



HOT FLASHES AND OTHER MIDLIFE MYTHS

A decade or two ago, it was considered indiscreet to even mention the word “menopause” in public.

Thanks to an unprecedented \$80 million nationwide research project focusing on women at the midlife, scientists today are not only using the word, they’re beginning to find out what it really means.

If you believe the myths, all women who go through menopause suffer hot flashes, memory loss, sexual dysfunction, osteoporosis, and profound mood swings. But the truth is a different matter.

For starters, says Mary Fran Sowers, a professor of epidemiology and principal investigator (Michigan) of the largest-ever national study of the menopausal transition, as many as one-third of American women who go through menopause “just don’t report having” hot flashes. Another one-third of the female population experiences hot flashes but isn’t bothered by them. So why the widespread misconception that they’re a hallmark of the midlife?

“Most of the studies out there are of women who’ve been specifically recruited from menopausal clinics,” Sowers says, “and such women tend to have substantial problems. It creates a bias, in that people come to believe that the health issues of these women reflect the health issues of all women.”

Unlike previous studies—many of which focused on white subjects in clinical settings—the Study of Women’s Health Across the Nation, or SWAN, an \$80 million research project funded by the National Institutes of Health, is collecting data annually from a population-based, multi-ethnic sample of over 3,000 women throughout the United States. Sowers directs one of seven nationwide SWAN centers, is a member of the steering committee for the overall project, and is principal investigator for key components of the study, including SWAN’s genetics program and its lab-specimen repository.

Recently, the NIH renewed funding for the project, giving Sowers and her colleagues five additional years for data collection and analysis. Already, though, SWAN is yielding valuable insights into researchers’ understanding of health at the midlife and the contribution of the menopausal transition. Sowers says it’s like being two-thirds of the way through “a really good novel and trying to guess if

the end is what you think. You want to skip to the last 20 pages, but you know you have to read through to the end.”

SWAN findings suggest that women should begin working to prevent osteoarthritis before, rather than after, menopause.

Simply put, menopause is one of the more profound changes the human organism experiences. In its effect on both physical and mental health, its closest parallel is puberty. Researchers are just beginning to grasp its full significance to women’s physiology.

“SWAN gives us the opportunity to look at what is a pre-existing condition, what conditions are developing before the menopause, and where menopause fits in,” says Siobán Harlow, an associate professor of epidemiology and co-principal investigator (Michigan) for the study, who is using SWAN data to develop a system for identifying the stages women experience as they transition out of reproductive life.

Harlow is part of a University of Michigan research team working on the massive study, whose 3,300 participants come from seven different U.S. regions and a range of ethnic backgrounds, including white, African-American, Latin-American, Chinese, and Japanese. Each participant was between 42 and 52 years old when she enrolled in the study eight years ago, and since then each has undergone a detailed yearly evaluation that elicits data on a variety of topics, from social and environmental factors to medical history, diet, lifestyle practices, and self-perception of health. Study participants also provide specimens for laboratory analysis.

According to Sowers, who also directs the Center for Integrated Approaches to Complex Diseases, SWAN has to date amassed in its repository more than a half-

million laboratory specimens, or assays. Roderick Little, the Richard D. Remington Collegiate Professor of Biostatistics and a SWAN co-investigator, says few studies accumulate “such a detailed set of measurements over a long period for such a large cohort.” The statistical challenges of evaluating the SWAN data are immense, Little adds.

The data collection itself is challenging. Some Asian cultures have no word for “hot flash,” and so women from these cultures may report symptoms in ways that aren’t immediately discernible. African-American women are more likely to report hot flashes than white women. “So trying to translate the data in meaningful ways is a challenge,” says John Randolph, a professor in the UM Medical School’s Department of Obstetrics and Gynecology and a co-principal investigator (Michigan) of SWAN.

By the time the study ends, Randolph notes, SWAN will have accumulated a decade’s worth of data. Besides the obvious challenge of interpreting so much information—especially as it changes over time—there is the underlying difficulty posed by menopause itself, which is a far more elusive process than puberty.

Says Little, “Trying to get a handle on the different stages of menopause is a very tricky problem.”

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It’s a challenge Harlow knows well. Although researchers developed a staging system decades ago for understanding the human transition into reproductive life, or puberty, only a rudimentary system exists for menopause. “The physiology of the hot flash was only described in 1979,” Harlow points out.

Harlow is using data from SWAN and five other studies to identify the common stages of menopause and midlife changes in reproduction. “Yes, there’s variation,” she says, “but there is in fact a defined set of patterns, and if we can have a better understanding of the length of time from the first long menstrual cycles to the end of reproduction, then we can help women predict what to expect.”

In turn, she says, women could make more informed decisions about if and when to adopt interventions to ease the symptoms of menopause or to address changes in cardiovascular or osteoporosis risk.

One of the biggest questions researchers are asking is when does menopause start. “Changes in the ovaries start to accelerate when women are in their late thirties,” Randolph explains. “But the conventional wisdom is that menopause starts at around age 50.” Nor is it clear when menopause ends—or what signals its end. Is it merely the cessation of menstrual periods? Or could it be the onset of other symptoms, such as bone loss?

Randolph admits he doesn’t know the answers. Asked whether he finds this subject perplexing, he nods his head and grins. “Every day.”

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Researchers are certain about one thing: menopause plays a critical role in women’s overall health, and therefore has profound implications for public health. “This is an important study because we’re not talking about ‘disease’ and ‘therapy,’” says Sowers. “We’re really talking about what initiates health-related processes.”

