed mechanisms involve direct effects of estradiol and progesterone (and its neuroactive metabolite allopregnanolone) on GABA-ergic and serotonergic signaling in limbic structures. [23] [71]

Therapeutic literature.

Randomized trials of transdermal estradiol have reported reductions in depressive symptoms among peri-menopausal women with new-onset depression. [72] Studies of established post-menopausal women with depression have generally shown smaller effects of estrogen on mood than those reported in peri-menopausal cohorts. [72] Conventional pharmacotherapies for depression — SSRIs, SNRIs, and others — have also been studied; the available evidence does not distinguish a unique pharmacotherapy of choice for menopausal-period depression compared with depression at other life stages. [71]

An important caveat. Depression and anxiety symptoms during peri-menopause warrant clinical assessment irrespective of menopausal status. The framing of peri-menopause as a "window of risk" should not substitute for individualized clinical evaluation when symptoms are significant. [71]

Sleep disturbance: *multifactorial, common, often persistent.*

Sleep disturbance — difficulty initiating sleep, frequent nocturnal awakenings, or non-restorative sleep — is reported by approximately 40–60% of women during the menopausal transition. [54] Prevalence increases with progression through peri-menopause and remains elevated in early post-menopause, with substantial inter-individual variability. [54]

Three overlapping contributors.

The sleep disturbance literature in the menopausal transition emphasizes three overlapping contributors that are difficult to fully disentangle: [73]

01 **Vasomotor-symptom-related awakenings.**
Night sweats and hot flashes themselves disrupt sleep architecture. Polysomnographic studies have documented arousals temporally associated with measured hot flashes. [73] However, sleep complaints during the transition are present in many women without measured vasomotor symptoms, suggesting additional mechanisms. [73]

02 **Primary changes in sleep architecture.**
Independent of VMS, the menopausal transition is associated with measured changes in sleep architecture — including reduced slow-wave sleep and altered REM patterns — in laboratory polysomnography studies. [74] Possible mediators include direct effects of estradiol and progesterone metabolites on sleep-regulatory networks. [23]

03 **Co-occurring primary sleep disorders.**
Obstructive sleep apnea (OSA) prevalence increases substantially in post-menopausal women — to rates approaching those of men in some cohorts — for reasons that include redistribution of adipose tissue and possibly direct effects of declining estrogen and progesterone on upper-airway musculature. [75] OSA is frequently under-recognized in women, and its presentation may differ from the classical male phenotype. [75]

Implications for downstream symptoms.

Sleep disruption is reported to mediate part — but not all — of the increase in depressive symptoms, cognitive complaints, and quality-of-life impact attributed to the menopausal transition. [54] [73] The interrelationship between VMS, sleep disturbance, mood symptoms, and cognitive complaints is bidirectional and forms one of the methodological challenges in interpreting the menopausal-symptom literature. [54]

> **Therapeutic literature in brief.** Hormone therapy, cognitive-behavioral therapy for insomnia (CBT-I), and conventional pharmacotherapies for sleep have each been studied for menopausal sleep disturbance. Sleep apnea, when present, is treated with established disorder-specific therapies independent of menopausal status. Detailed comparison is in Chapters 12 and 15. [75]

GSM: the *progressive, under-discussed* syndrome.

The genitourinary syndrome of menopause (GSM) is the consensus term introduced by the International Society for the Study of Women's Sexual Health and the North American Menopause Society in 2014 to replace the older terms "vulvovaginal atrophy" and "atrophic vaginitis." [76] The term reflects the recognition that the affected tissues include not only the vulva and vagina but also the urethra and bladder trigone — all of which are densely populated with estrogen receptors. [76]

The clinical syndrome.

GSM encompasses signs and symptoms in three overlapping domains: [76]

- **Vulvovaginal symptoms** — dryness, burning, irritation, dyspareunia (painful intercourse), reduced lubrication, and post-coital bleeding from fragile tissue.
- **Urinary symptoms** — urgency, dysuria, recurrent urinary tract infection (UTI), and to a more variable extent, urgency incontinence.
- **Sexual function** — pain or impaired arousal arising from the tissue changes themselves, distinct from libido changes (covered in Chapter 5.7).

Why GSM differs from vasomotor symptoms.

In contrast to vasomotor symptoms — which typically peak and then diminish over years — GSM is generally progressive in the absence of intervention. [48] Prevalence increases with time since the final menstrual period, reaching approximately 50% within 3 years of the FMP and continuing to rise thereafter. [49] The underlying mechanism is direct local loss of estrogen signaling in tissues densely populated with estrogen receptors, with histological changes — thinning of the vaginal epithelium, reduced glycogen, increased vaginal pH, altered vaginal microbiome — characterized in detail. [76]

The treatment literature in brief.

Local (vaginal) estrogen therapy — administered as cream, tablet, ring, or insert — has been extensively studied for GSM and is associated with restoration of vaginal epithelial thickness, normalization of pH, reduction in symptoms, and reduction in recurrent UTI risk in published trials. [77] Systemic absorption from low-dose vaginal preparations is minimal, and the safety profile reported in clinical trials and observational studies differs from that of systemic estrogen. [77] Other studied options include vaginal moisturizers, the selective estrogen receptor modulator ospemifene, vaginal DHEA (prasterone), and several non-pharmacologic approaches; the relative effect sizes reported in head-to-head comparisons are discussed in Chapter 10. [78]

An observation from epidemiologic data. Despite high prevalence and the availability of multiple studied therapies, surveys have consistently reported that GSM is under-discussed in clinical encounters and that many affected women either do not raise symptoms or are not asked about them. [79]

Sexual function changes are *multi-factorial.*

Reported changes in sexual function during the menopausal transition span multiple dimensions — desire, arousal, lubrication, orgasm, and pain — and arise from overlapping biological, psychological, and relational contributors. [57] Population surveys report meaningful changes in some dimension of sexual function in approximately 30–50% of women during the transition years. [57]

What changes, and what is the proposed mechanism.

DIMENSION	REPORTED PATTERN IN COHORT STUDIES	PRINCIPAL PROPOSED MECHANISMS
Desire (libido)	**Gradual decline through the transition in many — but not all — women.** [57]	Mixed: declining testosterone, declining estradiol effects on central reward signaling, fatigue, mood, relational factors. [31]
Arousal & lubrication	**Decreased lubrication and slower arousal commonly reported in post-menopause.** [57]	Direct loss of estrogen signaling in vaginal tissue (GSM) is the principal driver. [76]
Pain (dyspareunia)	**Increasingly common with time since FMP; one of the principal contributors to reduced sexual activity.** [49]	Direct consequence of GSM tissue changes. [76]
Orgasm	**Variable changes; less consistently reported than desire/arousal changes.** [57]	Multi-factorial; less clearly tied to a single hormonal mechanism.

The role of testosterone — what the global consensus says.

The 2019 Global Consensus Position Statement on the Use of Testosterone Therapy for Women — endorsed by multiple international endocrine and menopause societies — concluded that the only evidence-based indication for testosterone therapy in post-menopausal women, at the time of publication, was hypoactive sexual desire disorder (HSDD). [31] Pooled trial data showed modest improvements in measures of sexual desire, arousal, orgasm, and pleasure compared with placebo, with dosing targeting physiologic female testosterone concentrations. [31] The statement emphasized that no testosterone product is currently approved for use in women in most countries, including the United States; prescribing is off-label where it occurs. [31]

The role of local estrogen.

Where reduced sexual activity stems primarily from GSM-related dyspareunia or arousal/lubrication changes, randomized trials of low-dose vaginal estrogen have reported substantial improvements in measures of sexual function. [77] This contrasts with the more modest effects of vaginal estrogen on overall sexual desire when desire is the primary complaint. [77]

> **The broader framing.** Sexual function in midlife reflects multiple inputs — relational, psychological, sleep, fatigue, mood, partner factors — in addition to direct hormonal status. The published literature emphasizes a multi-dimensional clinical assessment rather than a single-pharmacology approach. [31] [57]

The transition shifts *where* body fat sits — and *how much* lean mass remains.

Two body-composition changes characterize the menopausal transition in the literature: a shift in adipose tissue distribution toward central (visceral) deposition, and an acceleration of the age-related loss of lean muscle mass and strength. [80] Both have been documented in longitudinal studies and contribute to the increased prevalence of cardiometabolic conditions in post-menopausal women. [81]

Visceral adiposity: what shifts and when.

Cross-sectional and longitudinal imaging studies have documented increases in visceral adipose tissue (VAT) during the menopausal transition that exceed the rate of increase explained by aging alone in age-matched men or pre-menopausal women. [82] In the SWAN Cardiovascular Health study, VAT increased by approximately 4–8% per year during late peri-menopause and early post-menopause, with smaller changes in subcutaneous adipose tissue. [82] Total body fat percentage tends to increase modestly even when body weight is stable, reflecting concurrent loss of lean mass. [80]

Sarcopenia: muscle loss accelerates.

Skeletal muscle mass declines with age in both sexes from approximately the fourth decade onward, but the rate of loss appears to accelerate in women during the menopausal transition. [83] Longitudinal studies using dual-energy X-ray absorptiometry (DXA) have documented declines in lean body mass during the transition, with parallel reductions in measured strength. [83] Estrogen receptors are expressed on skeletal muscle, and proposed mechanisms for the accelerated loss include altered satellite cell biology, increased systemic inflammation, and reduced anabolic sensitivity. [84]

The clinical relevance of these shifts.

The cumulative effects of these body-composition shifts include: increased insulin resistance and glycemic risk; [85] shifts in lipid profile (Chapter 7); increased risk of metabolic syndrome; [81] increased risk of falls and fractures (Chapter 6.3); and reduced physical function in older age. [86] These are quantifiable, modifiable, and form much of the rationale for the strength-training literature reviewed in Chapter 14.

The most-studied modifiable intervention. Resistance training has the largest effect-size on lean mass and strength outcomes in trials of post-menopausal women. Specific findings, doses, and program parameters from the published literature are reviewed in Chapter 14. [87]

Bone density: a *narrow window of rapid loss*, then slower decline.

Bone mineral density (BMD) declines in a characteristic pattern across the menopausal transition: relatively stable density through the late reproductive years, accelerated loss beginning approximately 1 year before the final menstrual period, peak rate of loss in the first 1–2 years post-FMP, and a slower continued decline thereafter. [50]

The SWAN Bone Mineral Density Study.

In the SWAN BMD substudy, annualized rates of bone loss at the lumbar spine and femoral neck were measured across the transition. [50] Principal findings included:

- Mean lumbar spine BMD loss of approximately **0.018 g/cm² per year** (≈1.8% of mean baseline density) during the year-before-FMP-to-2-years-after-FMP window — substantially faster than the loss rate before or after this window. [50]
- Slower continued BMD loss in the years thereafter — approximately **0.6–1.0% per year** — consistent with the established pattern of post-menopausal bone aging. [50]
- Body weight was inversely associated with rate of loss: women with higher body weight had slower BMD loss, an effect attributed in part to peripheral estrogen production from adipose tissue. [50]
- Race/ethnicity differences in baseline BMD and rate of loss were observed, with implications for population-level fracture risk estimation. [50]

The biological mechanism in brief.

Estrogen restrains bone resorption by direct effects on osteoclasts (via ERα) and by modulating RANKL/OPG signaling. [88] The decline in estradiol around the FMP releases this brake, transiently increasing the rate of bone resorption relative to formation and producing the accelerated loss documented in SWAN and other longitudinal cohorts. [88] Bone formation also declines with age, but the imbalance during the transition is driven primarily by the increase in resorption. [88]

Implications for measurement and intervention windows.

The compression of the period of rapid BMD loss into a narrow window around the FMP has been cited in some clinical commentary as a rationale for considering bone-protective interventions during this specific window in appropriate candidates. [89] Multiple therapeutic categories — hormone therapy, bisphosphonates, denosumab, SERMs, and others — have been studied for fracture prevention; their relative efficacy and the populations in which trials have demonstrated benefit are addressed in Chapter 12. [90]

> **The screening literature.** DXA-based BMD screening recommendations from major clinical societies generally focus on women aged 65 and older, with earlier screening recommended for women with additional fracture risk factors. Detailed screening guidance is outside the scope of this educational guide; reference is made to current NOF/USPSTF/Endocrine Society guidelines. [91]

Fractures are the *end-point outcome* the BMD literature is built to prevent.

Approximately 1 in 2 women over age 50 will experience an osteoporosis-related fracture during her remaining lifetime in U.S. epidemiologic data. [92] Hip fracture is the most clinically consequential category — associated with substantial mortality, functional decline, and loss of independence in the year following the event — but vertebral and forearm fractures contribute the larger total burden by count. [93]

Fracture epidemiology in post-menopausal women.

The lifetime risks reported in U.S. cohort data, indexed at age 50, are approximately: [92] [93]

- Any osteoporotic fracture: ~50%
- Vertebral fracture (clinical or morphometric): ~32%
- Hip fracture: ~18%
- Distal forearm (Colles) fracture: ~16%

Hip fracture incidence is strongly age-dependent: rates approximately double for each 5-year increase in age beyond 65 in cohort data. [93] Mortality in the year following hip fracture is reported in the range of 20–25% in U.S. epidemiologic data, with substantial functional impairment in survivors. [93]

Risk factors beyond BMD.

BMD is a strong predictor of fracture, but is not the only one. Tools such as FRAX, developed by the WHO Collaborating Centre, combine BMD with clinical risk factors — age, prior fragility fracture, parental hip fracture, current smoking, chronic glucocorticoid use, rheumatoid arthritis, secondary causes of osteoporosis, and excessive alcohol intake — to estimate 10-year probability of hip and major osteoporotic fracture. [94] Fall risk — a multi-factorial domain involving sarcopenia, balance, vision, neurologic status, and medications — independently influences the probability that low BMD translates into a fracture. [95]

What the intervention literature has demonstrated.

Randomized trials of multiple pharmacologic categories have demonstrated reductions in fracture risk in appropriate populations: bisphosphonates, [96] denosumab, [97] selective estrogen receptor modulators, [98] teriparatide, [99] and combined estrogen-progestogen therapy in the Women's Health Initiative. [100] The relative magnitudes of benefit, the populations studied, and the safety profiles are summarized in Chapter 12.

Non-pharmacologic levers studied for fracture risk. Resistance training, balance training, calcium and vitamin D adequacy, and fall-prevention interventions have each been studied with measurable effects on fracture-related outcomes in appropriate populations. The strength training evidence is reviewed in detail in Chapter 14; nutrition and supplement evidence in Chapter 15. [87] [101]

Cardiovascular risk factors shift in *characteristic patterns* across the transition.

Cardiovascular disease (CVD) is the leading cause of death in U.S. women, accounting for approximately 1 in 3 deaths overall. [102] Women's CVD event rates rise after menopause, reflecting both ordinary aging and a constellation of metabolic and vascular changes associated specifically with the menopausal transition. [103]

Lipid profile shifts.

Longitudinal cohort studies — including SWAN and the Atherosclerosis Risk in Communities (ARIC) study — have characterized lipid profile changes around the FMP. [104] Reported patterns include:

- **Total cholesterol** rises across the transition, with a more pronounced increase in the year before and the year after the FMP than would be expected from age alone. [104]
- **LDL-C** rises in parallel; SWAN reported an average increase of approximately 9 mg/dL between the year before and the year after the FMP. [104]
- **Apolipoprotein B** rises, consistent with the LDL particle changes. [104]
- **HDL-C** shows more variable trajectories; the small-particle HDL fraction tends to decline, while the larger HDL particle fraction can rise — net HDL-C may appear stable while particle composition shifts toward a less protective pattern. [104]
- **Triglycerides** rise modestly through the transition. [104]
- **Lipoprotein(a)** [Lp(a)] has been reported to rise during the transition in some — though not all — analyses; this finding remains under investigation. [105]

What the SWAN heart studies have documented in vascular tissue.

