Chapter 2: The Menopause and Aging

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Dramatic increases in life expectancy have led to women expecting to live more than a third of their lives after menopause.

Key Points[a]

1. Dramatic increases in life expectancy have led to women expecting to live more than a third of their lives after menopause.
2. The onset of menopause may affect progressive age-related changes in function and structure of body tissues and systems.
3. There is a lack of consensus as to whether the biological and psychological changes occurring during the menopause transition or presenting later in life are attributable to menopause and reduced ovarian function or to aging.
4. The timing of menopause may substantially influence subsequent morbidity and mortality.
5. Menopause cannot be said to have occurred until there have been 12 months of amenorrhea for which there is no other obvious pathological or physiological cause. Contraception is still needed during the menopause transition.
6. Endocrine changes begin years earlier. FSH and estradiol changes are maximal in the year of the FMP.
7. The endocrine changes of menopause do not include any acute or sudden decrease in androgens.
8. Menopause research has to address identified methodologic difficulties.
9. There is considerable individual and racial/ethnic variation among women in the age of menopause and in their manifestation of perimenopausal signs, symptoms, and menopause-related sequelae.
10. Influences of the menopause on health may affect a woman's quality of life.

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[a] Evidence categories are given in square brackets. A = randomized controlled trials (rich body of data); B = randomized controlled trials (limited data); C = nonrandomized trials and observational epidemiologic studies; D = Panel expert judgement. (See also table 1–1.)

1. Introduction

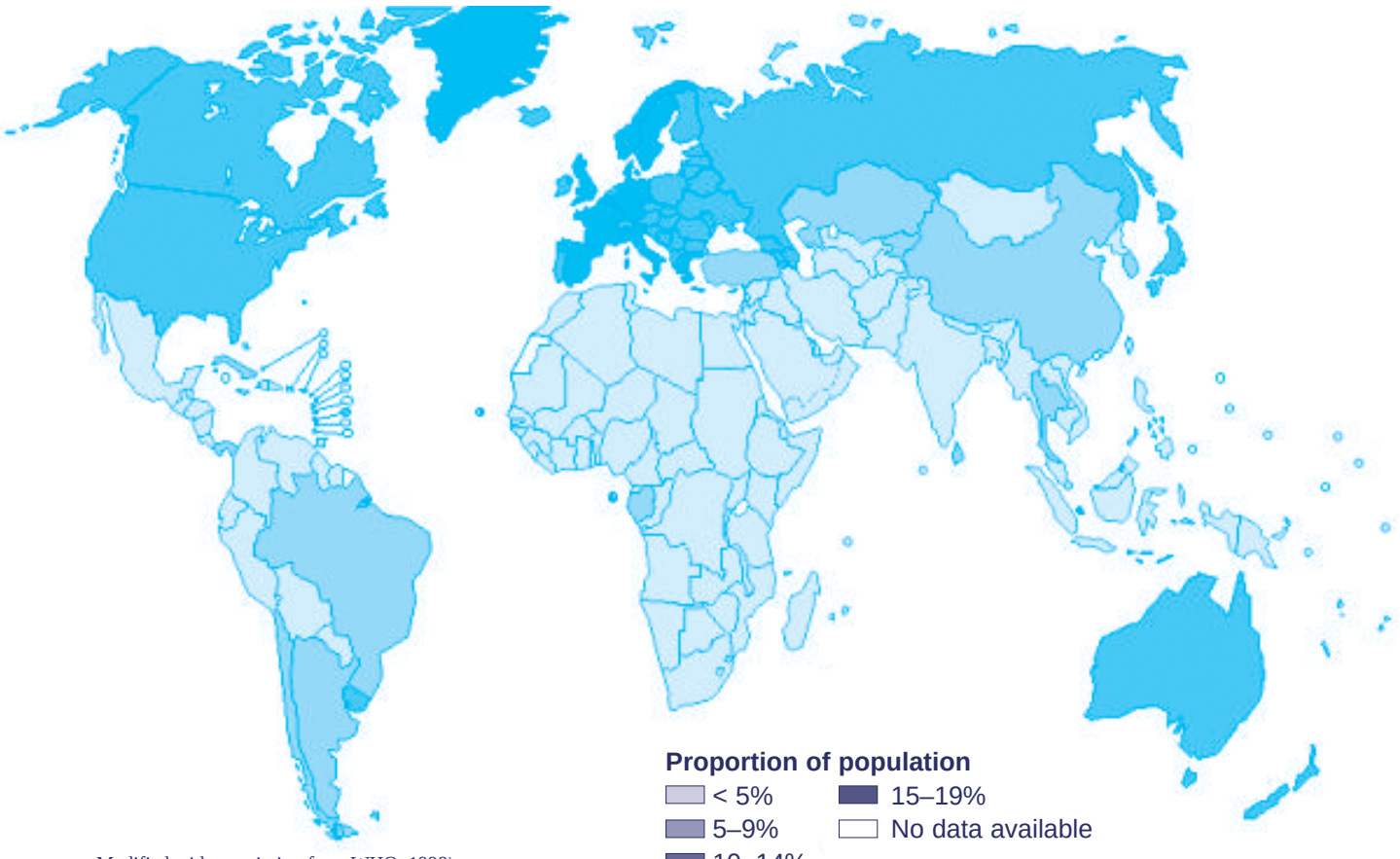
The third millennium begins with vast potential from unprecedented advances in medicine, technology, and public health. Major achievements over the past century in the conquest of infectious and parasitic diseases, progress in nutrition and education, reductions in maternal and infant mortality, although occurring unevenly on a global scale, have resulted in dramatic increases in life expectancy and burgeoning numbers of older individuals (figs. 2–1 and 2–2).[1] Although the world's elderly have been increasing in number for some time, the pace of population aging has accelerated during the past century, resulting in the "graying" of societies across the world as striking reductions in mortality have combined with declines in fertility to produce a rate of expansion of the older population that has outpaced total population growth.[2]

…Remarkable increase in the proportion of women over fifty in the population, which has tripled since the turn of the 19th century.

In the industrialized nations of Europe, Asia, and North America, this phenomenon has been a prominent issue. However, accelerated population aging in less-developed countries, where increases in the rate of growth of the older population are surpassing those in more-developed nations, has been underappreciated. Accommodating increases in the proportion of older individuals may be especially challenging to countries that are less-devel-

Figure 2–1

An Aging Population: Population Aged 65 and Above, 1996



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oped and are less prepared to address the economic, social, cultural, and medical uncertainties, competing priorities vis-à-vis enhanced life expectancy, and the desire to maintain quality of life into the very late years of life.[2]

In the developed world, mean life expectancy for women since 1900 has increased from 50 to 81.7 years. Particularly striking is the remarkable increase in the proportion of women over fifty in the population, which has tripled since the turn of the 19th century.[2] Population projections estimated approximately 467 million women in the world to be aged 50 years and older in 1990. By the year 2030, this number is expected to grow dramatically to 1,200 million. The numbers of postmenopausal women in the developing world are anticipated to increase much more rapidly than those in the industrialized world. From 1990 to 2030, the rate of growth of the postmenopausal population will decrease from 1.5 to 1.0 percent in the industrialized world, while averaging between 2 and 3.5 percent in less-developed countries. Therefore, during this period, the proportion of postmenopausal women in more developed countries is expected to decline from 40 to 24 percent, whereas it will increase from 60 to 76 percent in less-developed countries.

Accelerated population aging has led to a major epidemiological transition in the leading causes of death from infections and acute diseases to the chronic and degenerative diseases of old age (such as malignant neoplasms (see ch. 11), cardiovascular and cerebrovascular diseases (see ch. 8), osteo-

