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# Menopausal

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FOR CLINICIANS WHO PROVIDE CARE FOR WOMEN

## Evaluating and treating insomnia in menopausal women

► BETH A. MCAVEY, MD, AND GENEVIEVE S. NEAL-PERRY, MD, PHD

Sleep of adequate duration and quality is essential for maintaining health, peak daytime performance, and quality of life. Amazingly, most people spend nearly one third of their life sleeping, an observation that underscores the importance of sleep. While the need for sleep is unquestionable, the amount and quality of sleep

change with advancing age and can differ according to sex. A newborn, for example, requires an average of 16 hours of sleep per day, while an adult needs about 7 hours daily.<sup>1</sup> Among adults, premenopausal women have better sleep quality than men, and men require less sleep. However, the menopausal transition and the onset of the menopause are characterized by a striking increase in the incidence of sleep disturbances, especially insomnia.<sup>2</sup>

This article reviews how to evaluate for insomnia in patients presenting with sleep disturbances, especially women entering the menopausal transition or menopause, and discusses treatment strategies that can help patients attain their sleep requirements.

### Definition and classifications of insomnia

Insomnia is characterized by difficulty initiating sleep, maintaining sleep, waking too early, or reports of sleep that is nonrestorative or poor in quality. For a diagnosis of insomnia the patient must also report that the sleep difficulty occurs despite adequate opportunity for sleep and that daytime functioning is impaired.<sup>3</sup> Insomnia

is classified according to the length of symptom duration. Short-term insomnia is temporary, usually less than 1 month, and associated with an acute stressor (TABLE 1).<sup>4</sup> The sleep problem should resolve when the stressor is eliminated. Insomnia lasting longer than 1 month is considered chronic and is characterized as either primary or secondary (TABLE 2).<sup>4,5</sup>

The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) specifies that for a diagnosis of primary insomnia, symptoms must have existed for at least 1 month and impair everyday activities in the absence of a pre-existing mental disorder (TABLE 3).<sup>6</sup> Primary insomnia does *not* occur as a direct consequence of a medical disorder or pharmacotherapy. Primary insomnia is sometimes referred to as psychophysiological or idiopathic, resulting from a prolonged period of stress that often results in poor sleep hygiene. Primary insomnia does not occur exclusively as a result of narcolepsy, a sleep-related breathing disorder (SBD), a circadian rhythm sleep disorder, or a parasomnia (defined as an abnormal behavior that occurs during sleep). In contrast, secondary

CONTINUED ON PAGE 53

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#### Disclosures

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#### IN THIS ISSUE

#### S2 From the editor

► NANETTE F. SANTORO, MD

#### S8 What's new about menopause and cardiovascular risk?

► KAREN MATTHEWS, PHD, AND  
KIM SUTTON-TYRRELL, DRPH

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## FROM THE EDITOR



***Don't it always seem to go that you don't know  
what you've got till it's gone?***

—Joni Mitchell

I couldn't agree more. When it comes to sleep, most of us take it for granted that we will get a restful, uninterrupted, hours-long snooze every single night (or at least those nights when we are not on call). The human body's ability to refresh itself through sleep is a truly spectacular feat that we generally don't appreciate—until this ability is lost. Animals deprived of sleep, even if they are adequately fed and sheltered, will die within 2 weeks' time. The absence of sleep is not simply wakefulness. For some women, it is akin to torture.

In this issue, Dr Beth McAvey and Dr Genevieve Neal-Perry review the current literature on sleep, aging, and menopause and help us to connect the dots in this rapidly evolving field of science. Conventional wisdom has held that hot flushes lead to sleep disruption and that sleep disruption in turn leads to adverse mood, and thus that the menopausal transition initiates a cascade of symptomatology. The reality is more complex, however, as insomnia can occur through various pathways. Understanding these processes and how to best screen and treat our patients will help bring about more restorative sleep.

In our second feature, Dr Karen Matthews and Dr Kim Sutton-Tyrrell summarize a body of work that has accrued over the past decade indicating that the pathophysiologic model of heart disease in women differs from that in men, and clinicians need to be sensitive to the issues that affect women. Did you know that emotional stress significant enough to cause menstrual cycle disturbances is also significant enough to be associated with a worsened cardiovascular risk profile? The authors lead us through a maze of complex associations to a newly recognized paradigm that more tightly and clearly links the cardiovascular and reproductive systems.

As you read through this issue of *Menopausal Medicine*, keep in mind that it is not only observed signs and symptoms that lead us to a diagnosis: sometimes what is *not* there matters most.

