



MENOPAUSE CARE UPDATES

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Menopause Care Updates presents summaries 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 summary is accompanied by commentary from a recognized expert that addresses the article's clinical relevance. Oversight for this e-newsletter was by Barbara A. Soltes, MD, Editor of *Menopause Care Updates* and Chair of the 2021 NAMS Education Committee. Opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or by Dr. Soltes.

Study looks at relationship between breastfeeding and risk of early menopause

Langton CR, Whitcomb BW, Purdue-Smithe SC, et al. Association of parity and breastfeeding with risk of early natural menopause. *JAMA Netw Open*. 2020;3(1):e1919615.

Summary. Researchers conducted a population-based cohort study within the Nurses' Health Study II cohort (1989-2015) that included premenopausal participants aged 25 to 42 years at baseline. Response rates were 85% to 90% for each cycle, and follow-up continued until menopause, age 45 years, hysterectomy, oophorectomy, cancer diagnosis, loss to follow-up, death, or end of follow-up in May 2015. Hypotheses were formulated after data collection.

Parity (the number of pregnancies lasting ≥ 6 months) was measured at baseline and every 2 years. History and duration of total and exclusive breastfeeding were assessed three times during follow-up. Menopause status and age were assessed every 2 years.

At baseline, 108,887 premenopausal women aged 25 to 42 years (mean age, 34.1 y; 102,246

[93.9%] non-Hispanic white) were included in the study. In multivariable models, higher parity was associated with lower risk of early menopause. Hazard ratios (HRs) were attenuated with adjustment for breastfeeding but remained significant. Compared with nulliparous women, those reporting 1, 2, 3, and 4 or more pregnancies lasting at least 6 months had HRs for early menopause of 0.92 (95% confidence interval [CI], 0.79-1.06), 0.84 (95% CI, 0.73-0.96), 0.78 (95% CI, 0.67-0.92), and 0.81 (95% CI, 0.66-1.01), respectively (P for trend = .006).

In multivariable models also adjusted for parity, HRs for duration of exclusive breastfeeding of 1 to 6, 7 to 12, 13 to 18, and 19 or more months were 0.95 (95% CI, 0.85-1.07), 0.72 (95% CI, 0.62-0.83), 0.80 (95% CI, 0.66-0.97), and 0.89 (95% CI, 0.69-1.16), respectively, compared with less than 1 month of exclusive breastfeeding (P for trend = .001).

In a stratified analysis of parous women, risk of early menopause was lowest among those reporting exclusive breastfeeding for 7 to 12 months in each level of parity.

In this study, an inverse association of parity with risk of early menopause was observed. Breastfeeding was associated with significantly

lower risk, even after accounting for parity. Breastfeeding at levels consistent with current recommendations may confer an additional benefit of lower risk of early menopause.

Commentary by



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The Nurses' Health Study II (NHS2) is a seminal observational population-based cohort that has contributed immensely toward enhancing our understanding of the overall health consequences of reproductive aging.

In this recent publication based on retrospective analyses of data from the NHS2 cohort, Langton and associates have examined the relationship between parity and breastfeeding with the likelihood of early natural menopause. The authors provide evidence in support of higher parity and longer duration of breastfeeding with reduced likelihood for early menopause. They conclude that breastfeeding at levels consistent with current recommendations may confer an additional benefit of lower risk of early menopause.

The rationale for the pursued analyses was based on an assumption that the suppression of ovulation that is attained during the course of pregnancy and subsequent breastfeeding should translate to reduced attrition of ovarian follicles, and thereby, confer protection against early ovarian failure.

The authors are to be commended on a meaningful undertaking to examine the relationship between aspects of reproductive history with risk for early menopause. However, despite the robustness of the studied population

and concordance of their findings with an earlier report by Mishra and associates, certain caveats are apparent that limit extrapolation of the observed findings beyond “associative.”¹ Notwithstanding the statistical robustness of this work, it is difficult to separate the “chicken from the egg”

Higher parity and longer duration of breastfeeding are intuitively entangled, as reflected in the magnitude of the relationship between parity and early menopause when breastfeeding was included in the statistical model. Information on factors that could relate to low parity that may have a direct effect on the relevance to ovarian biology (such as endometriosis, ovarian reserve, psychological well-being)²⁻⁶ is lacking.