Figure 2–2

An Aging Population: Population Aged 65 and Above, 2020

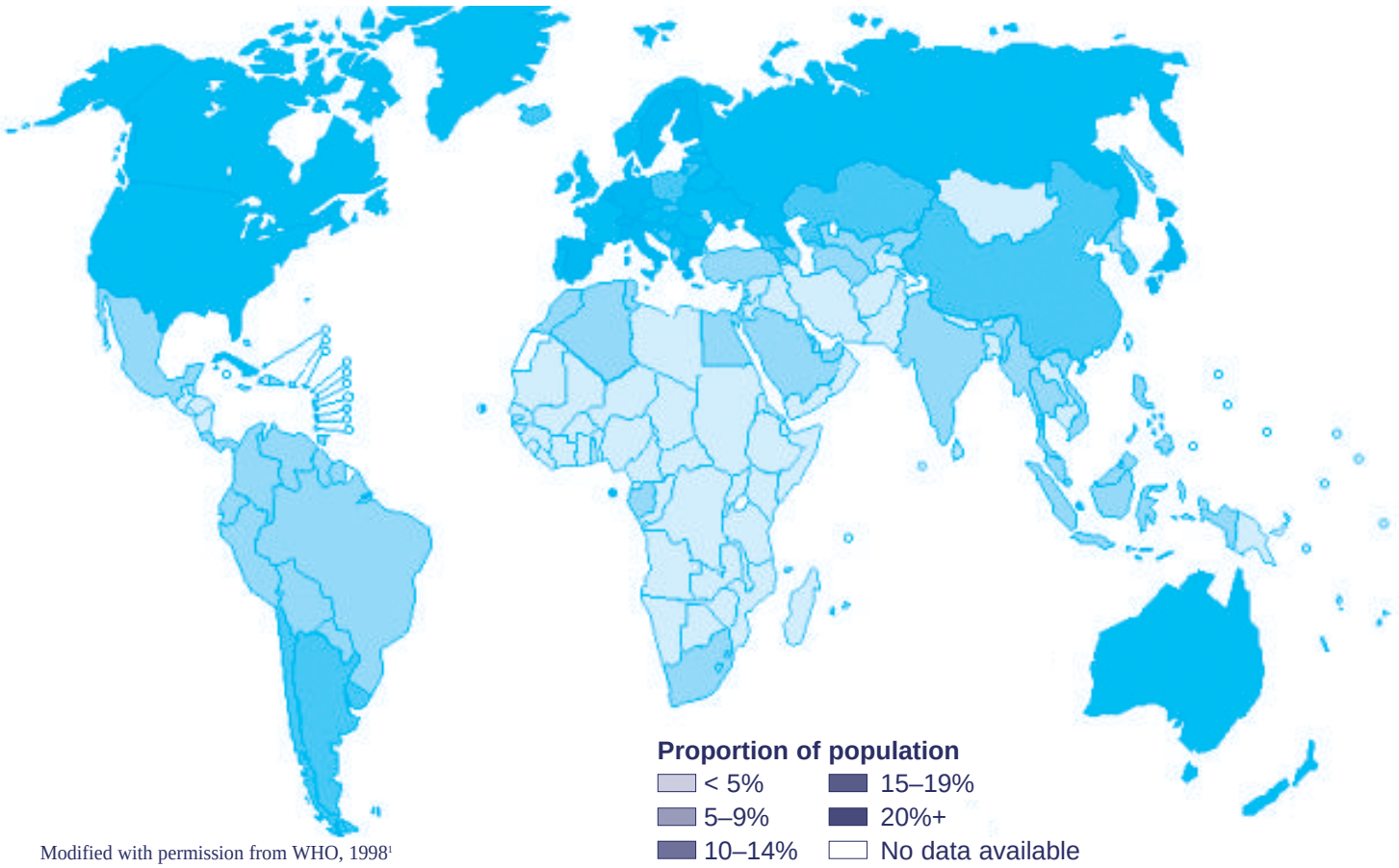

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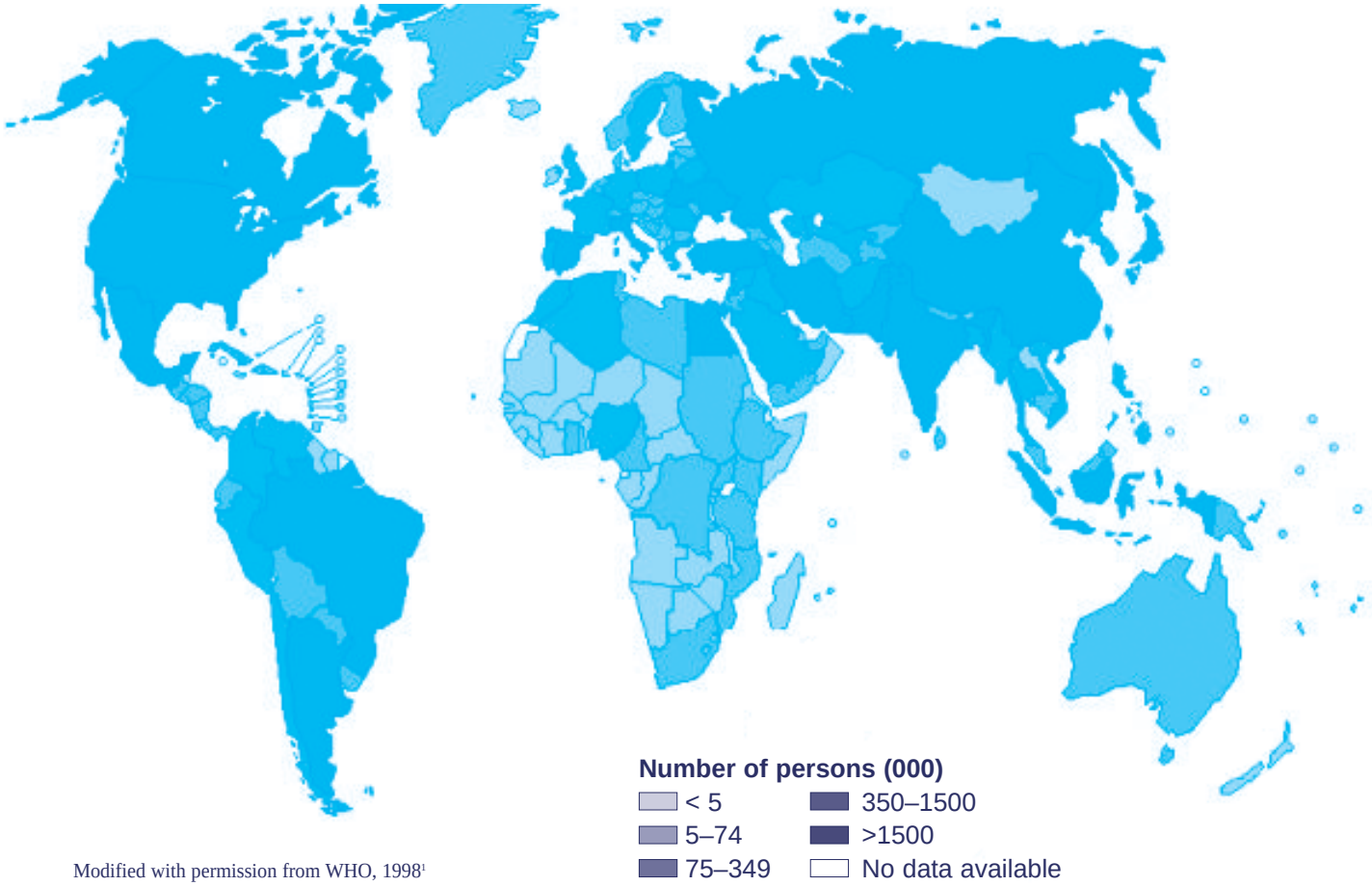
FIGURE 2–3

Diabetes Mellitus. Estimated Prevalence Among Adults, 1997



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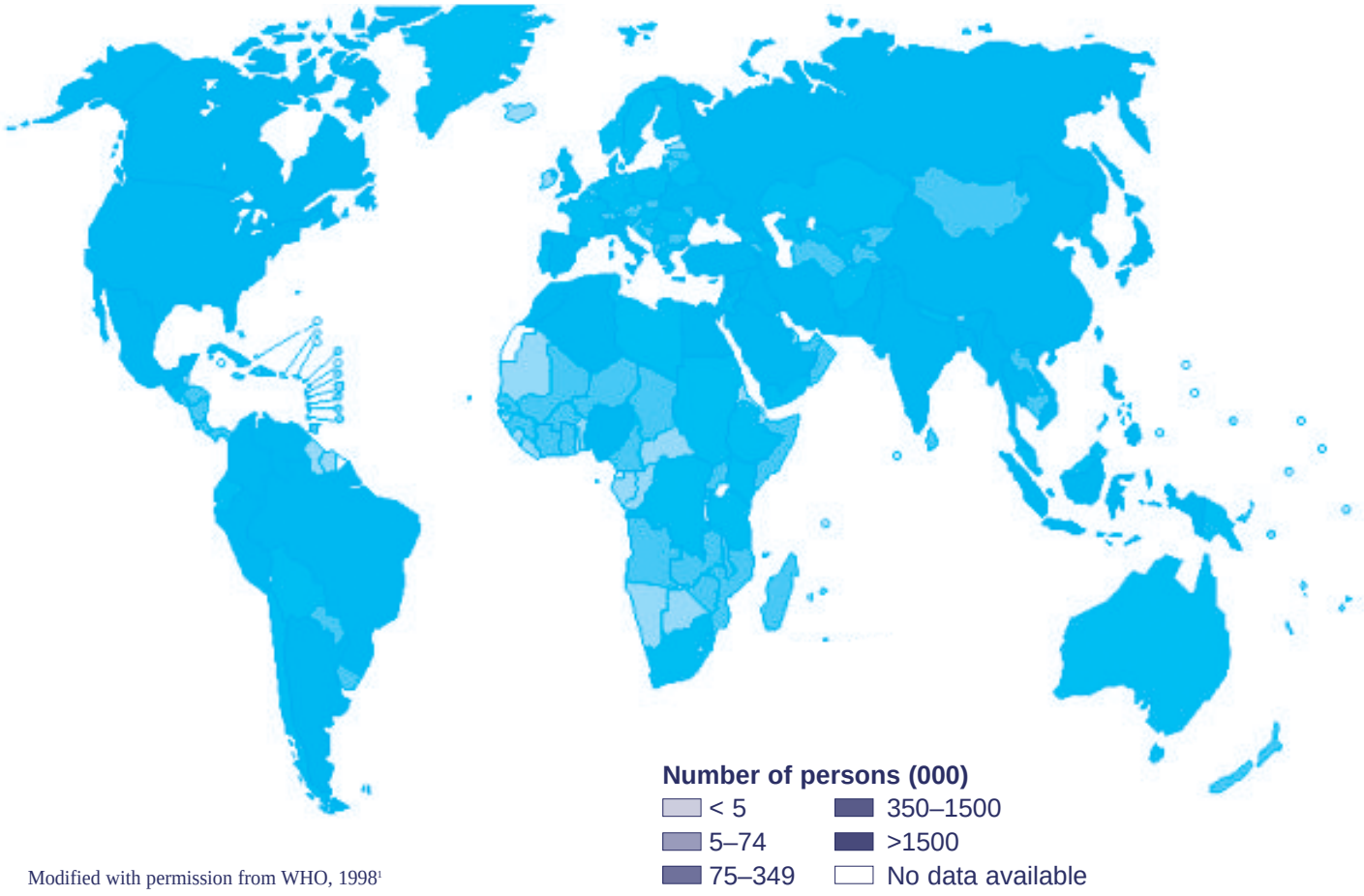
Approximately 467 million women in the world … aged 50 years and older in 1990. By the year 2030, this number is expected to grow dramatically to 1,200 million.

porosis (see ch. 9), and dementia (see ch. 12). The incidence of some metabolic diseases, such as diabetes mellitus, is increasing (figs. 2–3 and 2–4).[1] Degenerative processes, such as macular degeneration or progressive lens opacity, have been linked to prolonged estrogen deficiency.[3] Another study shows that HRT has a positive influence on intraocular pressure increasing with age.[4] However, increasingly sophisticated research in aging since the mid-1970s has led us to challenge the concept of an inevitable, inexorable, unified progression toward debility and infirmity before death. Now aging is appreciated as the heterogeneous product of a genetic disposition being revealed under variable environmental, behavioral, psychosocial, and economic conditions, many of which are amenable to profound change with existing as well as emerging new strategies.

Aging is associated with progressive structural, functional, endocrine, and metabolic alterations in a variety of tissues and systems, many of which have been implicated in subsequent impairments in physiological, physical, psychosocial, and cogni-

Figure 2–4

Diabetes Mellitus. Estimated Prevalence Among Adults, 2025



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tive functioning. A critical tenet in aging research, which is aimed at understanding, modifying, or preventing age-related morbidity, disability, and death, is the importance of differentiating changes due to disease and other pathologic processes from those attributable to aging *per se*. To better understand the etiology of age-related disease in women, it is important to additionally ascertain the independent role of menopause and its interaction with aging. There is little consensus as to the significance of menopause in healthy aging, and considerable controversy exists as to the scope of the physiological and psychological changes surrounding menopause or presenting later in life that are attributable to menopause and reduced ovarian function. Future advances in preventing and managing diseases and disorders in middle-aged and older women will require more careful delineation of those diseases and disorders that are attributable to menopause and reduced ovarian hormone levels versus those diseases that are not. Such advances are critically needed to clarify ambiguities in the presentation of age-related disease, to improve diagnosis and treatment, and to constrain health care costs.

The most profound and universal alteration in the mature aging endocrine system occurs in women and is due to menopause. However, while menopause is a universal phenomenon in women,

there is considerable individual variation among women in the age of menopause and in the manifestation of perimenopausal signs and symptoms as well as what may be considered menopause-related *sequelae*. The perimenopausal and postmenopausal experience encompasses a complex interaction of sociocultural, psychological, and environmental factors as well as biological changes relating strictly to altered ovarian hormone status or deficiency. In the United States and many Western countries, the perimenopausal experience is usually perceived largely in negative terms—as a transitional phase dominated by disturbing physical and mental symptoms. It has been suggested that highly negative characterizations of menopause may be due to an over-sampling of clinic-based populations of perimenopausal women, who, seeking treatment for symptoms, were more readily available for study and whose experiences represented the extremes of a difficult transition. Importantly, our knowledge base on menopause is extremely narrow in that the majority of studies have been of white women (of northwest European ancestry); very little is known about the range of perimenopausal experiences in women of other racial/ethnic groups. The sociocultural and behavioral antecedents and consequences of menopause have also not been well addressed, and major gaps exist in understanding factors that may profoundly influence the perception of, and response to, perimenopausal symptoms and *sequelae*. (See ch. 4).[5]

Smoking is associated with a menopause which occurs 1 to 2 years earlier than in nonsmokers.

The age of menopause and the timing of the onset of changes in the endocrine milieu may have profound implications for subsequent morbidity and even mortality. Women reporting an earlier menopause are reported to be at greater risk of CVD disease[6] and osteoporosis[7] but at a reduced risk of breast cancer.[8] However, data are conflicting, and methodological difficulties in assessing the relationship between age at menopause and the risk of subsequent conditions and diseases of aging abound in the literature base.

Although estimates for the median age of menopause range from 45–55 years of age worldwide[9] and between 50 and 52 years of age in white women from industrialized countries, our understanding of the determinants of, or factors which influence the age at, menopause is limited, with conflicting findings between studies commonly found. A prominent role appears to be played by race/ethnicity and lifestyle and sociocultural factors.[10] Recent studies have suggested that compared to white women, menopause is experienced at a later age in Japanese women and at a younger age in African-American[11] and Latin American[12] women and in women living in less-developed countries. Of all the variables studied, the most consistent relationship has been for smoking, which is associated with a menopause which occurs 1 to 2 years earlier than in nonsmokers.[13] Reproductive variables, including later age at menarche, oral contraceptive use, longer menstrual cycle length, and parity, have been (albeit inconsistently from study to study) associated with an older age at natural menopause. Other studies have shown an earlier menopause to be associated with lower socioeconomic status, lower educational attainment, low body mass index (BMI), or being on a weight-reducing diet.[14]

2. Aging In Women

Aging is associated with profound changes in body composition. For reasons that are incompletely understood, as they age, both men and women lose bone and muscle and increase their proportion of fat mass. These changes are of great public health significance, particularly as their associated structural (e.g., diminished muscle and bone strength) and metabolic (e.g., glucose intolerance, hyperinsulinemia) *sequelae* have been implicated in the development of frailty and morbidity (including heart disease, hypertension, osteoporotic fractures, and osteoarthritis).