**Nanette F. Santoro, MD**

**TABLE 1 Stressors associated with short-term insomnia****ENVIRONMENTAL CHANGES**

- Light
- Temperature
- Noise
- Travel across time zones
- Night-shift worker

**LIFE CHANGES**

- Death
- Divorce
- Unemployment
- Recent illness, surgery, or pain

**WITHDRAWAL FROM STIMULANTS**

- Caffeine
- Cocaine
- Methamphetamines

**WITHDRAWAL FROM OTHER SUBSTANCES**

- Alcohol
- Antidepressants

**COMMON MEDICATIONS**

- $\beta$ -blockers
- Thyroid replacement hormone
- Steroids

**TABLE 2 Disorders associated with chronic insomnia****MENTAL HEALTH DISTURBANCES**

- Depression
- Anxiety
- Post-traumatic stress disorder

**MEDICAL ILLNESSES**

- Cardiovascular disease
- Headaches
- Chronic fatigue syndrome
- Diabetes mellitus
- Renal/urologic disease

**SLEEP-RELATED BREATHING DISORDER (SBD)**

- Obstructive sleep apnea
- Central sleep apnea
- Sleep-related hypoventilation/hypoxemia syndromes
- Asthma

**NEUROLOGIC DISORDERS**

- Parkinson disease
- Alzheimer disease

**CIRCADIAN RHYTHM DISTURBANCES**

- Shift-work sleep disorder
- Jet lag disorder
- Delayed sleep phase disorder
- Advanced sleep phase disorder

**SLEEP-RELATED MOVEMENT DISORDERS**

- Restless leg syndrome
- Periodic limb movement disorder
- Sleep-related bruxism (grinding of teeth)
- Sleep-related rhythmic movement disorder

**PARASOMNIAS**

- Non-rapid eye movement (NREM) related parasomnias
- Rapid eye movement (REM) related parasomnias

insomnia can occur in response to medical or mental illness, pharmacotherapy, or exclusively during narcolepsy, an SBD, a circadian rhythm sleep disorder, or a parasomnia.

### Evaluating the patient with insomnia

The evaluation of insomnia starts with a detailed sleep history, including a description of sleep times and disturbances over a typical 24-hour period for at least 1 week. The time of bedtime, time to the onset of sleep (sleep latency), number and duration of awakenings, final awakening time, and the time and length of any naps should

also be determined. Volitional sleep deprivation by the patient should be ruled out. Patients who cannot provide an adequate sleep history or who experience considerable day-to-day or night-to-night variability should complete a daily sleep diary. Interviewing the bed partner may complement the patient's report, as the patient may be unaware of what happens during sleep.<sup>7</sup>

A detailed medical history, psychiatric history, and a depression screen should be obtained. It is important to note all medications (past or current) used and the use of any alcohol or toxic substances. A physi-

cal examination may reveal evidence of medical conditions that are associated with insomnia. Particular attention should be focused on excessive oropharyngeal tissue, extremity swelling, depressed mood, and abnormal mental status. Laboratory evaluation should include thyroid function tests, fasting glucose, serum creatinine, and iron levels to rule out comorbidities. When an underlying sleep disorder is suspected or if the insomnia has not responded to treatment, polysomnography is indicated. This is a formal sleep study conducted in a sleep disorders center that records stages of sleep architecture, bodily movements

**TABLE 3 Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for primary insomnia<sup>6</sup>**

- The predominant complaint is difficulty initiating or maintaining sleep or having nonrestorative sleep for *at least 1 month*
- The sleep disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning
- The sleep disturbance does *not* occur exclusively during the course of narcolepsy, sleep-related breathing disorder, circadian rhythm sleep disorder, or a parasomnia
- The disturbance does *not* occur exclusively during the course of another mental disorder (eg, major depressive disorder, generalized anxiety disorder, a delirium)
- The disturbance is *not* due to the direct physiologic effects of a substance (eg, a drug of abuse, a medication) or a general medical condition

during deep sleep (eg, limbs), electroencephalographic activity, and breathing patterns.<sup>8</sup> Alternatively, actigraphy, which uses a wrist monitor to record activity and bodily movements during sleep, may be used for outpatient evaluation over several days.<sup>9</sup>

**Treatment options for insomnia**

After ruling out physiologic causes of insomnia and trying basic sleep hygiene measures, nonpharmacologic and pharmacologic options are available. Treatment modalities are often combined in insomnia management.

