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This e-newsletter presents reviews of important, recently published scientific articles selected by The North American Menopause Society (NAMS), the leading nonprofit scientific organization dedicated to improving women's health and quality of life through an understanding of menopause. Each has a commentary from a recognized expert that addresses the clinical relevance of the item. Oversight for this e-newsletter issue was by Peter F. Schnatz, DO, Chair-Elect, 2008-2009 NAMS Professional Education Committee. Opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or Dr. Schnatz. Disclosures are available on request. Past issues of this e-newsletter may be viewed on the NAMS Web site ([www.menopause.org/news.html](http://www.menopause.org/news.html)).

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## Cognition, menopause, and HT

Greendale GA, Huang MH, Wight RG, et al. Effects of the menopause transition and hormone use on cognitive performance in midlife women. *Neurology* 2009;72:1850-1857. **Level of evidence: II-2.**

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**BACKGROUND:** There is almost no longitudinal information about measured cognitive performance during the menopause transition (MT). **METHODS:** We studied 2,362 participants from the Study of Women's Health Across the Nation for 4 years. Major exposures were time spent in MT stages, hormone use prior to the final menstrual period, and postmenopausal current hormone use. Outcomes were longitudinal performance in three domains: processing speed (Symbol Digit Modalities Test [SDMT]), verbal memory (East Boston Memory Test [EBMT]), and working memory (Digit Span Backward). **RESULTS:** Premenopausal, early perimenopausal, and postmenopausal women scored higher with repeated SDMT administration ( $p < \text{or} = 0.0008$ ), but scores of late perimenopausal women did not improve over time ( $p = 0.2$ ). EBMT delayed recall scores climbed during premenopause and postmenopause ( $p < \text{or} = 0.01$ ), but did not increase during early or late perimenopause ( $p > \text{or} = 0.14$ ). Initial SDMT, EBMT-immediate, and

EBMT-delayed tests were 4%-6% higher among prior hormone users ( $p < \text{or} = 0.001$ ). On the SDMT and EBMT, compared to the premenopausal referent, postmenopausal current hormone users demonstrated poorer cognitive performance ( $p < \text{or} = 0.05$ ) but performance of postmenopausal nonhormone users was indistinguishable from that of premenopausal women. **CONCLUSIONS:** Consistent with transitioning women's perceived memory difficulties, perimenopause was associated with a decrement in cognitive performance, characterized by women not being able to learn as well as they had during premenopause. Improvement rebounded to premenopausal levels in postmenopause, suggesting that menopause transition-related cognitive difficulties may be time-limited. Hormone initiation prior to the final menstrual period had a beneficial effect whereas initiation after the final menstrual period had a detrimental effect on cognitive performance.

**Comment.** SWAN is a landmark multicenter, multiethnic, community-based observational study of the menopause transition within the United States. At cohort inception, women were pre- or perimenopausal with an intact uterus and not currently using hormone therapy (HT). Cognitive assessment was initiated 3 years after cohort inception, at which time the mean age was 50 years, and 8% of the women

in the sample were still premenopausal. Participants were administered brief cognitive measures of processing speed (SDMT; a 90-second task in which women call out numbers corresponding to one of nine pictured symbols depicted on a printed key), verbal memory (EBMT; a 36-word story presented for immediate and delayed recall), and working memory (the familiar digit span backward test). Results of these three tasks administered annually over an additional 4 years form the basis of the report by Greendale et al.

Test score changes over time were modeled as a function of reproductive stage (pre-, early peri-, late peri-, and postmenopause) and HT use. Analyses considered use of HT prior to SWAN enrollment and, among postmenopausal women, current use of HT. Analyses excluded premenopausal and perimenopausal women during the time they used HT (including oral contraceptives).

One important result was the absence of any significant difference in test scores at time of initial testing, when women in the early peri-, late peri-, and postmenopause groups were compared to the premenopause group. A second finding was that test score trajectories within each reproductive stage improved with repeated administration, although the magnitude of improvement was not always significant. Third, test score trajectories of early peri-, late peri-, and postmenopausal women did not differ significantly from that of premenopausal women. The study conclusion that perceived memory difficulty during perimenopause is associated with “a decrement in cognitive performance” is based on positive trajectories that were “marginally different” from the slope of the premenopausal referent.

