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*J Am Coll Cardiol* 2019 Jun 18; 73:2915

**Aspirin for Primary Cardiovascular Prevention: Assessing the Pros and Cons**

*Estimates from a meta-analysis suggest that the risks outweigh the benefits for most primary prevention patients.*

Deciding whether to take aspirin for primary cardiovascular (CV) prevention can be vexing for patients. Investigators published an updated meta-analysis with useful estimates of CV outcomes, mortality, and adverse effects for this prevention strategy.

The researchers identified 15 randomized trials that compared aspirin with a control for primary prevention, had at least 1 year of follow-up, and focused on clinical outcomes. The trials covered 165,502 patients (weighted mean follow-up, 6.4 years).

Aspirin, compared with control, did not reduce the risk for death (4.75% and 4.82%) or CV death. Aspirin was associated with a lower risk for myocardial infarction (MI; 2.07% vs. 2.35%), but aspirin and control did not significantly differ in risks for fatal MI, coronary revascularization, angina, or symptomatic peripheral arterial disease. Overall stroke rates were similar in both groups, but the aspirin group had a lower rate of ischemic stroke than the control group (1.29% vs. 1.49%) and a nonsignificant trend toward an increase in hemorrhagic strokes (0.29% and 0.23%). The risk for major bleeding was

significantly higher with aspirin than control (1.47% vs. 1.02%). Aspirin was not associated with cancer incidence or mortality.

**COMMENT:** This meta-analysis provides estimates of the trade-offs with aspirin for the primary prevention of CV disease. The number needed to treat to prevent 1 MI is 357; for nonfatal MI, 400; and for ischemic stroke, 500. The number needed to harm to cause 1 bleeding event is 222; for intracranial bleeding, 1000. Benefits and risks differ among individuals, particularly by baseline risks, but aspirin for primary prevention is not a winning strategy overall.

**CITATION(S):** Abdelaziz HK et al. Aspirin for primary prevention of cardiovascular events. *J Am Coll Cardiol* 2019 Jun 18; 73:2915. (<https://doi.org/10.1016/j.jacc.2019.03.501>)

Pignone M. What is so hard about aspirin for primary prevention? *J Am Coll Cardiol* 2019 Jun 18; 73:2930. (<https://doi.org/10.1016/j.jacc.2019.03.502>)

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*Gut* 2019 Jun 17

## **Eat Your Yogurt**

*Men who consumed at least two servings per week had decreased risk for adenomas.*

Yogurt consumption has been associated with lower colorectal cancer (CRC) risk, but its relation to polyp risk is unknown. To investigate this issue, researchers assessed yogurt consumption and risk for conventional adenomas and serrated lesions among nearly 90,000 participants in the Health Professionals Follow-up Study and Nurses' Health Study. The analyses were adjusted for demographic and lifestyle factors, and dietary information was updated every 4 years.

Men who consumed  $\geq 2$  yogurt servings/week had significantly lower risk for conventional adenomas compared with nonconsumers (adjusted odds ratio, 0.81). The association was stronger for high-risk adenomas ( $\geq 1$  cm or with villous component or high-grade/severe dysplasia, or  $\geq 3$  adenomas), for which the risk reduction was 26%, and for colon adenomas compared with rectal adenomas. No association was seen for serrated lesions, except for large ( $\geq 1$  cm) lesions (aOR, 0.48). In women, there were no associations between yogurt consumption and either conventional adenomas or serrated lesions.

**COMMENT:** Yogurt may exert its beneficial effects in CRC prevention by a variety of mechanisms, including favorable microbiome alterations. Regular consumption of yogurt may be a marker of other healthy lifestyle factors that decrease the risk for CRC and its precursor lesions. The lack of benefits observed in women, however, is not clear. In any case, the regular consumption of yogurt is a reasonable recommendation to help decrease CRC risk, in addition to healthy eating habits, exercise, and avoidance of smoking.

**CITATION(S):** Zheng X et al. Yogurt consumption and risk of conventional and serrated precursors of colorectal cancer. *Gut* 2019 Jun 17; [e-pub]. (<https://doi.org/10.1136/gutjnl-2019-318374>)

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## Nonmedical Prescription Opioid Use Is Associated with Later Heroin Initiation in Teens

*The association with heroin initiation was stronger for teens using nonmedical prescription opioids than for those using nonopioid substances.*

Adolescents commonly obtain prescription opioids from friends and family for nonmedical reasons. Cross-sectional reports have suggested an association between prior nonmedical opioid prescription use and subsequent initiation of heroin.