Could the relationship between low parity and early menopause reside in the cause for low or no parity? Interpretation of biologic underpinnings to age at menopause is limited in the absence of information on family history of early menopause.^{3,4,7} History of smoking alone does not capture the breadth of occupational exposures that nurses are at risk for.⁸ Similarly, vegetable protein intake alone does not capture the nutritional nuances that are recognized to relate to ovarian function and ovarian reserve.⁹

The premise that suppression of ovulation, as occurs in pregnancy and with breastfeeding, translates to elimination or mitigation of attrition in ovarian follicles, although intriguing, is speculative. Based on data in users of hormone contraceptives, ultrasound evidence of ongoing ovarian follicular growth is commonly detected despite successful suppression of ovulation.¹⁰

Major strengths of this work include the large sample size of the NHS2, a well-characterized study population. Another strength is the detailed information on breastfeeding that allowed the authors to examine a dose-response in the relationship between breastfeeding and early menopause. Given the unique characteristics of the study population, any

interpretation of the observed associations is limited in the absence of the unique challenges faced by nurses.

Conclusions to this effort should therefore be interpreted in the context of the retrospective analytic approach. Any observational cohort that lacks information on some highly relevant variables may alter a conclusion because of one or more of the many missing considerations.

Nonetheless, this work by Langton and colleagues represents a laudable effort in our collective quest for improving our understanding of the *how's* and *why's* of early menopause.

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Surgery for urinary stress incontinence improves sexual function in women

Glass Clark SM, Huang Q, Sima AP, Siff LN. Effect of surgery for stress incontinence on female sexual function. *Obstet Gynecol.* 2020;135(2):352-360.

Summary. Researchers conducted a secondary analysis combining data from large two surgical trials that evaluated outcomes in women who underwent surgery for stress incontinence. Data from the Stress Incontinence Surgical Treatment Efficacy Trial (SISTER) and the Trial of Mid-Urethral Slings (TOMUS) was used. In the SISTER trial, patients underwent an autologous fascial sling or Burch colposuspension surgery for stress incontinence. In the TOMUS trial, patients underwent a retropubic or transobturator sling for stress incontinence. Data from the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12) was collected before surgery and then at 12 and 24 months after surgery. They included 924 women in their analysis and found that PISQ scores increased after any surgical intervention for stress incontinence, with no differences between specific procedures.

Commentary by



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Urinary incontinence (UI) is common and affects up to 41% of women.¹ Minassian

and colleagues studied women surveyed about their health and symptoms of incontinence and found that 73% reported that they had incontinence for more than 2 years, with 72% reporting moderate to severe symptoms. Incontinence is defined as *stress*—happening with increased pressure on the pelvic floor, such as with coughing or sneezing, or *urge*—happening with an urge or on the way to the bathroom.

Coital incontinence, or losing urine during sexual activity, also is common and can occur in 24% to 66% of women.² Coital incontinence can be a mix of both stress and urge incontinence happening with penetration or orgasm, respectively. Although incontinence is common, many women do not seek treatment or mention it to their healthcare providers.

One large Norwegian population-based study found that in women with incontinence, only 25% discussed their symptoms with a healthcare provider. On average, women who discussed their symptoms with their healthcare providers tended to be older and have more severe symptoms.³

Female sexual dysfunction is also a common cause, with lifetime reported rates of 38% to 70%, with even fewer (12%) reporting this to their healthcare providers.

Stadnicka and colleagues studied the psychosocial effects of incontinence and found that stress incontinence significantly affected feelings of emotional comfort, social and professional activities, sexual frequency, and desire.⁴ They also found that self-imposed social limitations were greater as the severity of their incontinence increased. Patients felt that embarrassment about having incontinence and wearing incontinence products, fear of smelling like urine, psychological distress, coital incontinence, and less self-esteem overall contributed to sexual dissatisfaction.

