Effects of menopause and depressive symptoms on sleep

Maintenance insomnia from night sweats and hot flashes seems to be the major type of insomnia in postmenopausal women


Summary. Researchers aimed in this study to evaluate subjective sleep quality in premenopausal and postmenopausal women and to study its association with night sweats, hot flashes, and depressive symptoms. A total of 158 women (107 premenopausal and 51 postmenopausal) used the Basic Nordic Sleep Questionnaire to evaluate sleep quality, a specific symptom questionnaire to evaluate night sweats and hot flashes, and the Beck Depression Inventory to evaluate depressive symptoms.

In the postmenopausal women, general sleep quality was poorer ($P < .001$), sleep was more restless ($P = .020$), and there were more nocturnal awakenings ($P = .015$). Regardless of menopause status, depression symptoms disturbed sleep. Researchers concluded that maintenance insomnia (from night sweats and hot flashes) seems to be the major type of insomnia in postmenopausal women. Sleep aspects not affected by menopause included initiation of sleep and daytime vitality.

Comments. The causes of poor sleep quality in women during and after the menopause transition are multifold with likely co-occurrence of several factors. Age-related changes occur as women make the transition from premenopause to perimenopause to postmenopause. These changes include a worse perception of sleep quality and more involuntary awakenings on electroencephalography, resulting in less non-rapid eye movement deep sleep and greater sleep fragmentation. Independent of age-related changes, there are important sources of sleep disturbance that occur commonly in midlife women, including vasomotor symptoms, psychological symptoms of depressed mood and anxiety, and primary sleep disorders of sleep apnea and restless legs/periodic limb movement disorder. Each of these conditions disrupts sleep in this population. They are common sources of sleep problems because vasomotor symptoms are the primary symptom manifestation of the menopause transition, whereas depressed mood is more common during the transition, and sleep apnea increases specifically during and after the menopause transition. These sources of sleep disruption can co-occur and may
independently and jointly contribute to poor sleep quality.

Results of this cross-sectional survey highlight the importance of assessing for the co-occurrence of common sources of sleep disturbance among midlife women during and after menopause. Sleep quality was compared between premenopausal and postmenopausal women, who were on average 10 years older than the premenopausal women (mean ages, 46 y vs 56 y), raising the possibility that age-related changes in sleep contributed to some of the findings, an important limitation of the study. The authors found that factors contributing to poor sleep quality included postmenopausal status, vasomotor symptoms, and depressive symptoms. The sleep disturbance that occurred more commonly in the postmenopausal group was sleep maintenance, not sleep-onset insomnia. Night sweats likely explain this sleep maintenance condition in postmenopausal women, but they are a less likely explanation in premenopausal women. In contrast, low mood was equally likely to explain poor sleep quality in both younger/premenopausal and older/postmenopausal women. Vasomotor and depressive symptoms commonly co-occurred as sources of sleep disruption.

This study extends findings from other studies showing that vasomotor symptoms cause sleep interruption rather than sleep-onset problems and that depressive symptoms can further contribute to poor sleep. The novel contribution in this paper is to highlight that these common sources of sleep problems co-occur, emphasizing how important it is to assess for different components of sleep quality and also possibly identify more than one underlying problem to address with treatment. The authors recognize that there are age differences between the two menopause status groups, which might explain some of their findings but do not fully address that age-related changes in sleep might increase susceptibility to other disruptive problems interrupting sleep.

Genetic breast cancer protection in Latinas on 6q25

There is a stronger association for estrogen receptor-negative disease than estrogen receptor-positive disease with these variants


Summary. This genome-wide association study of breast cancer in Latinas identified a
significant risk variant, the minor allele of which is strongly protective. It originates from indigenous Americans and is not correlated with other risk variants at 6q25. This risk variant has a stronger association for estrogen receptor-negative disease than for estrogen-receptor-positive disease. It is also associated with mammographic breast density.

**Comment.** This multicenter clinical evaluation shows a novel finding of a cancer-protective allele in several Latina populations extending from San Francisco into the Northern California Breast and Cancer Registry, and it is controlled with a multiethnic cohort group.