HT, however, did have significant effects. For SDMT and EBMT, prior HT users scored significantly *better* at cognitive baseline than women who had not used HT in the past. Conversely, prior HT use was associated with significantly *lower* trajectories in test score change on these tasks. Comparisons between

postmenopausal users and postmenopausal nonusers showed significant differences in slope trajectories on immediate and delayed recall components of the EBMT (*worse* trajectories for HT users). Test trajectories were also significantly *lower* among postmenopausal current users in comparison to premenopausal nonusers for SDMT and for EBMT delayed recall.

These new, interesting, and important findings from SWAN investigators are consistent with cross-sectional and longitudinal observations in other cohorts that the natural menopause transition is not accompanied by overall change in cognitive skills.<sup>1-4</sup> However, there may be “marginal” decrements in trajectories of test score improvement during perimenopause that resolve after postmenopause is reached. Also interesting is that prior HT users showed a cognitive advantage at the time of initial testing. Whether differences were due to biological effects of prior HT use or to unrecognized confounding is not easily decided with observational data. Because prior hormone users showed less tendency to improve with practice, these differences were attenuated or eliminated during the course of the menopause transition, and current HT use after menopause was associated with lower cognitive trajectories in the present study.

Effects of HT on midlife cognitive outcomes can best be answered through well-designed clinical trials in this age group, such as are beginning to emerge.<sup>5</sup>

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## Psychosocial influences on sexual function

Hess R, Conroy MB, Ness R, et al. Association of lifestyle and relationship factors with sexual functioning of women during midlife. *J Sex Med* 2009;6:1358-1368. **Level of evidence: II-3.**

This report by Hess et al was part of an ongoing 5-year longitudinal study that conducted a cross-sectional analysis of sexual functioning data of 677 women ages 41 to 68. The goal was to examine the effects of physical activity, sleep difficulties, and social support on partnered sexual activity and sexual functioning in women at the stages of the menopause transition.

Of the women in the study, 68% had participated in any partnered sexual activities (ie, were sexually active) during the past 6 months. Reasons for sexual inactivity included lack of a partner (70%), lack of interest in sex (12%) or in the current partner (5%), and physical problems (4%). The sexually active participants tended to be younger, married, more educated, have more social support in general, fewer comorbid medical illnesses, lower body mass index, and higher prevalence of vaginal dryness. For the sexually active women, scores for engagement in activities that ranged from kissing to sexual intercourse were higher if they were physically active, had more social support, and did not have sleeping difficulties. Similarly, scores for sexual enjoyment were higher if they were physically active, had more social support, and lacked vaginal dryness. Marital status and other factors did not affect the scores.

The authors concluded that midlife women who have social support and are physically active have enhanced sexual engagement and enjoyment.

**Comment.** Although the data presented by Hess et al make intuitive sense—that peri- and postmenopausal sexuality is affected not only by endocrinologic and physical health factors, but also by psychological and social factors—the conclusion that “psychosocial influences” significantly impact sexual health during the menopause transition should be cautiously applied to clinical practice. Attributing psychosocial etiologies to any female or male dysfunction, regardless of organ system, should not evolve to the point that this type of etiology becomes the first line rather than an etiology of exclusion.

When distressing symptoms, such as anorgasmia, inability to attain sexual excitement, hypoactive sexual desire disorder, dyspareunia, or vaginismus are immediately and strongly linked to psychological and social factors, the patient does not benefit and neither does the advancement of medical care. How many couples are lured into “procreation vacations” at hotels that offer several fertility enhancers such as sea moss elixirs, oysters, dark chocolate, Spanish fly, maca, and other aphrodisiacs because of the myth that stress is causing their infertility? Vacation will not lead to pregnancy in the infertile woman who is prematurely postmenopausal or who has blocked fallopian tubes.

The same is true with regard to sexual health. In fact, for decades—with some carryover even in today’s healthcare system—sexual function was not considered a valid medical issue that should involve practitioners. This is no longer the case. Clearly, dyspareunia in peri- and postmenopausal women with vaginal atrophy can be linked to hypoestrogenism, regardless of the woman’s psychological wellness or social status. For men, the advances in treating erectile dysfunction also support the role of medical etiologies for sexual issues.