Sarcopenia, defined as reduced muscle mass, is a well-known consequence of aging and occurs in parallel with reductions in muscle strength and, to some extent, muscle quality.[15] Importantly, decreased muscle mass and strength can impair physical performance in the elderly and are associated with an increased risk of physical frailty, declines in functional capacity, impaired mobility, and falls.[16]

A recent study suggests that the menopause transition is associated with deleterious changes in body composition and fat distribution, promoting the selective accumulation of fat in the intra-abdominal compartment. However, while increases in total and central adiposity were observed, no differences in fat-free mass were noted, which suggests that menopause may have less impact on the processes promoting muscle loss.[17]

As both men and women age, collagen synthesis is reduced, and the skin becomes progressively thinner and wrinkled. The decrease in collagen synthesis is similar in other connective tissues and in tissues rich in collagen, such as the conjunctiva and articulation capsules. Although ERs are present in the skin,[18] thus defining this tissue as a target tissue—and it is widely believed that estrogen deficiency affects epithelial tissues—there is a dearth of prospective observational data using validated methods to assess skin quality in different racial/ethnic groups exposed to varying environmental factors. Importantly, the ability to differentiate the effects of menopause from those of aging is very limited as skin quality can be substantially influenced over time by genetic, smoking, and environmental influences, particularly ultraviolet exposure, which can cause premature aging of the skin. There is evidence from experimental studies that estrogen can stimulate collagen biosynthesis and maturation in animal models[19] and increase skin collagen content in humans.[20] Estrogen use in humans has been associated with greater collagen content, thickness, elasticity, and vascularization.[21] Increases in facial hair, temporal hair loss, and deepening of the voice often observed in elderly women have been linked to the relative androgen dominance after menopause. Evidence suggests that estrogen administration can prevent hair loss,[18,22] and the frequent complaint of "dry eyes" (*keratoconjunctivitis sicca*).[23] However, there have been few RCTs demonstrating major benefits of HRT on the skin, hair, or sensory organs, such as the eye.

Recent studies have suggested that compared to white women, menopause is experienced at a later age in Japanese women and at a younger age in African-American and Latin American women and in women living in less-developed countries.

Because aging is associated with decrements in both skin thickness and BMD, it has often been postulated that measurement of the thickness of skin can be used to predict the risk of osteoporosis after menopause. However, despite significant statistical correlations between skin thickness and bone mineral content (BMC), the risk for osteoporosis cannot be accurately deduced from skin thickness in an individual patient.[24, 25]

3. Definitions

The word "menopause" ("ménespausie") was used for the first time in 1816 by Gardanne.[26] Initially, the phenomenon of menopause was explained as a deficiency of ganglionic regulatory functions. In 1910, Marshall[27] recognized that the ovary should be classified as an endocrine organ. From the endocrine perspective, the menopause represents a primary ovarian insufficiency and has an inception between the ages of 40 and 56 years, with a mean age of 51 years.[28] From a scientific perspective, natural menopause coincides with the FMP, and this cannot be determined until there have been[12] months of amenorrhea.[9] This definition is based on clinical epidemiological evidence that the probabil-

ity of resumption of menstruation after 12 months of amenorrhea is vanishingly small.[29,30]

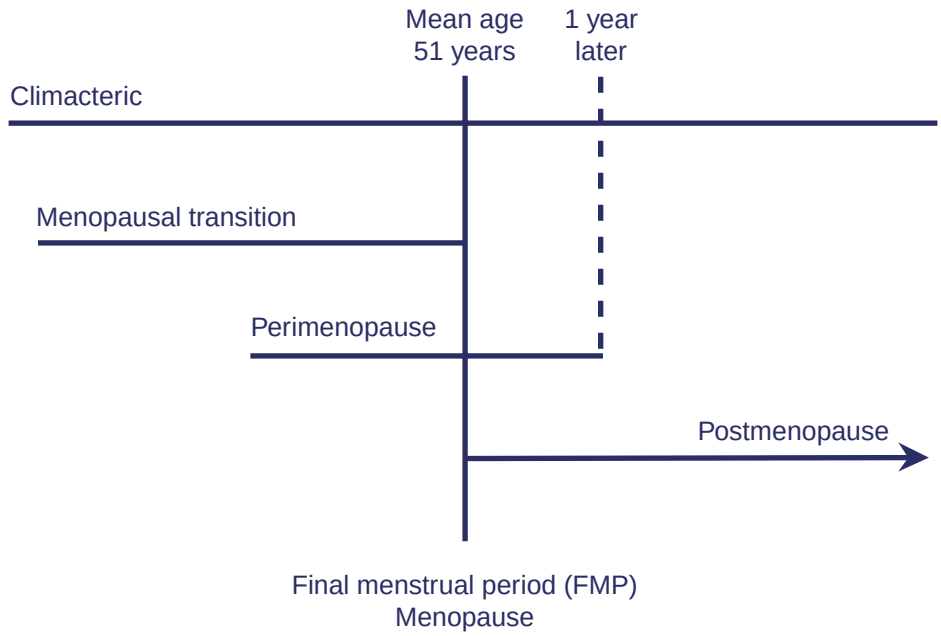
Much confusion has been caused by differing definitions used in relationship to changing ovarian status. Definitions were provided by the World Health Organization (WHO) Scientific Group on Research on the Menopause in the 1990s.[9] More recently, these definitions and others were considered by the Council of Affiliated Menopause Societies (CAMS) of the International Menopause Society (IMS). The only change recommended to the WHO definitions was the inclusion of the term "climacteric," considered by many clinicians to be descriptive of this phase of life. The list of menopause-related definitions given below was approved by the IMS in October 1999, in Yokohama, Japan.[31]

TERMS	SOURCE
Menopause (natural menopause)	**WHO**

The term "natural menopause" is defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity. Natural menopause is recognized to have occurred after 12 consecutive months of amenorrhoea, for which there is no other obvious pathological or physiological cause. Menopause occurs with the FMP, which is known with certainty only in retrospect a year or more after the event. An adequate biological marker for the event does not exist.

FIGURE 2–5

Relationships Between Different Time Periods Surrounding the Menopause



Perimenopause **WHO**

The term "perimenopause" should include the period immediately prior to the menopause (when the endocrinological, biological, and clinical features of approaching menopause commence) and the first year after menopause.

Menopausal transition **WHO**

The term "menopausal transition" should be reserved for that period of time before the FMP when variability in the menstrual cycle is usually increased.

Climacteric **IMS**

This phase in the aging of women marks the transition from the reproductive phase to the nonreproductive state. This phase incorporates the perimenopause by extending for a longer variable period before and after the perimenopause.

Climacteric syndrome **IMS**

The climacteric is sometimes, but not necessarily always, associated with symptomatology. When this occurs, it may be termed the "climacteric syndrome."

Premenopause **WHO**

The term "premenopause" is often used ambiguously to refer to the 1 or 2 years immediately before the menopause or to refer to the whole of the reproductive period prior to the menopause. The group recommended that the term be used consistently in the latter sense to encompass the entire reproductive period up to the FMP.

Postmenopause **WHO**

The term "postmenopause" is defined as dating from the FMP, regardless of whether the menopause was induced or spontaneous.

Premature menopause **WHO**

Ideally, premature menopause should be defined as menopause that occurs at an age more than two standard deviations below the mean estimated for the reference population. In practice, in the absence of reliable estimates of the distribution of age at natural menopause in populations in developing countries, the age of 40 years is frequently used as an arbitrary cutoff point, below which menopause is said to be premature.

Induced menopause **WHO**

The term "induced menopause" is defined as the cessation of menstruation, which follows either surgical removal of both ovaries (with or without hysterectomy) or iatrogenic ablation of ovarian function (e.g., by chemotherapy or radiation).

Figure 2–5 shows the relationships between different time periods surrounding the menopause.

4. Physiology

The process of the menopausal transition appears to take about a decade. The earliest signs of this transition are (1) shorter menstrual cycles by 2–3 days and (2) infertility. After birth, the number of oocytes continuously decreases. At puberty, 1 million oocytes are left.[32] This number decreases to 0.3 million by the age of 20 years.[32] Menopause is marked by the exhaustion of the ovarian supply of oocytes.[33] Although only approximately 400 follicles or less than 0.01 percent of all oocytes proceed through ovulation between menarche and menopause,[33,34] long-standing amenorrhea or the prolonged intake of a contraceptive pill does not seem to postpone menopause.[13] Reduced fertility due to the aging process of the oocytes and to abnormal follicular maturation is the first sign of ovarian aging. After the age of 40, about 30–50 percent of all cycles show an abnormal basal temperature.[35,36] Two to eight years before menopause, the incidence of luteal insufficiency and anovulatory cycles increases,[37] resulting in a higher incidence of persisting follicles and dysfunctional bleeding. Shorter menstrual cycles appear to be detectable at about age 38–40.[38,39] The subtle but common shortening of the intermenstrual interval is clinically valuable, as it seems to be predictive of other perimenopausal changes.

Subtle reproductive hormonal changes occur in the face of these minor cycle changes. FSH appears to rise throughout reproductive life, but the elevation becomes obvious in the late thirties/early forties in women.[40] Although it is elevated for most of the menstrual cycle, early follicular phase FSH concentrations are most easily discriminated from "normal" concentrations on cycle days 2–5. An elevated FSH is a harbinger of menopause, although it may still be many years away, and has clearly been shown to augur poorly for future fertility.[41] It is a poor predictor of age at menopause, however, and the clinician cannot make any conclusions on the timing of an individual woman's menopause based upon the presence or degree of FSH elevation.[42]

On the other hand, as long as the active follicular phase permitting the maturation of healthy follicles remains stable and the luteal phase normal, fertility is maintained. Therefore, contraception is still needed during the menopause transition, despite moderately elevated FSH levels. An isolated elevated serum FSH level is not proof of the occurrence of menopause and is not sufficient to consider a perimenopausal woman infertile so that she could cease reliable contraception.[43]

4.1 Clinical Factors

Environmental influences may alter the ovarian aging process. Smoking advances the age of menopause by about 2 years.[28] Recent studies suggest that high levels of galactose consumption may do the same. However, most of the determinants of menopause are innate. Familial and genetic factors appear to be the most predictive at present.[44] One recent study described an ERα polymorphism that is associated with a 1.1 year advancement in the age at menopause and a nearly threefold RR of hysterectomy for benign disease.[45] Ovarian surgery, adhesions, and pelvic endometriosis appear to be associated with poor ovarian stimulation for in vitro fertilization and perhaps are also risk factors for early age at menopause.[46]

Menstrual cyclicity is currently the best indicator of menopausal status. The large variability in intermenstrual intervals that occurs at this time of life probably reflects a combination of short cycles[38] and skipped cycles. Treloar et al.[37] reported a detailed analysis of intermenstrual intervals of women encompassing over 20,000 menstrual cycles. Variability of cycle length was enormous in both the perimenarcheal years and the years of menopausal transition. Cycle length shortening is probably due to elevated FSH levels in the early follicular phase/late luteal phase of the cycle.

The classic characterization of the menopause transition was provided by Sherman and Korenman (1975).[47] Six women were followed in detail up to and including the actual last menstrual period. Their data described the key features of the menopause transition, which are still under investigation today, almost 20 years later: (1) a monotropic rise in FSH secretion, (2) continued folliculogenesis and evidence of ovulation up to the FMP, and (3) periods of hypoestrogenemia concomitant with large FSH rises. The loss of inhibin restraint was first hypothesized by this group.

