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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 and healthy aging. Each review has a commentary from a recognized expert that addresses the clinical relevance of the item. Oversight for this e-newsletter issue was by Chrisandra L. Shufelt, MD, MS, NCMP, Chair-elect of the 2012-2013 NAMS Professional Education Committee. Opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or Dr. Shufelt.

The metabolism of hot flashes

Vasomotor symptoms related to insulin resistance in women in the SWAN Study.

Thurston RC, El Khoudary SR, Sutton-Tyrrell K, et al. Vasomotor symptoms and insulin resistance in the Study of Women's Health Across the Nation. *J Clin Endocrinol Metab* 2012;97:3487-3494. **Level of evidence: I.**

Summary. Although emerging research suggests there is an association between menopausal hot flashes and cardiovascular disease (CVD) risk, the underlying mechanism is not clear because hot flash physiology is not fully understood. The authors examined the associations between hot flashes/night sweats and glucose and insulin resistance over 8 years, controlling for cardiovascular risk factors and reproductive hormones. The 3,075 participants from the Study of Women's Health Across the Nation (SWAN) ranged in age from 42 to 52 upon entry. Women completed questionnaires (hot flashes and night sweats: none, 1-5 d, ≥ 6 d, past 2 wk), physical measures (blood pressure, height, weight), and a fasting blood draw (serum glucose, insulin, E^2 , FSH) annually. Hot flashes and night sweats were examined in relation to glucose and the homeostasis model assessment (HOMA)—an estimate of insulin resistance—in mixed models, adjusting for demographics, cardiovascular risk factors, medications, and E^2 /FSH. The authors concluded that hot flashes

were associated with a higher HOMA index and to a lesser extent higher glucose, indicating that metabolic factors may be relevant to understanding the link between hot flashes and CVD risk.

Comment. The prevalence and symptomatic burden of menopausal vasomotor symptoms are well known, but it is less widely recognized that these symptoms may have health implications beyond their impact on a woman's quality of life. In particular, a growing body of literature has examined the relationships between vasomotor symptoms and systemic cardiovascular health. Analyses of both the Women's Health Initiative (WHI) Hormone Therapy Clinical Trials¹ and the Heart and Estrogen/Progestin Replacement Study² suggested that the increased risk of coronary heart disease (CHD) observed with late hormone therapy was amplified among women who had experienced vasomotor symptoms. Several studies have found increased surrogate CVD risk markers among women with vasomotor symptoms.³⁻⁵ In contrast, we previously found that among women participating in the WHI Observational Study, the risks of stroke, CVD events, and all-cause mortality were decreased among women who reported onset of vasomotor symptoms around the time of menopause, with increased risks of CHD and all-cause mortality observed only among the much smaller group of women who

experienced onset of vasomotor symptoms in the later postmenopausal years.⁶

Thurston et al have made a valuable contribution to this area of research by investigating the relationships between vasomotor symptoms and insulin resistance among women participating in SWAN. In this study, both hot flashes and night sweats were associated with increased HOMA index. Vasomotor symptoms were also associated with higher fasting glucose to a lesser degree.

It is currently unclear what the possible pathophysiologic mechanisms of these interesting associations may be. The direction of causality is also unknown—do vasomotor symptoms predispose to insulin resistance or vice versa? Gaining a deeper understanding of the causal mechanisms underlying these associations is hindered by the intrinsic limitations of observational studies. Since all studies examining associations between vasomotor symptoms and outcomes are observational (as women cannot be “assigned” to having or not having vasomotor symptoms), these limitations are unavoidable.

While the nature of the relationships between vasomotor symptoms and insulin resistance are not fully understood at this time, future studies will be helpful in further exploring these relationships and the influence of potential modifying factors such as timing and duration of vasomotor symptoms. We are also reminded of the need for lifestyle modifications and therapies aimed at prevention of diabetes and CVD in all women, regardless of whether they experience vasomotor symptoms or not.

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The critical window of HT & Alzheimer’s disease

Use of unopposed HT within 5 years of menopause onset was associated with a 30% reduced risk of Alzheimer’s disease, but use 5 years or more following menopause onset was not.

Shao H, Breitner JC, Whitmer RA, et al. Hormone therapy and Alzheimer disease dementia: New findings from the Cache County Study. *Neurology* 2012;79:1846-1852. **Level of evidence: II-2.**

Summary. This prospective cohort study from Cache County, Utah, followed 1,768 women for an average of 7 years and assessed for incident Alzheimer’s disease (AD). In total, 176 women received diagnoses of definite, probable, or possible AD. Use of hormone therapy (HT), including timing, duration, and type, was assessed by a Women’s Health Questionnaire. Results indicated that 63% of women had used some form of HT. Most women (93%) used oral therapies so all types were considered together, and 37% used a progestogen. Overall, use of HT was not associated with a reduced risk of AD, nor was HT use when 5 years or more after menopause associated with a reduced risk.