Overall, the data from this survey study are important because the researchers did find a statistically significant association between social and psychological factors and sexual functioning. These data also support the existing theory that sexual function is the end product of multidimensional factors. But the results of this study should also be interpreted cautiously and not steer clinicians down a path that encourages them to quickly diagnose most sexual complaints as being caused by lifestyle, emotional instability, or both. Do not forget the prolonged time period in Western Europe and the United States when the many premenstrual and menstrual symptoms that we now associate with an increased synthesis of prostaglandins were placed under the umbrella etiology of female hysteria.

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## Is atherosclerosis affected by prolactin levels?

Georgiopoulos GA, Stamatelopoulos KS, Lambrinouadaki I, et al. Prolactin and preclinical atherosclerosis in menopausal women with cardiovascular risk factors. *Hypertension* 2009;54:98-105. **Level of evidence: II-3.**

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Hyperprolactinemia has been associated with endothelial dysfunction and an adverse cardiovascular risk profile, possibly as a result of the vasoconstrictive properties of prolactin. In this cross-sectional study, we examined the hypothesis that prolactin contributes to the increased cardiovascular risk occurring in early menopause by studying apparently healthy women without hyperprolactinemia. Prolactin serum levels were measured by immunoassay in 76 women aged 54.4 $\pm$ 4.9 years in menopause

for 4.9 $\pm$ 2.8 years, and possible correlations with traditional cardiovascular risk factors and surrogate markers of preclinical atherosclerosis, arterial stiffening, and endothelial and microcirculatory function were examined. Positive correlations between prolactin serum levels and arterial blood pressure, but no other traditional risk factors, were found. Prolactin also correlated with central aortic systolic ( $r=0.337$ ;  $P=0.002$ ) and diastolic ( $r=0.272$ ;  $P=0.012$ ) blood pressures and pulse wave velocity ( $r=0.264$ ;  $P=0.02$ ), a marker of aortic stiffness, but not with endothelial or microcirculatory function or carotid intima-media thickness. By multivariate regression analysis, prolactin levels determined, independent of traditional risk factors, both blood pressures and aortic stiffness. Notably, prolactin correlated with European Society of Cardiology HeartScore ( $r=0.364$ ;  $P=0.002$ ), a composite index that predicts 10-year cardiovascular mortality. Prolactin levels  $>8.0$  ng/mL had 100% sensitivity to predict a high peripheral blood pressure. Prolactin may play a role in accelerated arteriosclerosis in early menopause by affecting central/peripheral blood pressure and arterial stiffness. In contrast, no correlation was observed with other risk factors or surrogate markers of atherosclerosis. Prospective studies to assess whether prolactin is an additional hormone increasing cardiovascular risk are warranted.

**Comment.** This is an interesting cross-sectional (and therefore only a hypothesis-generating) study from a respected group of researchers. It suggests by mechanistic inference that prolactin may be associated with aortic stiffness and hypertension. Strengths of the study include a standardized blood pressure measurement (absent from many of our offices!). There were safeguards against interpretation bias, and there was reporting of observer variation. Average lipid levels among women in the study were not optimal and are considered out of control for postmenopausal women. Endothelial dysfunction does occur with dyslipidemia. Please note that the  $r$  values for associations are weak. Association does not

mean cause and effect. There are many other possible reasons for these findings.

I would have liked to have seen a test of association with an index of tissue estrogenization. The authors do not report DHEAS levels, which historically have been related to prolactin levels and which also may have implications for longevity. I would have also liked to have seen a test of association with physiologic and/or psychological stress. In the statistical methods, I did not see safeguards against multiple testing, and there was no description of how many comparisons were made. To infer a mechanistic bridge, I would have liked to have seen discussion of mechanistic studies and basic and/or animal studies addressing this potential association.

Further studies are needed, in my opinion, to help determine if there is any clinical relevance here. On the other hand, this study is creative; we know that vascular damage occurs in hypoerogenic environments associated with prolactin excess. All levels studied here were within the normal range. Prior studies that I am aware of had prolactin levels that were abnormal. Differences between these and the current one where prolactin levels were normal should be noted. The bottom line to me is that this topic, though interesting, requires more study to help determine its significance.