Metcalf followed perimenopausal women longitudinally throughout their forties and fifties.[48] This characterization of the perimenopause included the observation that the key feature of passage "through" menopause was the subsequent complete absence of luteal activity. Therefore, a permanent failure of ovulation is the cardinal observation. Within the first year after a woman's FMP, variable estrogen excretion was observed; thereafter, estrogen excretion was abidingly low and basal.[48,49] These results have been confirmed by others in serum studies.

Using 6 years of prospective annual measures, Burger et al. reported that mean FSH levels began to increase from about 2 years before the FMP, increasing most rapidly about 10 months before the FMP, and had virtually plateaued by 2 years after the FMP.[50] Mean estradiol levels started to

decrease about 2 years before the FMP, decreased most rapidly around the time of the FMP, and had virtually plateaued by 2 years after the FMP.

Klein et al. reported the endocrinology of follicles and peripheral hormones in women in their early forties.[51] Shortened follicular phases, apparent accelerated folliculogenesis, and a monotropic FSH rise were all confirmed in these women. Follicle fluid was aspirated and compared to younger controls. Follicle fluid in reproductively aged women contained more estradiol and less insulin-like growth factors than younger women, despite fewer granulosa cells per follicle.[51] Oocytes contained aberrant meiotic spindles in abundance, evidence for chromosomal damage to the oocyte either due to its age alone or to inappropriate paracrine/endocrine cues.[52] These data emphasize that reproductive aging begins earlier than previously believed (as early as age 40) and is happening in a very significant way before menstrual cycles become irregular and certainly before women notice any symptoms. This becomes particularly poignant in the office setting when healthy women in the older reproductive age group are informed of their poor fertility potential despite their robust, asymptomatic status.

Santoro et al.[53] observed a small cohort of women in the mid-perimenopausal years when menstrual cyclicity was beginning to deteriorate. Compared to younger women, these perimenopausal women had evidence of greater estrogen excretion in conjunction with elevated FSH and LH concentrations and decreased luteal phase progesterone metabolite excretion.[53] Irregularities of menstrual cyclicity were characterized by occasionally dramatic excursions of estrogen well beyond the normal range for younger women. Thus, "skipped" cycles in the perimenopause may be due to either failure of folliculogenesis and hypoestrogenemia or accelerated and sustained estrogen secretion. These findings have recently been confirmed in a larger, epidemiologic sample of perimenopausal women.[54] The common gynecological problems of women in the perimenopause, such as dysfunctional uterine bleeding, growth of uterine leiomyomata, and the frequent utilization of dilatation and curettage (D&C) and hysterectomy for women in this age group, may be explained by the persistence of these hormonal patterns.

4.2 FSH, Inhibins, and Reproductive Aging

The monotropic rise in FSH that accompanies the onset of the menopause transition has been known since the 1970s.[47] At that time, the prevailing notion was that a lack of inhibin "restraint" of FSH caused the elevation, the so-called "inhibin hypothesis."[47] Inhibins are molecules in the transforming growth factor-β (TGF) peptide superfamily. (See also ch. 5, sec. 6.) They are produced by the granulosa cells of the ovary. They are heterodimeric, consisting of a common alpha subunit and a specificity-providing beta subunit. Inhibin A appears to be expressed in large, dominant follicles and the corpus luteum while inhibin B appears to be a product of small follicles.[55] Although they were believed to act via specific binding to a cell surface receptor, inhibin receptors have only recently been identified.[56]

The available data shows that after hysterectomy menopause occurs earlier.

Thus, two decades after it was proposed, the inhibin hypothesis has been confirmed by measurement. Diminished inhibin A and B have been reported in the circulation of older reproductive-aged women.[57–60] Elevated FSH in perimenopause may be more tightly linked to this loss of inhibitory tone, rather than to decreased estradiol production by the perimenopausal ovary. At the early stages of the menopause transition, women appear to be estrogen replete and do not demonstrate evidence of decreased estradiol until they are within several years of their FMP.[50–53] In fact, in some perimenopausal women, the elevated FSH may lead to "overshoot" and the consequent production of supraphysiological amounts of estradiol.[53–61] Follicular phase inhibin B appears to be detectably decreased

in the early perimenopause, concomitant with the rise in FSH.[50] As the transition progresses, follicular phase inhibin A declines detectably as well, perhaps as a later event.[50]

In addition to these early changes in inhibin A and B, activin A has been shown to be elevated in perimenopausal women.[58,60] Activins are the beta homodimers of the inhibin molecules and exist as activin A and B. While they clearly play a local role in pituitary FSH secretion, their ability to act as endocrine factors influencing the production of FSH is not established. Moreover, activins circulate bound to follistatin, their serum-binding protein. The relatively high affinity of follistatin for activin, as well as its abundance in serum, suggests that activin may exert most of its effects in a paracrine or autocrine, and not endocrine, fashion.

Considering the high incidence of hysterectomy in some countries, this observation is clinically relevant.

4.2.1 Androgens in the Perimenopause

Circulating androgens in women reflect contributions from adrenal, ovarian, and peripheral sources. When relatively stable adrenal hormones, such as dehydroepiandrosterone sulfate, are measured, a dramatic decline is observed across the adult lifespan.[62, 63] An independent effect of the process of menopause on circulating adrenal androgens has not been observed.

Together with the age-related decline in adrenal androgen production, ovarian androgens, particularly testosterone and androstenedione, decrease throughout adult life as well.[64,65] Metabolites of dihydrotestosterone demonstrate the most precipitous declines between the ages of 20 to 40 years.[63] While some studies suggest that a small menopause-associated decrease in testosterone occurs,[66,68] other longitudinal, prospective studies have not documented any acute decrease in testosterone or androstenedione associated with the menopause transition.[69,70] The modification of testosterone bioavailability by sex hormone binding globulin (SHBG) may play a role in perimenopausal physiology; however, it is controversial as to which direction SHBG changes across menopause, with some studies observing a decline[67,70] and others an increase.[69] It seems clear that the major decline in circulating testosterone occurs well before the menopause transition.[65] Based upon current well-designed studies and including observations about both adrenal and ovarian androgens, the medical "myth" that menopause is associated with an acute drop in androgens does not appear to be tenable any longer.

4.2.2 Neuroendocrine Changes

The loss of "positive feedback," that is, the ability to respond to an estradiol challenge with an LH surge, appears to be another feature of the perimenopause which leads to potential morbidity for women.[71] It is unclear why this ability is lost, as it appears to be regained in the postmenopause, when LH surges in response to estrogen challenge have been well documented.[72,73] Perhaps the other concurrent abnormalities of the endocrine milieu predispose women to this temporary state. It may be the result of enhanced susceptibility to the negative feedback of estradiol.[60,74]

Whereas in young premenopausal women estradiol is the major circulating estrogen, estrone becomes the dominant estrogen after menopause. Estrone is produced primarily by peripheral aromatization of androgens.[75] Aromatization takes place in the adipose tissue, muscle, bone marrow, skin, brain, and other tissues. Estrone is less potent than estradiol. The postmenopausal concentration (20 to 60 pg/mL) of estrone equals or surpasses the range observed in healthy premenopausal women. The conversion of androgens to estrogens (mostly estrone) increases from approximately 1.4 to 2.7 percent in premenopausal compared to postmenopausal women.

4.3 Menstrually Defined Menopausal Status

Most observational studies of changes in health outcomes related to menopause have tried to subcharacterize the perimenopausal years based on changes in menstrual status.[76] The Korpilampi Workshop in 1985[77] defined the boundary between the premenopausal and perimenopausal states by the reporting of changes in menstrual flow and/or regularity. They identified that the reliability of such definitions for predicting the further movement to postmenopause had not been sufficiently studied.

Brambilla et al.[29] proposed a method for operationally defining the onset of perimenopause as (1) a self-report of 3 to 12 months of amenorrhea, and (2) for those without amenorrhea a self-report of increased menstrual irregularity. They stated that validation of this definition would require the examination of longitudinal hormonal changes with changes in the menstrual cycle.

Using prospective data, the Melbourne Women's Midlife Health Project[76] found that women who reported not having had a menstrual period in the last 3–1 months were older, had lower estradiol and inhibin levels and higher FSH, and were more likely to report hot flushes and to self-rate themselves as having started the menopausal transition, compared with women who had menstruated in the last 3 months. Subsequent analysis from the same project compared retrospective self-reports of menstrual status with prospectively kept menstrual diary data[78] for women reporting at least one menstrual period during the previous 3 months. This study found that no significant agreement exists between retrospective self-reports and prospective diary-based measures of change for cycle frequency nor for flow. Thus, retrospective self-reports at interview of changes in menstrual frequency and flow should not be regarded as reliable measures for the purpose of determining menopausal status.

4.3.1 Hormone Measures

Relatively few studies have undertaken any hormonal determinations. Endocrine change occurs for some years prior to the cessation of menopause,[50] so it is important to acquire measures while women are still menstruating regularly, some years before menses cease. Other issues involved in hormone measures have been those of the frequency of sampling (annual versus daily or weekly), type of sampling (plasma, urine, salivary), phase of the cycle sampled, and the presence of floor effects due to the lack of sensitivity of assays at the lower levels of estradiol and inhibin, which occur in the postmenopause.

4.3.2 Age and Length of Followup

Age at baseline and length of followup are important issues. Followup has often been only in the order of 3 years.[79–81] The Melbourne Women's Midlife Health Project found that after 3 years of followup, only 12 percent of women had become naturally postmenopausal (12 months of no bleeding after reaching their FMP). At the end of 7 years of followup, only 39 percent of the women in this cohort were naturally postmenopausal, reflecting splintering of the sample as well as length of followup.

Whereas in young premenopausal women estradiol is the major circulating estrogen, estrone becomes the dominant estrogen after menopause.

4.4 Natural Menopausal Transition Versus Induced Menopause

A major problem in menopause research has been to establish the health experiences associated with natural menopause and how these may differ when menopause is induced. A number of studies suggest that symptom experience is likely to be worse when women have undergone surgical menopause.[82] Documentation of medical treatment, which may impact ovarian functioning (surgery, chemotherapy, irradiation), and documentation of medication

taken by women are needed so that these women may be treated separately in the analysis. The available data show that after hysterectomy menopause occurs earlier. The mean age of ovarian failure in the hysterectomized group was 45.4 ± 4.0 years (standard deviation) and was significantly lower than the mean age of 49.5 ± 4.04 years in the nonhysterectomized control group ($p < 0.001$).[83] Considering the high incidence of hysterectomy in some countries, this observation is clinically relevant. In the United States, one woman in three undergoes hysterectomy by age 65. The rate in the European Union nations ranges from 6 to 20 percent.[84] In the 1980s, of a total sample of women in six European countries, 11.4 percent had undergone hysterectomy, the highest percentage being found in Italy (15.5 percent) and the lowest in France (8.5 percent).[85] In Europe, the prevalence of surgical procedures is higher in privately insured persons than in persons with only basic insurance. Among 25- to 74-year-old privately insured women, the lifetime prevalence of a hysterectomy is 30 percent with low educational status and 13 percent with high educational status ($p < 0.001$).[86] A European woman without education has a RR of 2.2 (1.1–4.4) for hysterectomy compared to an educated woman.[87] Similar data are reported from the United States.[88] In the United States, hysterectomy rates increased with age, and rates for black women slightly exceeded the rates for whites.[89] Hysterectomy with ovarian preservation is associated with increased risk of high diastolic blood pressure, diagnosis of hypertension, and increased BMI but is not associated with other heart diseases.[90] Women who underwent hysterectomy reported more discomfort and frequent symptoms of urogenital atrophy.[91]

4.5 Exogenous Hormones

Exogenous hormones may mask the effects of changing ovarian function, so that women taking the oral contraceptive pill or any HRT must also be treated separately in analyses. In many countries, an increasing number of women are choosing to adopt HRT, and this may lead to a splintering of the sample and even to insufficient numbers to examine the effects of the natural menopausal transition. Holte reported that sample size in a longitudinal study over 5 years was reduced from 200 to 56.[92]

Prospective studies allow the profile of those who adopt HRT to be compared with that of nonusers, in order to elucidate any biases which are related to hormone selection and which may affect the endpoint.[93]

5. Qualtiy of Life and Menopause

Concepts of quality of life vary from measures of subjective well-being, symptoms, or other indicators of health status to that of functional status. Assessing the impact of a condition on quality of life is particularly relevant. A range of measurement tools are available for monitoring how climacteric symptoms affect patients with regard to their well-being, sleep disturbance, other somatic symptoms, and cognitive and sexual functioning. Only standardized and well-validated measurement tools should be used.