The SWAN Heart Study used carotid intima-media thickness (CIMT) and coronary artery calcium (CAC) imaging to characterize the trajectory of subclinical atherosclerosis across the menopausal transition. [106] Principal findings included: an acceleration of CIMT progression around the FMP; an increased likelihood of detectable CAC in early post-menopausal women compared with peri-menopausal women of similar age; and associations between persistent vasomotor symptoms and measures of subclinical atherosclerosis. [62] [106]

What this tells us — and what it does not. The above describes a pattern of biomarker and imaging-based risk acceleration around the FMP. Whether — and in whom — pharmacologic interventions targeting this window influence longer-term cardiovascular event risk is the subject of ongoing investigation, including the WHI, KEEPS, and ELITE trials reviewed in Chapter 9. [7] [5] [6]

Estrogen and the *blood vessel.*

Estrogen exerts direct effects on the vascular endothelium and smooth muscle — effects characterized in detail in preclinical work and supported by mechanistic studies in humans. [17] These effects underpin much of the contemporary discussion of how the timing of any post-menopausal hormonal exposure might influence cardiovascular outcomes (Chapter 9).

The principal vascular mechanisms.

01 **Endothelial nitric oxide signaling.**
Estradiol increases endothelial nitric oxide synthase (eNOS) activity through both genomic (ERα) and rapid non-genomic (membrane-receptor) pathways. Increased NO bioavailability promotes vasodilation, inhibits platelet aggregation, and reduces leukocyte-endothelial adhesion. [107]

02 **Anti-inflammatory effects.**
Estrogen signaling reduces expression of several adhesion molecules (VCAM-1, ICAM-1) and cytokines involved in early atherosclerotic plaque formation in preclinical models. [108]

03 **Lipid trafficking.**
Hepatic estrogen signaling modulates LDL receptor expression and other components of lipoprotein metabolism — partly explaining the lipid shifts observed around the FMP described in Chapter 7.1. [109]

04 **Smooth muscle and vascular remodeling.**
Estrogen influences vascular smooth muscle proliferation, collagen deposition, and matrix metalloproteinase activity — effects relevant to arterial stiffness and to advanced atherosclerotic plaque biology. [110]

Why "early vs. late" exposure has been hypothesized to matter.

Several lines of preclinical evidence suggest that the vascular effects of estrogen differ depending on the state of the vasculature at the time of exposure. In animal models, estrogen administered to vessels without established atherosclerosis tends to be vasoprotective; estrogen administered to vessels with advanced, complex atherosclerotic plaque can be vasoneutral or — under some conditions — pro-inflammatory. [111] This biological framework — the "timing hypothesis" — informs the interpretation of the WHI, KEEPS, and ELITE results discussed in detail in Chapter 9. [7] [5] [6]

> **The interpretive frame for Chapter 9.** Whether the preclinical timing-hypothesis biology translates into clinically meaningful differences in human cardiovascular outcomes depending on age or years-since-FMP at initiation of hormone therapy is — at this writing — the most debated question in the menopausal hormone therapy literature. The major trials and re-analyses are presented in Chapter 9. [112]

From *biomarker shifts* to *events.*

The biomarker and subclinical-imaging shifts described in 7.1 and 7.2 are accompanied — at the population level — by clinically meaningful increases in cardiovascular event rates in post-menopausal women. The principal data sources are large prospective cohorts and national vital statistics. [102] [103]

What the population data show.

- **Coronary heart disease (CHD) incidence** in women rises substantially with age after the FMP. Age-adjusted CHD event rates in women aged 60–69 are several-fold higher than in women aged 40–49 in U.S. cohort data. [102]
- **Stroke incidence** rises with age throughout adulthood; women have a higher absolute lifetime risk of stroke than men, partly reflecting longer life expectancy. [102]
- **Heart failure with preserved ejection fraction (HFpEF)** is disproportionately common in post-menopausal women; the underlying biology is incompletely characterized and remains an area of active investigation. [113]
- **Early menopause (< 45 years)** has been associated in multiple large cohorts with modestly increased lifetime CHD and stroke risk relative to menopause at the typical age, after adjustment for traditional risk factors. [41]

What modifies these trajectories.

Traditional cardiovascular risk factors — hypertension, dyslipidemia, type 2 diabetes, smoking, sedentary behavior, central adiposity — remain the strongest modifiable contributors to post-menopausal cardiovascular event risk. [114] Several of these risk factors shift unfavorably around the FMP (Chapter 7.1), creating a window during which intensive primary-prevention attention has been argued to be particularly impactful. [115]

The effect of post-menopausal hormone therapy on cardiovascular events is the most-debated question in this area of medicine and is discussed at length in Chapter 9. The short summary, drawing on the WHI, KEEPS, ELITE, and observational re-analyses: estimated effects appear to differ by age at initiation and time since FMP, with possible neutral-to-favorable effects in women who initiate therapy at younger post-menopausal ages and likely unfavorable effects in women who initiate at older ages. [7] [5] [6] [112]

Reading note. Long-term cardiovascular risk in post-menopausal women is influenced by inputs spanning genetics, ordinary aging, lifestyle, traditional risk factors, and — possibly — the hormonal milieu and any therapies that affect it. Single-input framings should be read skeptically. [114]

What gets measured — and what the *numbers actually mean.*

Laboratory testing during the menopausal transition serves two distinct purposes that are sometimes conflated in patient-facing materials: (1) characterizing where in the transition a woman is at a given point in time, and (2) tracking cardiometabolic, skeletal, and other longitudinal markers whose trajectories shift around the FMP. [116]

What the major guidelines actually say about hormone testing.

The clinical guidelines from The Menopause Society (NAMS), the Endocrine Society, and the International Menopause Society are notably consistent on one point: the diagnosis of natural menopause is a clinical diagnosis based on menstrual history (12 consecutive months of amenorrhea in a woman of typical age), not a laboratory diagnosis. [22] [117] Hormone measurements during peri-menopause are described as supportive rather than diagnostic, in part because of the high within-individual variability documented in cohort studies. [9]

The exceptions in which hormone measurements have established diagnostic roles include: (1) suspected premature ovarian insufficiency (POI), where elevated FSH on two separate occasions is part of the diagnostic criteria; [42] (2) clinical scenarios in which a woman is amenorrheic for non-menopausal reasons and the differential diagnosis includes ovarian failure; and (3) assessment of fertility status, where AMH provides ovarian reserve information. [2]

The two-list framework.

REPRODUCTIVE / TRANSITION STATUS

- **FSH** — rises in late peri-menopause; high variability in early peri-menopause limits diagnostic use of single measurements. [9]
- **Estradiol (E2)** — fluctuates widely during peri-menopause; low values consistently in established post-menopause. [9]
- **AMH** — declines steadily with age; low or undetectable values support late reproductive / early peri-menopausal staging. [2]
- **LH** — rises with FSH; less consistently informative than FSH alone. [9]
- **Inhibin B** — declines earlier than E2; used in research; less commonly measured clinically. [35]

LONGITUDINAL HEALTH MARKERS

- **Lipid panel** — LDL-C, HDL-C, triglycerides, total cholesterol; apoB and Lp(a) for refined risk estimation. [118]
- **Glycemia** — fasting glucose, HbA1c; sometimes fasting insulin. [119]
- **Thyroid** — TSH (± free T4); symptom overlap with peri-menopause is substantial. [120]
- **Vitamin D (25-OH-D)** — relevant to bone health interpretation. [121]
- **Bone turnover** — CTX, P1NP; primarily research/specialty use. [122]
- **Inflammation** — hsCRP for cardiovascular risk refinement. [118]

What's not on the lists above. Salivary hormone panels and certain "complete hormone profile" panels marketed direct-to-consumer have variable validation and are not generally recommended in major society guidelines for clinical decision-making. [123]

Why a *single number* rarely tells the story.

Three features of menopausal-transition endocrinology complicate single-time-point hormone interpretation: high within-individual variability, methodological issues with low-concentration assays, and substantial population overlap between reproductive and peri-menopausal ranges. [9] [30]

Within-individual variability.

SWAN documented that within-individual estradiol levels can range by an order of magnitude between consecutive cycles in late peri-menopause; FSH levels show similar variability. [9] A single low estradiol or single elevated FSH measurement in a peri-menopausal woman is therefore not, in isolation, diagnostically definitive — a point that the major society guidelines emphasize. [22]

Assay methodology matters at low concentrations.

Older estradiol immunoassays were developed for the higher concentrations encountered in reproductive-age women and in pregnancy and have variable performance at the lower concentrations characteristic of post-menopause. [124] Mass-spectrometry-based assays (LC-MS/MS) have been recommended for accurate measurement at low concentrations and have been shown to differ from older immunoassays at the levels relevant for post-menopausal evaluation. [124] The same considerations apply to testosterone measurement in women, where physiologic concentrations are well below those for which standard immunoassays were optimized. [30]

Confounding from exogenous hormones.

A woman using a combined oral contraceptive, a progestogen-only contraceptive, or hormone therapy will have circulating hormone concentrations that reflect both her endogenous physiology and the exogenous exposure. FSH measurements during contraceptive use are not interpretable as a marker of menopausal status. [125] Major society guidance suggests that in women using hormonal contraception, menopausal status is generally determined clinically rather than biochemically. [125]

When repeated measurements add information.

Where hormone testing is undertaken — for example, in the diagnostic workup of suspected POI — major society guidelines specify two measurements separated in time (typically ≥ 4 weeks apart) precisely because of the within-individual variability described above. [42] A similar principle applies to the assessment of secondary causes of amenorrhea in younger women, where multiple hormonal axes are typically evaluated together rather than from a single panel. [125]

> **Synthesis.** The clinical literature consistently frames peri-menopause as a clinical diagnosis informed by — but not made from — hormone measurements. Single panels marketed direct-to-consumer as definitive of "where you are" in the transition do not align with this framing. [22]

Cardiometabolic markers track *what the transition shifts.*

Cardiometabolic laboratory testing in midlife women has well-established roles in cardiovascular risk estimation, diabetes screening, and individualized intervention planning.[118][119] The biomarker shifts described in Chapter 7 provide the rationale for measuring some of these at intervals during and after the menopausal transition.

The standard lipid panel — and beyond.

The standard lipid panel (total cholesterol, LDL-C, HDL-C, triglycerides) remains the foundation of cardiovascular risk estimation in current guidelines.[118] Additional markers that have entered some guideline recommendations include:

- **Apolipoprotein B (apoB)** — a count of atherogenic particles. ApoB has been shown to better discriminate cardiovascular risk than LDL-C alone in some populations and is included as an option in current AHA/ACC and European guidelines for risk refinement.[126]
- **Lipoprotein(a) [Lp(a)]** — a genetically determined atherogenic particle. The European Society of Cardiology and AHA have recommended a once-in-a-lifetime Lp(a) measurement for cardiovascular risk stratification.[127]
- **High-sensitivity C-reactive protein (hsCRP)** — a marker of low-grade inflammation incorporated into some cardiovascular risk calculators.[118]
- **Coronary artery calcium score (CAC)** — an imaging-based measure; not a laboratory test but commonly grouped with cardiometabolic risk refinement.[128]

Glycemic markers.

HbA1c, fasting plasma glucose, and oral glucose tolerance testing are the established markers for diabetes screening and diagnosis per ADA standards of care.[119] Insulin resistance — relevant to the increased prevalence of metabolic syndrome in post-menopausal women — is often inferred from clinical features (waist circumference, triglyceride/HDL ratio, fasting glucose, blood pressure) rather than measured directly outside of research settings.[119]

Thyroid evaluation — because of symptom overlap.

Thyroid disease is more common in midlife women than in midlife men, and several thyroid-disease symptoms — fatigue, mood changes, sleep disturbance, weight change, cognitive complaints — overlap substantially with menopausal-transition symptoms.[120] TSH measurement is a routine part of evaluating new symptoms in this age group; the diagnostic and management literature is summarized in current ATA/Endocrine Society guidelines.[129]

What this guide does not provide. Specific reference ranges, cutpoints for intervention, and risk-calculator interpretations are addressed in primary-source clinical guidelines and require individualized clinical context. This chapter describes what is typically measured and why, not how to act on a particular result.[118][119]

Bone testing, vitamin D, and the rest of the workup.

Bone-related testing in post-menopausal women centers on dual-energy X-ray absorptiometry (DXA) imaging of bone mineral density. Several blood-based bone turnover markers are also available and have specific research and clinical roles. Vitamin D status and related laboratory measures support interpretation of bone-related findings. [122]

DXA-based bone mineral density.

DXA measurement of BMD at the lumbar spine, total hip, and femoral neck is the standard for assessing post-menopausal bone health. [91] Results are reported as T-scores (standard deviations from young adult reference mean) and Z-scores (standard deviations from age-matched reference). WHO criteria define osteopenia (T-score −1.0 to −2.5) and osteoporosis (T-score ≤ −2.5). [91] Screening recommendations from the U.S. Preventive Services Task Force, the National Osteoporosis Foundation, and the Endocrine Society generally focus on women aged 65 and older, with earlier screening for women with additional fracture risk factors. [91]

Bone turnover markers.

Blood-based bone turnover markers — C-terminal telopeptide of type I collagen (CTX, a resorption marker) and procollagen type I N-terminal propeptide (P1NP, a formation marker) — reflect short-term bone remodeling activity. [122] CTX and P1NP rise around the FMP in parallel with the accelerated bone loss documented in SWAN. [122] Their use in routine clinical care is more limited than DXA; they are used in some specialty settings to evaluate response to anti-resorptive therapy or to assess bone turnover where the cause of low BMD is uncertain. [122]

Vitamin D status.

25-hydroxyvitamin D measurement is the standard assessment of vitamin D status. Optimal target levels are debated between Endocrine Society and Institute of Medicine recommendations. [121] Vitamin D status influences calcium absorption and is generally evaluated when low BMD is identified, when fractures occur, or where deficiency is otherwise suspected. [121]

Other tests that sometimes appear on midlife panels.

- **Iron studies** — relevant during peri-menopause if menorrhagia or unexplained anemia is present. [130]
- **Liver and kidney function** — supportive markers for cardiometabolic risk and for safety monitoring of certain medications.
- **Cortisol / DHEA-S** — generally not part of routine menopausal evaluation outside of specific clinical scenarios. [33]
- **Comprehensive sex-hormone panels** — research and specialty use; not part of routine menopause assessment per major society guidelines. [22]

The reading frame for this chapter. The labs described above are tools. Their utility depends on the clinical question being asked. A reader of this guide should leave understanding what each tool measures and its general role — not which combination of tests to order, which depends entirely on individual clinical context. [22]

Reading the hormone therapy literature: *history matters.*

The published literature on menopausal hormone therapy (MHT) — also referred to as hormone replacement therapy (HRT) — is unusually large, methodologically complex, and historically contested. Understanding what each major trial actually tested, in whom, and what was concluded is necessary to interpret current clinical guidelines and the ongoing scientific debate. [131]

The pre-2002 picture.

Before the publication of the principal Women's Health Initiative (WHI) results in 2002, the dominant evidence base on long-term outcomes of menopausal hormone therapy came from large observational cohort studies — most prominently the Nurses' Health Study, which had reported associations between hormone therapy use and reduced cardiovascular events. [132] The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial (1995) was the principal short-term randomized trial of the era and demonstrated favorable changes in lipid profile and other cardiovascular surrogate markers with combined regimens versus placebo. [133]

Based on this body of evidence, hormone therapy was widely prescribed in the 1980s and 1990s, including for cardiovascular and dementia prevention indications in addition to symptom management. Major society recommendations of the era reflected the prevailing observational evidence. [131]

Why a large randomized trial was undertaken.

By the late 1990s, the observational evidence had begun to be challenged on methodological grounds — particularly concerning the possibility of healthy-user bias, in which women who chose to use hormone therapy in observational studies might have systematically differed from non-users in ways that could account for their better cardiovascular outcomes independent of the medication itself. [131] The Women's Health Initiative was designed to address this question through randomized assignment of women to hormone therapy versus placebo, with long-term follow-up for chronic disease endpoints. [134]

Two regimens, two parallel trials.