In recent years, there have been more studies looking at changes in sexual function after

treatment of incontinence. Treatments for stress incontinence can include pelvic floor exercises, pelvic floor physical therapy, an incontinence pessary, or surgery.

Serati and colleagues assessed improvements in sexual function before and after 3 months of pelvic floor physical therapy for stress incontinence and found significant improvement in sexual function, even in women with known sexual disorders.⁵

Handa and colleagues randomized women with stress incontinence to treatment with a pessary, pelvic floor physical therapy, and a combination of a pessary and physical therapy. They assessed changes in sexual function 3 months after treatment and found that when women had improvement in their incontinence, they had greater improvement in sexual function overall, less coital incontinence, and fewer restrictions on sexual activity because of a fear of incontinence.⁶

When comparing a pessary to pelvic floor physical therapy or a combination of pessary and pelvic floor physical therapy, they found that any treatment with physical therapy had greater improvement than the pessary group in improving both incontinence and sexual function.

There are many types of surgery for stress incontinence, including most commonly a midurethral sling (transobturator or retropubic), fascial sling, or a Burch colposuspension. There has been concern that surgical intervention, including the placement of a permanent mesh or foreign body, can worsen sexual function. Many of the studies demonstrate that improvement in incontinence symptoms improves sexual function.

In 2017, Szell and colleagues conducted a meta-analysis to look at changes in sexual function after sling procedures for stress incontinence. They found that that there was no change in sexual function after 67% of sling procedures, but there was a 33% improvement in orgasm.⁷

In 2018, Bicudo-Furst and colleagues conducted a systematic review looking at sexual function after surgical treatment of stress incontinence and found mixed results.⁸ They found that some studies showed an increase in sexual function, whereas others did not.

The present study significantly adds to the literature and helps to answer the question: does improving stress incontinence with surgery improve sexual function? They used results from two large, randomized, controlled trials to show that sexual function improves after surgical treatment for stress incontinence irrespective of the type of surgery.

Their study demonstrates that when we treat stress incontinence, we improve female sexual function. This increasing body of literature can motivate all providers to ask their patients about both incontinence and sexual function and treat the incontinence with behavior therapy or surgery. Treatment improves both incontinence and sexual function, with dramatic improvements in quality of life and self-esteem.

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PALB2 emerges as an important, highly penetrant breast cancer-associated gene

Yang X, Leslie G, Doroszuk A, et al. Cancer risks associated with germline *PALB2* pathogenic variants: an international study of 524 families. *J Clin Oncol*. 2020;38(7):674-685.

Summary. To estimate age-specific relative and absolute cancer risks of breast cancer and to estimate risks of ovarian, pancreatic, male breast, prostate, and colorectal cancers associated with germline *PALB2* pathogenic variants (PVs), because these risks have not been extensively characterized, researchers analyzed data from 524 families with *PALB2* PVs from 21 countries.

Complex segregation analysis was used to estimate relative risks (RRs; relative to country-specific population incidences) and absolute risks of cancers. The models allowed for residual familial aggregation of breast and ovarian cancer and were adjusted for the family-specific ascertainment schemes.

They found associations between *PALB2* PVs and risk of female breast cancer (RR, 7.18; 95% confidence interval [CI], 5.82-8.85; $P=6.5 \times 10^{-76}$), ovarian cancer (RR, 2.91; 95% CI, 1.40-6.04; $P=4.1 \times 10^{-3}$), pancreatic cancer (RR, 2.37; 95% CI, 1.24-4.50; $P=8.7 \times 10^{-3}$), and male breast cancer (RR, 7.34; 95% CI, 1.28-42.18; $P=2.6 \times 10^{-2}$). There was no evidence for increased risks of prostate or colorectal cancer.

The breast cancer RRs declined with age (P for trend= 2.0×10^{-3}). After adjusting for family ascertainment, breast cancer risk estimates on the basis of multiple case families were similar to the

estimates from families ascertained through population-based studies (P for difference=.41).