Notably, however, HT initiated early—within 5 years of menopause onset—was associated with a 30% reduced risk of AD. There was some evidence of a duration effect; when continued for 10 or more years, early HT was associated with a 37% reduced risk of AD. For type of HT, both opposed and unopposed therapies were associated with a similar magnitude of reduced risk, though only unopposed HT reached statistical significance.

Comment. A 2003 report from Cache County was instrumental in providing evidence in support of the critical window hypothesis in noting a new finding of “an apparent limited window of time during which sustained HRT exposure seems to reduce the risk of AD.”¹ That conclusion was based on findings examining the joint effect of current versus past HT use and duration of use. Specifically, former HT use was associated with a significant reduction in AD, but current use was associated with a reduced risk only if women had used HT for 10 or more years. This current publication from this cohort reflects newly collected information on type, timing, and duration of HT to more directly test the critical window hypothesis. The report finds support for the hypothesis and provides new insights into the factors that might confer protection, including use within 5 years of the menopause, longer use, and use of ET alone.

At first glance, many might think that the new data run counter to the findings from the Women’s Health Initiative Memory Study (WHIMS).^{2,3} Instead, a close examination of the new Cache County findings reveals remarkable consistency with WHIMS regarding the effects of HT on dementia among women initiating HT at older ages. Shao et al found that initiation of opposed HT—but not unopposed HT—shortly before the study baseline was associated with a nearly double risk of AD though this effect did not quite reach statistical significance. The mean age of HT users at baseline was 73. In comparison, the WHIMS also found that opposed HT—but not unopposed HT—was associated with a doubling of the risk for all-

cause dementia, and the mean age was in the early 70s. WHIMS did not evaluate women younger than age 65 at baseline and therefore cannot address the critical window of HT and AD. Nevertheless, the consistency of findings among women who initiated later in life suggests that both the WHIMS findings and the Cache County findings might be valid and that timing of initiation is a critical factor in understanding the effects of HT on AD risk.

Overall, given the observational nature of the Cache County study, however, the findings do not warrant a change in guidelines about HT and dementia prevention. No women should initiate HT solely for dementia prevention. Instead, these findings may be helpful in counseling patients about the adverse effects of initiating HT for other indications, particularly vasomotor symptoms, early in perimenopause. Specifically, these new findings suggest that the risk of AD observed in WHIMS may not generalize to those younger women and that HT may confer some reduced risk of AD when initiated early.

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Midlife fitness lowers chronic disease risk later

Fitness earlier in life associated with fewer chronic disease outcomes in older age.

Willis BL, Gao A, Leonard D, Defina LF, Berry JD. Midlife fitness and the development of chronic conditions in later life. *Arch Intern Med* 2012;172:1333-1340. **Level of evidence: II-2.**

Summary. In order to study the association between midlife fitness and nonfatal chronic disease outcomes in later life, 18,670 healthy participants from the Cooper Center Longitudinal Study were linked with Medicare claims from January 1, 1999, to December 31, 2009. Fitness estimated by Balke treadmill time was analyzed as a continuous variable in metabolic equivalents (METs) and according to age- and sex-specific quintiles. Eight common chronic conditions were defined using validated algorithms, and associations between midlife fitness and the number of conditions were assessed using a modified Cox proportional hazards model that stratified the at-risk population by the number of conditions while adjusting for age, body mass index, blood pressure, cholesterol and glucose levels, alcohol use, and smoking. The authors found that, after 120,780 person-years of Medicare exposure, fitness was significantly associated with a lower risk of developing chronic disease outcomes during 26 years of follow-up. These findings suggest that higher midlife fitness may be associated with the compression of morbidity in older age.

Comment. Clinical practice teaches us that all patients care about something. Many simply wish to age better than their parents. Healthy aging can be difficult to achieve, and, as noted in 2011 by Mosca et al,¹ the list of barriers includes “health care professionals who are time-limited and burned out,” and the “ineffective uni-dimensional interventions” we too often deliver with one hand on the door such as “you need to lower your cholesterol.” This article by Willis et al provides information we

can share with our patients to encourage realistic goals.

In this study, fitness data from participants in the Cooper Center study were compared with their chronic condition burden after age 65 obtained through Medicare claims reports. Fitness levels were divided into quintiles, and each quintile was compared to summation of eight chronic condition diagnoses such as ischemic heart disease, stroke, and diabetes mellitus. The results were controlled for cigarette use, BMI, blood pressure, glucose levels, and alcohol consumption. A higher level of fitness at midlife was associated with fewer chronic conditions in women as well as in men. Also, in participants in the higher fitness quintiles, their life curves were more rectangular, with less time in unhealthy decline.