**Nonpharmacologic therapies**

Cognitive behavioral therapy (CBT) is often recommended as the initial treatment for insomnia and is the foundation for sustained sleep im-

provement. CBT usually includes 8 to 10 weekly sessions that focus on stimulus control, sleep restriction, and sleep hygiene. While CBT may be the first line of intervention, most often it is recommended in conjunction with pharmacotherapy. Numerous clinical trials have evaluated the efficacy of CBT and pharmacotherapy separately.<sup>10</sup> Recently, a prospective randomized controlled trial evaluating the added value of pharmacotherapy versus CBT alone for acute treatment of insomnia revealed that long-term resolution was optimized when medication was discontinued during maintenance CBT for persistent insomnia.<sup>11</sup>

Relaxation therapy is another mode of therapy, involving progressive muscle relaxation, that helps promote restfulness and reduce insomnia. Relaxation therapy is sometimes combined with biofeedback therapy to reduce somatic arousal. Another nonpharmacologic intervention is stimulus-control therapy. Stimulus-control therapy is based on the concept that some people with insomnia have learned to associate the bedroom with staying awake rather than sleeping. This treatment approach requires that the patient spend no more than 20 minutes lying in bed trying to fall asleep. If sleep does not occur, the patient should get up and pursue another relaxing activity until sleepiness returns.<sup>12</sup>

Sleep hygiene is a term used to describe the habits, practices, and environmental factors that are important to sound sleep. Improving sleep hygiene refers to actions that a patient can take to improve and maintain good sleep, such as keeping a regular sleep schedule and ensuring a bedroom environment conducive to sleep (TABLE 4). Sleep hygiene alone has *not* been directly compared to placebo in a randomized trial setting. However,

numerous clinical trials have used sleep hygiene as the control intervention and have demonstrated improved sleep following initiation of good sleep hygiene techniques.<sup>13</sup>

Phototherapy is often an effective therapy for patients who have insomnia secondary to a delayed sleep phase syndrome or a disruption in their circadian rhythm such that falling asleep is difficult. This treatment involves sitting in front of a light box for 30 minutes after waking up. A randomized trial of nonpharmacologic therapy that compared sleep hygiene instructions to sleep hygiene instructions and phototherapy found that the combined treatment produced a significant benefit in reducing sleep latency.<sup>13,14</sup>

**Pharmacologic therapies**

Pharmacologic treatment may be recommended if insomnia significantly interferes with daytime functioning and nonpharmacologic interventions do not improve the sleep disturbances (TABLE 5). Patients whose insomnia has been successfully treated with medications are likely to report fewer daytime symptoms and improved daytime function, quality of life, and comorbidities.

**TABLE 4 Techniques for good sleep hygiene**

- Maintain a regular sleep schedule
- Sleep as much as necessary to feel rested and then get out of bed
- Try not to force sleep
- Avoid caffeinated beverages after lunch
- Avoid alcohol near bedtime
- Avoid smoking
- Do not go to bed hungry
- Adjust the bedroom environment as needed to decrease stimuli
- Resolve concerns or worries before bedtime



**TABLE 5 Pharmacologic treatments for primary insomnia**

DRUG CLASS	DRUG NAME	DOSE	DURATION
Benzodiazepines	Flurazepam (Dalmane)	15-30 mg QHS	≤2 weeks
	Lorazepam (Ativan)*	2-4 mg QHS	
	Quazepam (Doral)	7.5-15 mg QHS	
	Triazolam (Halcion)	0.125-0.25 mg QHS	
Nonbenzodiazepines	Eszopiclone (Lunesta)	2 mg QHS	2-6 weeks
	Zaleplon (Sonata)	10 mg QHS	
	Zolpidem (Ambien)	5-10 mg QHS	
Melatonin agonist	Ramelteon (Rozerem)	8 mg QHS	Long term

QHS = nightly at bedtime.

\*Not FDA approved for use in the treatment of insomnia.

Benzodiazepines, including lorazepam and triazolam, are a class of medications that bind to the gamma-aminobutyric acid (GABA) type A receptor subtypes; they are effective in reducing sleep-onset latency and the number of awakenings, while improving sleep duration and quality.<sup>15</sup> They also cause sedation, muscle relaxation, and can lower anxiety levels, thus promoting sleep. Benzodiazepines are generally recommended for short-term insomnia and limited use because long-term daily use (greater than 2 weeks) may cause dependence.

Nonbenzodiazepine GABA receptor agonists, including zolpidem, eszopiclone, and zaleplon, are a newer class of medications with a shorter half-life that are used to treat insomnia. Therefore, patients experience fewer and less severe adverse side effects than those often associated with benzodiazepines. Nonetheless, patients should be warned that nonbenzodiazepines may also cause dependence with long-term use.

Depression and insomnia often co-exist; hence it is important to perform a detailed mental health examination in any patient presenting with

insomnia. Antidepressants are not FDA approved to treat primary insomnia. But if a depressed patient has secondary insomnia, it is prudent to treat with an antidepressant first. In some patients, antidepressant therapy pre-

**Depression and insomnia often co-exist; hence it is important to perform a detailed mental health examination in any patient presenting with insomnia.**

cipitates insomnia; consultation with a psychiatrist may be helpful when choosing an alternative therapy. A randomized, placebo-controlled trial was performed in 545 patients who met DSM-IV criteria for both major depressive disorders and insomnia and who were receiving fluoxetine for depression. Patients were randomized to 3 mg of eszopiclone or placebo nightly for 8 weeks. Patients in the eszopiclone group had significantly decreased sleep latency, decreased wake time after sleep onset, and increased total sleep time and sleep quality compared with placebo-treated patients.