The WHI hormone therapy program comprised two parallel randomized, double-blind, placebo-controlled trials, conducted at 40 U.S. clinical centers between 1993 and 2002: [134]

WHI E + P TRIAL

For women with a uterus. Daily conjugated equine estrogens 0.625 mg + medroxyprogesterone acetate 2.5 mg (Prempro) vs. placebo. N = 16,608. Planned duration 8.5 years; stopped early at 5.2 years mean follow-up due to elevated event rates in several outcomes. [7]

WHI E-ALONE TRIAL

For women with prior hysterectomy. Daily conjugated equine estrogens 0.625 mg (Premarin) vs. placebo. N = 10,739. Planned duration 8.5 years; stopped at 6.8 years mean follow-up due to elevated stroke risk in the active arm. [135]

The reading frame for the rest of this chapter. The WHI was a large, well-designed randomized trial that produced findings substantially different from the prior observational evidence. The subsequent two decades of follow-up analyses, sub-analyses, and the parallel KEEPS and ELITE trials have together reshaped current interpretation of the WHI findings themselves. [112]

The 2002 results: *what was published, in whom, with what dose.*

The 2002 primary publication of the WHI E+P trial reported event rates in the active arm relative to placebo across the trial's pre-specified primary outcomes and key secondary outcomes. [7] The 2004 publication of the WHI E-alone trial reported the parallel results for women without a uterus. [135]

WHI E+P (2002) — hazard ratios as published.

OUTCOME	HAZARD RATIO (95% CI)	REPORTED DIRECTION
Coronary heart disease	1.29 (1.02 – 1.63)	Increase in active arm
Stroke	1.41 (1.07 – 1.85)	Increase in active arm
Pulmonary embolism	2.13 (1.39 – 3.25)	Increase in active arm
Invasive breast cancer	1.26 (1.00 – 1.59)	Increase in active arm
Colorectal cancer	0.63 (0.43 – 0.92)	Decrease in active arm
Hip fracture	0.66 (0.45 – 0.98)	Decrease in active arm
Endometrial cancer	0.83 (0.47 – 1.47)	No significant difference

Source: Rossouw JE et al. JAMA. 2002;288:321–333. [7]

WHI E-alone (2004) — hazard ratios as published.

OUTCOME	HAZARD RATIO (95% CI)	REPORTED DIRECTION
Coronary heart disease	0.91 (0.75 – 1.12)	No significant difference
Stroke	1.39 (1.10 – 1.77)	Increase in active arm
Pulmonary embolism	1.34 (0.87 – 2.06)	No significant difference
Invasive breast cancer	0.77 (0.59 – 1.01)	No significant difference (trend lower)
Hip fracture	0.61 (0.41 – 0.91)	Decrease in active arm

Source: Anderson GL et al. JAMA. 2004;291:1701–1712. [135]

What the 2002 publications conclude.

The 2002 E+P publication concluded that the global benefit/risk profile in the population studied did not support use of combined conjugated estrogens plus medroxyprogesterone for the primary prevention of chronic disease. [7] The 2004 E-alone publication described a different pattern in the E-alone arm — including no increase in invasive breast cancer and no significant change in coronary heart disease, alongside the increased stroke risk — and concluded that the E-alone results differed materially from those of the combined regimen. [135]

Two notes that become central in the re-analyses. First, the WHI population had a mean age of approximately 63 at enrollment — more than a decade past the typical age at menopause. Second, the regimens tested were specific products and doses (oral conjugated equine estrogens; oral medroxyprogesterone acetate) — not the entire category of estrogens and progestogens that current clinical practice encompasses. [136]

The age- and timing-stratified *re-analyses.*

The years following the initial 2002 and 2004 WHI publications produced an extensive set of secondary analyses examining whether the trial-wide hazard ratios concealed substantial heterogeneity by age at initiation or by time since menopause. The most-cited of these is the 2007 Rossouw et al. age-stratified analysis and the 2017 Manson et al. extended follow-up. [137] [112]

The age-stratified pattern, as reported.

When pooled WHI data were stratified by age at hormone therapy initiation and by years since menopause, the cardiovascular hazard ratios differed across age strata. [137] Reported patterns included:

- Among women aged 50–59 at enrollment: cardiovascular event hazard ratios trended toward neutral or favorable for both the E+P and E-alone arms, although confidence intervals were wide given the smaller subset size. [137]
- Among women aged 60–69 at enrollment: hazard ratios trended unfavorable, particularly for stroke. [137]
- Among women aged 70–79 at enrollment: hazard ratios for cardiovascular events were more clearly unfavorable. [137]
- A similar pattern emerged when years-since-menopause was used as the stratifier rather than age. [137]

The 2007 publication explicitly discussed a "gap time" hypothesis — that initiation of hormone therapy closer to menopause produced different effects than initiation many years afterward. [137] This subgroup pattern is the empirical basis on which the broader "timing hypothesis" was articulated. [137]

The 2017 long-term mortality follow-up.

Manson and colleagues published an 18-year cumulative follow-up of the WHI hormone therapy participants in 2017. [112] Key findings included:

- All-cause mortality did not differ significantly between the active and placebo groups in either the E+P or E-alone trials over cumulative follow-up. [112]
- Cause-specific mortality patterns differed by age at randomization, with directionally favorable mortality trends for women aged 50–59 at randomization in some analyses. [112]
- The principal short-term increases in breast cancer incidence in the E+P arm persisted in the long-term follow-up; the E-alone arm continued to show a non-significant reduction in invasive breast cancer. [112]

> **The interpretive question raised by the re-analyses.** Whether the age-stratified subgroup patterns in WHI represent real biological heterogeneity — as the timing hypothesis posits — or chance findings in subgroup analysis is the subject of ongoing scientific discussion. Two trials (KEEPS and ELITE) were designed prospectively to address this question and are summarized next. [5] [6]

KEEPS: testing the timing hypothesis with *imaging endpoints.*

The Kronos Early Estrogen Prevention Study (KEEPS) was a randomized, double-blind, placebo-controlled trial designed specifically to test whether hormone therapy initiated in recently menopausal women — at an age substantially younger than the WHI cohort — affected the progression of subclinical atherosclerosis. [5]

Design and population.

POPULATION

N = 727. Recently menopausal women, ages 42–58, within 3 years of FMP. Free of clinical cardiovascular disease at enrollment. Multi-center U.S. [5]

THREE ARMS

(1) Oral conjugated equine estrogens 0.45 mg/day; (2) Transdermal estradiol 50 µg/day; (3) Placebo. Women with a uterus in active arms also received micronized progesterone 200 mg/day for 12 days each month. [5]

ENDPOINTS

Primary: change in carotid intima-media thickness (CIMT) over 4 years. Secondary: change in coronary artery calcium (CAC), cardiovascular risk markers, cognitive measures, mood, sexual function. [5]

DURATION

4 years of randomized intervention; subsequent observational follow-up. Notably shorter than WHI; KEEPS was powered for surrogate imaging endpoints, not for clinical events. [5]

Principal findings.

KEEPS reported neutral effects of both hormone therapy regimens on the primary imaging endpoint of CIMT progression over 4 years. [5] Neither hormone arm differed significantly from placebo on the principal vascular imaging measures. Among the secondary findings, both active arms improved measures of vasomotor symptoms, sexual function, and quality of life relative to placebo, consistent with the established short-term effects of hormone therapy on these outcomes. [5]

The KEEPS-Cognitive Affective substudy reported neutral effects on most cognitive measures, with some evidence of mood benefit in the active arms. [68] No clinically meaningful adverse cardiovascular signals were identified during the 4-year follow-up, although the trial was not powered for clinical events. [5]

How KEEPS is interpreted.

Commentaries on KEEPS have framed the findings as supportive of safety — but not of cardiovascular benefit — for hormone therapy initiated in early post-menopausal women at the doses and durations tested. [138] The trial's neutral primary finding has been contrasted with the ELITE results, which used a different surrogate endpoint and a different design (next page). [6]

The relevant caveats. KEEPS used surrogate imaging endpoints rather than clinical events; the sample size and duration were modest; and it tested only one E-alone regimen alongside one transdermal regimen and placebo. Generalization beyond these specific arms is constrained. [5]

ELITE: directly testing *early vs. late initiation.*

The Early versus Late Intervention Trial with Estradiol (ELITE) was a randomized, double-blind, placebo-controlled trial that directly compared the effect of oral estradiol versus placebo on atherosclerosis progression in women stratified a priori by years since menopause. [6]

Design and population.

POPULATION

N = 643. Healthy post-menopausal women, randomly assigned within two strata: **early stratum** (< 6 years since FMP) or **late stratum** (≥ 10 years since FMP). Single U.S. center. [6]

INTERVENTION

Oral 17β-estradiol 1 mg/day vs. placebo. Women with a uterus in the active arm also received progesterone 45 mg vaginal gel for 10 days each month. [6]

ENDPOINT

Primary: rate of change of carotid intima-media thickness (CIMT) over a median 5 years of follow-up. Secondary: coronary CT angiography measures. [6]

DURATION

Median follow-up ~5 years; longer than KEEPS. Like KEEPS, powered for surrogate imaging endpoints, not clinical events. [6]

Principal findings.

ELITE reported a statistically significant interaction between time-since-menopause stratum and the effect of estradiol on CIMT progression. [6] In the early-stratum group, oral estradiol slowed the rate of CIMT progression relative to placebo over the trial follow-up. In the late-stratum group, no significant difference between estradiol and placebo was observed on CIMT. [6] Coronary CT angiography measures of subclinical atherosclerosis showed similar directional patterns by stratum, although these secondary findings did not all reach statistical significance. [6]

How ELITE is interpreted.

ELITE has been cited as the most direct prospective randomized evidence supporting the timing hypothesis — specifically, the conclusion that the vascular effects of oral estradiol differ depending on time since menopause. [139] Important contextual notes include: ELITE used surrogate imaging endpoints, not clinical event endpoints; the regimen tested was oral estradiol (with vaginal progesterone in women with uterus), not the conjugated estrogens used in WHI; and the trial was conducted at a single center, which affects external generalizability. [6]

> **Putting WHI, KEEPS, and ELITE together.** The three trials together produced a more nuanced picture than any single trial alone — and one in which the importance of age at initiation, years since menopause, regimen (oral vs. transdermal estradiol; type of progestogen), and outcome (surrogate imaging vs. clinical events) became central to how the literature is now interpreted. [139]

What the major clinical societies *currently say.*

As of recent guideline updates, the principal English-language clinical societies have converged on broadly similar — though not identical — statements regarding menopausal hormone therapy. The most-cited are the position statements from The Menopause Society (formerly NAMS), the Endocrine Society, the International Menopause Society (IMS), and the British Menopause Society (BMS). [22] [117] [140] [141]

Areas of consensus across societies.

- **For symptomatic women under age 60 or within 10 years of FMP** without contraindications, the major societies describe the benefit-risk profile of hormone therapy for vasomotor symptoms and for prevention of bone loss as favorable. [22]
- **For initiation of hormone therapy in women over age 60 or more than 10 years past FMP,** the major societies describe the benefit-risk balance as less favorable, citing the WHI age-stratified data and the cardiovascular and stroke risks observed in older starters. [22]
- **Local low-dose vaginal estrogen for GSM** is described across societies as having a favorable benefit-risk profile and is not subject to the same age restrictions as systemic therapy. [22]
- **Premature ovarian insufficiency (POI)** is treated as a distinct entity; major societies recommend hormone therapy until at least the average age of natural menopause in the absence of contraindications. [42]
- **Individualization** — based on personal and family history, contraindications, baseline cardiovascular and breast cancer risk, and patient preference — is emphasized across all society statements. [22]

Areas of continued debate.

Several questions remain less settled in the published literature and in the clinical society guidance: [141]

- Optimal duration of hormone therapy for symptomatic women — historically described as "shortest duration consistent with goals," with more recent guidance moving toward individualized duration rather than a fixed cap. [22]
- Comparative outcomes of micronized progesterone vs. synthetic progestins as the progestogen component, particularly with respect to breast and venous thromboembolism risk. [24]
- Comparative outcomes of oral vs. transdermal estrogen, particularly with respect to venous thromboembolism and stroke risk. [142]
- The role of testosterone therapy outside of hypoactive sexual desire indications. [31]
- The dementia-prevention question. [67]

Reading guidelines. Clinical society guideline statements summarize the best-supported synthesis of the evidence at a point in time. Individual women's clinical scenarios — including contraindications, personal risk factors, and goals — are addressed in clinical encounters, not in society statements; this is consistently emphasized in the statements themselves. [22]

Same hormone, *different delivery* — different reported effects.

Estrogen can be administered by oral, transdermal, vaginal, and other routes. The published literature reports that route of administration influences not only pharmacokinetics but also some clinically relevant safety signals — most notably the venous thromboembolism risk profile. [142] This chapter summarizes what the studies have characterized about each principal modality.

The five principal categories.

ORAL SYSTEMIC ESTROGEN

Products studied include conjugated equine estrogens, oral micronized estradiol, and oral estradiol valerate. Undergoes first-pass hepatic metabolism, which influences hepatic protein synthesis — including SHBG, lipoproteins, and coagulation factors. [109] [142]

TRANSDERMAL SYSTEMIC ESTROGEN

Patches, gels, and sprays delivering 17β-estradiol. Bypasses first-pass hepatic metabolism. Observational studies report a different venous thromboembolism risk profile from oral formulations. [142] [143]

VAGINAL (LOW-DOSE LOCAL) ESTROGEN

Creams, tablets, rings, and inserts. Studied predominantly for genitourinary syndrome of menopause. Systemic absorption from low-dose preparations is minimal in published pharmacokinetic studies. [77]

TISSUE-SELECTIVE ESTROGEN COMPLEX

Conjugated estrogens combined with bazedoxifene (a SERM). Approved for vasomotor symptoms and prevention of osteoporosis in women with a uterus; the SERM provides endometrial protection in lieu of a progestogen. [144]

ESTROGEN-CONTAINING CONTRACEPTIVE PRODUCTS

Combined oral contraceptives (typically ethinyl estradiol with a progestin). Higher hormone doses than menopausal hormone therapy; used in peri-menopause for contraception and cycle control in appropriate candidates. [125]

COMPOUNDED "BIOIDENTICAL" PREPARATIONS

Pharmacy-compounded estrogen products. The term "bioidentical" denotes molecules identical to endogenous human hormones (estradiol, progesterone). Multiple FDA-approved bioidentical products exist; compounded preparations differ in that they are not subject to standardized FDA approval testing. [145]

Terminology note. "Bioidentical" and "compounded" are not synonymous. FDA-approved transdermal estradiol patches, oral estradiol tablets, and micronized progesterone capsules are all bioidentical preparations. Compounded preparations may use bioidentical molecules but are produced by individual pharmacies rather than by manufacturers subject to standardized FDA review. [145]

Why route matters: *the first-pass effect.*

Oral and transdermal estrogen produce similar therapeutic effects on vasomotor symptoms and on bone density in head-to-head studies, but they differ pharmacologically in ways that influence several reported safety signals. [142] The principal pharmacological difference is hepatic first-pass exposure.

What the first-pass effect means biochemically.

Oral estrogen passes through the portal circulation and is delivered to the liver at high concentration before reaching the systemic circulation. This hepatic exposure increases the synthesis of several proteins — including: [109] [142]

- Sex hormone-binding globulin (SHBG), which binds circulating sex steroids;
- Several coagulation factors (factor VII, factor X, prothrombin) and reduced antithrombin activity, shifting the hemostatic balance modestly toward thrombosis;
- Angiotensinogen and triglyceride-rich lipoproteins;
- C-reactive protein (a marker of inflammation often used in cardiovascular risk estimation).

Transdermal estradiol bypasses portal delivery and produces a much smaller effect on these hepatic protein measurements at therapeutically equivalent doses. [142]

The principal reported safety difference: venous thromboembolism.

Multiple large observational studies — including the French E3N cohort, the U.K. CPRD analyses, and meta-analyses across cohort studies — have reported a higher venous thromboembolism (VTE) risk with oral estrogen than with transdermal estradiol. [143] [146] The reported VTE relative risk with oral estrogen vs. placebo in WHI was approximately 2-fold; observational analyses of transdermal preparations have reported risk estimates closer to that of non-users in some — though not all — studies. [146] No large randomized trial has directly compared VTE outcomes between oral and transdermal estrogen. [142]

Stroke and gallbladder disease.

Stroke risk has been reported to be lower with transdermal preparations at standard doses compared with oral estrogen in some observational studies, though this finding has not been confirmed in a randomized trial designed to compare the two routes. [147] Cholestatic effects of oral estrogen on bile composition are associated with modestly increased gallbladder disease risk; transdermal preparations have not been associated with the same effect. [148]

> **How this is integrated into guidelines.** Major society guidelines describe transdermal estradiol as a preferred initial route in women with elevated baseline VTE risk, with hepatic considerations, or with hypertriglyceridemia. [22] The clinical decision integrates these factors with patient preference, cost, and other considerations.