In a longitudinal cohort study, researchers surveyed 3396 students at 10 high schools in Los Angeles every 6 months for 42 months, starting in ninth grade. Students who had used heroin at baseline were excluded. The remaining cohort of 3298 participants was 54% girls and 48% Hispanic, 17% Asian, 16% non-Hispanic white, and 5% African-American.

Seventy students (2.1%) initiated heroin by 42 months; they were more likely to be boys and to report lower parental monitoring and higher delinquent behavior at baseline. Overall, 596 students (18.1%) reported nonprescription opioid use. In adjusted multivariable models, prior and current use of nonmedical prescription opioids were significantly associated with subsequent heroin use (hazard ratios, 2.09 and 3.18, respectively), as were female sex and family history of substance use. The associations with heroin initiation were stronger for nonmedical prescription opioid use than for use of nonopioid substances.

**COMMENT:** These findings suggest pediatricians should do all that they can to keep teenagers — boys and girls — away from prescription opioids. This report provides compelling evidence that the risk of exposure to nonmedical prescription opioids and initiation of heroin may increase during adolescence as teenagers are exposed to new peers and adults who may provide access to these drugs. Pediatricians should take careful histories around exposure to illegal substances and degree of parental monitoring as these factors may confer an increased risk for the initiation of heroin.

**CITATION(S):** Kelley-Quon LI et al. Association of nonmedical prescription opioid use with subsequent heroin use initiation in adolescents. *JAMA Pediatr* 2019 Jul 8; [e-pub]. (<https://doi.org/10.1001/jamapediatrics.2019.1750>)

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## Feeding Evaluation Decreases Need for Frenotomy in Poor Breast-Feeders

*Among 115 infants referred for surgical intervention for ankyloglossia, 63% did not require surgery following feeding evaluation.*

Ankyloglossia (tongue tie) is often considered in evaluation of infants having challenges with breast-feeding. In a prospective, observational, quality improvement study, 115 infants (median age, 34 days, 59% boys) who were referred to a surgical center for breast-feeding difficulties first underwent a comprehensive feeding evaluation by a pediatric speech and language specialist. The feeding evaluation included anatomical and functional assessments and resulted in recommendations of feeding techniques to be implemented at home for 3 to 14 days prior to determination of the need for surgery. Infants were referred for surgery if functional sucking or attachment impairment was due to anatomical ankyloglossia.

Seventy-two patients (63%) did not undergo surgery. Among the 43 patients (37%) who did undergo surgery, procedures included: labial frenotomy alone (10 patients), both labial and lingual frenotomy (32 patients), and frenotomy alone (1

patient). As a reference point, prior to this study, 95% of patients referred to this specialty clinic for suspected ankyloglossia underwent a surgical procedure.

**COMMENT:** I suspect that many pediatricians already practice this clinical approach prior to surgery; however, it serves as a great reminder that a comprehensive breast-feeding consultation, typically performed by a nurse or lactation specialist, can eliminate unnecessary procedures. Because this study was conducted as a quality improvement effort, important outcomes such as costs, long-term outcomes, and parent perceptions of care weren't available. The good news is that two thirds of the infants were able to continue breast-feeding without needing a procedure.

**CITATION(S):** Caloway C et al. Association of feeding evaluation with frenotomy rates in infants with breastfeeding difficulties. *JAMA Otolaryngol Head Neck Surg* 2019 Jul 11; [e-pub]. (<https://doi.org/10.1001/jamaoto.2019.1696>)

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*JAMA Intern Med* 2019 Jul 1;

## Effectiveness of Weight Loss Interventions on Nonalcoholic Fatty Liver Disease

*Formal weight loss programs were associated with improved biomarkers for liver disease in patients with NAFLD.*

As there is no licensed pharmacologic therapy for the treatment of nonalcoholic fatty liver disease (NAFLD), clinical guidelines recommend counseling patients to lose weight through modifying diet and exercise. However, guidelines fall short of recommending any specific weight loss intervention.