Furthermore, there was a greater magnitude of the antidepressant effect.<sup>16</sup>

Ramelteon is a melatonin receptor agonist that binds to the MT<sub>1</sub> and MT<sub>2</sub> receptors in the suprachiasmatic nucleus of the hypothalamus. Ramelteon is FDA approved for insomnia in patients who have a delayed sleep phase syndrome. In a recent study, 20 healthy peri- and postmenopausal women with insomnia received 8 mg of ramelteon for 6 weeks. Participants completed daily sleep-wake diaries and reported measures of sleep impairment, daytime functioning, and quality of life. Analysis revealed significant decreases in latency to sleep onset, improvements in total sleep time, sleep efficiency, and daytime functioning, quality of life, and mood, in self-reported measures.<sup>17</sup> Ramelteon is the only insomnia pharmacologic agent approved by the FDA for long-term use and does *not* exhibit potential for dependence/abuse; hence it has the advantage of being a nonscheduled drug. However, while ramelteon provides a promising alternative for patients with insomnia, additional randomized controlled trials are needed to further evaluate its efficacy. In addition, patients should be counseled that there

have been rare case reports describing complex sleep-related behaviors (sleep-driving, cooking or eating food, and making phone calls) observed with some of the nonbenzodiazepines.

Numerous alternative therapies, including herbal and botanical products, such as valerian root, have been used to treat insomnia. Most studies show, however, that herbal treatments are no more effective than placebo.<sup>18</sup> A meta-analysis of randomized clinical trials comparing valerian preparations with placebo suggests that valerian might improve subjective but not objective parameters of insomnia.<sup>19</sup> Notably, many herbal products have not been tested for dosing efficacy and their interaction profiles with commonly used drugs have not been described. Therefore, use of alternative herbal remedies in a nonstudy format is not recommended.

### Sleepless in menopause

Women in early menopause and those transitioning into menopause often experience vasomotor symptoms or hot flashes. Women often describe the hot flush as an acute sensation of heat, followed by a flush that results in diaphoresis and a subsequent reduction in core body temperature. Of note, a large percentage of women (33% to 51%) complain that hot flashes significantly disturb their sleep.<sup>2</sup> In cross-sectional studies of women aged 40 to 55 years, there is mixed evidence relating menopausal status to insomnia. In one small study, self-reported sleep disturbances and follicle-stimulating hormone levels or menstrual bleeding patterns were not correlated and waking episodes were not associated with hot flashes or night sweats.<sup>20</sup> In contrast, a 3-year longitudinal study of 213 women *not* taking hormone therapy (HT) during the menopausal transition suggested a significant increase

in the incidence of sleep disturbances during the change from pre- to postmenopausal status.<sup>21</sup>

Conflicting evidence most likely reflects inherent variations in baseline sleep patterns among women and the methods used across studies to define sleep disturbances. Nonetheless, self-reports from middle-aged women support the hypothesis that sleep disturbances increase as women make the transition into menopause. The research and clinical challenge is to discern whether the increased prevalence of sleep disturbances in middle-aged women results directly from hormonal flux and the characteristic dysregulation of the hypothalamic-pituitary-ovarian (HPO) axis that often characterize the menopausal

**Before a diagnosis of primary insomnia is assigned to a woman making the transition into the menopause, clinicians must rule out all other secondary causes.**

transition or as a consequence of other morbidities that increase with age. It is important for clinicians to remember that although sleep disorders in the menopause have historically been attributed to age-related HPO disruption, other causes frequently emerge as women age. These include an increase in SBD and consequences or contributors of these disorders, such as systemic hypertension and obesity. Most important, before a diagnosis of primary insomnia is assigned to a woman making the transition into the menopause, clinicians must rule out all other secondary causes.

Nonbenzodiazepines may be a practical treatment option for menopausal women with insomnia. In a

double-blind, placebo-controlled study randomizing 410 peri- or early postmenopausal women with insomnia to 3 mg of eszopiclone or placebo nightly for 4 weeks, those patients receiving treatment reported improvements in sleep induction, sleep maintenance and duration, sleep quality, next-day functioning, and fewer total awakenings secondary to nocturnal hot flashes relative to placebo.<sup>22</sup> The results of this study suggest that targeting sleep disturbance in peri- and postmenopausal women who present with insomnia in combination with other menopause-related symptoms has beneficial effects and may improve quality of life.