Low-dose vaginal estrogen for GSM: *a distinct safety profile.*

Low-dose vaginal estrogen preparations — administered as cream, intravaginal tablet, low-dose ring, or insert — are the most-studied therapy for the genitourinary syndrome of menopause (GSM). Their pharmacokinetic and safety profiles in the published literature differ substantially from those of systemic hormone therapy. [77]

Reported effects on GSM endpoints.

Randomized trials of low-dose vaginal estrogen have consistently reported: [77] [149]

- Reduction in symptoms of vaginal dryness, burning, and dyspareunia;
- Restoration of vaginal epithelial maturation index toward pre-menopausal patterns;
- Reduction in vaginal pH toward the lower (pre-menopausal) range;
- Reduction in recurrent urinary tract infection frequency in studied populations;
- Improvements in measures of sexual function where impaired arousal/lubrication or dyspareunia is the predominant contributor.

Pharmacokinetics and systemic absorption.

Pharmacokinetic studies of low-dose preparations have generally reported minimal systemic estradiol absorption, with circulating concentrations remaining within the post-menopausal range during steady-state use. [77] The very-low-dose insert and the low-dose intravaginal tablet have been particularly characterized in this regard. [149] Higher-dose vaginal preparations — including conventional creams used at higher cumulative doses — can produce measurable systemic absorption. [77]

Endometrial safety in women with a uterus.

Because systemic absorption from low-dose vaginal preparations is minimal, major society guidelines describe routine progestogen addition as unnecessary when low-dose vaginal estrogen is used at recommended doses for GSM in women with a uterus. [22] Endometrial surveillance is generally not recommended in this population in current guidance, though clinical assessment of any vaginal bleeding is standard. [22]

Use in women with breast cancer history — the labeling question.

Current U.S. labeling of estrogen-containing products lists breast cancer as a contraindication. The application of this labeling to low-dose vaginal preparations in women with breast cancer history has been the subject of substantial discussion in the gynecologic and oncologic literature, given the minimal systemic absorption characterized in pharmacokinetic studies. [150] Some specialty society statements describe low-dose vaginal estrogen as an option to consider — after discussion with the patient's oncologist — for severe symptomatic GSM in this population. [150]

The aromatase-inhibitor caveat. Women on aromatase inhibitors (e.g., letrozole, anastrozole) for breast cancer are treated as a separate population in the literature, given the mechanism of those medications. The decision around vaginal estrogen in that specific context is described in the literature as requiring multidisciplinary discussion. [150]

Doses studied in the published trials.

This page presents the doses of various estrogen preparations as studied in the clinical trial literature and as listed in current product information. These figures are descriptive of published research and not recommendations for any individual reader. [22]

Systemic preparations in major studies.

PREPARATION	DOSE AS STUDIED	SOURCE / CONTEXT
Conjugated equine estrogens (CEE), oral	0.625 mg/day	Standard dose in WHI E+P and E-alone trials. [7] [135]
CEE, oral	0.45 mg/day	Lower-dose arm in KEEPS. [5]
17β-estradiol, oral	1 mg/day	Dose used in ELITE. [6]
17β-estradiol, transdermal patch	50 µg/day	Standard-dose patch arm in KEEPS. [5] Other patch strengths range from 25 to 100 µg/day in various studies. [142]
17β-estradiol, transdermal gel/spray	Variable	Gel and spray formulations dose by metered applications; product-specific. [142]
Conjugated estrogens + bazedoxifene	CEE 0.45 mg + bazedoxifene 20 mg/day	Approved tissue-selective estrogen complex. [144]

Low-dose vaginal preparations as studied.

PREPARATION	DOSE AS STUDIED	SOURCE / CONTEXT
Conjugated estrogens vaginal cream	0.5 g cream 1–3×/wk	Standard low-dose regimen in trials. [77]
17β-estradiol vaginal tablet	10 µg tablet 2×/wk after loading	Pharmacokinetic studies report minimal systemic absorption at this dose. [149]
17β-estradiol low-dose vaginal ring	7.5 µg/day, replaced q90 days	Continuous low-dose delivery; specific to the lower-dose ring product. [77]
Estradiol vaginal insert	4 µg or 10 µg softgel, daily then 2×/wk	Very-low-dose insert. [149]

Doses for women with surgical or premature menopause.

Women with surgical menopause at a young age or premature ovarian insufficiency are noted in major society guidelines as a population in whom higher estrogen doses than those listed above are sometimes studied or used — targeting approximate physiologic reproductive-age estradiol concentrations. [42] Specific dose ranges and durations are described in ESHRE and Endocrine Society POI guidelines. [42]

Reading note. All dose values above describe regimens studied in published research. Dose decisions in clinical care are based on individual medical history, symptom severity, response over time, and clinical judgment — not on tables in educational guides.

Progesterone and progestins: *what the comparative literature reports.*

Progestogens — comprising natural progesterone (administered as oral micronized progesterone) and the broader class of synthetic progestins — are used alongside estrogen in women with a uterus to protect against estrogen-induced endometrial hyperplasia and endometrial cancer. [21] [22] Different progestogens have different reported clinical profiles outside of their endometrial-protective role.

The principal categories used in menopausal hormone therapy.

PROGESTOGEN	COMMON DOSE STUDIED	NOTABLE FEATURES IN THE LITERATURE
Micronized progesterone (oral)	100 mg/day continuous; 200 mg/day cyclic	Bioidentical. Studied in PEPI [133] and E3N. [146] Sleep effects via allopregnanolone metabolite. [23]
Medroxyprogesterone acetate (oral)	2.5 mg/day continuous; 5–10 mg cyclic	Synthetic progestin used in WHI E+P. [7] The increased breast cancer signal in WHI was specific to this regimen. [7]
Norethindrone acetate	0.1–0.5 mg/day	Synthetic progestin available in combined oral and transdermal preparations. [22]
Levonorgestrel-releasing IUD	52 mg device (5–7 yr duration)	Local intrauterine progestin delivery. Used off-label in some countries for endometrial protection during estrogen therapy. [151]
Vaginal progesterone (cyclic)	45 mg gel × 10 days/month	Regimen used in ELITE. [6] Alternative route avoiding oral progesterone side effects.

Comparative outcomes — what's reported and what isn't.

The most-cited comparative observational data come from the French E3N cohort, which reported lower breast cancer risk associations with combinations of estradiol plus micronized progesterone compared with combinations of estradiol plus synthetic progestins. [146] Several smaller observational and randomized studies have reported metabolic and breast tissue differences between micronized progesterone and synthetic progestins. [24]

The principal limitation of this evidence base is the absence of large, long-term randomized trials directly comparing different progestogens with hard clinical endpoints. The micronized-progesterone arm in the major prospective trials (PEPI, ELITE) was studied for surrogate endpoints rather than for long-term breast cancer or cardiovascular events. [133] [6]

> **How this gets summarized in clinical guidance.** Some major society statements describe micronized progesterone as the preferred progestogen when the choice is otherwise neutral, acknowledging the suggestive but not definitive comparative evidence. [141] Other guidance emphasizes individualization given the limitations of the evidence base. [22]

Testosterone therapy in women: *the evidence as it stands.*

As described in Chapter 2, testosterone declines gradually in women from approximately the mid-twenties and continues to decline through and after menopause. Whether testosterone therapy is appropriate for any clinical indication in women — and at what dose — has been the subject of multiple randomized trials, meta-analyses, and a 2019 Global Consensus Position Statement. [31]

The 2019 Global Consensus Position Statement.

Endorsed by The Menopause Society, the International Menopause Society, the Endocrine Society, the European Menopause and Andropause Society, the International Society for the Study of Women's Sexual Health, the Royal College of Obstetricians and Gynaecologists, and others, the 2019 statement reached the following conclusions: [31]

- **Hypoactive sexual desire disorder (HSDD)** is the only evidence-based indication for which testosterone therapy could be considered in post-menopausal women, with pooled trial data showing modest improvements in measures of sexual desire, arousal, orgasm, pleasure, and sexual responsiveness compared with placebo. [31]
- Doses should approximate physiologic premenopausal testosterone concentrations; supraphysiologic dosing was not supported by the evidence reviewed. [31]
- Evidence was judged **insufficient** to recommend testosterone therapy for cognitive performance, mood, body composition, musculoskeletal symptoms, cardiovascular health, or other potential indications. [31]
- Use in premenopausal women was not supported in the evidence base reviewed. [31]
- No clearly defined "deficiency" syndrome was found; testosterone measurement was not recommended for screening or diagnosis of an indication for therapy, but rather to exclude pre-existing supraphysiologic concentrations before starting therapy. [31]

Practical issues described in the literature.

No testosterone preparation is currently FDA-approved for use in women in the United States. Prescribing in U.S. practice occurs off-label, typically using compounded preparations or fractionated doses of male-approved transdermal testosterone products. [31] One transdermal testosterone product for women is approved in Australia. [31] The literature on long-term safety in women is limited; the trials underlying the consensus statement were typically 6–12 months in duration. [31]

Reported adverse effects with physiologic-dose testosterone in trials have generally been mild — acne and increased facial/body hair are the most commonly reported. [31] Supraphysiologic concentrations — sometimes encountered with male-product dosing translated to female use — have been associated with more clinically significant androgenic effects and are described in the literature as inappropriate for women. [31]

Where the evidence gaps are. The position statement explicitly identified large evidence gaps: no long-term safety data, no consistent dose-response data for non-sexual outcomes, and limited data in premenopausal women. Active research is ongoing in several of these areas. [31]

DHEA: *much marketing, narrow evidence base.*

Dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S) decline progressively with age in both sexes — a pattern sometimes termed "adrenopause." [33] Whether oral DHEA supplementation produces clinically meaningful benefit in post-menopausal women has been studied in multiple trials. Vaginal DHEA (prasterone) is approved for a specific indication and is supported by different evidence than oral DHEA. [152]

Oral DHEA supplementation.

The DHEAge study (Baulieu et al., 2000), the multicenter DHEA and Well-being trial, and several other randomized studies of oral DHEA in older adults reported small or null effects on most measured outcomes — including bone density, body composition, cognition, mood, and quality of life — at the doses studied. [153] A 2014 Endocrine Society Clinical Practice Guideline concluded that the available evidence did not support routine DHEA supplementation outside of specific conditions (e.g., adrenal insufficiency). [154]

Vaginal DHEA (prasterone) for GSM.

In contrast to oral DHEA, intravaginal prasterone (a 6.5 mg DHEA insert) was studied in randomized trials for moderate-to-severe dyspareunia due to GSM and reported improvements in dyspareunia, vaginal cell maturation, and pH compared with placebo. [152] The product is FDA-approved for this specific indication. The mechanism is believed to involve local conversion of DHEA to estrogens and androgens within the vaginal tissue (intracrinology), with minimal systemic absorption of the precursor. [152]

DHEA-S as a laboratory marker.

DHEA-S is sometimes measured in clinical contexts including evaluation of adrenal disorders, polycystic ovary syndrome, and certain androgen-related symptoms. Its routine measurement in the context of the menopausal transition is not part of standard society guidance, although it appears on some specialty hormone panels. [33]

> **The summary picture.** Oral DHEA is marketed widely and supported by relatively narrow randomized evidence for clinically meaningful effects outside of specific clinical conditions. Vaginal DHEA (prasterone) is supported by a distinct, indication-specific evidence base for moderate-to-severe dyspareunia due to GSM. These are not interchangeable considerations. [152] [154]

The published benefit-risk framework: *three categories of evidence.*

Major society guidelines characterize the benefit-risk profile of menopausal hormone therapy as varying along three principal axes: the woman's age and proximity to menopause at initiation, the specific regimen used, and the indication for which therapy is considered. [22] [117]

Benefits well-documented in randomized trials.

- **Reduction in vasomotor symptoms.** The most consistently demonstrated effect across randomized trials, with effect sizes substantially larger than non-hormonal pharmacologic alternatives. [22]
- **Prevention of bone loss and fracture.** The WHI demonstrated a reduction in hip and clinical fracture risk in both the E+P and E-alone arms. [7] [135]
- **Improvement in GSM.** Local vaginal estrogen specifically; systemic estrogen also reduces GSM but with the systemic considerations. [77]
- **Mood improvement in peri-menopausal new-onset depression.** Reported for transdermal estradiol specifically. [72]
- **Improvements in some quality-of-life measures.** Reported across multiple trials. [22]

Risks documented in randomized trials.

- **Venous thromboembolism.** Higher with oral than transdermal preparations. [142]
- **Stroke.** Elevated risk reported in WHI; observational data suggests lower stroke risk with low-dose transdermal preparations. [147]
- **Breast cancer (combined E+P regimens).** Modest absolute increase reported in WHI E+P arm using conjugated equine estrogens and medroxyprogesterone; the absolute increase was approximately 8 additional cases per 10,000 women-years. [7] The signal differs by progestogen choice. [146]
- **Endometrial hyperplasia/cancer.** Risk arises with unopposed systemic estrogen in women with a uterus; mitigated by appropriate progestogen co-administration. [21]
- **Gallbladder disease.** Modest excess with oral preparations. [148]

Outcomes where age at initiation appears to matter.

As described in Chapter 9, the age-stratified WHI re-analyses and the KEEPS/ELITE trials together suggest that cardiovascular outcomes, all-cause mortality, and possibly cognitive outcomes differ by age at hormone therapy initiation and by time since FMP — with neutral-to-favorable profiles reported in women initiating within the first decade after menopause and less favorable profiles in women initiating later. [112] [137]

How to read absolute vs. relative numbers. Reported risk increases in the literature are often expressed as relative risks or hazard ratios. The absolute change in event rate per 10,000 women-years — given typical baseline event rates — is generally more interpretable for an individual reader. Major society guidelines and the WHI publications provide both formats. [22]

Contraindications as listed in *major society guidelines.*

Major society guidelines list a relatively concise set of conditions that contraindicate or strongly caution against systemic menopausal hormone therapy. The list below reflects the convergent guidance from The Menopause Society, the Endocrine Society, and the International Menopause Society as of recent updates. [22] [117] [140]

Listed contraindications.

- **Known, suspected, or history of breast cancer.** (See discussion of low-dose vaginal estrogen in Chapter 10 for the GSM-specific context.) [22]
- **Known or suspected estrogen-dependent malignancy.**
- **Undiagnosed vaginal bleeding.**
- **Active or recent venous thromboembolism (deep vein thrombosis or pulmonary embolism).**
- **Active or recent arterial thromboembolic disease (e.g., stroke, myocardial infarction).**
- **Untreated hypertension that is severely uncontrolled.**
- **Active liver disease with abnormal hepatic function.**
- **Known hypersensitivity to the specific preparation.**
- **Pregnancy.**

Conditions requiring individualized assessment.

Several conditions are not listed as absolute contraindications but are described in major guidelines as requiring particular individualized consideration: [22]

- Migraine with aura;
- Active gallbladder disease;
- Hypertriglyceridemia (with potential preference for transdermal preparations);
- Strong family history of estrogen-dependent malignancy;
- Established cardiovascular disease;
- Diabetes mellitus with vascular complications;
- Multiple cardiovascular risk factors that have not been addressed;
- Endometriosis (particularly with respect to progestogen choice);
- Smoking, particularly in women aged over 35 considering oral preparations.

Duration considerations.

Earlier guidance recommended hormone therapy use for the "shortest duration consistent with goals." More recent major society statements have moved toward duration individualization rather than a categorical time limit, emphasizing periodic reassessment of indication, benefit, and risk over time. [22] The 2022 NAMS Hormone Therapy Position Statement explicitly addressed the case of women aged 65 and older — noting that continuation of hormone therapy in this group, while requiring particular attention to risk-benefit, was not categorically inappropriate when justified by ongoing indication. [22]

> **The principal reading frame.** Contraindication lists and individualized-assessment conditions in clinical guidelines are tools for clinical decisions. They describe categories that warrant attention; they do not determine the outcome of any individual decision. Decisions are made in clinical encounters with full medical history available. [22]

Non-hormonal interventions *that have been studied* in randomized trials.

Multiple non-hormonal interventions have been evaluated in randomized trials for menopausal symptoms — particularly vasomotor symptoms. The literature includes pharmacologic and non-pharmacologic categories. This chapter summarizes what has been studied, in whom, and what was reported. [155]

Pharmacologic options with FDA approval for VMS.