Based on the combined data, the estimated risks to age 80 years were 53% (95% CI, 44-63%) for female breast cancer; 5% (95% CI, 2-10%) for ovarian cancer; 2% to 3% (95% CI females, 1-4%; 95% CI males, 2-5%) for pancreatic cancer; and 1% (95% CI, 0.2-5%) for male breast cancer.

The researchers say that these results confirm *PALB2* as a major breast cancer susceptibility gene and establish substantial associations between germline *PALB2* PVs and ovarian, pancreatic, and male breast cancers. These findings will facilitate incorporation of *PALB2* into risk-prediction models and optimize the clinical cancer risk management of *PALB2* PV carriers, they say.

Commentary by



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The United States Preventive Services Task Force (USPSTF), the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), and other organizations recommend cancer risk assessment and counseling for patients at high risk for harboring a PV in a gene associated with hereditary cancer.¹⁻³ The introduction of next-generation sequencing technology for multigene cancer panel testing has changed the clinical approach to genetic testing for patients and their families. It is critical that precise estimates of cancer risk of these “panel genes” beyond *BRCA1* and *BRCA2* be quantified to optimize risk management, taking into account the

influence of gene-gene or gene-environment interactions.

PALB2 is a partner and localizer of *BRCA2* and a Fanconi anemia gene (in patients with biallelic inheritance). Pathogenic variants in *PALB2* have been observed in 0.6% to 3% of families with a history of breast cancer. The incidence of this mutation varies by population, and risk estimates have been variable because of the relative rarity of the mutation and small sample size of studies described to date.

Nevertheless, *PALB2* has emerged as an important, highly penetrant breast cancer-associated gene. A meta-analysis of three studies estimated a relative risk (RR; compared with populations in the United Kingdom) of 5.3 (90% confidence interval [CI], 3.0-9.4) for breast cancer in carriers of a *PALB2* mutation.⁴

A consistent finding confirmed in the present study is that breast cancer risk in *PALB2* mutation carriers is significantly higher for women from more recent birth cohorts,⁵ and there is some evidence suggesting a possible association of triple-negative breast cancer in patients who harbor *PALB2* mutations.⁵⁻⁷ The only prospective study of *PALB2* patients with breast cancer published by Cybulski and colleagues showed a 10% risk of contralateral breast cancer and a 10-year survival of 48% compared with 72% in *BRCA1* mutation carriers and 75% in noncarriers ($P<.001$).⁸

Previous studies involving small numbers of patients have suggested an increased risk for ovarian cancer,^{5,9,10} male breast cancer,⁵ and pancreatic cancer, but evidence has been inconsistent and insufficient to inform clinical decisions.

The present study by Yang and associates looking at 17,906 persons from 524 families in 21 countries provided the numbers of patients needed to characterize age-specific relative and absolute risks of breast cancer and to estimate risks of ovarian, pancreatic, male breast, prostate,

and colorectal cancer with statistical significance in this group.

Caution must be observed, however, in interpreting the data because the population may represent very high-risk families that are being followed by various academic institutions rather than those generally clinically identified by panel testing. In addition, there is no control population provided for *PALB2* rates and associated cancer rates in the general population. For breast and ovarian cancer, a residual polygenic familial component (polygenic risk score estimate) was added to the single-gene estimates for risk modeling.

The authors found associations between *PALB2* PVs and the risk of female breast cancer, ovarian cancer, pancreatic cancer, and male breast cancer. There was no evidence for increased risk of prostate or colorectal cancer. Estimated risks to age 80 years were 53% for female breast cancer, 5% for ovarian cancer, 2% to 3% for pancreatic cancer, and 1% for male breast cancer. Breast cancer relative risk estimates declined with age. The absolute risk of developing breast cancer to age 50 years was 16.9% and to age 80 years, 52.8%. Breast cancer risks did vary by birth cohort, however, as has been previously seen.⁵ The risk to age 50 years was reported to be 34.3% for those born after 1969. This might reflect under-reporting of cancers in earlier decades; changes in lifestyle, reproductive, or other environmental factors; or more intensive cancer surveillance in recent decades. This level of risk to age 50 years is similar to that of patients with *BRCA* mutations (followed prospectively)¹¹ in whom a discussion of the option of risk-reducing mastectomy is recommended.²