In the current systematic review and meta-analysis of randomized, controlled trial data, researchers assessed the impact of weight loss interventions on biomarkers (laboratory, radiologic, and histologic) of liver disease. Twenty-two studies were included, examining behavioral interventions (15 studies), pharmacotherapy (6 studies), and surgery (1 study) among 2588 total participants (mean age, 45 years; 66% men). The median treatment duration was 6 months. Researchers assessed the intensity of interventions based on the degree of behavioral support, prescribed energy deficit, or pharmacologic dose.

Compared with no or minimal weight loss support or a lower-intensity intervention, a more-intensive weight loss intervention was significantly associated with greater weight change (−3.61 kg), lower alanine aminotransferase level (−9.8 IU/L), improved hepatic steatosis as measured histologically or radiologically, lower histologic NAFLD score, and reduced presence of nonalcoholic steatohepatitis. However, weight loss interventions did not improve liver fibrosis. In subgroup analysis, behavioral interventions improved liver steatosis, but pharmacotherapy did not. Estimates were largely unaffected when excluding 12 studies at high risk for bias and 7 at unclear risk.

**COMMENT:** Formal weight loss interventions appear to improve biomarkers for liver disease in patients with NAFLD. Pharmacotherapy alone did not impact liver steatosis, which is in line with current evidence indicating that no pharmacologic therapy appears to be effective in NAFLD. Unfortunately, liver fibrosis did not improve, but this is not surprising given the short treatment duration. I agree with authors of an accompanying editorial that these results should encourage all clinicians to incorporate formal weight loss programs into their treatment of NAFLD.

**CITATION(S):** Koutoukidis DA et al. Association of weight loss interventions with changes in biomarkers of nonalcoholic fatty liver disease: A systematic review and meta-analysis. *JAMA Intern Med* 2019 Jul 1; [e-pub]. (<https://doi.org/10.1001/jamainternmed.2019.2248>)

Adler E and Brandman D. Treatment of fatty liver disease — Time to implement common sense measures. *JAMA Intern Med* 2019 Jul 1; [e-pub]. (<https://doi.org/10.1001/jamainternmed.2019.2244>)

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## A Simple, Easy-to-Use Scoring System Identified Advanced Fibrosis in Patients with Nonalcoholic Fatty Liver Disease

*A new scoring system uses readily available demographic and laboratory data to identify patients with higher risk for advanced fibrosis.*

Several noninvasive scoring systems are used to identify advanced fibrosis in nonalcoholic-fatty-liver-disease (NAFLD) patients. These systems help to avoid liver biopsies, but some use proprietary assays (see NEJM JW Gastroenterology Feb 2019 and Clin Gastroenterol Hepatol 2018 Nov 21; [e-pub]), some require specialized equipment (transient elastography), and others have moderate accuracy and variable performance depending on patient characteristics (NAFLD fibrosis score [NFS] and FIB-4).

These authors devised the Hepamet Fibrosis scoring system, a noninvasive system using readily available standard variables. They compared it with NFS and FIB-4 scoring methods for identifying advanced fibrosis in an international cross-sectional study of nearly 2500 consecutive, biopsy-proven NAFLD patients (mean age, 51 years; 54.5% male; 20.6% with advanced fibrosis) who had demographic, anthropometric, and laboratory data collected at time of biopsy.

In univariate analysis, they identified variables independently associated with advanced fibrosis and then employed multivariate analysis to develop their system that includes gender, age, homeostatic model assessment score, presence of diabetes, AST, albumin, and platelet count. The area under the curve for Hepamet was significantly better than for NFS or FIB-4, 0.85 versus 0.80 ( $P=0.0001$ ). Furthermore, the rate of indeterminate results was lower with Hepamet than with NFS and FIB-4 (20% vs. 30%). In the validation set, with cut-off values of 0.12 and 0.47, the negative predictive value was 92% and positive predictive value was 76.3%.

**COMMENT:** This large study identified readily available demographic and laboratory data that allow primary care clinicians to identify patients with higher risk for advanced fibrosis. The Hepamet Fibrosis score is available online at [www.hepamet-fibrosis-score.eu](http://www.hepamet-fibrosis-score.eu).