AGENT	CLASS	REPORTED EFFECT ON VMS AND KEY FINDINGS
Paroxetine 7.5 mg	**SSRI (low dose)**	FDA-approved non-hormonal therapy for moderate-to-severe VMS. Reduced hot flash frequency by ~33–65% in pivotal trials. [156]
Fezolinetant	**NK3R antagonist**	FDA-approved 2023 for moderate-to-severe VMS. Targets the KNDy/NK3R pathway. SKYLIGHT trials reported ~45–55% reduction in hot flash frequency. [157]

Pharmacologic options studied off-label for VMS.

AGENT	CLASS	REPORTED EFFECT
Venlafaxine	**SNRI**	Reduced VMS frequency and severity in multiple randomized trials. [158]
Escitalopram	**SSRI**	Reduced VMS frequency and severity in the MsFLASH trial. [159]
Desvenlafaxine	**SNRI**	Reduced VMS in randomized trials; pharmacokinetics may differ from venlafaxine. [158]
Gabapentin	**Anticonvulsant**	Modest reduction in VMS in randomized trials; some sedation utility for night-sweat-related sleep disturbance. [160]
Oxybutynin	**Anticholinergic**	Reduced VMS in randomized trials; anticholinergic side effects limit some use. [161]
Clonidine	**Centrally acting α2-agonist**	Reduced VMS modestly; older literature; less commonly used than newer options. [162]

Effect-size context. Across the non-hormonal pharmacologic options, reported effect sizes on VMS are generally smaller than those reported for systemic estrogen — but the absolute reductions in hot flash frequency can still be clinically meaningful for individual women who cannot or choose not to use hormone therapy. [155]

Fezolinetant and the *NK3R antagonist class.*

Neurokinin 3 receptor (NK3R) antagonists represent the first mechanism-based non-hormonal class developed specifically for vasomotor symptoms. The class targets the KNDy/NK3R signaling described in Chapter 5.2. [60] Fezolinetant became the first FDA-approved member of the class in 2023. [157]

The SKYLIGHT program.

Fezolinetant's pivotal evidence comes from the SKYLIGHT 1 and SKYLIGHT 2 randomized, double-blind, placebo-controlled trials, with a 52-week safety extension (SKYLIGHT 4). [157] Reported findings included:

- Reduction in moderate-to-severe vasomotor symptom frequency at 4 weeks (~50% reduction vs. placebo) maintained through 12 weeks; [157]
- Reduction in VMS severity scores at 12 weeks; [157]
- Improvements in sleep measures, consistent with the role of night sweats in sleep disruption; [157]
- Hepatic transaminase elevations in a subset of participants — leading to recommendations for baseline and periodic liver function monitoring in product labeling. [157]

Mechanism and class implications.

Fezolinetant blocks NK3R signaling on the KNDy neurons that drive thermoregulatory dysfunction during the menopausal transition. [60] Because this mechanism is non-hormonal, it provides an option for women with contraindications to or preferences against estrogen-based therapy. Additional NK3R antagonist molecules are in clinical development, and a dual NK1R/NK3R antagonist (elinzanetant) has been studied in phase 3 trials. [163]

Non-pharmacologic options with randomized evidence.

Several non-pharmacologic interventions have been studied in randomized trials for VMS and related menopausal symptoms: [155]

- **Cognitive behavioral therapy (CBT) for menopausal symptoms.** Reduced reported symptom interference and improved related outcomes in randomized trials. [164]
- **Clinical hypnosis.** Reduced VMS frequency and bother in randomized trials. [165]
- **Mindfulness-based stress reduction.** Modest effects on symptom bother in randomized trials. [166]
- **Aerobic exercise.** Mixed evidence on direct VMS effects; established benefits on related cardiovascular, mood, and sleep outcomes. [167]
- **Acupuncture.** Reduced VMS in some trials; meta-analyses report heterogeneous findings with placebo-controlled comparisons. [168]

> **Reading note.** The non-pharmacologic literature is heterogeneous in design, quality, and reported effect size. Major society statements describe CBT and clinical hypnosis as having the most consistent supporting evidence among non-pharmacologic options. [22]

Resistance training: the *largest-effect non-pharmacologic lever* for sarcopenia and BMD.

Among non-pharmacologic interventions studied for post-menopausal body composition, bone density, and physical function outcomes, resistance training has the largest reported effect sizes and the most consistent evidence base. [87] [169]

Effects on lean mass and strength.

Meta-analyses of randomized trials in post-menopausal women have reported that supervised resistance training programs produce measurable increases in lean body mass (typically ~1–2 kg over 3–12 month interventions) and substantial increases in measured strength (often 20–100% in the trained movements) compared with non-training controls. [169] Effect sizes scale with training intensity, frequency, and duration; programs incorporating progressive overload of major compound movements have generally reported larger effects than low-intensity or single-movement programs. [170]

Effects on bone mineral density.

The effect of resistance training on BMD in post-menopausal women has been studied in numerous randomized trials and meta-analyses. Principal findings include: [171]

- Resistance training is associated with attenuation of post-menopausal BMD loss at the lumbar spine and femoral neck in pooled analyses; [171]
- Higher-intensity protocols — including the LIFTMOR trial of high-intensity resistance and impact training — reported modest increases in lumbar spine BMD over 8 months in osteopenic and osteoporotic post-menopausal women; [172]
- Combined resistance plus impact (weight-bearing) training has reported larger effects than resistance alone in some trials; [173]
- BMD effects are smaller in magnitude than those reported with pharmacologic anti-resorptive therapies — but with different risk profiles and additional benefits on strength, balance, and quality of life. [87]

Effects on fall risk and fracture-related outcomes.

Resistance training in combination with balance training has been studied in multiple randomized trials for fall prevention in older adults, including post-menopausal women. Pooled analyses report reductions in fall rates and in the proportion of participants experiencing a fall. [174] Direct fracture endpoint evidence from exercise-based interventions is more limited (because of sample size requirements), but reductions in falls and improvements in fall-related risk factors provide an indirect pathway by which exercise interventions may reduce fractures. [95]

Effects on cardiometabolic markers.

Resistance training has been associated with improvements in measures of insulin sensitivity, blood pressure, lipid profile, and waist circumference in randomized trials in post-menopausal women. [175] Effect sizes are typically smaller than those reported for substantially higher doses of aerobic training but are complementary; combined aerobic-plus-resistance protocols have reported additive benefits in several outcomes. [175]

Practical protocols studied. Programs producing the effects above generally comprised 2–3 supervised sessions per week, with progressive overload across multi-joint compound movements (squat, hinge, push, pull patterns). Specific program parameters — sets, reps, intensities — are detailed in primary trial reports and in evidence syntheses. [87]

Aerobic exercise and combined modalities.

Aerobic exercise — including walking, jogging, cycling, swimming, and structured cardiovascular training — has been studied extensively in post-menopausal women for cardiovascular, metabolic, mood, and bone outcomes. Combined aerobic-plus-resistance programs are commonly recommended in current guidelines. [175] [176]

Cardiovascular and metabolic effects.

Higher doses of aerobic exercise are associated with reduced cardiovascular event risk in observational cohort data and with favorable changes in cardiovascular risk markers in randomized trials. [176] Reported effects in post-menopausal populations include: reductions in blood pressure, improvements in lipid profile, increased VO_2 max, improvements in fasting glucose and insulin sensitivity, and reductions in visceral adiposity. [177]

Effects on vasomotor symptoms — what trials report.

Randomized trials of aerobic exercise interventions on VMS have produced mixed results. [167] A 2014 Cochrane review concluded that the evidence was insufficient to support exercise as effective for hot flashes specifically. [167] The downstream benefits of regular aerobic exercise on sleep, mood, and related quality-of-life outcomes — even when direct VMS effects are equivocal — are well-documented. [177]

Effects on bone density.

Weight-bearing aerobic exercise — walking, running, dance, jumping — has been studied for BMD outcomes. Effect sizes are generally smaller than those of resistance training; the largest effects appear with high-impact or high-velocity loading, with the caveat that such loading may not be appropriate for women with established osteoporosis without medical guidance. [171] Combined high-impact + resistance protocols (e.g., LIFTMOR) reported larger BMD effects than aerobic-only training. [172]

Effects on mood and cognitive symptoms.

Regular aerobic exercise is associated with improvements in depressive symptoms in randomized trials across age groups, including in post-menopausal women. [178] Effect sizes for moderate-intensity aerobic exercise on depressive symptoms in some trials approach those reported for first-line pharmacotherapies. [178] Effects on cognitive function are more variable; long-term cohort and trial evidence support broad cardiometabolic risk reduction as a likely mediator of any cognitive benefit. [179]

Current public health guidance. The 2018 Physical Activity Guidelines for Americans recommend at least 150–300 minutes per week of moderate-intensity aerobic activity (or 75–150 minutes of vigorous), plus muscle-strengthening activities on 2 or more days per week, for adults of all ages. [180] Similar guidance appears in WHO and several other national bodies. [181]

Protein intake: *the most-studied dietary lever* for sarcopenia.

Among modifiable dietary factors with implications for post-menopausal body composition, protein intake has the most consistent supporting evidence — particularly when combined with resistance training. Current intake recommendations from clinical and research bodies have evolved upward from the RDA-era 0.8 g/kg/day in light of accumulating evidence. [182]

Recommendations from research bodies.

The U.S. RDA for protein (0.8 g/kg/day) was established to prevent deficiency, not to optimize body composition or healthy aging outcomes. Multiple research consensus statements have recommended higher intakes for older adults and for adults engaged in resistance training: [182]

- The PROT-AGE Study Group and ESPEN consensus papers recommended **1.0–1.2 g/kg/day for healthy older adults** and 1.2–1.5 g/kg/day for older adults with acute or chronic disease. [183]
- Multiple resistance-training studies have used protein intakes in the range of **1.6–2.0 g/kg/day** in conjunction with progressive resistance training to support hypertrophy in older adults. [184]
- The recommendation is generally framed as **per-meal** distribution — approximately 25–40 g of high-quality protein per meal — based on muscle protein synthesis kinetics in mechanistic studies. [185]

Protein quality considerations.

"High-quality" protein in this context refers to protein with a complete profile of essential amino acids — particularly leucine, which has been characterized as a primary trigger of muscle protein synthesis in mechanistic studies. [186] Animal-source proteins (whey, dairy, eggs, meat, fish) and several plant-source proteins (soy, pea protein isolate) provide high-quality protein. Mixed plant-protein patterns can also meet requirements with appropriate combination across meals. [186]

The interaction with resistance training.

Protein intake and resistance training are studied in the literature as complementary inputs: resistance training provides the stimulus for muscle protein synthesis, and protein intake provides the substrate. Trials examining protein supplementation in older adults without a concurrent resistance training stimulus have generally reported smaller effects than trials combining the two. [184]

> **Population-level intake patterns.** Survey data suggest that a substantial fraction of older U.S. women consume below 1.0 g/kg/day of protein. [187] The literature on whether moving from typical intake toward the higher recommended ranges produces meaningful clinical outcomes — independent of training — remains active. [183]

Calcium and vitamin D: *foundational, often misunderstood.*

Adequate calcium and vitamin D intake form the foundation upon which most bone health interventions — pharmacologic and non-pharmacologic alike — are layered in clinical guidelines. [188] The literature on whether supplementation beyond dietary adequacy reduces fracture risk in the general population is more nuanced than commonly portrayed.

Calcium — intake recommendations and source.

The Institute of Medicine RDA for calcium in women aged 51+ is 1200 mg/day from all sources combined. [188] Most major society guidance — including from the National Osteoporosis Foundation and the Endocrine Society — favors achieving this intake through dietary sources first, with supplementation reserved for shortfall. [188]

The WHI Calcium and Vitamin D supplementation arm tested 1000 mg calcium plus 400 IU vitamin D_3 daily versus placebo in 36,282 post-menopausal women. [189] Principal findings included a modest reduction in hip BMD loss but a non-significant reduction in hip fracture in the intention-to-treat analysis; a per-protocol analysis (women with high adherence) reported a larger reduction. [189] Concern was raised in subsequent observational analyses regarding cardiovascular risk associations with high-dose calcium supplementation; the relationship remains debated. [190]

Vitamin D — adequacy thresholds and supplementation.

Optimal serum 25-hydroxyvitamin D thresholds are debated between Institute of Medicine and Endocrine Society guidance, with the Endocrine Society favoring 30 ng/mL minimum and the IoM defining adequacy at 20 ng/mL. [121] [191] A 2010 IOM report concluded that vitamin D deficiency was over-diagnosed and that supplementation above adequacy thresholds had not been shown to reduce non-skeletal outcomes; subsequent guidance has refined but generally not overturned this position. [191]

Recent large randomized trials of vitamin D supplementation in vitamin-D-replete populations — including the VITAL trial — have reported neutral findings on cancer, cardiovascular events, and fracture outcomes in the primary analyses. [192] Pre-specified subgroup analyses suggested possible benefits in subgroups with lower baseline 25-OH-D, but these are hypothesis-generating rather than definitive. [192]

How current guidance integrates this.

Major society guidance generally recommends targeting adequacy through dietary sources where possible, identifying deficiency through 25-OH-D measurement in selected populations, and supplementing to correct deficiency — but does not generally support routine high-dose supplementation in vitamin-D-replete populations. [188] Supplementation forms the backdrop on which fracture-prevention interventions (pharmacologic and non-pharmacologic) are typically tested in trials. [90]

A clarification. Calcium and vitamin D adequacy do not, in randomized trials of generally-replete populations, substitute for fracture-prevention medications in women at established high fracture risk. They are foundational to the broader bone-health framework, not stand-alone fracture-prevention interventions in higher-risk populations. [188]

Creatine, omega-3, magnesium, and the rest of the supplement landscape.

Several additional supplements have an established literature in post-menopausal women — some with substantial randomized evidence for specific outcomes, others marketed widely with limited supporting evidence. [193]

Creatine monohydrate.

Creatine monohydrate is among the most-studied performance and body-composition supplements. Meta-analyses of randomized trials in older adults — including post-menopausal women — have reported small but consistent benefits when combined with resistance training: increased lean mass, increased measured strength, and improved performance on functional tasks. [194] Without a resistance training stimulus, effects on body composition are smaller. [194] Doses studied are typically 3–5 g/day. The safety profile in healthy adults at standard doses has been characterized as favorable in long-term studies. [195]

Omega-3 fatty acids (EPA + DHA).

Omega-3 supplementation has been studied for cardiovascular, mood, and inflammatory outcomes in multiple populations. The 2018 VITAL omega-3 arm and the 2018 ASCEND trial reported neutral findings for major cardiovascular events in primary prevention populations at modest doses (~1 g/day). [196] Higher-dose icosapent ethyl in the REDUCE-IT trial reported cardiovascular event reduction in a hypertriglyceridemic population on statin therapy — a different clinical scenario. [197] Evidence for omega-3 supplementation on VMS, joint pain, and mood symptoms is mixed and generally underpowered. [193]

Magnesium.

Magnesium adequacy is associated in observational studies with multiple outcomes including BMD, cardiovascular markers, sleep quality, and insulin sensitivity. [198] Randomized trial evidence for magnesium supplementation in post-menopausal women is more limited. Magnesium glycinate, citrate, and other organic forms are commonly used; magnesium oxide has lower bioavailability. [198] Population intake data suggest a meaningful fraction of U.S. adults consume below the RDA. [198]

Soy isoflavones / phytoestrogens.

Soy isoflavones — particularly genistein and daidzein and the daidzein metabolite equol — have been extensively studied for VMS and bone outcomes. Pooled randomized trial evidence reports a modest reduction in hot flash frequency with isoflavone preparations versus placebo; effect sizes are smaller than those of estrogen-based therapy. [199] The S-equol-producing subset of women has been reported to derive larger benefits in some — though not all — analyses. [200] Bone density effects in randomized trials have been modest and inconsistent. [199]

Black cohosh and other botanicals.

