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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 Gloria Bachmann, MD, Chair-Elect, 2011-2012 NAMS Professional Education Committee. Opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or Dr. Bachmann.

Obesity does not protect against fracture

Compston JE, Watts NB, Chapurlat R, et al, for the Glow Investigators. Obesity is not protective against fracture in postmenopausal women: GLOW. *Am J Med* 2011;124:1043-1050. **Level of evidence: III.**

Summary. This multinational, prospective, observational, population-based study was carried out by 723 physician practices at 17 sites in 10 countries, including 60,393 women age 55 or older. Researchers found that fracture prevalence in obese women (at baseline, 222 per 1,000, and at 2 years, 61.7 per 1,000) was similar to rates in non-obese women (227 and 66.0 per 1,000, respectively).

Incidence of ankle and upper leg fracture risk was significantly higher in obese than in non-obese women, while the risk of wrist fracture was significantly lower. Obese women with fracture were more likely to have experienced early menopause, to report two or more falls in the past year, and to have self-reported asthma, emphysema, and type 1 diabetes than non-obese women with incident fracture. At 2 years, 27% of obese women with incident fracture were receiving bone protective therapy, compared with 41% of non-obese and 57% of underweight women. Compston et al concluded that postmenopausal obesity does not protect against

fracture and is associated with increased risk of ankle and upper leg fracture.

Comment. Uncertainty exists about the relationship between body mass index (BMI) and skeletal health. It is well documented that bone mineral density (BMD) measured by DXA closely correlates with body weight after adjusting for age;¹ thin women typically have below-average BMD values while heavy women usually have values in the upper normal range. This relationship is the basis of the recommendation by The North American Menopause Society that postmenopausal women younger than age 65 who are thin (<127 lbs [57.7 kg] or BMI <21 kg/m²) be screened with DXA testing.²

As the Global Longitudinal Study of Osteoporosis in Women (GLOW) documents, the relationship between BMI and fracture risk is more complex, confirming previous observations that low body weight is a risk factor for fractures related to osteoporosis (eg, spine, hip, wrist), while increased BMI does not protect from these fractures. This relationship is greatly reduced after adjusting for BMD, indicating that BMD is an important intermediary or confounder. Importantly, BMD was not considered in the GLOW study. However, fractures of the ankle and lower extremity were increased among the obese

GLOW cohort. These data are consistent with other studies demonstrating an increased risk of nonvertebral (mostly lower extremity) fractures among heavy adults.

Fractures occur when the load applied to bone exceeds its capacity to withstand it. Fractures typical of osteoporosis (fragility fractures) occur when weakened bone encounters normal or even minimal trauma. On the other hand, stress fractures of the weight-bearing skeleton (predominantly the lower extremity) occur as a result of increased trauma such as new or excessive exercise (long-distance running, military training), heavy work on hard surfaces, or increased mechanical loading due to excessive weight. These load-related fractures occur predominantly in the lower extremity; fractures of the ankle and foot are not frequently seen in patients with osteoporosis. Thus, some fractures are primarily related to impaired bone strength (fragility or osteoporotic fractures) while others are due to excessive mechanical loading (stress fractures). The GLOW data are consistent with this concept; underweight and obese cohorts displayed different patterns of increased fracture risk, probably due to skeletal fragility and excessive mechanical loading, respectively.

What are the implications of these data for clinicians? We must appreciate that all fractures do not carry the same implication about skeletal fragility or the need for bone-active drugs. The diagnosis of osteoporosis can be made and treatment with an osteoporosis drug is indicated in a postmenopausal woman who presents with a hip or spine fracture. In contrast, stress fractures and most other non-hip fractures of the lower extremity in postmenopausal women deserve evaluation but should not always be construed as a sign of skeletal fragility or an indication for pharmacologic therapy. We have no evidence that our osteoporosis drugs reduce the incidence of fracture related to an increase in mechanical loading.

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Heart failure & socioeconomic status

Shah RU, Winkleby MA, Van Horn L, et al. Education, income, and incident heart failure in post-menopausal women: the Women's Health Initiative Hormone Therapy Trials. *J Am Coll Cardiol* 2011;58:1457-1464.
Level of evidence: II-2.

Summary. This study of 26,160 healthy postmenopausal women from the Women's Health Initiative (WHI) Hormone Therapy Trials examined the association between education, income, and incident heart failure (HF) hospitalization. Statistical analyses were done with chi-square tests, analysis of variance, and proportional hazards models (adjusted for demographics, comorbid conditions, behavioral factors, and hormone and dietary modification assignments).