Ovarian cancer is the most lethal gynecologic malignancy, responsible for 13,000 deaths per year in the United States. It is estimated that up to 20% of women with ovarian cancer (including fallopian tube cancer or primary peritoneal cancer) harbor a mutation in DNA repair genes of which mutations in *BRCA1* and *BRCA2* are most prevalent. The identification of women at an elevated risk because of an inherited *BRCA*

mutation offers an opportunity for risk-reducing bilateral salpingo-oophorectomy (RRSO), which has been associated with significant reductions in ovarian cancer risk and all-cause mortality.¹²

It is important to evaluate the effect of other genes on ovarian cancer risk with the ultimate goal of offering surgical risk reduction to all known women at high risk. Before the publication of this report, guidelines have not recommended salpingo-oophorectomy for patients with the *PALB2* PV in the absence of a strong family history because risk estimates have been inconsistent between studies.

These statistically significant data involving 173 cases of ovarian cancer in carriers of *PALB2* pathogenic variants may inform guidelines encouraging surgical risk reduction and age at recommended surgery. The absolute risk of developing ovarian cancer for women born between 1950 and 1959 was 0.6% (95% CI, 0.3-1.3%) to age 50 years and 4.8% (95% CI, 2.4-9.7%) to age 80 years. These data are in line with a review of a large series of unselected comprehensively sequenced patients with ovarian cancer showing a 6- to 8-fold RR of ovarian cancer similar to *BRIP1*, *RAD51C*, and *RAD51D* mutations carriers.¹⁰

These findings confirm *PALB2* as an important, highly penetrant breast cancer gene (albeit likely in high-risk families) and with more precise quantification of age-related risks will facilitate discussions around *PALB2* and risks for breast cancer (female and male), ovarian cancer, and pancreatic cancer. Current NCCN guidelines advise screening with an annual mammogram (with consideration of tomosynthesis and breast magnetic resonance imaging with contrast) beginning at age 30 years (or 5-10 y earlier than the youngest diagnosis in the family) and discussion of the option of risk-reducing mastectomy.² This latter discussion (including degree of protection, reconstruction options, and risks) may be undertaken more frequently in younger women given the data presented but must be balanced with discussions around a patient's personal and family history. Currently,

per NCCN, evidence is deemed insufficient for recommendation of RRSO (“manage based on family history”), but the present data may inform consideration of surgery in this setting. Per current NCCN guidelines, pancreatic cancer screening can be offered to patients with *PALB2* mutations and a family history of pancreatic cancer in a first- or second-degree relative (from the same side of the family as the germline pathogenic variant).²

Finally, given the similar cancer spectrum and underlying role in DNA repair, the presence of germline *PALB2* pathogenic variants may ultimately have therapeutic implications similar to *BRCA* (eg, PARP inhibitors and platinum-based chemotherapy regimens). These findings will help to promote more precision recommendations for patients with germline *PALB2* mutations, and studies will continue to further define risks.

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Other Noteworthy Research

NAMS presents summaries of other recently published articles for your consideration

Did the juries get it right? Did powder really cause ovarian cancer?

O’Brien KM, Tworoger SS, Harris HR, et al. Association of powder use in the genital area with risk of ovarian cancer. *JAMA*. 2020;323(1):49-59.

The relationship between use of powder in the genital area and ovarian cancer has not been established. Positive associations reported in case-control studies have not been confirmed in cohort studies.

To estimate the association between use of powder in the genital area and ovarian cancer using prospective observational data, researchers pooled data from four, large, US-based cohorts: the Nurses’ Health Study (n=81,869), the Nurses’ Health Study II (n=61,261), the Sister Study (n=40,647), and the Women’s Health Initiative Observational Study (n=73,267). In the pooled sample of 252,745 women (median age at baseline, 57 y), 38% self-reported use of powder in the genital area—10% reported long-term use (≥ 20), and 22% reported frequent use (≥ 1 /wk).

The primary analysis examined the association between ever use of powder in the genital area and self-reported incident ovarian cancer. Covariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models.