### Using hormone therapy for insomnia

Hormone therapy has long been accepted as the standard treatment for vasomotor symptoms of menopause. Clinical studies suggest that HT may improve sleep disturbances in menopausal women, as estradiol has been hypothesized to shorten sleep latency, reduce nocturnal restlessness and awakenings, improve sleep efficiency, and increase the phase of rapid eye movement (REM) sleep.<sup>23</sup> It is also hypothesized that progesterone stimulates breathing; this could explain why women appear to be protected from SBD during their reproductive years.<sup>24</sup> Furthermore, polysomnography studies have shown that estradiol decreases the frequency of nocturnal movements.<sup>25</sup>

A longitudinal cohort study of women enrolled in the multicenter Study of Osteoporotic Fractures tested the hypothesis that HT use in postmenopausal women is associated with better sleep.<sup>25</sup> Actigraphy was performed in more than 3000 postmenopausal women categorized by current HT use. Women using HT, compared with never-users, were less likely to have their sleep interrupted by waking



after falling asleep and they experienced fewer wake episodes. Additionally, women who never used HT had significantly greater odds of experiencing wake episodes after sleep onset and longer wake episodes.<sup>25</sup>

Well-established data from the Women's Health Initiative (WHI) trials have concluded that HT use in the postmenopause has an adverse vascular and cardiac risk profile, and therefore its use should be considered carefully and tailored to each patient. While HT is used for treating menopausal vasomotor symptoms that may or may not result in insomnia, it should *not* be exclusively used as a treatment for insomnia or other sleep disturbances.

## Conclusion

The incidence of insomnia is disproportionately increased in menopausal women and those making the menopausal transition, raising the question of whether gonadal failure predisposes women to develop insomnia. However, studies designed to determine whether HPO dysregulation or failure affects the risk for insomnia in aging women have produced inconsistent conclusions. Of note, discrepancies in conclusions regarding the relationship between HT and insomnia are most striking when studies that rely on subjective reports are compared to studies that rely on objective parameters. Further research is therefore

needed to investigate the appropriateness of currently used methods for diagnosing insomnia in menopausal women.

Although HT has traditionally been used as the initial treatment for menopausal women with vasomotor symptoms complaining of insomnia, a full evaluation for insomnia must be undertaken before initiating any pharmacotherapy. The potential for adverse side effects warrants judicious use of HT in all patients. Moreover, it may be prudent to first recommend nonhormonal therapies, especially in women who are at high risk for HT-associated adverse outcomes. ■

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# What's new about menopause and cardiovascular risk?

► KAREN MATTHEWS, PHD, AND KIM SUTTON-TYRRELL, DRPH

It has long been recognized that postmenopausal women are at increased risk for cardiovascular disease (CVD). Women who have an early menopause, especially those who have undergone bilateral oophorectomy, have higher rates of CVD than those who have a later menopause. Higher levels of cardiovascular risk factors, however, predict age at menopause.<sup>1</sup> Women's rates of CVD neither increase exponentially at menopause nor differ from those of age-matched men.<sup>2</sup> Thus, some have questioned whether menopause even matters for cardiovascular risk in women.<sup>2</sup> That perspective, however, does not take into account the many sex differences in the pathophysiology, manifestation, and treatment of CVD or newly emerging data from observational studies that have assessed cardiovascular risk factors during the perimenopause.

In this article, we provide an overview of what's new concerning the influence of the menopausal transition on cardiovascular risk. The discussion draws data from such impor-

tant studies as the Women's Health Initiative (WHI), Women's Ischemia Syndrome Evaluation (WISE), clinical trials summarized by Shaw et al,<sup>3</sup> and the Study of Women's Health Across the Nation (SWAN). We also discuss implications of this accumulating evidence for treatment and prevention by clinicians who care for peri- and postmenopausal women. Note that by definition what we describe as new herein may not be the final word, as evidence continues to evolve.

**Surprisingly, women have higher rates of myocardial ischemia and mortality compared with similar-aged men.**

## Women and ischemic heart disease

Women with heart disease have less obstructive coronary artery disease (CAD) and better-preserved left ventricular function than do men. Surprisingly, however, women have higher rates of myocardial ischemia and mortality compared with similar-aged men. Shaw et al suggest that sex differences in microvascular dysfunction, abnormal coronary reactivity, and plaque erosion/distal microembolization may account for these discrepancies.<sup>3</sup> They propose that this condition in women may more appropriately be labeled "ischemic heart disease," because this term more accurately encompasses the

symptoms and diagnoses most often seen in women. Shaw et al also propose that hormonal factors, especially decreased estradiol levels, influence the accumulation of risk factors that, in turn, lead to chronic inflammation, exacerbated by autoimmune diseases (FIGURE 1). Changes from normal artery structure and function, which eventually lead to obstructive disease, are marked by abnormal coronary reactivity and increased coronary remodeling. Thus, rather than focusing solely on the determinants of obstructive CAD in women, Shaw et al emphasize the pathophysiologic processes that are more prevalent in women, especially those related to microvascular dysfunction.<sup>3</sup>