The close association between lifestyle and health is generally recognized. Much is still to be learned about the reciprocal influences of lifestyle, decision to use HRT, and quality of life. The most relevant factors influencing a woman's quality of life during the menopause transition appear to be her previous emotional and physical health, her social situation, her experience of stressful life events (particularly bereavements and separations), as well as her beliefs about menopause and aging. Those who seek medical help for menopausal problems tend to report more physical and psychological problems in general. They are more likely

to be under stress and to hold particular beliefs about the menopause.[94]

Health and quality of life related to menopause may be enhanced by providing: (1) balanced information about the menopause to women and to their families; (2) discussion of attitudes towards the menopause, with the promotion of positive attitudes towards aging and menopause; and (3) health promotion sessions focusing upon healthy lifestyles of balanced diet, daily exercise, and cessation of smoking.[94]

6. Future Needs

- Markers of a woman's proximity to menopause are lacking. More menstrual diary research studies with concurrent hormone measures are needed to identify biomarkers of menopausal status.
- More research is needed on fertility and contraception in the perimenopause.
- Further understanding is needed about the reciprocal influences of lifestyle, decision to use HRT, and quality of life.
- Providing women and their families with balanced information about menopause, fostering positive attitudes towards aging and menopause, and encouraging healthy lifestyles may improve their health and quality of life related to menopause.

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Chapter 3: Symptoms and the Menopause

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Key Points[a]

1. Conflicting findings regarding which symptoms are related to hormonal changes of menopause reflect different research methodologies and their limitations.
2. When symptom checklists are used, middle-aged women are highly symptomatic.
3. Age related symptoms may be differentiated from those related to the menopausal phase.
4. Only vasomotor symptoms, vaginal atrophic symptoms, and breast tenderness consistently vary with the phase of the menopause transition and are significantly affected by the administration of hormones in double blind RCTs [A].
5. Other symptoms, such as insomnia and mood, may be affected by the presence of bothersome vasomotor symptoms.
6. Symptoms are influenced by psychosocial and lifestyle factors.

Conflicting findings regarding which symptoms are related to hormonal changes of menopause reflect different research methodologies and their limitations.

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[a] Evidence categories are given in square brackets. A = randomized controlled trials (rich body of data); B = randomized controlled trials (limited data); C = nonrandomized trials and observational epidemiologic studies; D = Panel expert judgement. (See also table 1–1).

1. Introduction

A large number of symptoms have been variously linked with the menopause transition. Important clinical questions include the following:

1. What are the most frequent symptoms experienced by middle-aged women?
2. Which of these are related to the hormonal events reflected in the different phases of the menopausal transition, and which relate to aging?
3. What is the role of other psychosocial and lifestyle factors in determining women's experience of symptoms?
4. What evidence is there for the effectiveness of treatment interventions for symptoms linked to the transition to menopause?

2. Quality of Life and Symptoms

Symptoms are influenced by psychosocial and lifestyle factors.

The term "quality of life" refers to a subjective perception on the part of both researcher and subject. Areas covered range from health status (SF–36),[1] life satisfaction,[2] coping,[3] and depression (Center for Epidemiologic Studies Depression scale)[4] to scales measuring symptoms thought to be characteristic of specific states, such as menopause. This breadth of coverage and absence of a single, widely accepted definition may be a limiting feature of the concept of quality of life.[5] There are two different types of measures: global quality of life or aspects specific to a particular disease (such as osteoporosis) or a physiological state such as the hormonal changes underlying the menopause transition. Scales designed to measure the latter make the assumption that the more symptoms are present and the more severe those symptoms are, the lower is the ensuing quality of life. Yet there has been surprisingly little research linking symptom presence with the other more global aspects of quality of life described above.

There is debate as to whether the term "sign" or "symptom" should be used when referring to the events of the menopausal transition. The term "sign" is often used to refer to objective clinical manifestation of a disease, such as a lump or a bruit, whereas the term "symptoms" is used to refer to those bodily perceptions presented as complaints by the individual. This chapter uses the term "symptom" in this context.

3. Methodological Aspects of Measuring Symptoms

Conflicting findings as to the etiology of symptoms in midlife reflect some of the methodological difficulties inherent in menopause research as well as specific issues pertaining to the measurement of symptoms, such as sample selection, validity of symptom measures, age at baseline and length of followup, separation of the effects of the natural menopausal transition from that of induced menopause, statistical and experimental design. The most obvious methodological issue is the potential to confuse studies evaluating the effects of estrogen or differences between estrogen users and nonusers on various outcomes as "studies of menopause." In order to distinguish menopause-related changes (due to changes from altered levels of estrogen and/or other sex hormones) from those of aging or disease, it is necessary to elucidate the processes of the transition from premenopause to postmenopause. Although there is an abundance of studies and findings on the effects of ERT on various physiological and psychological outcomes, the actual processes and mechanisms of follicular depletion which underlie the transition to menopause are poorly understood.

3.1 Study Type

Clearly a number of different research modes can be used to explore whether the menopause transition affects quality of life, varying from studies of primates (often involving extirpative surgery and then hormonal intervention), to clinical trials of

women who may have reached natural menopause or had menopause induced. However, clinical experience is based on a small proportion of self-selecting, predominantly ill women and may not be representative of most women's experience of the menopause.[6,7] Population-based studies have demonstrated that women who seek treatment differ in systematic ways from those who do not.[6,7] Patient-based samples are biased in terms of education, socioeconomic status, other health problems, and incidence of general depression.[8] Clinical trial samples often included women who had undergone surgical menopause, and the hormones administered were usually synthetic, so these studies do not inform us of the relationship of symptoms to the natural menopause transition. Only studies of women derived randomly from the general population provide findings which can be confidently generalized to be the experience of most women of that particular culture and geographic location. Reliable transcultural comparisons are rare because rating scales and questionnaires cannot be easily translated to other languages: a specific term may not exist in the target language or may have a slightly different meaning. This problem exists even for translations within the group of western languages and points to the importance of validation.

There are intercultural and intracultural differences in symptom reporting. Kaufert and Syrotuik[9] describe how stereotypes held by differing social and cultural groups act as a framework within which an individual can select and organize and label experience. Moreover, in menopause research there is a risk that stereotypes will become operative whenever subjects know the topic of the research.

3.2 Rating Scales

Health outcomes and their determinants can be measured by validated rating scales. The failure to use adequately validated scales has been a major problem in menopause research. In the classical Kuppermann Menopausal Index,[10] a numerical summation of 11 menopausal complaints derived from clinical experience in New York in the 1950s, as well as in other rating scales, the importance of "neurovegetative symptoms" is overestimated, whereas other changes are neglected. This particularly applies to the measurement of sexuality and of symptom experience. For example, with regard to sexuality, relatively few of the population-based studies of the menopause transition have made any inquiry about sexual functioning. Differing measures of sexual functioning have been used but studies often fail to offer any data on the validity or reliability of these measures in their local population. The research process itself may result in response bias. This includes interviewer bias in the phrasing of questions and specification bias if the variable under study is not well specified to the full understanding of the subject.

3.3 Symptom Measure

A major methodological issue is that of the symptom measure utilized and its validity and reliability for the cultural group studied. The standard method used for collecting information on the prevalence and severity of symptoms has been a checklist of symptoms. But the checklist in itself introduces a number of biases, including the problem of elicitation. For example, Wright,[11] interviewing women of the Navajo tribe, found that virtually all respondents reported no bodily changes since menopause in relation to open-ended questions, but most responded positively to symptoms in the checklist. Holte[12] noted that the sounder the methodology, the lower the prevalence of symptoms. When frequency or bothersomeness of complaint are included, the reporting rate goes down further: irritability was reported by 57 percent of premenopausal women as being present occasionally, but only 10 percent of the same women reported that it was there frequently.[12] The presence of symptoms "occasionally" does not indicate their impact on the woman and may not be clinically relevant or indicative of treatment needs. Porter et al.[13] assessed the impact and prevalence of symp-

toms in a Scottish postal survey of 6,096 women aged 45–54. Fifty-seven percent of the cohort had experienced a hot flush, but only 22 percent said that it had been a problem. Similar disparity existed for night sweats (55 percent and 24 percent) and dry vagina (34 percent and 14 percent). Only 4 percent had experienced none of the symptoms.

The most frequently used checklist has been based on a numerical summation of 11 menopausal complaints, the Kupperman Menopausal Index, derived from clinical experience in New York in the 1950s. The index was a combination of self-report and physician ratings. The index included 11 symptoms (vasomotor, paraesthesia, insomnia, nervousness, melancholia, vertigo, weakness (fatigue), arthralgia and myalgia, headaches, palpitations and formication) rated on a 4-point scale. In a critical review, Alder[14] noted that terms were ill defined, categories included overlapping scores, and scores were summed without being based on independent factors. Symptoms seemed to be arbitrarily selected; omitted were measures of vaginal dryness, dyspareunia, and breast tenderness. The following year Kupperman and coworkers, including Blatt,[15] described a modification, which allowed for some symptoms to be weighted more than others. Weighting was used without statistical justification. Later, investigators, such as Neugarten and Kraines,[16] extended the list to 28 symptoms but found that only 9 of these distinguished menopausal women from those at other developmental phases. These authors, and many since, arbitrarily categorized groups of symptoms. Greene[17] was the first to use factor analysis as the basis for categorizing symptoms into three factors, vasomotor, somatic, and psychological. But Greene's study contained a number of flaws. Although his 30-symptom list was constructed from the scale of Neugarten and Kraines,[16] he failed to include breast pain, somewhat curiously as Neugarten and Kraines had found this symptom to be associated with menopausal women. Nor did he include symptoms of vaginal atrophy. These symptoms (mastalgia and atrophy) were still not included in a later amended 20-item list.[18]

Whether psychological complaints vary with the menopause transition has been a key concept, yet the capacity of most symptom checklists to adequately measure psychological morbidity is unknown.[9] In their Manitoba study, symptoms measuring psychological morbidity had to conform to scales used by psychological epidemiologists, and concurrent validity was sought. The symptom checklist was not restricted to items with an association with menopause but was embedded in an 18-item general symptom list adapted from one used in a community health survey. The 11 symptoms forming the menopausal index were derived from the International Health Foundation studies (hot flush, night sweats, dizziness, rapid heart beat, pins and needles in hands and feet, tiredness, irritability, headaches, depression, nervous tension, and insomnia). Interestingly, the list did not include vaginal atrophy symptoms, yet the International Health Foundation list was supposedly chosen as a "succinct summary of the core symptoms as described in the clinical literature." Four factors were found. Hot flushes and night sweats group together as a separate factor, and five symptoms burdened on a psychological factor. These were five of the six symptoms in the International Health Foundation arbitrary classification of "symptoms of the nervous system." A strong association was found between the five psychological symptoms and the two standardized measures of psychological morbidity used for concurrent validity.