The meta-analyses were enhanced reasonably to 7.2 million markers that overlapped between the data sets. Statistically, this was an overwhelming evaluation of a single genome association recomputed by regional plotting and fine mapping at 6q25. Previous reports of similar associations in Latinas were used to rectify the close $P$ value of .05 in several series studied and in the references. Interpretation of the data, although written lucidly, shows many areas in which the final statistics require a more comprehensive designation. The variant is an estrogen receptor 1 gene (ESF1.6 of the 25 region). I find these results remarkably interesting, and they may lead into a new characteristic such as the historical positive/negative evaluation of the estrogen receptor itself.

To clarify, it would seem that direct responses in other diverse Latina populations would serve for local similarities. These variants need a clearer definition in order to be reproduced directly or on tissue culture. The potential of this study should also be more evident from pathology seen after activity.

Bernard A. Eskin, MS, MD
Professor of Obstetrics and Gynecology
Drexel University College of Medicine
Philadelphia, PA

**Effect of sex and menopause status on telomere length and aortic stiffness**

*Telomere lengths were similar in men and women and inversely correlated with age*


**Summary.** Researchers evaluated the relationship between relative leukocyte telomere length (determined using quantitative real-time polymerase chain reaction assays) and carotid-femoral (aortic) pulse wave velocity (PWV; determined using carotid and femoral application tonometry) in 580 randomly recruited participants of black African descent.

Telomere lengths were similar in men and women and inversely correlated with age before and after adjustment for confounders. There was no interaction between telomere length and either sex or menopause status independently associated with PWV. Telomere length was independently correlated with PWV in women and in men. Researchers concluded that sex and premenopausal status do not affect age-related decreases in telomere length and associations between telomere length and PWV.

**Comment.** In 2009, Elizabeth Blackburn, Carol Greider, and Jack Szostak achieved the Nobel Prize for the discovery of how chromosomes are protected by telomeres and the telomerase enzyme. Telomere length is believed to be a marker of oxidative stress and cellular senescence and hence has been postulated to be a marker of human aging.

Multiple studies have examined telomere length in varied phenotypes. Within any individual person, there is variability in telomere length from one tissue to another. The most consistent results have been with age, sex, and race. In general, increased age shows decreased
telomere length. Male sex and white race are associated with mean telomere length that is several hundred base pairs shorter than in women or those of black African descent, respectively. The findings are empirically present, but mechanistic explanations for these relationships are presently not known. Telomere markers of subclinical cardiovascular disease have been inconsistent. Studies of carotid or femoral intima-media thickening, ankle-brachial index, coronary calcium, and PWV have all had conflicting relationships to telomere length.

In this paper, Raymond and colleagues set out to discern the effect of sex and menopause status on relationships between aging and aortic stiffness as indexed by leukocyte telomere length in participants of black African descent. Their conclusion, after very detailed methodology and adjustments for many confounders, was that in this relatively large, cross-sectional study, in which telomere length did not differ by sex, age-related decreases in telomere length were similar in men and women. Moreover, independent of chronologic age, relationships between biological age, as indexed by relative leukocyte telomere length and aortic stiffness (carotid-femoral PWV) were not reduced in women, including premenopausal women, compared with men.

In considering the differences between men and women, it is clear that women have greater longevity. This has been associated with lengthening of the telomeres. The regulation of telomere reverse transcriptase by the estrogen response element has been offered as a mechanism of the increase on telomerase activity within cells and the estrogen-associated preservation of telomere length.1

Adipocyte hypertrophy, obesity, and diabetes mellitus have been strongly associated with telomerase shortening. Oxidative stress in these conditions is thought to provoke damage to the telomere by free radicals, resulting in telomere shortening.2

The age range of those considered to be in menopause was 44 ± 18 years, and the measure of follicle-stimulating hormone was 25.6 ± 28.6 IU/l, clearly indicating great variations in menopause status and in estrogen production. Therefore, it would be impossible to differentiate the menopausal women from the premenopausal women in this sample.

The marked difference in body mass index between the men and the women (24.6 ± 4.8 vs 30.5 ± 7.3), in addition to the lower incidence of diabetes in men, raises the question of whether these women, in the face of their increase in oxidative stress from obesity and diabetes, would have a definitive confounding reason for telomere shortening. Therefore, the ability to make comparisons is obliterated.