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## Mammographic density unchanged by isoflavones

Maskarinec G, Verheus M, Steinberg FM, et al. Various doses of soy isoflavones do not modify mammographic density in postmenopausal women. *J Nutr* 2009;139:981-986. **Level of evidence: I.**

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Soy isoflavones have functional similarity to human estrogens and may protect against breast cancer as a result of their antiestrogenic activity or increase risk as a result of their estrogen-like properties. We examined the relation between isoflavone supplementation and mammographic density, a strong marker for breast cancer risk, among postmenopausal women. The Osteoporosis Prevention Using Soy (OPUS) study, a multi-site, randomized, double-blinded, and placebo-controlled trial assigned 406 postmenopausal women to 80 or 120 mg/d of isoflavones each or a placebo for 2 y. Percent densities were assessed in digitized mammograms using a computer-assisted method. The mammogram reader did not know the treatment status and the time of mammograms. We applied mixed models to compare breast density by treatment while considering the repeated measures. The mammographic density analysis included 358 women, 88.2% of the OPUS participants; 303 had a complete set of 3 mammograms, 49 had 2, and 6 had only 1 mammogram. At baseline, the groups were similar in age, BMI, and percent density, but mean breast density differed by study site ( $P = 0.02$ ). A model with all mammograms did not show a treatment effect on any mammographic measure, but the change over time was significant; breast density decreased by 1.6%/y across groups ( $P < 0.001$ ). Stratification by age and BMI did not reveal any effects in subgroups. In this randomized 2-y trial, isoflavone supplements did not modify breast density in postmenopausal women. These findings offer reassurance that isoflavones do not act like hormone replacement medication on breast density.

**Comment.** Despite epidemiological and experimental evidence suggesting that soy isoflavones may reduce breast cancer risk, there has been some concern in recent years that the reverse might be true—that is, that soy isoflavones might increase the risk. That concern was largely the result of reports that isoflavones bind and transactivate estrogen

receptors, induce proliferation and estrogenic markers in MCF-7 breast cancer cells, and produce estrogenic changes in rodent reproductive tissues. Fortunately, the studies of the MCF-7 cells and the rodent studies were of little translational value as was shown later in studies of nonhuman primates and women.

Maskarinec et al report that the administration of two doses of soy isoflavones (80 or 120 mg/d) to postmenopausal women had no effect on mammographic density. Their finding is reassuring, especially since it involved a large group of women (n = 358) that was a part of the Osteoporosis Prevention Using Soy (OPUS) study. As a stand-alone observation, mammographic density is of uncertain value in predicting breast cancer risk; however, the indication that soy isoflavone treatment does not increase breast cancer risk has been supported by recent cellular and molecular studies. Cheng et al<sup>1</sup> administered either 60 mg of soy isoflavones or placebo to postmenopausal women and, as a part of their evaluation of effects on menopause symptoms and plasma lipoprotein concentrations, investigated whether there were any adverse effects on breast. Breast biopsies were taken before the soy isoflavone treatment and after 12 weeks. Expression levels of estrogen receptors  $\beta$ ,  $\alpha$ , and  $\beta\chi$  along with progesterone receptors A and B and proliferation rates as measured by the proliferation marker Ki67 did not change as a result of the isoflavone treatment. Those observations are consistent with extensive studies done in monkeys and reported by Wood et al.<sup>2</sup>

The soy isoflavone preparation used by Maskarinec and coworkers was derived from the germ of soybeans and thus has different relative amounts of isoflavones than the usual soy protein made from the entire soybean. Their preparation was daidzein rich, genistein poor, and contained large amounts of glycitein. The soy preparations made from the whole soybean (and the ones used widely) are genistein rich, daidzein poor, and with very small amounts of glycitein. Consequently, it remains uncertain the extent to which their observations can be generalized to the more usual soy preparations.

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1. Cheng G, Wilczek B, Warner M, Gustafsson J, Landgren B. Isoflavone treatment for acute menopausal symptoms. *Menopause* 2007;14:1-6.
2. Wood C, Register T, Franke A, Anthony M, Cline M. Dietary soy isoflavones inhibit estrogen effects in the postmenopausal breast. *Cancer Res* 2006;66:1241-1249.