Greene[18] compared the findings of seven factor analytic studies. Despite different methodologies and sampling, he found that vasomotor symptoms (hot flushes, night sweats) always formed a separate cluster, totally independent of other symptoms. There was also agreement that a number of symptoms cluster together to form a general somatic or perhaps psychosomatic factor: pressure or tightness in head or body, muscle and joint pains,

numb-tingling feelings, headaches, feeling dizzy or faint, breathing difficulties, and loss of feeling in hands or feet. A further group of symptoms cluster together to form a psychological factor, which in some studies can be subdivided into anxiety and depression.

3.4 Cross-Sectional Versus Longitudinal Design

As indicated above, observational studies of population-based samples are the best way to determine the symptom experience of women in relationship to the phases of the natural menopause transition. However, they often suffer from being cross-sectional in design[19] rather than having the power of longitudinal analysis of the same women through the menopause transition.[20] Cross-sectional studies can only indicate whether associations exist and are unable to determine causality. Cross-sectional studies have certain advantages. They are more convenient and less expensive to carry out. Subjects are only asked to participate on one occasion so that the response rate is likely to be higher than when subjects are asked to contribute time for assessments on a regular basis. Those who accept to participate in a longitudinal study may differ in certain systematic ways from those who decline and this may introduce bias into the sample.[21] Thus, the sample participating in a cross-sectional study may be more similar to a general population sample than that of a longitudinal study sample.

Splintering of the study population can continue for other reasons during the accrual process.[22] From the target group, only those persons available to the investigator are potentially eligible for study. Further splintering occurs after applying inclusion and exclusion criteria. After being admitted to the study, the subject's records must be properly filled in: missing data on some variables can lead to exclusion of the subject with some analytic techniques. If the reason for drop-out or premature early termination of the study is related to the studied endpoint, this can induce further bias. Another source of error is that of confounding, which necessitates the need for multivariate analytic methods to control for the influence of the various factors that can affect an outcome. The majority of community-based studies have been cross-sectional and thus limit researchers to inferring apparent associations. Cross-sectional studies cannot control for premenopausal characteristics nor separate the effects of aging from those of menopause.

These studies are less satisfactory than longitudinal studies in which the same women are followed over time with the same instruments, so that what is being observed is change in the same population with time. Longitudinal cohort designs facilitate the identification of causal pathways and allow the effects of aging to be disentangled from those of menopause.[8] However, most longitudinal studies have used inadequate statistical methods, often resorting to a cross-sectional approach to data, which, as repeated measures, are no longer independent in nature.[23] Longitudinal collection of data reduces reliance on memory for long recall periods. The length of the recall period in cross-sectional studies can lead to further inaccuracy of data. This is not only true for the studied endpoints, but also for possible covariates at the time of occurrence. In longitudinal studies, there is the opportunity for measures to be made prospectively (such as menstrual diaries) rather than relying on self-recall, which may be substantially less accurate. When change over time is the key concern, a prospective design is mandatory.

3.5 Statistical Analysis

Most studies have only utilized univariate analysis and thus been unable to take into account the role of confounding or interacting factors. The findings of these studies are thus often contradictory. A major problem in the longitudinal studies has been the lack of a sensitive enough statistical analysis, which would use a within-subject-repeated-measures method, allowing for the various factors which may affect the quality-of-life measure, changes in those factors, and interactions with the menopausal transition to be identified.[23]

The analysis of longitudinal studies becomes more complex as the temporal dimension is added to the other possible components of the study. Many statistical approaches are possible. A simple and powerful technique is to calculate mean values prior to and following an event such as the FMP. To allow for the influence of multiple factors, linear regression is preferred to logistic regression where continuous data are available. For more information about evolution in time, more complex techniques are needed. A suitable technique is repeated measures multivariate analysis of variance using a number of contrasts to estimate various effects. Simple split plot or randomized block designs cannot be recommended as they often violate compound symmetry assumptions. For series involving more than 100 observations for each subject, time series and spectral analysis techniques should be considered. Structural equation modeling is recommended for examination in detail of a range of factors that may influence the studied endpoint, the presence of feedback and of latent or nonmeasurable variables.

In reviewing the extensive observational literature in this field accessible in Medline, we will concentrate on those studies which use adequate study design.[24] These include random sampling; describing the study as a general health survey, so that bias caused by emotional response to menopause is lessened; collecting information on current symptomatology, so that the problem of recall bias is minimized; utilizing an age range that encompasses the menopause transition, for example, 45–55 years for cross-sectional studies or a younger (mean) age group for longitudinal studies of the menopause transition, to ensure that women are premenopausal at outset; longer followup in longitudinal studies; and collection of data on menstrual status, hormone usage, and induced menopause, so that the phase of the menopause transition can be adequately determined. Where there are methodological problems such as poor response rate, these are outlined.

4. Prevalence of Symptoms in Middle-Aged Women: Relationship to Hormonal Events of the Menopause Transition and Aging

A few studies have tried to address this question by examining different symptom experiences for women of different age groups and menopausal status.

Two studies compared symptom checklist results for men and women of different age groups using lists from general practices. Results were presented by age groups rather than by menopausal status. Bungay et al.,[25] in a United Kingdom postal survey, found that four different patterns occurred by age and sex. Peaks of prevalence of flushing and sweating were closely associated with the mean age of the menopause. Less impressive peaks of minor mental symptoms were associated with an age just preceding the mean age of menopause. Complaints about aching breasts, irritability, and low backache diminished after menopause. Male and female curves were parallel for loss of appetite, crawling or tingling sensations on skin, headaches, difficulty with intercourse, indigestion, constipation, diarrhea, shortness of breath, coldness of hands and feet, dryness of skin, dryness of hair, aching muscles, aching joints, feelings of panic, feelings of depression, and stinging on passing urine.

A Dutch national study[26] of the symptoms in the Kupperman index experienced by men and women aged over 25 years, reported female/male ratios for each symptom. Only transpiration (excessive sweating) showed a significant increase at age 45–54, compared to younger age groups and then remained raised. No other symptom showed a significant increase in the age group 45–54, including the General Health Questionnaire score of mental health.

Most observational studies using symptom checklists find that middle-aged women are highly symptomatic. An Australian study[27] of women aged 45–54 found the symptoms most commonly experienced in the prior 2 weeks to be very dry skin (68 percent), backache (49 percent), forgetfulness

(47 percent), problems sleeping (39 percent), irritability (37 percent), and mood swings (36 percent). Hot flushes were reported by 25 percent of women (rank order 10) and sweating attacks by 13 percent (rank order 19). Vaginal dryness and discomfort was reported by 16 percent (rank order 17).

As noted earlier, there is consensus about the marked temporal relationship of vasomotor symptoms to menopause.[28] These begin to increase in perimenopause, reach a peak within 1–2 years of the FMP,[12] and remain elevated for up to 10 years.[29–31] McKinlay et al.,[32] in a followup study over 4 years of 1,178 premenopausal women, found increasing hot flushes—10 percent in early premenopause, 30 percent in early perimenopause increasing to 50 percent of women 1 year prior to the FMP—coinciding with late perimenopause, with reports of hot flushes starting to decline significantly 2 years after FMP and reaching 20 percent of women 4 years after FMP. Thus, hot flushes are not the most frequent symptoms reported, nor are they pathognomonic of menopause, being reported by younger menstruating women. A number of studies have shown an association between hot flushes and night sweats,[33] and some show an association between these vasomotor symptoms and insomnia.[34] Women who had an artificially induced menopause were more likely to still report flushing than were naturally menopausal women and to report more symptoms.[34] Only a few studies included any reported measure of dryness of the vagina. Oldenhave reports that dry vagina increased in the perimenopause to postmenopause, with a slight decrease > 10 years postmenopause, which may be explained by lack of a partner.[31] This complaint is related to hot flush reporting. There was less consistency regarding other symptoms. A number of cross-sectional studies, including the two Ede studies,[29,31] report a small but transient increase in nonvasomotor symptoms in perimenopause. There was no attempt to differentiate whether any increase in such symptoms is due to distress caused by vasomotor symptoms. A Norwegian 5-year prospective study found that vasomotor symptoms, vaginal dryness, heart palpitations, and social dysfunction increased with the menopausal transition, but that headache and breast tenderness decreased.[35] However, these results were based on only 59 of the 200 premenopausal women selected for the study. The author notes that the finding of heart palpitations must be treated with caution since it differs from all previous factor analytic studies.[35] Recently released results from the cross-sectional phase of the Study of Women's Health Across the Nation (SWAN) study have also found an increase in vasomotor symptoms and in psychological and psychosomatic symptoms related to menopause.[36] Analyses of data from 14,906 women aged 40 to 55 years found vasomotor symptoms burden on a different factor to psychosomatic symptoms. Perimenopausal and postmenopausal women, HRT users, and women who had a surgical menopause were all significantly more likely to report vasomotor symptoms compared to premenopausal women, with postmenopausal women having the higher OR. Psychosomatic symptoms (tense, depressed, irritable, forgetful, headaches) were reported more often by perimenopausal women, hormone users, and women with a surgical menopause than by premenopuase or postmenopausal women. A number of other studies, including recent longitudinal studies using validated mood scales, have not found an association between mood and menopausal status.[37]

The Melbourne Women's Midlife Health Project reported on the analysis of those women who after 7 years of followup had progressed through the menopause transition. Annual measures included a 33-item symptom checklist. Increasing significantly from early to late perimenopause were the total number of symptoms, hot flushes, night sweats, and dry vagina. Breast soreness/tenderness (mastalgia) decreased significantly with the menopause transition. Trouble sleeping showed a smaller increase, which was found to in part reflect bothersome hot

flushes.[38] (See figs. 3–1 to 3–5.) The onset of hot flushes was found to be related to decreased estradiol levels ($p < 0.01$), and the onset of night sweats was related to the change in estradiol level ($p < 0.05$).[38] Interestingly, breast tenderness was not included in the SWAN study reported above. The SWAN study found that vaginal dryness was related to vasomotor symptoms but did not reach the criteria for inclusion in the factor analysis, and results were not reported by menopausal status.[36]

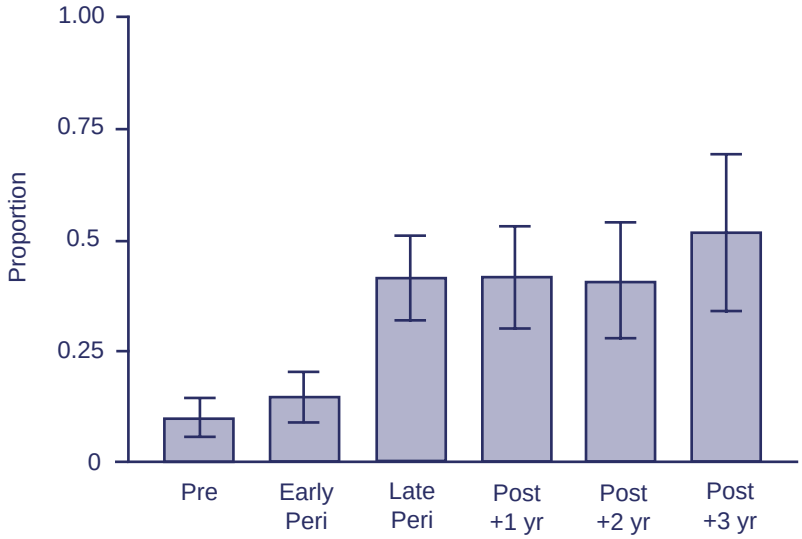
Epidemiological studies have found that only vasomotor and vaginal atrophic symptoms significantly increase as women pass through the natural menopause transition.

Longcope et al.[39] also report a significant negative association of hot flushes with estrone and estradiol levels amongst their sample of 241 Massachusetts women followed for 3 years. Thus, a number of epidemiological studies have found that only vasomotor and vaginal atrophic symptoms significantly increase as women pass through the natural menopause transition.