Black cohosh has been studied for VMS with heterogeneous trial results. Cochrane analyses have generally not supported a clear benefit beyond placebo at standardized doses. [201] Several other botanicals (red clover, evening primrose, dong quai) have insufficient randomized evidence to support clinical recommendations as of current major society guidance. [22]

Reading note for this chapter. Supplement supply is largely unregulated for therapeutic claims. Specific brands, doses, and product characteristics affect both efficacy and safety. The literature summary above describes what's been measured in research; it is not product recommendation guidance. [193]

Sleep interventions: *CBT-I leads the evidence base.*

As described in Chapter 5.5, sleep disturbance during the menopausal transition is multifactorial. Among studied interventions, cognitive behavioral therapy for insomnia (CBT-I) has the strongest evidence base for chronic insomnia symptoms — including in midlife women. [202]

CBT-I — what it is and what trials report.

CBT-I is a structured short-term psychological intervention combining sleep restriction, stimulus control, cognitive restructuring, sleep hygiene, and relaxation techniques. [202] Randomized trials in midlife and post-menopausal women have reported reductions in insomnia severity, improvements in sleep efficiency, and improvements in related quality-of-life outcomes — with effects generally maintained at long-term follow-up. [203] Multiple specialty societies — including the American Academy of Sleep Medicine and the American College of Physicians — recommend CBT-I as first-line treatment for chronic insomnia in adults. [202]

Pharmacologic sleep aids.

Pharmacologic agents studied for sleep in post-menopausal women include benzodiazepines, non-benzodiazepine sedative-hypnotics ("Z-drugs"), orexin receptor antagonists, low-dose doxepin, and others. Major society guidance generally describes these as second-line to CBT-I, with attention to dependence, fall risk, and cognitive considerations in older adults. [202] Hormone therapy improves sleep measures in trials, particularly in women whose sleep disturbance is mediated substantially by night sweats. [204]

Sleep apnea — under-recognized in women.

As noted in Chapter 5.5, obstructive sleep apnea prevalence rises substantially in post-menopausal women. Sleep apnea presents differently in women than in men in some cohort data, and may be under-diagnosed. [75] Where OSA is present, established disorder-specific therapies (positive airway pressure devices, oral appliances, behavioral and weight measures) are addressed independently of menopausal status. [75]

Sleep hygiene and lifestyle factors.

Standard sleep hygiene recommendations — consistent sleep timing, dark and cool sleep environment, limited evening caffeine and alcohol, reduced screen exposure before bed, regular exercise outside the immediate pre-sleep window — have varied evidence in formal trials but are widely incorporated into clinical sleep guidance as a foundation. [205] Bedroom temperature in particular has been studied in the context of night sweats; cooler bedroom environments have been reported to reduce night sweat frequency and severity in some experimental studies. [206]

Stress as a sleep input. Cortisol patterns, perceived stress, and sleep are linked bidirectionally. Mind-body interventions including mindfulness-based stress reduction and yoga have been studied for sleep quality with modest reported effects — generally smaller than CBT-I but with potential complementary benefit. [166]

Questions worth bringing into the room.

The information collected across this guide is at most a foundation for an informed conversation with a clinician. The following are categories of question that the published literature suggests are commonly under-asked in routine clinical encounters — included here as a reference, not as a script.

Questions about staging and assessment.

- Where am I in the menopausal transition, based on my menstrual history and any laboratory testing? Do I fit STRAW+10 staging?
- Which of my current symptoms are likely related to the transition, and which warrant separate evaluation?
- What laboratory testing — hormonal and non-hormonal — is appropriate for me at this point? What will the results tell us, and what would change based on the results?
- What is my cardiovascular risk profile, and how does it inform the decisions I'm considering?
- What is my fracture risk profile, and how does it inform the decisions I'm considering?

Questions about hormone therapy, if considered.

- Am I a candidate for hormone therapy given my personal and family medical history? Are there contraindications I should know about?
- If I am a candidate, what regimen (oral vs. transdermal estrogen; type of progestogen; vaginal vs. systemic) would you recommend for me, and why?
- What are the specific reported benefits and risks of that regimen, in absolute terms, given my profile?
- What does ongoing monitoring look like — what tests, what frequency, what indication for stopping or changing the regimen?
- How will we evaluate whether the therapy is working, and on what timeline?
- What is your view on duration of use? When and how would we revisit the decision?

Questions about non-hormonal options.

- What non-hormonal options have you considered for my most bothersome symptoms — pharmacologic and non-pharmacologic?
- What is the evidence for those options in someone like me, in terms of effect size and timeline?
- How would we layer interventions if one alone isn't sufficient?

Questions about the broader picture.

- How do bone health, cardiometabolic health, sleep, and mental health interact with the menopausal-transition decisions we're making?
- What lifestyle interventions — training, nutrition, sleep — should be foundational, regardless of any other decisions?
- What should prompt me to come back sooner than the next scheduled visit?

If a clinician isn't engaging with these questions. The literature on women's health care quality consistently reports that women are not always provided with detailed information about hormone therapy options in routine primary-care encounters. [79] A second opinion from a clinician with menopause-specific training (e.g., a Menopause Society Certified Practitioner) is one path forward when questions remain unanswered. [22]

Every citation, *traced to source.*

The references below correspond to the superscript numbers used throughout the preceding chapters. Where available, PubMed identifiers are included for direct lookup. References to clinical society position statements include the publishing organization and year.

Note to readers and clinicians. This guide was compiled as an educational reference summarizing the published literature on peri- and post-menopause. Citations represent the principal supporting source for each clinical statement at the time of writing. **Readers and clinicians using this material to inform decisions are encouraged to verify each citation against the current PubMed record**, since this literature evolves and updated analyses may revise individual findings. This guide does not substitute for direct review of primary sources by a qualified clinician.

1 **Harlow SD, Gass M, Hall JE, et al.** Executive summary of the Stages of Reproductive Aging Workshop +10: addressing the unfinished agenda of staging reproductive aging. *J Clin Endocrinol Metab.* 2012;97(4):1159–1168. **PubMed 22344196**.

2 **Broer SL, Broekmans FJM, Laven JSE, Fauser BCJM.** Anti-Müllerian hormone: ovarian reserve testing and its potential clinical implications. *Hum Reprod Update.* 2014;20(5):688–701. **PubMed 24821925**.

3 **World Health Organization.** Research on the menopause in the 1990s. *WHO Technical Report Series 866.* Geneva: World Health Organization; 1996.

4 **Gold EB.** The timing of the age at which natural menopause occurs. *Obstet Gynecol Clin North Am.* 2011;38(3):425–440. **PubMed 21961711**.

5 **Harman SM, Black DM, Naftolin F, et al.** Arterial imaging outcomes and cardiovascular risk factors in recently menopausal women: a randomized trial (KEEPS). *Ann Intern Med.* 2014;161(4):249–260. **PubMed 25069991**.

6 **Hodis HN, Mack WJ, Henderson VW, et al.** Vascular effects of early versus late postmenopausal treatment with estradiol (ELITE). *N Engl J Med.* 2016;374(13):1221–1231. **PubMed 27028912**.

7 **Rossouw JE, Anderson GL, Prentice RL, et al.** Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA.* 2002;288(3):321–333. **PubMed 12117397**.

8 **Burger HG, Hale GE, Robertson DM, Dennerstein L.** A review of hormonal changes during the menopausal transition: focus on findings from the Melbourne Women's Midlife Health Project. *Hum Reprod Update.* 2007;13(6):559–565. **PubMed 17630397**.

9 **Randolph JF Jr, Zheng H, Sowers MR, et al.** Change in follicle-stimulating hormone and estradiol across the menopausal transition: effect of age at the final menstrual period (SWAN). *J Clin Endocrinol Metab.* 2011;96(3):746–754. **PubMed 21177999**.

10 **Santoro N, Crawford SL, Allshouse AA, et al.** Reproductive hormones and the menopause transition. *Obstet Gynecol Clin North Am.* 2011;38(3):455–466. **PubMed 21961713**.

11 **Davis SR, Wahlin-Jacobsen S.** Testosterone in women — the clinical significance. *Lancet Diabetes Endocrinol.* 2015;3(12):980–992. **PubMed 26358173**.

12 **Gruber CJ, Tschugguel W, Schneeberger C, Huber JC.** Production and actions of estrogens. *N Engl J Med.* 2002;346(5):340–352. **PubMed 11821512**.

13 **Simpson ER.** Sources of estrogen and their importance. *J Steroid Biochem Mol Biol.* 2003;86(3-5):225–230. **PubMed 14623515**.

14 **Holtorf K.** The bioidentical hormone debate: are bioidentical hormones (estradiol, estriol, and progesterone) safer or more efficacious than commonly used synthetic versions in hormone replacement therapy? *Postgrad Med.* 2009;121(1):73–85. **PubMed 19179815**.

15 **Heldring N, Pike A, Andersson S, et al.** Estrogen receptors: how do they signal and what are their targets. *Physiol Rev.* 2007;87(3):905–931. **PubMed 17615392**.

16 **Paterni I, Granchi C, Katzenellenbogen JA, Minutolo F.** Estrogen receptors alpha (ERα) and beta (ERβ): subtype-selective ligands and clinical potential. *Steroids.* 2014;90:13–29. **PubMed 24971815**.

17 **Prossnitz ER, Barton M.** The G-protein-coupled estrogen receptor GPER in health and disease. *Nat Rev Endocrinol.* 2011;7(12):715–726. **PubMed 21844907**.

18 **Hall JE.** Endocrinology of the menopause. *Endocrinol Metab Clin North Am.* 2015;44(3):485–496. **PubMed 26316238**.

19 **Stanczyk FZ, Hapgood JP, Winer S, Mishell DR Jr.** Progestogens used in postmenopausal hormone therapy: differences in their pharmacological properties, intracellular actions, and clinical effects. *Endocr Rev.* 2013;34(2):171–208. **PubMed 23238854**.

20 **Chlebowski RT, Anderson GL, Aragaki AK, et al.** Association of menopausal hormone therapy with breast cancer incidence and mortality during long-term follow-up of the Women's Health Initiative randomized clinical trials. *JAMA.* 2020;324(4):369–380. **PubMed 32721007**.

21 **Furness S, Roberts H, Marjoribanks J, Lethaby A.** Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. *Cochrane Database Syst Rev.* 2012;(8):CD000402. **PubMed 22895916**.

22 **"The 2022 hormone therapy position statement of The North American Menopause Society" Advisory Panel.** The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause.* 2022;29(7):767–794. **PubMed 35797481**.

23 **Schüssler P, Kluge M, Yassouridis A, et al.** Progesterone reduces wakefulness in sleep EEG and has no effect on cognition in healthy postmenopausal women. *Psychoneuroendocrinology.* 2008;33(8):1124–1131. **PubMed 18676087**.

24 **Fournier A, Berrino F, Clavel-Chapelon F.** Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. *Breast Cancer Res Treat.* 2008;107(1):103–111. **PubMed 17333341**.

25 **Davis SR, Lambrinoudaki I, Lumsden M, et al.** Menopause. *Nat Rev Dis Primers.* 2015;1:15004. **PubMed 27188388**.

26 **Burger HG.** Androgen production in women. *Fertil Steril.* 2002;77 Suppl 4:S3–S5. **PubMed 12007895**.

27 **Laughlin GA, Barrett-Connor E, Kritz-Silverstein D, von Mühlen D.** Hysterectomy, oophorectomy, and endogenous sex hormone levels in older women: the Rancho Bernardo Study. *J Clin Endocrinol Metab.* 2000;85(2):645–651. **PubMed 10690870**.

28 **Rosner W, Auchus RJ, Azziz R, et al.** Position statement: utility, limitations, and pitfalls in measuring testosterone: an Endocrine Society position statement. *J Clin Endocrinol Metab.* 2007;92(2):405–413. **PubMed 17090633**.

29 **Goldman AL, Bhasin S, Wu FCW, et al.** A reappraisal of testosterone's binding in circulation: physiological and clinical implications. *Endocr Rev.* 2017;38(4):302–324. **PubMed 28673039**.

30 **Stanczyk FZ, Cho MM, Endres DB, et al.** Limitations of direct estradiol and testosterone immunoassay kits. *Steroids.* 2003;68(14):1173–1178. **PubMed 14643877**.

31 **Davis SR, Baber R, Panay N, et al.** Global consensus position statement on the use of testosterone therapy for women. *J Clin Endocrinol Metab.* 2019;104(10):4660–4666. **PubMed 31498871**.

32 **Hall JE, Lavoie HB, Marsh EE, Martin KA.** Decrease in gonadotropin-releasing hormone (GnRH) pulse frequency with aging in postmenopausal women. *J Clin Endocrinol Metab.* 2000;85(5):1794–1800. **PubMed 10843156**.

References 33–64.

1. **Labrie F, Bélanger A, Cusan L, Gomez JL, Candas B.** Marked decline in serum concentrations of adrenal C19 sex steroid precursors and conjugated androgen metabolites during aging. *J Clin Endocrinol Metab.* 1997;82(8):2396–2402. **PubMed 9253307**.
2. **Sowers MR, Eyvazzadeh AD, McConnell D, et al.** Anti-Müllerian hormone and inhibin B in the definition of ovarian aging and the menopause transition. *J Clin Endocrinol Metab.* 2008;93(9):3478–3483. **PubMed 18593767**.
3. **Burger HG, Cahir N, Robertson DM, et al.** Serum inhibins A and B fall differentially as FSH rises in perimenopausal women. *Clin Endocrinol (Oxf).* 1998;48(6):809–813. **PubMed 9713572**.
4. **Santoro N, Brown JR, Adel T, Skurnick JH.** Characterization of reproductive hormonal dynamics in the perimenopause. *J Clin Endocrinol Metab.* 1996;81(4):1495–1501. **PubMed 8636357**.
5. **Avis NE, Crawford SL, Greendale G, et al.** Duration of menopausal vasomotor symptoms over the menopause transition. *JAMA Intern Med.* 2015;175(4):531–539. **PubMed 25686030**.
6. **Paramsothy P, Harlow SD, Greendale GA, et al.** Duration of the menopausal transition is longer in women with young age at onset: the multi-ethnic Study of Women's Health Across the Nation. *Menopause.* 2017;24(2):142–149. **PubMed 27676632**.
7. **Tepper PG, Randolph JF Jr, McConnell DS, et al.** Trajectories of estradiol and follicle-stimulating hormone over the menopause transition and early predictors of late reproductive trajectory. *J Clin Endocrinol Metab.* 2012;97(8):2872–2880. **PubMed 22659249**.
8. **Webber L, Davies M, Anderson R, et al.** ESHRE Guideline: management of women with premature ovarian insufficiency. *Hum Reprod.* 2016;31(5):926–937. **PubMed 27008889**.
9. **Maslow BS, Davis S, Brady M, et al.** Premature ovarian insufficiency. *Lancet.* 2010;376(9744):911–921. **PubMed 20708256**.
10. **Muka T, Oliver-Williams C, Kunutsor S, et al.** Association of age at onset of menopause and time since onset of menopause with cardiovascular outcomes, intermediate vascular traits, and all-cause mortality: a systematic review and meta-analysis. *JAMA Cardiol.* 2016;1(7):767–776. **PubMed 27627190**.
11. **Stuenkel CA, Davis SR, Gompel A, et al.** Treatment of symptoms of the menopause: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2015;100(11):3975–4011. **PubMed 26444994**.
12. **Rivera CM, Grossardt BR, Rhodes DJ, et al.** Increased cardiovascular mortality after early bilateral oophorectomy. *Menopause.* 2009;16(1):15–23. **PubMed 19034052**.
13. **Sukumvanich P, Case LD, Van Zee K, et al.** Incidence and time course of bleeding after long-term amenorrhea after breast cancer treatment: a prospective study. *Cancer.* 2010;116(13):3102–3111. **PubMed 20564648**.
14. **Arias E, Tejada-Vera B, Ahmad F, Kochanek KD.** Provisional life expectancy estimates for 2021. *NVSS Vital Statistics Rapid Release.* 2022;No. 23.
15. **Khosla S, Riggs BL.** Pathophysiology of age-related bone loss and osteoporosis. *Endocrinol Metab Clin North Am.* 2005;34(4):1015–1030. **PubMed 16310636**.
16. **Avis NE, Crawford SL, Greendale G, et al.** Vasomotor symptom trajectories: SWAN findings. *J Womens Health (Larchmt).* 2016;25(8):753–761.
17. **Portman DJ, Gass ML, Vulvovaginal Atrophy Terminology Consensus Conference Panel.** Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and The North American Menopause Society. *Maturitas.* 2014;79(3):349–354. **PubMed 25179577**.
18. **Palacios S, Castelo-Branco C, Currie H, et al.** Update on management of genitourinary syndrome of menopause: a practical guide. *Maturitas.* 2015;82(3):308–313. **PubMed 26330294**.
19. **Wright NC, Looker AC, Saag KG, et al.** The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. *J Bone Miner Res.* 2014;29(11):2520–2526. **PubMed 24771492**.
20. **Greendale GA, Sowers M, Han W, et al.** Bone mineral density loss in relation to the final menstrual period in a multiethnic cohort: results from the Study of Women's Health Across the Nation (SWAN). *J Bone Miner Res.* 2012;27(1):111–118. **PubMed 21976317**.
21. **El Khoudary SR, Aggarwal B, Beckie TM, et al.** Menopause transition and cardiovascular disease risk: implications for timing of early prevention: a scientific statement from the American Heart Association. *Circulation.* 2020;142(25):e506–e532. **PubMed 33251828**.
22. **Freeman EW, Sammel MD, Lin H.** Temporal associations of hot flashes and depression in the transition to menopause. *Menopause.* 2009;16(4):728–734. **PubMed 19188853**.
23. **Avis NE, Brockwell S, Randolph JF Jr, et al.** Longitudinal changes in sexual functioning as women transition through menopause: results from the Study of Women's Health Across the Nation. *Menopause.* 2009;16(3):442–452. **PubMed 19212271**.
24. **Magliano M.** Menopausal arthralgia: fact or fiction. *Maturitas.* 2010;67(1):29–33. **PubMed 20537835**.
25. **Stevenson S, Thornton J.** Effect of estrogens on skin aging and the potential role of SERMs. *Clin Interv Aging.* 2007;2(3):283–297. **PubMed 18044179**.
26. **Rance NE, Dacks PA, Mittelman-Smith MA, et al.** Modulation of body temperature and LH secretion by hypothalamic KNDy (kisspeptin, neurokinin B and dynorphin) neurons. *Front Neuroendocrinol.* 2013;34(3):211–227. **PubMed 23872331**.
27. **Lederman S, Ottery FD, Cano A, et al.** Fezolinetant for treatment of moderate-to-severe vasomotor symptoms associated with menopause (SKYLIGHT 1): a phase 3 randomised controlled trial. *Lancet.* 2023;401(10382):1091–1102. **PubMed 36924778**.
28. **Thurston RC, Aslanidou Vlachos HE, Derby CA, et al.** Menopausal vasomotor symptoms and risk of incident cardiovascular disease events in SWAN. *J Am Heart Assoc.* 2021;10(3):e017416. **PubMed 33474977**.
29. **Thurston RC, Sutton-Tyrrell K, Everson-Rose SA, et al.** Hot flashes and subclinical cardiovascular disease: findings from the Study of Women's Health Across the Nation Heart Study. *Circulation.* 2008;118(12):1234–1240. **PubMed 18765392**.
30. **Greendale GA, Karlamangla AS, Maki PM.** The menopause transition and cognition. *JAMA.* 2020;323(15):1495–1496. **PubMed 32228067**.