## Influence of menopause on cardiovascular risk factors

Increased levels of lipids and lipoproteins, blood pressure, glucose, and insulin, as well as adiposity and smoking, are well-established CVD risk factors. More recently, inflammatory and procoagulant states, as well as depression, have been recognized as risk factors for CVD in women. Although epidemiologic investigations have examined whether risk factor levels significantly increase as women change from premenopausal to postmenopausal status, many studies have been inconclusive, primarily because they were designed for purposes other than for examining the influence of the menopausal transition on CVD risk. Some studies, for example, assessed risk factors at in-

### Karen Matthews, PhD

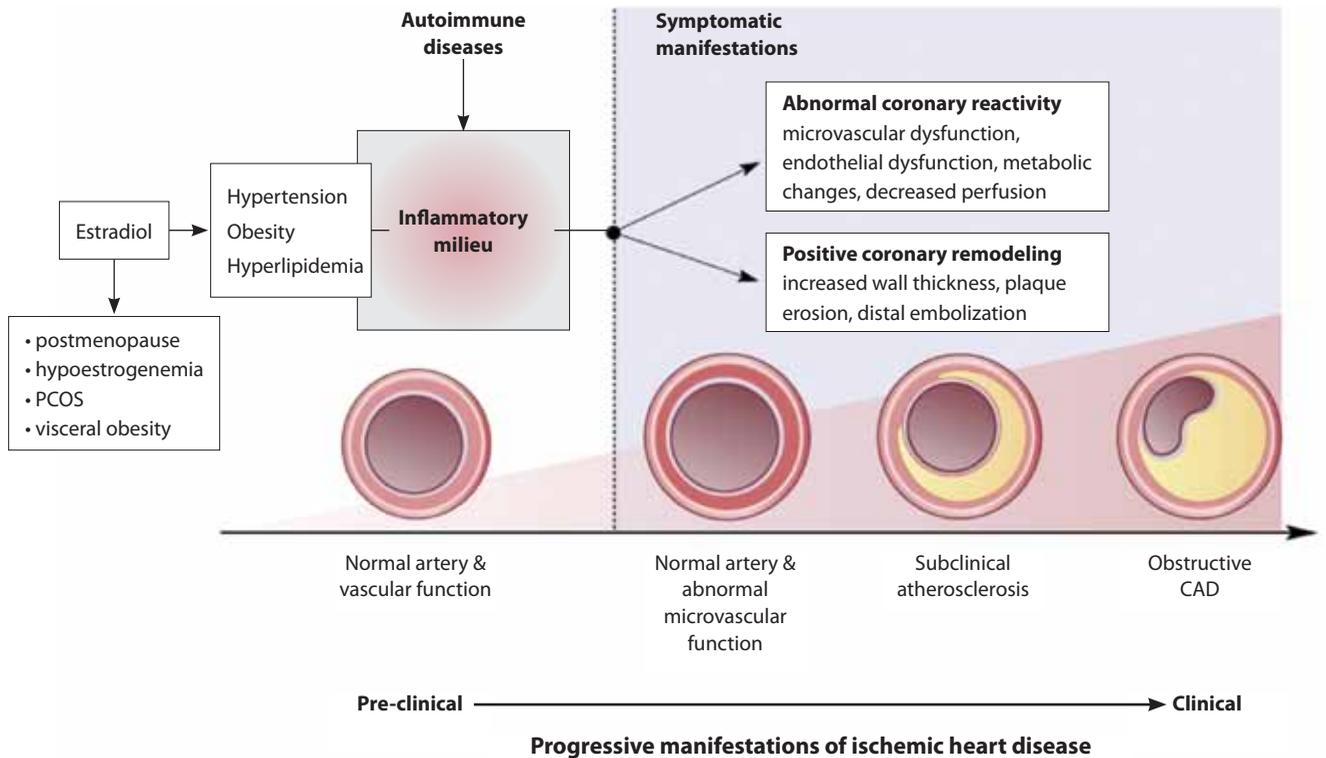
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### Disclosures

Dr Matthews and Dr Sutton-Tyrrell report no relevant commercial or financial relationships.



**FIGURE 1.** Model of the development of ischemic heart disease in women.

Reprinted with permission.<sup>3</sup> CAD, coronary artery disease; PCOS, polycystic ovarian syndrome.

tervals as broad as 5 years. Such long intervals are suboptimal for assessing changes in menopausal status, since a woman might well traverse the entire menopausal transition over a 5-year period. In addition, prior studies did not take into account newly emerging risk factors.