Although many theories have been suggested to explain the mechanism of menopausal flushing, none provide a satisfactory explanation.[40] Core body temperature elevations precede the menopausal hot flush and serve as one trigger of this heat loss phenomenon.[41] What is responsible for the core temperature elevation is a matter of speculation. Although vasomotor symptoms are associated with increasing FSH and decreasing estradiol levels,[38,42] it may be that vasomotor symptoms relate to the activity of another substance, in whose absence the activity of the thermoregulatory center is disturbed.[42] This substance may be common to both ovaries and testes and explain the fact that the male flushes after orchidectomy and the woman after ovarian failure. Each hot flush is accompanied by a gonadotrophin-releasing hormone (GnRH) pulse with a consecutive episode of FSH and LH secretion.[43] Because hypophysec-

FIGURE 3–1

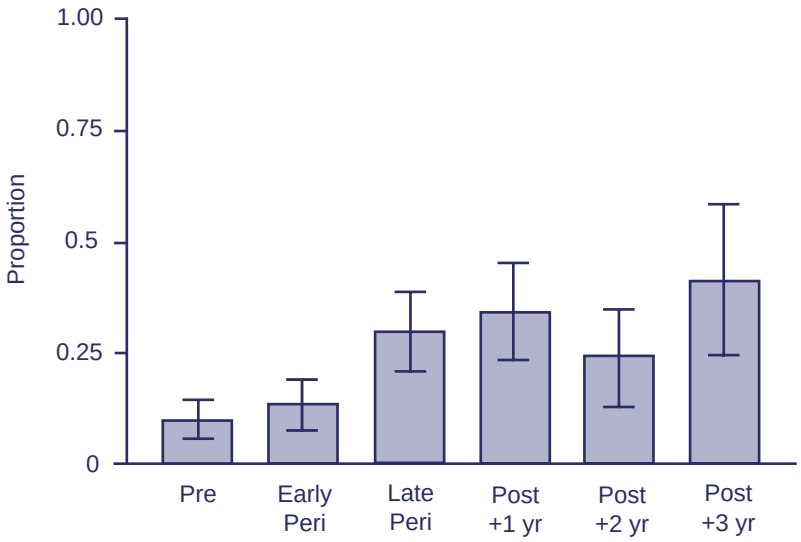
Proportion of Women Bothered by Hot Flushes by Menopausal Status



pre = premenopausal
early peri = change in menstrual frequency
late peri = 3–11 months amenorrhoea
post 1 year = 12–23 months amenorrhoea
post 2 years = 24–35 months amenorrhoea
post 3 years ≥ 36 months amenorrhoea

FIGURE 3–2

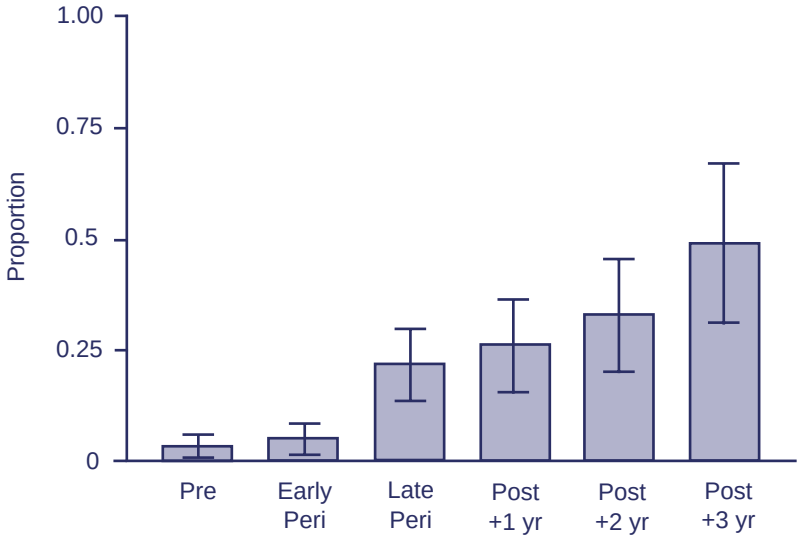
Proportion of Women Bothered by Night Sweats by Menopausal Status



pre = premenopausal
early peri = change in menstrual frequency
late peri = 3–11 months amenorrhoea
post 1 year = 12–23 months amenorrhoea
post 2 years = 24–35 months amenorrhoea
post 3 years ≥ 36 months amenorrhoea

FIGURE 3–3

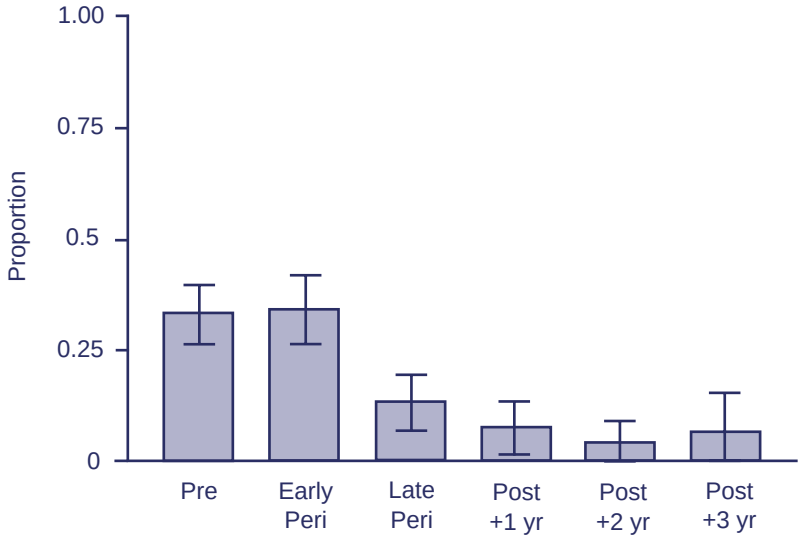
Proportion of Women Bothered by Dryness of Vagina by Menopausal Status



pre = premenopausal
early peri = change in menstrual frequency
late peri = 3–11 months amenorrhoea
post 1 year = 12–23 months amenorrhoea
post 2 years = 24–35 months amenorrhoea
post 3 years ≥ 36 months amenorrhoea

FIGURE 3–4

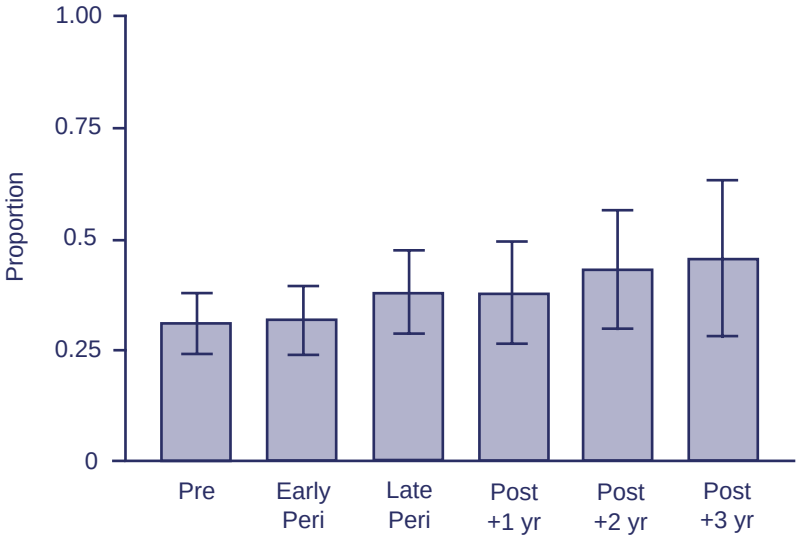
Proportion of Women Bothered by Breast Soreness by Menopausal Status



pre = premenopausal
early peri = change in menstrual frequency
late peri = 3–11 months amenorrhoea
post 1 year = 12–23 months amenorrhoea
post 2 years = 24–35 months amenorrhoea
post 3 years ≥ 36 months amenorrhoea

FIGURE 3–5

Proportion of Women Bothered by Trouble Sleeping by Menopausal Status



pre = premenopausal
early peri = change in menstrual frequency
late peri = 3–11 months amenorrhoea
post 1 year = 12–23 months amenorrhoea
post 2 years = 24–35 months amenorrhoea
post 3 years ≥ 36 months amenorrhoea

tomized hypogonadotropic women experience hot flushes in the same way as women with an intact pituitary, vasomotor instability is induced by a common higher cerebral center and not by the gonadotropin-pulse. The vasodilatation occurring during hot flushes leads to an increase of skin temperature and finger volume and to an augmented oxygen consumption.[44] Due to peripheral vasodilatation, there is an increase of the pulse rate by about 15 percent. Body core temperature then decreases. The increase of finger perfusion starts 1.5 min before the start of the hot flush and lasts for several minutes after its subjective end. Serum LH levels increase only after the beginning of peripheral vasodilatation and reach their maximal value approximately 12 minutes later. Most likely as a consequence of the cooling down of the body core temperature, an elevation of adrenocoticotropic hormone (ACTH) and of human growth hormone (hGH) occurs respectively 5 and 30 minutes after the rise of skin temperature. Because hot flushes occur not only after menopause, but also during the down-regulation by GnRH analogues, the primary decrease of serum estradiol is essential for vasomotor symptoms. Anorexia nervosa or other conditions of hypothalamic amenorrhea do not provoke hot flushes. Furthermore, hot flushes are only observed in women previously exposed to endogenous or exogenous estrogen activity. The pathophysiological mechanism provoking hot flushes involves catecholamines, catecholestrogens, serotonin, histamine, endorphins, and prostaglandins. The endorphin neurons are inactivated by low estrogen levels, a phenomenon that is reversible.

5. Role of Psychosocial and Lifestyle Factors in Determining Women's Experience of Symptoms

Cross-sectional studies have explored associations between symptom experience and a large range of other factors. In keeping with other studies from Australia, North America, Scandinavia, and Europe, an Australian study found lower symptom experience in the midlife years to be associated with increasing years of education, better self-rated health, the use of fewer nonprescription medications, absence of chronic conditions, a low level of interpersonal stress, not currently smoking, exercise at least once per week, and positive attitudes to aging and to menopause.[45]

A previous history of premenstrual complaints was reported to be associated with the occurrence of vasomotor symptoms during menopause in cross-sectional analyses of this population-based sample of midlife women.[42,46] Longitudinal analysis of the same cohort found that a prior history of both physical and psychological premenstrual complaints was associated with a more symptomatic perimenopause characterized by dysphoria, skeletal, digestive, and respiratory symptoms.[47]

The cross-sectional phase of the SWAN study found that reports of vasomotor symptoms were negatively associated with educational level and self-assessed health and positively associated with difficulty in paying for basics. Psychosomatic symptoms decreased with age and were reported less often by those with better self-reported health and with less difficulty in paying for basics.[36]

Cross-sectional studies have explored associations between symptom experience and a large range of other factors.

Longitudinal population-based studies are best able to establish the likely relationship between experience of symptoms, psychosocial and lifestyle factors. The Massachusetts Women's Health Study found that prior physical and psychological symptoms explained physical symptoms, while psychological symptoms were explained by low education and perceived health.[6] A further analysis of the 454 women from this sample who were premenopausal at baseline and postmenopausal by the

6th followup found that variables related to greater frequency of vasomotor reporting included a longer perimenopause, more symptoms reported prior to menopause, lower education, and more negative attitudes to menopause prior to menopause.[48] Symptom bothersomeness was related to a greater frequency of vasomotor symptom reporting, smoking, and being divorced. Variables that predicted consultations were greater frequency and bothersomeness of symptoms, higher education, and greater health care utilization.[48] Women with negative attitudes to menopause were more likely to subsequently experience bothersome symptoms.[49]

A British study[50] found that women who had experienced an early natural menopause had a strongly increased risk of vasomotor symptoms (hot flushes or night sweats), sexual difficulties (vaginal dryness or difficulties with intercourse), and trouble sleeping. However, there was little or no excess risk of the other somatic or psychological symptoms studied. In contrast, all types of symptoms were more common among women who had had a hysterectomy or were users of HRT. Using prospective data collected when the women were 36, symptom reporting was predicted by low education, stressful lives, or a previous history of poor physical and psychological health. Adjustment for these factors in a logistic regression model did not affect the relationship between symptoms and current menopausal status. For vasomotor symptoms, postmenopausal women had an adjusted OR of 4.7 (95 percent confidence internval (CI) 2.6–8.5), and perimenopausal women had an adjusted OR of 2.6 (95 percent CI 1.9–3.5) compared with premenopausal women. Corresponding adjusted ORs for sexual difficulties were 3.9 (95 percent CI 2.1–7.1) and 2.2 (95 percent CI 1.4–3.2) and for trouble sleeping were 3.4 (95 percent CI 1.9–6.2) and 1.5 (95 percent CI 1.1–2.0).