Note to readers: At the time we reviewed this paper, its publisher noted that it was not in final form and that subsequent changes might be made.

**CITATION(S):** Ampuero J et al. Development and validation of Hepamet Fibrosis scoring system — a simple, non-invasive test to identify patients with nonalcoholic fatty liver disease with advanced fibrosis. *Clin Gastroenterol Hepatol* 2019 Jun 10; [e-pub]. (<https://doi.org/10.1016/j.cgh.2019.05.051>)

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*J Bone Joint Surg Am* 2019 Jun 19; 101:1050.

## Surgery vs. Physical Therapy for Symptomatic Rotator Cuff Tears

*In 10-year follow-up of a randomized trial, outcomes generally were better with surgery.*

In 2004, researchers in Norway began a study in which 103 patients (mean age, 60) with symptomatic full-thickness rotator cuff tears not exceeding 3 cm were randomized to either surgical repair or physical therapy. In 2010 and 2015, 1-year and 5-year results were published: Several outcomes favored surgery statistically, but differences were considered to be “possibly clinically irrelevant” by the authors. Now, they report 10-year follow-up results, during which 14 of the 51 physical therapy patients had crossed over to surgery.

In intention-to-treat analyses, mean scores for most clinical outcomes (covering pain and function) remained significantly better in the surgery group than in the physical therapy group, with larger between-group differences than at 5 years. Good-to-excellent results were reported by 71% of surgical patients and by 42% of physical therapy patients. This difference of about 30 percentage points suggests that one person benefitted for every three or four who underwent surgery initially.

**COMMENT:** In patients with symptomatic small- to medium-sized full-thickness rotator cuff tears, 10-year outcomes were, on average, better with tendon repair than with physical therapy in this study. The authors believe that long-term follow-up is important: They note that in previous trials showing no significant benefit for surgery compared with physical therapy, follow-up generally was limited to 1 or 2 years.

**CITATION(S):** Moosmayer S et al. At a 10-year follow-up, tendon repair is superior to physiotherapy in the treatment of small and medium-sized rotator cuff tears. *J Bone Joint Surg Am* 2019 Jun 19; 101:1050. (<https://doi.org/10.2106/JBJS.18.01373>)

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*JAMA Psychiatry* 2019 Jun 12

## How to Understand Treatment Choice for PTSD

*A network meta-analysis reveals that psychotherapy is superior to pharmacotherapy in the long run, but we still know little about specific therapies.*

Established treatments for post-traumatic stress disorder (PTSD) include medications — especially selective serotonin reuptake inhibitors (SSRIs) — and psychotherapies. These researchers conducted a pairwise meta-analysis (directly comparing studies of 2 or 3 treatments) and a network meta-analysis (e.g., comparing treatments A versus B and B versus C, with inferences about A versus C) of 12 randomized, controlled trials involving 922 participants with PTSD and examining outcomes with psychotherapy (including cognitive-behavioral therapy, exposure therapy, prolonged exposure, seeking safety, and eye-movement desensitization and reprocessing), pharmacotherapy, and their combination.

At the end of treatment, the three conditions did not differ in outcomes. At the longest available follow-up in both meta-analyses, psychotherapy alone was significantly more effective than pharmacotherapy alone. At long-term follow-up (6 studies), combined treatment was superior to pharmacotherapy alone but only in the network meta-analysis. Dropouts before treatment completion were similar in all three conditions.

**COMMENT:** Network meta-analysis increases power and picks up more subtle differences, whereas pairwise meta-analysis has less power but allows more specific treatment comparisons. Agreement between the two meta-analysis types increases confidence in the result. Nevertheless, as editorialists note, treating all psychotherapies as equivalent and all pharmacotherapies as equivalent obscures individual differences in specific medications and psychotherapies. The meta-analyses' findings are limited by the differing goals and methodologies of relatively small studies. The take-home message about the current state of knowledge is that psychotherapy should be a first-line treatment for PTSD because it has more enduring benefit. Although patient preference seems to influence outcome, the additional factors to consider in choosing a specific therapy for a specific patient are unknown. If psychotherapy is not fully effective, an SSRI should be added, but we do not yet definitively know which augmentation strategy to consider and which medication to consider first.