Pronounced income and educational disparities in incident HF were found among the women without HF or coronary heart disease at baseline. Researchers found that women with yearly household incomes below \$20,000 had higher HF hospitalization incidence than those above \$50,000 (multivariable analyses showed that women with the lowest income levels had 56% higher risk than the women with highest income levels). Women with less than a high school education had higher HF hospitalization incidence than college graduates and above (multivariable analyses showed that women with the least education had 21% higher risk for incident HF hospitalization than women with the most education).

Comment. With a lifetime risk for men and women of 1 in 5,¹ HF is an important problem in the United States. The 5-year death rate is

approximately 50%.¹ While socioeconomic disparities in other cardiovascular diseases such as ischemic heart disease and stroke are well established, less is known about socioeconomic disparities in HF.

This study has several strengths. It addresses an important and underexamined issue and this analysis was performed in the WHI, which includes a large sample of women. Low socioeconomic status (SES) is a risk factor relevant to women, particularly older women, who are overrepresented in poverty statistics.^{2,3} Moreover, contrary to historic beliefs that SES disparities in health may be weaker among women than men, there is evidence that SES disparities in cardiovascular diseases may actually be stronger in women.² Other study strengths include the fact that multiple cardiovascular and demographic risk factors were measured and events were carefully adjudicated. However, this analysis was performed in the WHI Hormone Therapy Trials, and women had to meet specific inclusion criteria and be willing to be randomized to hormone therapy (or placebo). Thus, while the sample size is large, these women cannot be considered representative of the general female population. Moreover, these results cannot be generalized to men.

Curiously, the authors observed somewhat more robust associations for income than for education. Education and income are not directly interchangeable and may have somewhat different implications with respect to health.⁴ Income is generally considered a less optimal measure of SES among individuals in this age group, given that it may less accurately reflect available resources after retirement than at other points during adulthood.⁵ The authors do attempt to address this issue, stratifying the sample by age 66 and showing that the effect sizes were broadly similar. However, this method includes several assumptions about age and retirement that likely do not hold entirely true in this context. Stratification by employment would have been preferable. Researchers did not consider that the impact of income on a household's resources is

often dependent on the number of individuals supported by this income. Finally, income is best conceptualized as an acute SES measure, capturing one's acute resources at a given point in time and often fluctuating more over the adult life than education. Often, but not always, SES disparities in health occur over a long time.

What may explain these findings? HF is a heterogeneous condition, and because there was not further delineation of origins or subtypes (eg, ischemic vs non-ischemic, reduced vs preserved ejection fraction), we are limited in understanding the mechanisms giving rise to these disparities and how to best address them. However, the pronounced SES disparities in cardiovascular risk factors, such as smoking, diabetes, physical inactivity, and hypertension are well established. Most of these were statistically controlled in this study. Residual confounding must always be considered in observational studies, particularly when measured at one point or with brief self-report measures. However, these findings do suggest the consideration of other factors in the etiology of these disparities. The authors discuss issues such as unfavorable neighborhood factors including lack of walking environment, healthy food availability, safety, and social cohesion; lower access to or poorer quality of health care; and lower health literacy.

Because there are likely multiple processes that give rise to SES disparities in health, isolating a single pathway might not be possible. In fact, the persistence and pervasiveness of SES disparities in health lead some to conceptualize low SES as being a fundamental cause of disease,⁶ patterning the exposure to multiple risks throughout life. SES disparities are seen across many mental and physical health conditions. They are observed at all SES levels, even relatively high levels. They are generally not attributed solely to healthcare access—they are observed among countries with universal health care and among relatively high-SES insured individuals.⁷ Health disparities are also

seen among youth. In fact, disparities in preclinical markers of cardiovascular disease are seen among adolescents.⁸ Thus, the development of SES disparities in adult health is often conceptualized as the result of a lifetime of exposure to adverse physical and psychosocial conditions.⁴

The persistence of SES health disparities in the United States may lead one to wonder how to address them. There are many heated and diverse opinions on this topic, which are beyond the scope of this commentary. However, what these findings point to is the need for early and aggressive prevention efforts among low SES individuals to reduce the burden of disease throughout life.

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POF and resumption of ovarian function

Bidet M, Bachelot A, Bissauge E, et al. Resumption of ovarian function and pregnancies in 358 patients with premature ovarian failure. *J Clin Endocrinol Metab* 2011 Oct 12. [Epub ahead of print] **Level of evidence:III.**

Summary. This mixed retrospective and prospective study of 358 consecutive premature ovarian failure (POF) patients examined the prevalence of and predictive factors for spontaneous resumption of ovarian function. A total of 86 (24%) of patients resumed ovarian function; of these, 88% were within 1 y of POF diagnosis. In 15 patients, 21 spontaneous pregnancies (16 births, 5 miscarriages) occurred. Significantly predictive of ovarian resumption were a familial history of POF, secondary amenorrhea, presence of follicles at ultrasound, and inhibin B and estradiol levels, according to multivariate analysis by Cox proportional hazard model. Factors not predictive were association with an autoimmune disease, anti-Mullerian hormone levels, the presence of follicles on biopsy, and genetic abnormalities.