A postal survey of men and women aged between 49–55 years and registered with a London general practice[51] found no gender differences in reporting of self-rated health, life satisfaction, and health-related quality of life, although women reported more physical problems. Menopausal status was not significantly related to life satisfaction or to health-related quality of life. Significant predictors of health-related quality of life were serious illness, employment, and marital status. Sample size was relatively small in this study (n = 189), response rate was only 47 percent, and the age range may have meant that most women were already in the menopausal transition.

Using structural modeling of data from the first 6 years of followup of the Melbourne Women's Midlife Health Project, the presence of bothersome symptoms was found to adversely affect well-being.[52] Repeated measures multivariate analysis of covariance also found that bothersome symptoms adversely impacted negative mood.[37]

Greene[28] suggested a vulnerability model to explain the role of psychosocial factors in symptom experience during the menopausal transition. The Greene vulnerability model hypothesizes that adverse psychosocial factors render women vulnerable to develop nonspecific physical and psychological symptoms at this time. Response to stress interacts with personality and sensitivity to biological changes to determine the actual symptoms experienced.

Hot beverages can cause flushing through counter current heat exchange mediated through the thermoregulation center of the anterior hypothalamus. Foods containing nitrites and sulphites and spicy foods, such as those containing the active agent in red pepper or capsaicin, may also provoke severe flushing. Alcohol intake is also associated with flushing reactions, although there are no controlled trials examining the effect of alcohol intake on the severity of menopausal symptoms, in particular vasomotor symptoms. The mechanism of alcohol-provoked flushing is complex but is probably related to the fact that fermented alcoholic beverages contain tyramine or histamine, which induces flushing.[53]

5.1 Exercise

It has been suggested that physical activity may have a beneficial effect on reducing vasomotor symptoms in menopausal women. Physical exercise involving increased energy expenditure increases hypothalamic β-endorphin production, and β-endorphins are reported to stabilize thermoregulation.[54] However, conflicting evidence exists as to whether exercise has an effect on menopausal symptoms.

In a cross-sectional study of a population-based sample of 728 Australian-born women,[55] physical activity had no significant effect on women's experience of troubling symptoms, including those symptoms associated with their menopausal status, such as vasomotor symptoms. Hammar et al.[56] reported that women who participated in organized physical exercise on a regular basis had a lower prevalence of moderate to severe vasomotor symptoms compared with women of the same menopausal status from the population. A further study by these researchers[54] reported that from a population of 793 women, only 5 percent of highly physically active women experienced severe vasomotor symptoms as compared with 14–16 percent of women who had little or no weekly exercise. The latter study collected data on physical habits and on current and previous experience of vasomotor symptoms. There is the risk of women overestimating the time spent in physical activities as well as the problems of retrospective reporting of vasomotor symptoms. A prospective or intervention study would avoid these problems. However, the fluctuating nature of the experience of vasomotor symptoms and the expectations of participants could affect such studies. A case-control study[57] (82 cases and 89 controls) found that habitual exercise prior to the FMP did not reduce the likelihood of experiencing vasomotor symptoms during the perimenopause.

6. Effectivemess of Treatment Interventions for Symptoms Linked to the Transition To Menopause

Available treatments aimed at reducing symptoms related to the menopausal transition include HRT, phytoestrogens, and natural therapies, which have been shown to possess different degrees of efficacy.

6.1 Hormone Replacement Therapies (HRT)

Most RCTs of HRT have been carried out on postmenopausal women, many of whom have already received HRT and may have undergone a surgical menopause. Nevertheless, there is considerable consensus in findings that the symptoms which consistently respond to HRT are the vasomotor and vaginal atrophic symptoms. These beneficial effects of HRT persisted after adjusting for baseline symptom level and uterine status.[58]

Conflicting evidence exists as to whether exercise has an effect on menopausal symptoms.

There is a substantial body of evidence showing that HRT is effective in reducing hot flushes. Randomized double-blind placebo controlled trials have reported that CEE at dosages of 0.3, 0.625, and 1.25 mg/day significantly reduced hot flushes compared with placebo.[59–61] Similarly, other preparations of estrogen, administered either orally or by transdermal patch, have also shown effectiveness in the relief of vasomotor symptoms.[62–70] Gordon et al.[67] compared the efficacy of estradiol patches and oral conjugated estrogen and found no statistically significant difference between the preparations with regard to their effect on the reduction of hot flushes. The response to the 0.1 mg estradiol patch was greater, and the response to the 0.05 mg estradiol patch was less than the response to conjugated estrogens, although these differences were not statistically different. Percutaneous estradiol delivered in an alcohol-water gel has been reported to be effective in treating vasomotor symptoms.[71] The

use of either continuous or sequential progestins with estrogen does not reduce the efficacy of the preparation in the reduction of hot flushes.[58,65,72] Recently, an intranasal 17β-estradiol spray has been shown to be significantly better than placebo and similar to oral estradiol in reducing hot flushes and is also well tolerated.[73]

Considerable consensus in findings that the symptoms which consistently respond to HRT are the vasomotor and vaginal atrophic symptoms.

Vaginal symptoms related to atrophy have been reported to be alleviated by ERT. Local low-dose treatment with a small vaginal tablet of 25 micrograms of 17β-estradiol was shown to significantly relieve postmenopausal symptoms related to vaginal atrophy when compared to placebo.[74] Preparations of estradiol vaginal cream have a similar effect[75] and also result in an increase in plasma levels of estradiol. Percutaneous, transdermal, and oral estradiol treatments have all been reported to improve the vaginal cytology profile in comparison with placebo therapy.[67,71,76] Sleep disturbances do not appear to be helped by transdermal or oral ERT.[69,77] The benefits and risks of HRTs are discussed in other chapters.

A number of nonestrogen preparations have been evaluated for their effects on menopausal symptoms with varying results. The progestational agent megestrol acetate (20 mg twice daily) has been reported to significantly decrease the frequency of hot flushes in women with a history of breast cancer.[78] Veralipride, an antidopaminergic treatment, reduced vasomotor symptoms and was significantly more effective than placebo in three trials.[79–81] Other dopamine agonists and antagonists have also been found to be more effective than placebo in alleviating hot flushes.[78] In one trial, opipramol treatment was reported as being significantly better than placebo in reducing hot flushes.[82] Trials with clonidine,[83] propranolol,[84] and dong quai[85] have shown these treatments to be no more effective than placebo in controlling hot flushes. Dong quai did not have any effect on vaginal cell maturation.[85] More promising results for non-hormonal treatment of hot flushes have come from trials of antidepressants, particularly the selective serotonin reuptake inhibitors (SSRIs) and related drugs such as venlafaxine. Pilot studies presented at conferences have found significant reduction in hot flush frequency and severity, but evidence from larger double-blind randomized trials is needed.[86]

Studies of the effects of HRT on mood, cognitive and sexual functioning are discussed elsewhere. The symptom of breast soreness/tenderness (mastalgia) has been shown in clinical trials to be related to estrogen/progestin balance.[58] The Postmenopause Estrogen/Progestin Intervention (PEPI) trial[58] found a significant reduction in muscle and joint pain in women who adhered to estrogen- and progestin-containing regimes. This beneficial effect on muscle and joint pain was not evident in intention-to-treat analyses. Aches or stiff joints were reported by over 40 percent of women in the Melbourne Women's Midlife Health Project at each phase of the menopause transition,[38] although there was no demonstrable variation with the menopause transition. Given the prevalence of these symptoms among middle-aged women, further research is needed.

6.2 Phytoestrogens

Phytoestrogens are plant compounds that have a close similarity in structure to estrogens. Evidence for the effects of phytoestrogens on reducing menopausal symptoms, hot flushes, and vaginal dryness come from two main sources—observational studies and clinical trials. The first source is from epidemiological data of populations who have high dietary intakes of phytoestrogen compounds and who have a very low rate of hot flushes (for example, 5–10 percent of Japanese women report hot flushes compared with 70–80 percent of Western women).[87] Japanese women are reported

to consume 20–150 mg/day of isoflavones[88] compared to Western women, where less than 5 mg/day is consumed.[89]

The second source is from placebo-controlled clinical trials. Five studies[90–94] have reported improvement in hot flushes after dietary supplementation with phytoestrogens. In three of these studies,[90,93,94] there was no significant improvement in these symptoms in subjects in the treatment compared to the placebo group. In one study,[93] there was an increase in urinary isoflavone excretion in the placebo group. There was a strong negative correlation between the level of urinary isoflavone excretion and the incidence of vasomotor symptoms in both treatment and placebo groups. This further emphasises the problem with intervention studies using naturally occurring dietary compounds.

There are problems with both sources of information. Whether Japanese women do in fact experience a significantly lower frequency of hot flushes has been challenged,[95] and there is no data from this population on the prevalence of vaginal dryness. Evidence from controlled trials is limited by several problems—finding an effective control group, as phytoestrogens are present in so many foods that it is difficult to eliminate them from the diet, and the fact that natural improvement of menopausal symptoms occurs with time. Of five studies that looked at changes in vaginal cytology with and without phytoestrogen supplementation, there was a significant improvement in three instances[91,96,97] but not in two.[90,98] The variations in response may depend on populations studied, source of phytoestrogen, and study design, particularly with respect to duration of exposure.

6.3 Natural Therapies

Evening primrose oil, containing gamma-linolenic acid, has been evaluated as a therapy for treating hot flushes and sweating associated with menopause in a randomized, double-blind, placebo-controlled trial.[99] Although there is no good scientific rationale for the use of this preparation in treating hot flushes and although neither clinicians nor the pharmaceutical industry have ever promoted evening primrose oil for this purpose, there is a current view among the lay public that it is effective in the control of menopausal symptoms. Chenoy and colleagues[99] reported that gamma-linolenic acid provided by evening primrose oil offers no benefit over placebo in treating menopausal flushing.

7. Future Needs

Clearly there has been a great deal of research documenting the relationship of symptoms of the menopause transition. In this section, we expand on those areas that require further detailed studies.

In the field of observational studies, there is a need for better documentation of the processes of the natural menopause transition using prospective investigations to distinguish menopause-related changes from those of aging or disease. Design features needed in these longitudinal epidemiological studies are:

- Randomized population sampling including minority women of the country concerned
- Baseline age 45 or less, so that women are more likely to be premenopausal
- Symptom checklists which include all symptoms shown to vary directly (vasomotor, vaginal atrophic, breast tenderness) or indirectly (insomnia, mood) with hormonal change
- Validated measures of psychosocial and lifestyle factors which may mediate hormonal effects
- Prospectively kept menstrual calendars so that phase of the menopause transition can be determined without bias of retrospective recall
- Regular hormonal measures
- Power analysis for sample size, so that effects of hormones and other factors can be delineated

- Long-term followup until women are at least 10 years postmenopausal, so that longer term effects can be studied, including the natural history of untreated symptoms
- Studies of different populations worldwide, representing women from a broader array of racial-ethnic and socioeconomic backgrounds

In the field of treatment interventions, there have been many RCTs of different forms of HRT on symptoms, and larger studies are in progress. On the other hand, there is a need for—

- Questionnaires validating phytoestrogen intake against metabolic measures of metabolites in different cultural settings before either RCTs or observational studies of the role of phytoestrogens can proceed
- A larger RCT of phytoestrogen supplementations, including metabolic measures of metabolite levels

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