**CITATION(S):** Merz J et al. Comparative efficacy and acceptability of pharmacological, psychotherapeutic, and combination treatments in adults with posttraumatic stress disorder: A network meta-analysis. *JAMA Psychiatry* 2019 Jun 12; [e-pub]. (<https://doi.org/10.1001/jamapsychiatry.2019.0951>)

Stein MB and Norman SB. When does meta-analysis of a network not work?: Fishing for answers. *JAMA Psychiatry* 2019 Jun 12; [e-pub]. (<https://doi.org/10.1001/jamapsychiatry.2019.0902>)

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Exeltis USA, Inc.; 2019 Jun 6

## A New Progestin-Only Contraceptive Pill

*Andrew M. Kaunitz, MD*

*FDA approves a second drospirenone-only oral contraceptive.*

The FDA recently approved a new progestin-only pill (POP; Slynd); each pack contains twenty-four 4-mg drospirenone tablets and four inert tablets. This dosage is higher than the 3 mg found in ethinyl estradiol/drospirenone oral contraceptive (OC) formulations (Yasmin, Yaz, and generics).

In efficacy trials that included 953 participants aged ≤35, the Pearl index (percentage of women conceiving during the first year of use) was 4.0, comparable to the failure rate observed in U.S. trials of estrogen-progestin pills and patches. Incidence of scheduled bleeding or spotting fell from 81% in Cycle 1 to 26% in Cycle 13, whereas unscheduled bleeding or spotting fell from 61% to 40%. These observations suggest that, while scheduled withdrawal bleeding and spotting decreases with longer duration of use, unscheduled bleeding and spotting remain relatively common in users of this POP.

**COMMENT:** In the U.S., POP use is largely limited to postpartum and lactating women (who have relatively low fertility). Progestin-only contraceptives are appropriate for women in whom use of estrogen-progestin contraceptives may confer excess risk for adverse cardiovascular (CV) events; however, because of the low progestin dose and corresponding concerns about insufficient contraceptive efficacy, some clinicians are reluctant to use the norethindrone POP in fully fertile women (i.e., those not postpartum or lactating). Evidence indicates that, because “negligible” levels of progestin are excreted in breast milk, the new drospirenone POP seems appropriate for postpartum or lactating women (as well as those with CV risk factors). Bottom line: The availability of a second — and presumably more effective — POP represents good news for U.S. women.

**CITATION(S):** Exeltis USA, Inc. announces the approval of Slynd™, the first and only progestin-only pill providing pregnancy prevention with a 24/4 dosing regimen and 24-hour missed pill window [press release]. Florham Park, NJ: Exeltis USA, Inc.; 2019 Jun 6. (<https://www.prnewswire.com/news-releases/exeltis-usa-inc-announces-the-approval-of-slynd-the-first-and-only-progestin-only-pill-providing-pregnancy-prevention-with-a-244-dosing-regimen-and-24-hour-missed-pill-window-300863390.html>)

Drugs@FDA: FDA Approved Drug Products. Drospirenone. (<https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=211367>)

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*Obstet Gynecol* 2019 Jun; 133:1259

## A Clinician's Guide to Sexual Devices: What We Didn't Learn in School

*Knowledge about types and safe use of sexual devices can aid counseling of patients.*

More than half of all U.S. women (and three quarters of women who have sex with women) have used a vibrator, and almost one third have used a dildo. Sexual devices (“sex toys”) are readily available but unregulated; thus, clinicians should be prepared to educate patients about safe use, and perhaps to recommend devices for women with sexual dysfunction.

### Types of Devices

These may enhance sex or masturbation or be therapeutic for cases of decreased libido, anorgasmia, difficulty with vaginal penetration, partner's erectile dysfunction, and motor or sensory disabilities.

- Vibrator: Small motor creating vibrations for internal or external stimulation.
- Dildo: Phallus-shaped device for vaginal or rectal penetration; double-sided dildoes have two insertive ends for partnered use.
- Strap-on dildo: Wearable harness and dildo combination.
- Air pulse generator: Device emitting mild air puffs for clitoral stimulation.
- Collision dyspareunia aid: Donut-shaped bumper placed around penile base to prevent deep penetration.
- Anal plug: Triangular device with narrow base designed to be held within the rectum by the external anal sphincter.