References 65–104.

1. **Brinton RD.** Estrogen-induced plasticity from cells to circuits: predictions for cognitive function. *Trends Pharmacol Sci.* 2009;30(4):212–222. **PubMed 19299024**.
2. **Mosconi L, Berti V, Quinn C, et al.** Sex differences in Alzheimer risk: brain imaging of endocrine vs chronologic aging. *Neurology.* 2017;89(13):1382–1390. **PubMed 28855400**.
3. **Henderson VW.** Cognitive changes after menopause: influence of estrogen. *Clin Obstet Gynecol.* 2008;51(3):618–626. **PubMed 18677155**.
4. **Gleason CE, Dowling NM, Wharton W, et al.** Effects of hormone therapy on cognition and mood in recently postmenopausal women: findings from the randomized, controlled KEEPS-Cognitive and Affective study. *PLoS Med.* 2015;12(6):e1001833. **PubMed 26035291**.
5. **Shumaker SA, Legault C, Rapp SR, et al.** Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study (WHIMS). *JAMA.* 2003;289(20):2651–2662. **PubMed 12771112**.
6. **Freeman EW, Sammel MD, Lin H, Nelson DB.** Associations of hormones and menopausal status with depressed mood in women with no history of depression. *Arch Gen Psychiatry.* 2006;63(4):375–382. **PubMed 16585466**.
7. **Maki PM, Kornstein SG, Joffe H, et al.** Guidelines for the evaluation and treatment of perimenopausal depression: summary and recommendations. *Menopause.* 2018;25(10):1069–1085. **PubMed 30179986**.
8. **Soares CN, Almeida OP, Joffe H, Cohen LS.** Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women: a double-blind, randomized, placebo-controlled trial. *Arch Gen Psychiatry.* 2001;58(6):529–534. **PubMed 11386980**.
9. **Joffe H, Massler A, Sharkey KM.** Evaluation and management of sleep disturbance during the menopause transition. *Semin Reprod Med.* 2010;28(5):404–421. **PubMed 20845239**.
10. **Pengo MF, Won CH, Bourjeily G.** Sleep in women across the life span. *Chest.* 2018;154(1):196–206. **PubMed 29679598**.
11. **Mirer AG, Young T, Palta M, et al.** Sleep-disordered breathing and the menopausal transition among participants in the Sleep in Midlife Women Study. *Menopause.* 2017;24(2):157–162. **PubMed 27676636**.
12. **Portman DJ, Gass ML.** Genitourinary syndrome of menopause: new terminology. *Menopause.* 2014;21(10):1063–1068.
13. **Crandall CJ, Diamant A, Santoro N.** Safety of vaginal estrogens: a systematic review. *Menopause.* 2020;27(3):339–360. **PubMed 31913230**.
14. **Constantine GD, Bouchard C, Pickar JH, et al.** Vaginal-estrogen formulations and treatment of genitourinary syndrome of menopause. *Climacteric.* 2019;22(3):301–308.
15. **Manson JE, Kaunitz AM.** Menopause management — getting clinical care back on track. *N Engl J Med.* 2016;374(9):803–806. **PubMed 26962899**.
16. **Davis SR, Castelo-Branco C, Chedraui P, et al.** Understanding weight gain at menopause. *Climacteric.* 2012;15(5):419–429. **PubMed 22978257**.
17. **Carr MC.** The emergence of the metabolic syndrome with menopause. *J Clin Endocrinol Metab.* 2003;88(6):2404–2411. **PubMed 12788835**.
18. **Lovejoy JC, Champagne CM, de Jonge L, Xie H, Smith SR.** Increased visceral fat and decreased energy expenditure during the menopausal transition. *Int J Obes (Lond).* 2008;32(6):949–958. **PubMed 18332882**.
19. **Maltais ML, Desroches J, Dionne IJ.** Changes in muscle mass and strength after menopause. *J Musculoskelet Neuronal Interact.* 2009;9(4):186–197. **PubMed 19949277**.
20. **Geraci A, Calvani R, Ferri E, et al.** Sarcopenia and menopause: the role of estradiol. *Front Endocrinol (Lausanne).* 2021;12:682012. **PubMed 34122351**.
21. **Mauvais-Jarvis F, Manson JE, Stevenson JC, Fonseca VA.** Menopausal hormone therapy and type 2 diabetes prevention: evidence, mechanisms, and clinical implications. *Endocr Rev.* 2017;38(3):173–188. **PubMed 28323950**.
22. **Janssen I, Heymsfield SB, Ross R.** Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. *J Am Geriatr Soc.* 2002;50(5):889–896. **PubMed 12028177**.
23. **Beckwée D, Delaere A, Aelbrecht S, et al.** Exercise interventions for the prevention and treatment of sarcopenia. *J Nutr Health Aging.* 2019;23(6):494–502. **PubMed 31233067**.
24. **Khosla S, Oursler MJ, Monroe DG.** Estrogen and the skeleton. *Trends Endocrinol Metab.* 2012;23(11):576–581. **PubMed 22595550**.
25. **de Villiers TJ, Hall JE, Pinkerton JV, et al.** Revised global consensus statement on menopausal hormone therapy. *Climacteric.* 2016;19(4):313–315. **PubMed 27322027**.
26. **Cosman F, de Beur SJ, LeBoff MS, et al.** Clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int.* 2014;25(10):2359–2381. **PubMed 25182228**.
27. **U.S. Preventive Services Task Force.** Screening for osteoporosis to prevent fractures: US Preventive Services Task Force recommendation statement. *JAMA.* 2018;319(24):2521–2531. **PubMed 29946735**.
28. **Johnell O, Kanis JA.** An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int.* 2006;17(12):1726–1733. **PubMed 16983459**.
29. **Kanis JA, Johnell O, Oden A, et al.** Long-term risk of osteoporotic fracture in Malmö. *Osteoporos Int.* 2000;11(8):669–674. **PubMed 11095169**.
30. **Kanis JA, Oden A, Johansson H, et al.** FRAX and its applications to clinical practice. *Bone.* 2009;44(5):734–743. **PubMed 19195497**.
31. **Tinetti ME, Kumar C.** The patient who falls: "it's always a trade-off". *JAMA.* 2010;303(3):258–266. **PubMed 20085954**.
32. **Black DM, Cummings SR, Karpf DB, et al.** Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *Lancet.* 1996;348(9041):1535–1541. **PubMed 8950879**.
33. **Cummings SR, San Martin J, McClung MR, et al.** Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med.* 2009;361(8):756–765. **PubMed 19671655**.
34. **Ettinger B, Black DM, Mitlak BH, et al.** Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene (MORE). *JAMA.* 1999;282(7):637–645. **PubMed 10517716**.
35. **Neer RM, Arnaud CD, Zanchetta JR, et al.** Effect of parathyroid hormone on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med.* 2001;344(19):1434–1441. **PubMed 11346808**.
36. **Cauley JA, Robbins J, Chen Z, et al.** Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA.* 2003;290(13):1729–1738. **PubMed 14519707**.
37. **Tang BMP, Eslick GD, Nowson C, et al.** Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. *Lancet.* 2007;370(9588):657–666. **PubMed 17720017**.
38. **Benjamin EJ, Muntner P, Alonso A, et al.** Heart disease and stroke statistics — 2019 update: a report from the American Heart Association. *Circulation.* 2019;139(10):e56–e528. **PubMed 30700139**.
39. **El Khoudary SR, Thurston RC.** Cardiovascular implications of the menopause transition: endogenous sex hormones and vasomotor symptoms. *Obstet Gynecol Clin North Am.* 2018;45(4):641–661. **PubMed 30401547**.
40. **Matthews KA, Crawford SL, Chae CU, et al.** Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or to the menopausal transition? *J Am Coll Cardiol.* 2009;54(25):2366–2373. **PubMed 20082925**.

References 105–140.

1. **Anagnostis P, Galanis P, Chatzistergiou V, et al.** The effect of menopause on lipoprotein(a) concentrations: a systematic review and meta-analysis. *Maturitas.* 2017;99:27–36. PubMed 28364865.
2. **El Khoudary SR, Wildman RP, Matthews K, et al.** Progression rates of carotid intima-media thickness and adventitial diameter during the menopausal transition. *Menopause.* 2013;20(1):8–14. PubMed 22929034.
3. **Mendelsohn ME, Karas RH.** The protective effects of estrogen on the cardiovascular system. *N Engl J Med.* 1999;340(23):1801–1811. PubMed 10362825.
4. **Mendelsohn ME, Karas RH.** Molecular and cellular basis of cardiovascular gender differences. *Science.* 2005;308(5728):1583–1587. PubMed 15947175.
5. **Walsh BW, Schiff I, Rosner B, et al.** Effects of postmenopausal estrogen replacement on the concentrations and metabolism of plasma lipoproteins. *N Engl J Med.* 1991;325(17):1196–1204. PubMed 1922206.
6. **Murphy E.** Estrogen signaling and cardiovascular disease. *Circ Res.* 2011;109(6):687–696. PubMed 21885836.
7. **Hodis HN, Mack WJ.** The timing hypothesis and hormone replacement therapy: a paradigm shift in the primary prevention of coronary heart disease in women. *J Am Geriatr Soc.* 2013;61(6):1011–1018. PubMed 23692390.
8. **Manson JE, Aragaki AK, Rossouw JE, et al.** Menopausal hormone therapy and long-term all-cause and cause-specific mortality: the Women's Health Initiative randomized trials. *JAMA.* 2017;318(10):927–938. PubMed 28898378.
9. **Beale AL, Meyer P, Marwick TH, et al.** Sex differences in cardiovascular pathophysiology: why women are overrepresented in heart failure with preserved ejection fraction. *Circulation.* 2018;138(2):198–205. PubMed 29986961.
10. **Mosca L, Benjamin EJ, Berra K, et al.** Effectiveness-based guidelines for the prevention of cardiovascular disease in women — 2011 update. *Circulation.* 2011;123(11):1243–1262. PubMed 21325087.
11. **Maas AHEM, Rosano G, Cifkova R, et al.** Cardiovascular health after menopause transition: pregnancy complications and migraine; ESC consensus statement. *Eur Heart J.* 2021;42(10):967–984. PubMed 33495787.
12. **Grundy SM, Stone NJ, Bailey AL, et al.** 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol. *Circulation.* 2019;139(25):e1082–e1143. PubMed 30586774.
13. **The "2022 hormone therapy position statement" advisory panel.** 2022 NAMS Hormone Therapy Position Statement. *Menopause.* 2022;29(7):767–794.
14. **American Diabetes Association Professional Practice Committee.** Standards of Medical Care in Diabetes — 2023. *Diabetes Care.* 2023;46(Suppl 1):S1–S298.
15. **Garber JR, Cobin RH, Gharib H, et al.** Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Endocr Pract.* 2012;18(6):988–1028. PubMed 23246686.
16. **Holick MF, Binkley NC, Bischoff-Ferrari HA, et al.** Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2011;96(7):1911–1930. PubMed 21646368.
17. **Vasikaran S, Cooper C, Eastell R, et al.** International Osteoporosis Foundation and International Federation of Clinical Chemistry and Laboratory Medicine position on bone marker standards in osteoporosis. *Clin Chem Lab Med.* 2011;49(8):1271–1274. PubMed 21605012.
18. **Files JA, Ko MG, Pruthi S.** Bioidentical hormone therapy. *Mayo Clin Proc.* 2011;86(7):673–680. PubMed 21709134.
19. **Wallach JD, Sullivan PG, Trepanowski JF, et al.** Sex based subgroup differences in randomized controlled trials. *BMJ.* 2016;355:i5826. PubMed 27884868.
20. **Stampfer MJ, Colditz GA.** Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. *Prev Med.* 1991;20(1):47–63. PubMed 1826173.
21. **The Writing Group for the PEPI Trial.** Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA.* 1995;273(3):199–208. PubMed 7807658.
22. **Women's Health Initiative Study Group.** Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials.* 1998;19(1):61–109. PubMed 9492970.
23. **Anderson GL, Limacher M, Assaf AR, et al.** Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA.* 2004;291(14):1701–1712. PubMed 15082697.
24. **Manson JE, Chlebowski RT, Stefanick ML, et al.** Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA.* 2013;310(13):1353–1368. PubMed 24084921.
25. **Rossouw JE, Prentice RL, Manson JE, et al.** Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA.* 2007;297(13):1465–1477. PubMed 17405972.
26. **Lobo RA.** Where are we 10 years after the Women's Health Initiative? *J Clin Endocrinol Metab.* 2013;98(5):1771–1780. PubMed 23493437.
27. **Baber RJ, Panay N, Fenton A, IMS Writing Group.** 2016 IMS Recommendations on women's midlife health and menopause hormone therapy. *Climacteric.* 2016;19(2):109–150. PubMed 26872610.
28. **Hamoda H, Panay N, Pedder H, et al.** The British Menopause Society & Women's Health Concern 2020 recommendations on hormone replacement therapy in menopausal women. *Post Reprod Health.* 2020;26(4):181–209. PubMed 33045914.
29. **Mohammed K, Abu Dabrh AM, Benkhadra K, et al.** Oral vs transdermal estrogen therapy and vascular events: a systematic review and meta-analysis. *J Clin Endocrinol Metab.* 2015;100(11):4012–4020. PubMed 26544651.
30. **Canonico M, Plu-Bureau G, Lowe GDO, Scarabin PY.** Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. *BMJ.* 2008;336(7655):1227–1231. PubMed 18495631.
31. **Lobo RA, Pinkerton JV, Gass MLS, et al.** Evaluation of bazedoxifene/conjugated estrogens for the treatment of menopausal symptoms and effects on metabolic parameters and overall safety profile. *Fertil Steril.* 2009;92(3):1025–1038. PubMed 19635616.
32. **North American Menopause Society.** The 2020 genitourinary syndrome of menopause position statement. *Menopause.* 2020;27(9):976–992. PubMed 32852449.
33. **Renoux C, Dell'Aniello S, Garbe E, Suissa S.** Transdermal and oral hormone replacement therapy and the risk of stroke: a nested case-control study. *BMJ.* 2010;340:c2519. PubMed 20525678.
34. **Liu B, Beral V, Balkwill A, et al.** Gallbladder disease and use of transdermal versus oral hormone replacement therapy in postmenopausal women: prospective cohort study. *BMJ.* 2008;337:a386. PubMed 18617493.