Researchers also created a predictive score for resumption of ovarian function (age at diagnosis, presence of follicles at ultrasound, inhibin B level), which may help clinicians identify POF patients most likely to regain ovarian function.

Comment. Based on existing evidence in the literature, for years we have counseled our patients with POF with two quotations, which we ask them to write down, mark with a star, and save for future reference: 1) “Primary ovarian insufficiency is intermittent and unpredictable ovarian function that can go on for decades.” 2) “Primary ovarian insufficiency is not an early menopause.” We don’t need to change that based on the findings of this paper.

I never cease to be amazed by the surprises we encounter—I have seen a woman conceive a healthy pregnancy after having serum FSH levels over 100 IU/L, estradiol levels less than 20 pg/ml, and no ovaries visible on ultrasound. There is a case in the literature of a woman being diagnosed with the condition at age 27 and conceiving a healthy child and delivering at age 44. Rare pregnancies have even been reported in patients with Turner syndrome who presented with primary amenorrhea. In my view, efforts to develop predictive markers for return of ovarian function and pregnancy in this population are efforts better spent elsewhere. As Dr. Amy Cooper mentioned to me when we reviewed this paper, “Pregnancy is like survival from cancer, it is either 100% or 0% to the desiring individual.”

I wish the authors would have done some things differently. For one, other major journals have moved to Fuller Albright’s 1942 term “primary ovarian insufficiency” and away from the terms “premature menopause” and “premature ovarian failure.” These terms are scientifically inaccurate and stigmatizing to many women with the condition. Our data show that patients prefer the term “primary ovarian insufficiency.” It is hard for me to understand why a publication that further demonstrates potential return of ovarian function still uses the term “premature ovarian failure.” Many of our patients also would prefer that the authors not refer to “POF patients.” Using “women with POF” is preferred by those patients who object to their entire identity being defined by their disease. There is an entire movement along these lines called People First Language (<http://www.disabilityisnatural.com>).

I have concerns regarding this mixed approach of retrospective and prospective study. It is likely that this significantly underestimates the frequency of return of function in these women. This is the best we can do now in the current paradigm, but this paradigm needs to shift. Bidet et al highlight the need to establish an international registry for women with primary ovarian insufficiency.

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Editor’s picks from December 2011 *Menopause*

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

Gibson CJ, Thurston RC, Bromberger JT, Karmarck T, Matthews KA. Negative affect and vasomotor symptoms in the Study of Women’s Health Across the Nation Daily Hormone Study. *Menopause* 2011;18:1270-1277.

Although an association between self-reported vasomotor symptoms and measures of negative affect is commonly found, the temporal relationship between these factors is unclear. In an examination of this relationship using prospective data from daily diaries, negative affect was more likely to be reported on the same day of and the day after experiencing vasomotor symptoms.

Costa-Paiva L, Godoy CE, Antunes A, Caseiro JD, Arthuso M, Pinto-Neto AM. Risk of malignancy in endometrial polyps in premenopausal and postmenopausal women according to clinicopathologic characteristics. *Menopause* 2011;18:1278-1282.

The prevalence rate of malignancy in endometrial polyps was 2.5% and was higher in women with postmenopausal bleeding and advanced age.

Waetjen LE, Johnson WO, Xing G, et al, for the Study of Women’s Health Across the Nation. Serum estradiol levels are not associated with urinary incontinence in midlife women transitioning through menopause. *Menopause* 2011;18:1283-1290.

Annually measured values and year-to-year changes in endogenous estradiol levels had no effect on the development or worsening of urinary incontinence in women transitioning through menopause.

Woodard GA, Mehta VG, Mackey RH, et al. C-reactive protein is associated with aortic stiffness in a cohort of African-American and white women transitioning through menopause. *Menopause* 2011;18:1291-1297.

This study demonstrated a significantly stronger positive association between C-reactive protein and pulse wave velocity in a cohort of women who had reached late perimenopausal or postmenopausal status compared with women who were premenopausal or early perimenopausal.

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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- Identifying & Treating Depression in Midlife Women
- When Sex Hurts
- Cardiovascular Disease in Postmenopausal Women: Getting to the Heart of the Matter
- Debate: Is There Ever an Indication for HT in an Asymptomatic Postmenopausal Women?
- Addressing the Needs of Midlife Women Through & Beyond Breast Cancer
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