## Editor's picks from July-August *Menopause*

NAMS spotlights the most recent issue of the Society's official journal, *Menopause*, selected by its Editor-in-Chief, Dr. Isaac Schiff.

Huang AJ, Sawaya GF, Vittinghoff E, Lin F, Grady D. Hot flashes, coronary heart disease, and hormone therapy in postmenopausal women. *Menopause* 2009;16:639-643.

In a large randomized trial of estrogen plus progestogen in postmenopausal women with coronary heart disease (CHD), estrogen plus progestogen was associated with a substantially increased risk of early CHD events among women with hot flashes but not among women without hot flashes. These findings suggest that hormone therapy may selectively increase the risk of CHD events among older postmenopausal women who experience hot flashes.



Nguyen A, Lemler S, Haydn J, et al. Comparison of subjective and objective hot flash measures over time among breast cancer survivors initiating aromatase inhibitor therapy. *Menopause* 2009;16:653-659.

Findings indicated dissimilarities between measures. Hot flash frequency and hot flash intensity and bother did not significantly change over time, diary and event button flashes significantly changed but in dissimilar patterns, and few consistent predictors of change in hot flashes were identified.



Giles GG, Cicuttini FM, Hanna FS, et al. Women have increased rates of cartilage loss and progression of cartilage defects at the knee than men: a gender study of adults without clinical knee osteoarthritis. *Menopause* 2009; 16:666-670.

Women, in comparison to men, tend to lose more tibial and patellar cartilage volume and are more likely to show increased severity of cartilage defects. This may in part explain the increased risk of knee osteoarthritis in women compared with men. The mechanism for this gender difference remains unknown.



Joffe H, Soares CN, Thurston RC, et al. Depression is associated with worse objectively and subjectively measured sleep, but not more frequent awakenings, in women with vasomotor symptoms. *Menopause* 2009; 16:671-679.

Sleep quality and selected parameters of objectively measured sleep, but not sleep interruption, are worse in depressed women with vasomotor symptoms (VMS) than in nondepressed controls with VMS. The type of sleep disturbance seen in these depressed women was not consistent with the etiology of depression secondary to VMS-associated awakenings.



Kingsberg SA, Flyckt RL, Liu J, Frasure H, Wekselman K, Buch A. Comparison of salivary versus serum testosterone levels in postmenopausal women receiving transdermal testosterone supplementation versus placebo. *Menopause* 2009;16:680-688.

In postmenopausal women, serum concentrations of free, total, and bioavailable testosterone did not demonstrate a strong correlation with salivary testosterone concentrations. These results do not support the routine use of measuring salivary testosterone in postmenopausal women receiving testosterone supplementation.



Celiloglu M, Aydin Y, Balci P, Kolamaz T. The effect of alendronate sodium on carotid artery intima-media thickness and lipid profile in women with postmenopausal osteoporosis. *Menopause* 2009;16:689-693.

The effects of alendronate sodium on carotid artery intima-media thickness, the lipid profile, and apolipoprotein A-I and apolipoprotein B rates were investigated. Alendronate sodium resulted in a significant decrease in intima-media thickness during a 1-year period compared with matched controls. Alendronate was also associated with a positive effect on the apolipoprotein B/apolipoprotein A-I ratio.

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.

**NAMS 20TH ANNUAL SCIENTIFIC MEETING**

“A New Experience: Bringing Technology to Menopausal Health”

San Diego, California

September 30-October 3, 2009

There are many compelling reasons to consider attending this year’s meeting. The CME scientific program is outstanding, with all sessions focusing on exciting technological advances to enhance health. The cornerstones of the NAMS Annual Meeting—cutting-edge science, world-class experts, and networking—will take place against the backdrop of the spectacular Manchester Grand Hyatt.

In addition, this year’s meeting marks the last meeting for Dr. Wulf Utian as Executive Director before his retirement at year’s end. As a friend and colleague of Dr. Utian’s, you will no doubt want to offer your good wishes in person. A special session, “20 Years of Progress in Menopausal Medicine: The Utian Years,” has been planned, followed by an evening reception on Wednesday, September 30.

For more information, visit [www.menopause.org/meetings/2009HCP.aspx](http://www.menopause.org/meetings/2009HCP.aspx).

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