References 141–180.

141. **Pinkerton JV, Sánchez Aguirre F, Blake J, et al.** The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause.* 2022;29(7):767–794.
142. **Scarabin PY, Oger E, Plu-Bureau G; EStrogen and THromboEmbolism Risk Study Group.** Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk. *Lancet.* 2003;362(9382):428–432. PubMed 12927428.
143. **Vinogradova Y, Coupland C, Hippisley-Cox J.** Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. *BMJ.* 2019;364:k4810. PubMed 30626577.
144. **Lobo RA, Archer DF, Kagan R, et al.** A 17β-estradiol-progesterone oral capsule for vasomotor symptoms in postmenopausal women: a randomized controlled trial. *Obstet Gynecol.* 2018;132(1):161–170. PubMed 29889748.
145. **Files JA, Ko MG, Pruthi S.** Bioidentical hormone therapy. *Mayo Clin Proc.* 2011;86(7):673–680.
146. **Fournier A, Berrino F, Riboli E, et al.** Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. *Int J Cancer.* 2005;114(3):448–454. PubMed 15551359.
147. **Smith NL, Blondon M, Wiggins KL, et al.** Lower risk of cardiovascular events in postmenopausal women taking oral estradiol compared with oral conjugated equine estrogens. *JAMA Intern Med.* 2014;174(1):25–31. PubMed 24193300.
148. **Cirillo DJ, Wallace RB, Wu L, Yood RA.** Effect of hormone therapy on risk of hip and knee joint replacement in the Women's Health Initiative. *Arthritis Rheum.* 2006;54(10):3194–3204. PubMed 17009251.
149. **Simon JA, Lin VH, Radovich C, Bachmann GA; Estradiol Vaginal Insert Study Group.** One-year long-term safety extension study of a low-dose 17β-estradiol vaginal insert. *Menopause.* 2013;20(4):418–427.
150. **Faubion SS, Larkin LC, Stuenkel CA, et al.** Management of genitourinary syndrome of menopause in women with or at high risk for breast cancer: consensus recommendations from The North American Menopause Society and the International Society for the Study of Women's Sexual Health. *Menopause.* 2018;25(6):596–608. PubMed 29762200.
151. **Depypere H, Inki P.** The levonorgestrel-releasing intrauterine system as a postmenopausal hormone therapy. *Climacteric.* 2015;18(4):470–482. PubMed 26075876.
152. **Labrie F, Archer DF, Koltun W, et al.** Efficacy of intravaginal dehydroepiandrosterone (DHEA) on moderate-to-severe dyspareunia and vaginal dryness, symptoms of vulvovaginal atrophy, and of the genitourinary syndrome of menopause. *Menopause.* 2016;23(3):243–256. PubMed 26731686.
153. **Baulieu EE, Thomas G, Legrain S, et al.** Dehydroepiandrosterone (DHEA), DHEA sulfate, and aging: contribution of the DHEAge Study to a sociobiomedical issue. *Proc Natl Acad Sci U S A.* 2000;97(8):4279–4284. PubMed 10760294.
154. **Bornstein SR, Allolio B, Arlt W, et al.** Diagnosis and treatment of primary adrenal insufficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2016;101(2):364–389. PubMed 26760044.
155. **Nonhormonal Management of Menopause-Associated Vasomotor Symptoms Position Statement of The North American Menopause Society.** The 2023 nonhormonal management of menopause-associated vasomotor symptoms position statement of The North American Menopause Society. *Menopause.* 2023;30(6):573–590. PubMed 37252752.
156. **Simon JA, Portman DJ, Kaunitz AM, et al.** Low-dose paroxetine 7.5 mg for menopausal vasomotor symptoms: two randomized controlled trials. *Menopause.* 2013;20(10):1027–1035. PubMed 24045679.
157. **Johnson KA, Martin N, Nappi RE, et al.** Efficacy and safety of fezolinetant in moderate-to-severe vasomotor symptoms associated with menopause: a phase 3 RCT. *J Clin Endocrinol Metab.* 2023;108(8):1981–1997. PubMed 36734148.
158. **Loprinzi CL, Sloan J, Stearns V, et al.** Newer antidepressants and gabapentin for hot flashes: an individual patient pooled analysis. *J Clin Oncol.* 2009;27(17):2831–2837. PubMed 19332723.
159. **Freeman EW, Guthrie KA, Caan B, et al.** Efficacy of escitalopram for hot flashes in healthy menopausal women: a randomized controlled trial. *JAMA.* 2011;305(3):267–274. PubMed 21245182.
160. **Pinkerton JV, Kagan R, Portman D, et al.** Phase 3 randomized controlled study of gastroretentive gabapentin for the treatment of moderate-to-severe hot flashes in menopause. *Menopause.* 2014;21(6):567–573. PubMed 24149920.
161. **Leon-Ferre RA, Novotny PJ, Wolfe EG, et al.** Oxybutynin vs placebo for hot flashes in women with or without breast cancer. *JAMA Netw Open.* 2020;3(1):e1921519. PubMed 31935080.
162. **Pandya KJ, Raubertas RF, Flynn PJ, et al.** Oral clonidine in postmenopausal patients with breast cancer experiencing tamoxifen-induced hot flashes. *Ann Intern Med.* 2000;132(10):788–793. PubMed 10819701.
163. **Pinkerton JV, Simon JA, Joffe H, et al.** Elinzanetant for the treatment of vasomotor symptoms associated with menopause. *JAMA.* 2024;332(16):1343–1354.
164. **Hunter MS.** Cognitive behavioural therapy for menopausal symptoms. *Climacteric.* 2021;24(1):51–56. PubMed 32844687.
165. **Elkins GR, Fisher WI, Johnson AK, Carpenter JS, Keith TZ.** Clinical hypnosis in the treatment of postmenopausal hot flashes: a randomized controlled trial. *Menopause.* 2013;20(3):291–298. PubMed 23435026.
166. **Carmody JF, Crawford S, Salmoirago-Blotcher E, et al.** Mindfulness training for coping with hot flashes: results of a randomized trial. *Menopause.* 2011;18(6):611–620. PubMed 21372745.
167. **Daley A, Stokes-Lampard H, Thomas A, MacArthur C.** Exercise for vasomotor menopausal symptoms. *Cochrane Database Syst Rev.* 2014;(11):CD006108. PubMed 25431132.
168. **Chiu HY, Pan CH, Shyu YK, et al.** Effects of acupuncture on menopause-related symptoms and quality of life in women in natural menopause. *Menopause.* 2015;22(2):234–244. PubMed 25003620.
169. **Latham NK, Bennett DA, Stretton CM, Anderson CS.** Systematic review of progressive resistance strength training in older adults. *J Gerontol A Biol Sci Med Sci.* 2004;59(1):48–61. PubMed 14718486.
170. **Cermak NM, Res PT, de Groot LCPGM, Saris WHM, van Loon LJC.** Protein supplementation augments the adaptive response of skeletal muscle to resistance-type exercise training. *Am J Clin Nutr.* 2012;96(6):1454–1464. PubMed 23134885.
171. **Howe TE, Shea B, Dawson LJ, et al.** Exercise for preventing and treating osteoporosis in postmenopausal women. *Cochrane Database Syst Rev.* 2011;(7):CD000333. PubMed 21735380.
172. **Watson SL, Weeks BK, Weis LJ, et al.** High-intensity resistance and impact training improves bone mineral density and physical function in postmenopausal women with osteopenia and osteoporosis: the LIFTMOR randomized controlled trial. *J Bone Miner Res.* 2018;33(2):211–220. PubMed 28975661.
173. **Kemmler W, Bebenek M, Kohl M, von Stengel S.** Exercise and fractures in postmenopausal women: final results of the controlled Erlangen Fitness and Osteoporosis Prevention Study (EFOPS). *Osteoporos Int.* 2015;26(10):2491–2499. PubMed 25963237.
174. **Sherrington C, Fairhall NJ, Wallbank GK, et al.** Exercise for preventing falls in older people living in the community. *Cochrane Database Syst Rev.* 2019;(1):CD012424. PubMed 30703272.
175. **Strasser B, Schobersberger W.** Evidence for resistance training as a treatment therapy in obesity. *J Obes.* 2011;2011:482564. PubMed 20847892.
176. **Mora S, Lee IM, Buring JE, Ridker PM.** Association of physical activity and body mass index with novel and traditional cardiovascular biomarkers in women. *JAMA.* 2006;295(12):1412–1419. PubMed 16551713.
177. **Powell KE, King AC, Buchner DM, et al.** The scientific foundation for the Physical Activity Guidelines for Americans, 2nd Edition. *J Phys Act Health.* 2018;15(12):891–893. PubMed 30558473.

References 178–206.

1. **Cooney GM, Dwan K, Greig CA, et al.** Exercise for depression. *Cochrane Database Syst Rev.* 2013;(9):CD004366. **PubMed 24026850**.
2. **Erickson KI, Voss MW, Prakash RS, et al.** Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci U S A.* 2011;108(7):3017–3022. **PubMed 21282661**.
3. **Piercy KL, Troiano RP, Ballard RM, et al.** The Physical Activity Guidelines for Americans. *JAMA.* 2018;320(19):2020–2028. **PubMed 30418471**.
4. **Bull FC, Al-Ansari SS, Biddle S, et al.** World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *Br J Sports Med.* 2020;54(24):1451–1462. **PubMed 33239350**.
5. **Phillips SM, Chevalier S, Leidy HJ.** Protein "requirements" beyond the RDA: implications for optimizing health. *Appl Physiol Nutr Metab.* 2016;41(5):565–572. **PubMed 26960445**.
6. **Bauer J, Biolo G, Cederholm T, et al.** Evidence-based recommendations for optimal dietary protein intake in older people: a position paper from the PROT-AGE Study Group. *J Am Med Dir Assoc.* 2013;14(8):542–559. **PubMed 23867520**.
7. **Morton RW, Murphy KT, McKellar SR, et al.** A systematic review, meta-analysis and meta-regression of the effect of protein supplementation on resistance training-induced gains in muscle mass and strength in healthy adults. *Br J Sports Med.* 2018;52(6):376–384. **PubMed 28698222**.
8. **Moore DR, Churchward-Venne TA, Witard O, et al.** Protein ingestion to stimulate myofibrillar protein synthesis requires greater relative protein intakes in healthy older versus younger men. *J Gerontol A Biol Sci Med Sci.* 2015;70(1):57–62. **PubMed 25056502**.
9. **Pasiakos SM, McLellan TM, Lieberman HR.** The effects of protein supplements on muscle mass, strength, and aerobic and anaerobic power in healthy adults: a systematic review. *Sports Med.* 2015;45(1):111–131. **PubMed 25169440**.
10. **Berryman CE, Lieberman HR, Fulgoni VL III, Pasiakos SM.** Protein intake trends and conformity with the Dietary Reference Intakes in the United States: analysis of the National Health and Nutrition Examination Survey, 2001-2014. *Am J Clin Nutr.* 2018;108(2):405–413. **PubMed 29931213**.
11. **Institute of Medicine.** Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: National Academies Press; 2011. **PubMed 21796828**.
12. **Jackson RD, LaCroix AZ, Gass M, et al.** Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med.* 2006;354(7):669–683. **PubMed 16481635**.
13. **Bolland MJ, Avenell A, Baron JA, et al.** Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ.* 2010;341:c3691. **PubMed 20671013**.
14. **Ross AC, Manson JE, Abrams SA, et al.** The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine. *J Clin Endocrinol Metab.* 2011;96(1):53–58. **PubMed 21118827**.
15. **Manson JE, Cook NR, Lee IM, et al.** Vitamin D supplements and prevention of cancer and cardiovascular disease (VITAL). *N Engl J Med.* 2019;380(1):33–44. **PubMed 30415629**.
16. **Vannice G, Rasmussen H.** Position of the Academy of Nutrition and Dietetics: dietary fatty acids for healthy adults. *J Acad Nutr Diet.* 2014;114(1):136–153. **PubMed 24342605**.
17. **Candow DG, Forbes SC, Chilibeck PD, Cornish SM, Antonio J, Kreider RB.** Variables influencing the effectiveness of creatine supplementation as a therapeutic intervention for sarcopenia. *Front Nutr.* 2019;6:124. **PubMed 31448280**.
18. **Kreider RB, Kalman DS, Antonio J, et al.** International Society of Sports Nutrition position stand: safety and efficacy of creatine supplementation in exercise, sport, and medicine. *J Int Soc Sports Nutr.* 2017;14:18. **PubMed 28615996**.
19. **Manson JE, Cook NR, Lee IM, et al.** Marine n−3 fatty acids and prevention of cardiovascular disease and cancer. *N Engl J Med.* 2019;380(1):23–32. **PubMed 30415637**.
20. **Bhatt DL, Steg PG, Miller M, et al.** Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia (REDUCE-IT). *N Engl J Med.* 2019;380(1):11–22. **PubMed 30415628**.
21. **Volpe SL.** Magnesium in disease prevention and overall health. *Adv Nutr.* 2013;4(3):378S–383S. **PubMed 23674807**.
22. **Chen MN, Lin CC, Liu CF.** Efficacy of phytoestrogens for menopausal symptoms: a meta-analysis and systematic review. *Climacteric.* 2015;18(2):260–269. **PubMed 25263312**.
23. **Setchell KDR, Clerici C, Lephart ED, et al.** S-equol, a potent ligand for estrogen receptor beta, is the exclusive enantiomeric form of the soy isoflavone metabolite produced by human intestinal bacterial flora. *Am J Clin Nutr.* 2005;81(5):1072–1079. **PubMed 15883431**.
24. **Leach MJ, Moore V.** Black cohosh (Cimicifuga spp.) for menopausal symptoms. *Cochrane Database Syst Rev.* 2012;(9):CD007244. **PubMed 22972105**.
25. **Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD.** Management of chronic insomnia disorder in adults: a clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2016;165(2):125–133. **PubMed 27136449**.
26. **McCurry SM, Guthrie KA, Morin CM, et al.** Telephone-based cognitive behavioral therapy for insomnia in perimenopausal and postmenopausal women with vasomotor symptoms: a MsFLASH randomized clinical trial. *JAMA Intern Med.* 2016;176(7):913–920. **PubMed 27213646**.
27. **Cintron D, Lipford M, Larrea-Mantilla L, et al.** Efficacy of menopausal hormone therapy on sleep quality: systematic review and meta-analysis. *Endocrine.* 2017;55(3):702–711. **PubMed 27815752**.
28. **Irish LA, Kline CE, Gunn HE, Buysse DJ, Hall MH.** The role of sleep hygiene in promoting public health: a review of empirical evidence. *Sleep Med Rev.* 2015;22:23–36. **PubMed 25454674**.
29. **Freedman RR, Roehrs TA.** Effects of REM sleep and ambient temperature on hot flash-induced sleep disturbance. *Menopause.* 2006;13(4):576–583. **PubMed 16837879**.

End of References. This list covers references 1–206 cited throughout the preceding chapters. Where multiple citations point to the same general body of evidence (e.g., the cluster of WHI follow-up analyses, or the multiple NAMS position statements over time), the reader is encouraged to consult the cited primary source and to search PubMed for any subsequent updates published after this guide's compilation date.

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