A “MET” is the energy cost of physical activity.² Included as examples were: TV watching (1 MET), brisk walking (3 METs), and average jogging (7 METs). The study participants, with a median age of 49, were evaluated with a treadmill test measuring fitness in METs. When analyzed, the data demonstrated that for each additional MET the participants were able to obtain, their chronic disease burden was reduced by 6%. It follows that if our patients increase their midlife activity by even 1 MET, walking or biking more briskly, they are more likely to age in a fashion their children would want to mimic. Risk for cardiovascular disease and diabetes would be lower, and length of time with an end-of-life illness would be less.

While this study was limited to a population of healthy non-Hispanic whites, this considerable effort by Willis et al has provided us with useful information for our patients who desire to age with vitality.

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Screening Mammography: Does Overdiagnosis Overshadow Prevention of Advanced Breast Cancer?

Analysis of US data spanning 30 years suggests many mammographically detected tumors are destined to be harmless.

Bleyer A, Welch HG. Effect of three decades of screening mammography on breast-cancer incidence. *N Engl J Med* 2012;367:1998-2005.

Summary. Screening to lower cancer mortality should enable earlier detection of malignancies destined to be fatal while also facilitating early treatment of screen-detected cancers. U.S. investigators analyzed three decades of federal data to assess the long-term effects of screening mammography. Breast cancer rates from 1976 through 1978 (when mammography was uncommon) were used to estimate baseline incidence; data from 2006 through 2008 were used to estimate current incidence. To minimize confounding effects of menopausal hormone therapy, the transitory increase in incident breast cancers from 1990 through 2005 was not included. Models for determining the excess in screen-detected early-stage breast cancer as well as the reduction in diagnoses of late-stage cancer included the "best-guess" estimate, in which the underlying incidence of breast cancer was assumed to rise by 0.25% annually (the

known percent change in women who were younger than 40).

Incidence of early-stage breast cancer rose from 112 (baseline) to 234 (current) cases per 100,000 women. During the same 30-year interval, incidence of late-stage disease declined by 8 cases per 100,000. Overdiagnosis (i.e., identification of tumors destined not to progress to advanced disease) attributable to screening mammography affected an estimated 1.3 million women (including >70,000 women in 2008 alone, when overdiagnosis accounted for 31% of tumors identified in women 40 and older). During the study period, breast cancer mortality fell by 28% among women 40 and older and by 42% in women younger than 40, a group in which screening was not prevalent.

Comment. By promoting early diagnosis of breast cancer, screening mammography can save lives. However — and consistent with other reports^{1,2} — this study suggests that screening's contribution to the decline in breast cancer mortality is surpassed by improvements in treatment, and that the benefits of screening mammography are smaller and the harms associated with overdiagnosis greater than have been previously appreciated. This viewpoint supports the 2009 USPSTF recommendation that women begin biennial mammograms at age 50.³ In the future, comprehensive genetic analysis of breast tumors could allow cancers to be distinguished according to their potential to cause advanced disease.⁴ Until then, the pros and cons of mammography should be incorporated into the counseling that women receive as they decide whether and when to be screened.

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Menopause Editor's picks from November 2012

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

Bleil ME, Adler NE, Pasch LA, et al. Depressive symptomatology, psychological stress, and ovarian reserve: a role for psychological factors in ovarian aging? *Menopause* 2012;19:1176-1185.

Cross-sectional evidence suggests that women with low positive affect may experience accelerated antral follicle count decline (AFC) and low positive affect may be a vulnerability factor, or, alternatively, high positive affect may be a protective factor, in moderating the negative effects of psychological stress on AFC decline.



Tseng LA, El Khoudary SR, Young EA, et al. The association of menopause status with physical function: the Study of Women's Health Across the Nation. *Menopause* 2012;19:1186-1192.

Women with surgical or naturally occurring menopause are at nearly four-fold higher odds of reporting greater limitations in physical function than premenopausal women, independent of age, only partly explained by higher BMI and depressive symptoms. This suggests that physiologic changes of menopause could contribute directly to limitations in physical function.



Baro F, Cano A, Borrego RS, et al, for the FROSPE Study Group. Frequency of FRAX risk factors in osteopenic postmenopausal women with and without history of fragility fracture. *Menopause* 2012;19:1193-1199.

The aim of this study was to compare the frequency of risk factors for fractures included in the FRAX algorithm, as well as others, in osteopenic postmenopausal women with and without prior fragility fractures in Spain.



Jane A. Cauley, DrPH, Michelle E. Danielson, PhD, Gail A. Greendale, MD, Joel S. Finkelstein, MD, Yue-Fang Chang, PhD, Joan C. Lo, MD, Carolyn J. Crandall, MD, MS, Robert M. Neer, MD, Kristine Ruppert, DrPH, Leslie Meyn, MS, Beth A. Prairie, MD, MS, and MaryFran R. Sowers, PhD. Bone resorption and fracture across the menopausal transition: the Study of Women's Health Across the Nation. *Menopause* 2012;19:1200-1207.

Higher urinary cross-linked N-telopeptide of type 1 collagen (NTX) excretion measured before menopause and greater increases in NTX across menopause are associated with a higher risk for fracture over the menopausal transition.

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.

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