She and her colleagues are finding that lifestyle practices are even more important

than previously thought. Women who smoke, for instance, begin the menopausal transition at an earlier age, and studies have shown that women who transition earlier appear to have earlier deaths.

While prior studies suggested that bone loss occurs only after the menopausal transition, SWAN data reveals that women have substantial bone loss before menopause. This means that current interventions, such as weight training and other forms of physical exercise, which are now targeted to post-menopausal women, should be introduced earlier.

Similarly, SWAN findings suggest that women should begin working to prevent osteoarthritis before, rather than after, menopause. “You see no X-ray-defined osteoarthritis before age 40, but between 40 and 45 the prevalence is 8%, and between 45 and 50 it jumps to between 13 and 15%,” says Sowers.

Researchers have traditionally viewed arthritis as something that afflicts older-aged people, and so its potential impact on women at the midlife has been overlooked. “If you’re going to talk about movement and preventive practices,” Sowers notes, “it’s important to think in terms of the package. Once arthritis sets in, physical exercise hurts, and people are less likely to do it.”

SWAN may change other aspects of conventional wisdom as well. The study suggests, for example, that important markers of cardiovascular disease change with time, but not specifically with hormone changes leading to menopause. This information, combined with findings from the Women’s Health Initiative, a large NIH research study that focused on health in older women, may indicate why the practice of prescribing estrogen to help prevent heart disease is questionable. “It’s a paradox,” says Randolph, a reproductive endocrinologist by training. “Until a few years ago we thought estrogen replacement helped prevent heart disease. Now we’re back to where we were 50 years ago—if you have symptoms associated with menopause, take estrogen. If not, don’t.”



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Estrogen levels themselves are proving a poor indicator of the stages of the menopausal transition. Follicle-stimulating hormone, or FSH, which prompts the ovaries to produce estrogen, may be a better predictor of some health outcomes. But the scope of the role that hormones play in menopause is not entirely clear. Although the initial premise of the SWAN study was that hormones “drive everything,” Randolph now concedes this “may or may not be true. Some of what’s happening may be because of aging and time.”

What is clear is that women from different ethnic and cultural backgrounds can experience different hormonal levels. SWAN has shown that Chinese and Japanese women have lower-than-average levels of estradiol, the main estrogen, than African-American, Caucasian, or Hispanic women, but similar levels of FSH. Diet may have something to do with the differences, but until further studies are conducted, no one can know for certain. Sowers, who is directing a special study of estrogen metabolism aimed at understanding the role of diet, says it will be important to comprehend these differences because of the impact they may have on body tissues, such as blood vessels and bone, that respond to estrogen and other hormones.

Ethnic and cultural backgrounds may affect women’s perceptions of menopause, too. After analyzing data from SWAN focus groups, Carolyn Sampsel, the Carolyn K. Davis Collegiate Professor of Nursing and associate dean for research at the UM School of Nursing, as well as a co-investigator (Michigan) on the SWAN study, reported that African-American women are more likely to regard menopause as a normal part of the life process, whereas European-American women tend to view the transition as a significant—and inherently negative—sign of aging. “I don’t want to suggest that there aren’t African-American women who are having serious problems with hot flashes, but they seem to have much less angst about the experience of menopause,” says Sampsel.

Similar findings emerged from a series of focus groups conducted with postmenopausal Latina women in Detroit by Antonia Villarruel, an associate professor of nursing and an adjunct faculty member in the SPH Department of Health Behavior and Health Education. Villarruel found that a majority of women in her SWAN focus groups viewed the *cambio de vida*, or menopause, as an opportunity for reorientation and restructuring rather than as a medical problem. “For many, it was a good phase of life,” says Villarruel.



On the other hand, women who have a history of recurrent depression are more likely to experience symptoms of depression or poor social functioning in midlife, reports Joyce Bromberger, an associate professor of epidemiology and psychiatry at the University of Pittsburgh, who is conducting an ancillary study using SWAN data. Bromberger has also found that women with a recurrent history of depression have higher rates of carotid plaque, a subclinical measure of cardiovascular disease.

“These kinds of findings suggest that primary care doctors should pay more attention to lifetime histories of depression in women they see during midlife,” says Bromberger.

In other projects, Sampsel and Harlow are using SWAN data to try to identify predictors of severe urinary incontinence among midlife women. Fifty-seven percent of SWAN participants nationwide report some level of incontinence, and 25% report moderate-to-severe incontinence. Body mass index, or BMI, is a key factor. “It’s a question of obesity,” says Sampsel. Diabetes also appears to be linked to incontinence.

Like other SWAN researchers, Sampsel knows it will take time before findings from the study can be translated into advice that clinicians can pass on to their patients. Randolph agrees. Clinical trials typically reduce variables as much as possible, he notes, and can therefore be of immediate use to physicians, but observational studies such as SWAN include an array of variables and are far more complicated to decipher.

The strength of a study like SWAN, however, is that its findings are more likely to be relevant to a wider range of individuals, because the information comes from women who are more representative of the entire female population.

Says Sherry Sherman, program director of clinical research on reproductive hormones and aging for the National Institute on Aging, “SWAN is a unique and valuable study because it will make possible a key chapter on women’s health and aging that has previously been missing or underdeveloped.”

“This is a study that absolutely had to be done,” says Sampsel. “It’s criminal how little we know about the natural history of menopause. It’s only been ten years since we’ve even mentioned the word in polite company. People would just pretend that there was something wrong with the heat in the room. So there was just not a lot of impetus to study the whole phenomenon.”

But now there is. What’s more, Sowers says, SWAN is setting the stage for future research—so it’s a safe bet there’ll be a sequel to the novel she is so eager to finish reading. ■