### Screening Questions

- Have you ever or do you currently use a sexual device, alone or with a partner?
  - Follow up “yes” answers with questions to assess safe use (e.g., “How often do you clean the device?”).
- Would you consider using a sexual device if it would improve your sexual health and wellness?

### Device Safety

- Trauma: Devices inserted rectally should have flared bases to prevent rectal retention and should be lubricated to protect against trauma.
  - Glass devices should not be used rectally.
- Infection: Bacterial and viral infections can be transmitted through shared devices. Covering such devices with barriers (e.g., condoms), appropriate selection of materials, and routine cleaning are critical.
  - Human papillomavirus (HPV) can persist on devices.
  - One case of HIV has been documented to be device-transmitted between cisgender women.
  - Chlamydia, gonorrhea, syphilis, herpes simplex virus, and trichomoniasis are thought to be device transmissible.
  - Bacterial vaginosis can be transmitted between female partners sharing devices.

### Materials

- Nonporous materials (e.g., medical-grade silicone, hypoallergenic metals) are more effectively disinfected than porous materials (e.g., inexpensive rubber polymers).

### Cleaning and Disinfection

- Cleaning with soap and water after each use removes discharge and debris.
- Submerging devices in dilute household bleach (0.5% sodium hypochlorite) for 3 minutes or 70% isopropyl alcohol for 5 minutes may provide disinfection, although HPV can persist.
- Review manufacturer's instructions before using these techniques, as they may damage some materials.
- Autoclaving is the only method that eradicates pathogens; boiling water or a dishwasher sanitize cycle has unknown efficacy and may damage some devices.
- Ultraviolet light units promoted for disinfection of sexual devices may not live up to their claims.

**COMMENT:** In most practices, discussions of sexual health are limited by available time and the comfort levels of both clinician and patient; nonetheless, opportunities to address sexual issues do exist. For starters, explore device use with women having unexplained recurrent or persistent vaginal or sexually transmitted infections — or those experiencing sexual limitations due to chronic disease, decreased libido, or diminished sexual response.

**CITATION(S):** Rubin ES et al. A clinical reference guide on sexual devices for obstetrician-gynecologists. *Obstet Gynecol* 2019 Jun; 133:1259. (<https://doi.org/10.1097/AOG.0000000000003262>)

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*BMJ* 2019 Jun 26; 365:12327

## **Early Bird or Night Owl: Do Sleep Characteristics Influence Breast Cancer Risk?**

*British analysis suggests a preference for mornings can lower risk for breast cancer.*

Findings about the association between chronotype (morning or evening preference) and risk for breast cancer have been inconsistent. Mendelian randomization uses genetic variants highly associated with chronotype, sleep duration, and insomnia symptoms to help clarify this association. In addition to performing a multivariable regression analysis based on self-reported preferences for morning or evening among >150,000 women (age range, 40–70) participating in the U.K. Biobank, researchers used genetic variants identified in these women in a Mendelian randomization analysis to investigate how sleep traits might influence breast cancer risk. Prevalent and incident invasive breast cancers (during a median follow-up of 2.98 years) were assessed.

Among women with a preference for morning compared with evening, fully adjusted regression analysis showed a hazard ratio of 0.95 ( $P=0.002$ ) for breast cancer. Mendelian analysis also found that morning preference was associated with lower risk for breast cancer (HR, 0.85); however, this association did not achieve statistical significance. Neither analysis showed significant associations between breast cancer risk and sleep duration or insomnia.

**COMMENT;** Other studies in this U.K. cohort have suggested that the morning chronotype is associated with lower all-cause and cardiovascular mortality as well as lower risk for schizophrenia and depression. The cohort's lack of ethnic diversity is a limitation when examining chronotypes and breast cancer. Nonetheless, these findings represent encouraging news for women who are “morning people” — while also pointing out the need for more research on ways to diminish the stresses on our biological clocks.

et al. Investigating causal relations between sleep traits and risk of breast cancer in women: Mendelian randomisation study. *BMJ* 2019 Jun 26; 365:12327. (<https://doi.org/10.1136/bmj.12327>)

Schernhammer ES. Larks, owls, and breast cancer. *BMJ* 2019 Jun 26; 365:14267. (<https://doi.org/10.1136/bmj.14267>)

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