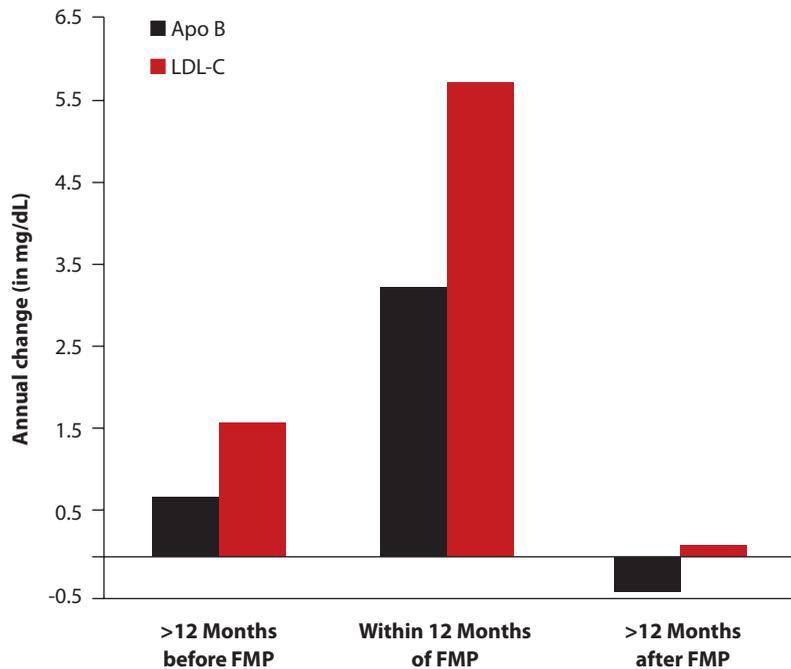
The SWAN investigation was designed specifically to assess the health changes that occur during the menopausal transition and, thus, is not subject to the types of limitations described above.<sup>4</sup> SWAN is a multi-site, multi-ethnic observational study of initially premenopausal women followed for up to 10 years as of 2009. In a sample of 1054 women from the SWAN cohort, we evaluated annual changes in lipids, lipoproteins, blood pressure, weight, and inflammatory and coagulation markers within a

1-year interval of the final menstrual period (FMP).<sup>4</sup> These changes were then compared with annual changes that occurred before or after that interval. Women were white, African American, or of Hispanic, Chinese, or Japanese descent.

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The SWAN results showed that low-density lipoprotein cholesterol (LDL-C), total cholesterol, and apolipoprotein B (apoB) increased exponentially around the FMP, as compared with either before or after (FIGURE 2).<sup>4</sup> These effects were similar in all ethnic

groups. In contrast, no other CVD risk factors—blood pressure, glucose, insulin, body weight, C-reactive protein, or fibrinogen—increased substantially relative to the FMP. Most risk factors increased gradually across the follow-up period, consistent with an effect of chronologic aging. Other data from SWAN suggested that not only do levels of LDL-C rise, but the composition of lipoprotein molecules changed as well. High-density lipoprotein cholesterol (HDL-C) particle size became smaller, indicating a prevalence of small HDL-C with fewer cardiovascular protective properties than large HDL-C. LDL-C particle concentration also changed, with proportionally more small, dense LDL-C, which is most strongly associated with CVD risk.<sup>5</sup> Taken together, these observational findings suggested that the increase in coronary heart



**FIGURE 2.** Annual changes in low-density lipoprotein cholesterol and apolipoprotein B at the time interval within 1 year of final menstrual period, compared to the interval >12 months before the final menstrual period and to the interval >12 months after the final menstrual period. Changes were adjusted for age at final menstrual period, ethnicity, site; baseline height, baseline log weight, and change in log weight; concurrent smoking and concurrent relevant medication use; total calories, percent of calories from fat and alcohol; physical activity from routine activities, sports/leisure, and household childcare from the most recent measurement.

Based on data from Matthews et al.<sup>4</sup>

Apo B, apolipoprotein B; FMP, final menstrual period; LDL-C, low-density lipoprotein cholesterol.

disease (CHD) in postmenopausal women may be partly due to accelerated increases in lipid levels and changes in their particle size and composition associated with the menopausal transition.

The SWAN study clearly showed that estrogens are not the sole potential explanation for why a woman’s risk for ischemic heart disease increases as she traverses the menopause. Data from SWAN and other studies point to sex hormone binding globulin (SHBG) and androgens as players that predispose women to CVD risk. SWAN data revealed that both low SHBG and high free testosterone levels are strongly

and consistently correlated with elevated CVD risk factors, including obesity, higher insulin, glucose, hemostatic and inflammatory markers, and adverse lipid levels.<sup>6</sup> In prospective analyses, baseline SHBG and free testosterone levels predict the metabolic syndrome,<sup>7</sup> as does the shift to a greater androgen/estrogen ratio.<sup>8</sup> The latter occurs because the decline in testosterone is smaller than the decline in estrogen.