During a median of 11.2 years' follow-up, 2,168 women developed ovarian cancer (58 cases/100,000 person-years). Ovarian cancer incidence was 61 cases per 100,000 person-years in ever users and 55 cases per 100,000 person-years in never users (estimated risk difference at age 70 y, 0.09% [95% CI, -0.02-0.19%]; estimated HR, 1.08 [95% CI, 0.99-1.17]). The estimated HR for frequent versus never use was 1.09 (95% CI, 0.97-1.23) and for long-term versus never use, the HR was 1.01 (95% CI, 0.82-1.25).

Although the estimated HR for the association between ever use of powder in the genital area and ovarian cancer risk in women with a patent reproductive tract was 1.13 (95% CI, 1.01-1.26), the *P* value for interaction comparing women with versus without patent reproductive tracts was .15.

In their analysis, researchers say they found no statistically significant association between use of powder in the genital area and incident ovarian cancer.

Alterations in vascular function in women progress within 1 year of the final menstrual period

Samargandy S, Matthews KA, Brooks MM, et al. Arterial stiffness accelerates within 1 year of the final menstrual period: the SWAN Heart Study [published online ahead of print January 23, 2020]. *Atherosclerosis Thromb Vasc Biol*.

Menopause may augment age-dependent increases in arterial stiffness, with black women having greater progression in midlife compared with white women. Researchers sought to determine whether and when women experience changes in arterial stiffness relative to

the final menstrual period (FMP) and whether these changes differ between black and white midlife women. They evaluated 339 participants from the SWAN (Study of Women's Health Across the Nation) Heart Ancillary study. Women had two or fewer carotid-femoral pulse-wave velocity (cfPWV) exams over a mean \pm SD of 2.3 ± 0.5 years' follow-up. Annual percentage changes in cfPWV were estimated in three time segments relative to FMP and compared using piecewise linear mixed-effects models.

At baseline, women were aged 51.1 ± 2.8 years, and 36% were black. Annual percentage change (95% CI) in cfPWV varied by time segments: 0.9% (-0.6-2.3%) for more than 1 year before FMP; 7.5% (4.1-11.1%) within 1 year of FMP; and -1.0% (-2.8-0.8%) for more than 1 year after FMP.

Annual percentage change in cfPWV within 1 year of FMP was significantly greater than the other two time segments ($P < .05$ for both comparisons). Adjusting for concurrent cardiovascular disease risk factors explained part of the change estimates but did not eliminate the difference. Black women had greater increase in cfPWV compared with white women in the first segment (P for interaction, .04).

The interval within 1 year of FMP is a critical period for women when vascular functional alterations occur. These findings underscore the importance of more intensive lifestyle modifications in women transitioning through menopause.

Menopause Editor's picks for March 2020

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

Heart fat and carotid artery atherosclerosis progression in recently menopausal women: impact of menopausal hormone therapy: the KEEPS trial

The use of hormone therapy in recently menopausal women modifies the associations between pericardial fat and carotid intima media thickness (CIMT). Oral conjugated equine estrogens may slow down the adverse effects of heart fat accumulation outside the pericardial sac on CIMT compared with 17 β -estradiol.

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Interaction between postmenopausal hormone therapy and diabetes on cataract

This study investigated whether postmenopausal hormone therapy (HT) use interacts with diabetes, a risk factor for several age-related eye diseases. It was found that long-term HT use and type 2 diabetes interact in their relationship with cataract such that the odds of cataract is highest in that group.

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Hot flashes are associated with altered brain function during a memory task

Preliminary data suggest that vasomotor symptoms may contribute to memory performance through effects on the hippocampus and prefrontal cortex. Larger studies are warranted to determine the robustness of these initial observations.

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Trajectory analysis of sleep maintenance problems in midlife women before and after surgical menopause: the Study of Women's Health Across the Nation (SWAN)

Sleep maintenance problems were relatively stable across time postsurgery. These data are remarkably consistent with trajectory results across the natural menopause, suggesting that presurgical assessment of sleep concerns could help guide women's expectations postsurgically.

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