In their excellent and exhaustive review of hundreds of telomere studies, Sanders and Newman discuss many variables and associations but not menopausal differences.3 In his review, Pines concludes that although estrogen has been shown to increase telomere length and modify telomerase activity, menopause itself (and whether estrogen is given exogenously) does not affect this process.4

Clearly, the issue of whether menopause shortens telomeres or shortened telomeres lead to earlier menopause is important. Equally significant is the relation to cardiovascular disease and the mechanisms of sex differences. Sadly, this Raymond paper does little to answer this question, although it will hopefully lead to a greater quest for answers.

Lila E. Nachtigall, MD, NCMP
Professor of Obstetrics and Gynecology
NYU School of Medicine
New York, NY

References

Does pelvic floor muscle training work for symptomatic mild prolapse?

In a 3-month trial, training was better than watchful waiting


Summary. Many women experience bladder and bowel symptoms from mild pelvic organ prolapse in which the leading edge of the prolapse is at or below the hymen. Treatment options include surgery, pessary placement, and pelvic floor muscle training. However, whether pelvic floor training is effective in the setting of mild prolapse is unclear. In a randomized, controlled trial, investigators in the Netherlands compared pelvic floor training with watchful waiting in 287 older women (age, ≥55) with symptomatic mild prolapse. The intervention consisted of training by pelvic floor physiotherapists combined with home exercises. The primary outcome was change in the Pelvic Floor Distress Inventory (PFDI)-20, which assesses urinary, bowel, and prolapse symptoms on a scale of 0 to 100.

At a median follow-up of 3.6 months, mean improvement in the PFDI-20 score was 18 points in the training group and 8 points in the watchful waiting group—a statistically significant difference (improvement of ≥15 points is considered to be clinically significant). Improvement in urinary symptoms accounted for most of the difference. More than half (57%) of women in the training group reported improvements in overall symptoms compared with only 13% in the watchful waiting group—also a significant difference.

Comment. Surgery is not appropriate or practical for many women with mild pelvic organ prolapse. In this trial, pelvic floor muscle training yielded symptomatic improvements over watchful waiting. Whether these results can be sustained after 3 months is unclear. Nonetheless, such training seems reasonable for affected women.

Paul S. Mueller, MD, MPH, FACP
Professor of Biomedical Ethics and Medicine
Chair, General Internal Medicine
Mayo Clinic
Rochester, MN


Menopause Editor’s picks from January 2015

NAMS spotlights selections from the most recent issue of the Society’s official journal, Menopause, chosen by its editor in chief, Isaac Schiff, MD.

Relationship between age at natural menopause and risk of heart failure.
Ifiat Rahman, PhD, Agneta Akesson, PhD, and Alicja Wolk, DrMedSci.

Cognitive functioning during long-term tamoxifen treatment in postmenopausal women with breast cancer.
Florien W. Boele, MSc, Christina M.T. Schilder, PhD, Mari-Lou de Roode, MSc, Jan Berend Deijen, PhD, and Sanne B. Schagen, PhD.

Extended maternal age at birth of last child and women’s longevity in the Long Life Family Study.
Fangui Sun, PhD, Paola Sebastiani, PhD, Nicole Schupf, PhD, Harold Bae, PhD, Stacy L. Andersen, BS, Avery McIntosh, BS, Haley Abel, BS, Irma T. Elo, PhD, and Thomas T. Perls, MD, MPH.
The level of evidence indicated for each study is based on a grading system that evaluates the scientific rigor of the study design, as developed by the US Preventive Services Task Force. A synopsis of the levels is presented below.

- **Level I** Properly randomized, controlled trial.
- **Level II-1** Well-designed controlled trial but without randomization.
- **Level II-2** Well-designed cohort or case-control analytic study.
- **Level II-3** Multiple time series with or without the intervention (eg, cross-sectional and uncontrolled investigational studies).
- **Level III** Meta-analyses; reports from expert committees; descriptive studies and case reports.

**Member Forum on [www.menopause.org](http://www.menopause.org)**

What are your clinical challenges? Post on our Member Forum to discuss January’s *First to Know* papers: [www.menopause.org/member-login?ReturnUrl=%2fforum](http://www.menopause.org/member-login?ReturnUrl=%2fforum)