Dehydroepiandrosterone sulfate (DHEAS) is a weak androgen secreted by the adrenal gland. In SWAN, a majority of women undergoing the menopausal transition experienced a

short-term rise in circulating DHEAS during late perimenopause.<sup>9</sup> The adrenal gland may thus play a role in the changing hormone milieu associated with the menopausal transition. Although these concepts are speculative, they do suggest a broader perspective on hormones, beyond estradiol, as important to setting the stage for women’s heart disease.

Depression and depressive symptoms are risk factors for CVD events in both initially healthy men and women and in patients with existing CVD, independent of standard CVD risk factors.<sup>10</sup> Mechanisms accounting for the risk associated with depression are not established. In SWAN, the risk for elevated depressive symptoms, measured by questionnaire, increased in women during the menopausal transition. The largest increase in risk occurred during late perimenopause (3 to 12 months without menses) compared with premenopause (menses within the last 3 months with no change in regularity) and early perimenopause (menses within the last 3 months with change in regularity).<sup>11</sup> The increase in risk for elevated depressive symptoms was statistically significant but not large, and other factors, such as experiencing high levels of stress, were more important predictors of depressive symptoms than was change in menopausal status. Nonetheless, depression and depressive symptoms prior to and during the transition may be important to follow. At one of the SWAN sites, the protocol included both diagnostic interviews to screen for major depression and coronary and aortic calcification examinations. Analyses showed that, independent of standard risk factors for CVD, a history of several episodes of major depression was associated with both coronary and aortic calcification in



women with no symptoms of heart disease or stroke.<sup>12</sup> These findings suggest that, to the extent that women become depressed during the menopausal transition, they may also be at increased risk for developing subclinical CVD and, later, CVD morbidity and mortality.

### Influence of menopause on subclinical cardiovascular disease

An ancillary SWAN study, SWAN Heart, has provided much information on how menopause may be linked to subclinical CVD. Conducted at 2 of the 7 SWAN sites, SWAN Heart assessed subclinical CVD by examining coronary calcification and carotid intimal medial thickness in African American and white women. Notably, a large adventitial diameter of the common carotid artery is consistently associated with high levels of risk factors and with existing CVD.<sup>13</sup> Adventitial diameter can be viewed as a barometer of vascular health, because increases in diameter reflect the vessel's adaptive response to control adverse levels of shear and tensile stress. An artery that is already dilated has less ability to adaptively control these pressures and, thus, can be viewed as more "vulnerable." SWAN Heart found that as women transitioned to menopause and estradiol levels declined, adventitial diameter increased.<sup>14</sup> This may be

due to estrogen's effects on the sympathetic nervous system (ie, a loss of arterial tone) or to degradation of collagen within the arterial wall.

These changes in arterial structure may be related to impairments in endothelial function. Postmenopausal women have altered endothelial function.<sup>15</sup> Risk factors for endothelial dysfunction include not only menopausal status, but also elevated lipids, which are clearly tied to the menopausal transition. In SWAN Heart, the occur-

### Perhaps abnormal vascular reactivity is an underlying factor in both hot flushes and CVD.

rence of hot flushes, independent of menopausal status, was associated with reduced endothelial function as measured by flow-mediated dilation of the brachial artery in response to reactive hyperemia.<sup>16</sup> Perhaps abnormal vascular reactivity is an underlying factor in both hot flushes and CVD. This is consistent with evolving literature suggesting that persistent vasomotor symptoms may be a marker of underlying CVD risk. In the Women's Health Initiative, among postmenopausal women quite distant from their FMP, cardiovascular events were highest in the subset of older women who

had moderate to severe vasomotor symptoms at baseline.<sup>17</sup>

### Implications for treatment

Current recommendations on hormone therapy (HT) indicate limited risk for its use in early postmenopausal women. Extensive evidence suggests that the effects of estrogens on the vasculature differ based on a woman's age and, possibly, the stage of atherosclerosis.<sup>18</sup> Estrogens are thought to benefit early postmenopausal women, but their thrombotic and pro-inflammatory effects outweigh this benefit once women become older.<sup>18</sup> In the SWAN study, we observed that declining endogenous estrogen is associated with worsening vascular tone. More importantly, the increase in arterial diameter with declining estrogen leaves the vasculature in a state that is more vulnerable to risk factors. Of particular concern are the higher levels of LDL-C and apoB that clearly rise with the transition. Thus, lipid profiles should be closely monitored and treated when appropriate in mid-life women, as adverse lipid levels will eventually translate into cardiovascular morbidity and mortality as these women age.

Finally, SWAN has shown a clear link between depression and early vascular disease. Women suffering from depression should be screened and treated for adverse levels of cardiovascular risk factors. ■

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