GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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Week of March 3 - 10, 2023

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Should We Use Cannabis for Chronic Pain?

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Cannabis-Based Products for Chronic Pain: A Systematic Review

McDonagh MS, Morasco BJ, Wagner J, et al. Cannabis-Based Products for Chronic Pain: A Systematic Review. *Ann Intern Med*. 2022;175(8):1143-1153. doi:10.7326/M21-4520

KEY TAKEAWAY: Synthetic and plant-extracted high tetrahydrocannabinol (THC)-to-cannabidiol (CBD) ratio products result in short term improvements in chronic neuropathic pain but increase the risk for dizziness and sedation.

STUDY DESIGN: Meta-analysis of 18 placebo controlled RCTs and 7 cohort studies (N=14,835)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: About 100 million people in the United States are affected by refractory chronic pain. Opioids may lack efficacy and have frequent adverse effects, driving the search for alternatives. Cannabis is being explored as an alternative pain treatment.

PATIENTS: Patients with chronic pain

INTERVENTION: Cannabis-products

CONTROL: Usual care

PRIMARY OUTCOME: Pain severity, function/disability, adverse events

METHODS (BRIEF DESCRIPTION):

- Patients enrolled in these studies were mostly white, female, middle aged individuals from several countries (United States, Canada, Netherlands, United Kingdom, Germany, Austria, Denmark, Finland, Brazil).
- Different studies were analyzed by THC-CBD ratio category (high, comparable, low) and source (synthetic vs. extracted)
- Magnitude of benefit was evaluated on scales and categorized into large (mean difference [MD], >2), moderate (MD, >1 to 2) or small (MD, 0.5 to 1) effect.
    - Perceived pain intensity was measured using a 0–10 numeric scale via the Fibromyalgia Impact Questionnaire (FIQ), Numeric Rating Scale (NRS), or Visual Analogue Scale (VAS), wherein 0 = no pain, 10 = worst/unbearable pain.
    - Perceived change in function due to pain interference was measured using a 0–10 numeric scale via the FIQ, VAS, Joint Disease Activity Score Scale, Pain Disability Index Scale, Brief Pain Inventory (BPI), SF-36 Physical Functioning Scale, or hybridized BPI-SF36 scale, wherein 0 = no interference at all, 10 = interferes completely.
- A ≥30% reduction in pain from baseline was deemed a clinically important pain response.

INTERVENTION (# IN THE GROUP): 7,012

COMPARISON (# IN THE GROUP): 7,823

FOLLOW-UP PERIOD: Four to 208 weeks

RESULTS:

- High THC-CBD ratio synthetic products:
    - Moderate improvement in pain severity (6 studies, n=390; MD –1.2; 95% CI, -2 to -0.5)
    - No improvement in overall function (MD 1.75; 95% CI, –0.5 to 4)
    - Moderate risk of sedation (3 studies, n=335; Relative Risk (RR) 1.7; 95% CI, 1.03–4.6)
    - Moderate risk of dizziness with dronabinol use (2 studies, n=302; RR 2.7; 95% CI, 1.4–6.9)
- Comparable THC-CBD ratio products:
    - Small improvement in pain severity (7 studies, n=702; MD –0.5; 95% CI, –1 to –0.2)
    - Small improvement in overall function (6 RCTs, n=616; MD –0.4; 95% CI, –0.7 to –0.2)
    - Large increase in dizziness (6 studies, n=866; RR 3.6; 95% CI, 2.4–5.6)
    - Large increase in sedation (6 studies, n=866; RR 5.0; 95% CI, 2.1–12)
    - Moderate increase in nausea (6 studies, n=866; RR 1.8; 95% CI, 1.2–2.8)

LIMITATIONS:

- There was inadequate evidence for some products and lack of study details such as unclear availability in the United States
- Studies under-reported adverse events such as psychosis, cannabis use disorder, and cognitive deficits, which may result in underestimation of harm.
- Studies excluded populations with higher risk of harm, further limiting harm risk assessment.

Celina Chapman, MD
SIU Family Residency Program
Quincy, IL

Was Stroke Incidence in COVID-19 Patients Overestimated?

Incidence of Stroke in Randomized Trials of COVID-19 Therapeutics: A Systematic Review and Meta-Analysis

Nagraj S, Varrias D, Hernandez Romero G, et al. Incidence of Stroke in Randomized Trials of COVID-19 Therapeutics: A Systematic Review and Meta-Analysis. *Stroke*. 2022;53(11):3410-3418. doi:10.1161/STROKEAHA.122.040233.

KEY TAKEAWAY: The <0.2% incidence of stroke within the 30-day follow-up window in patients undergoing treatment for COVID-19 is lower than previously reported.

STUDY DESIGN: Systematic review and meta-analysis of 77 randomized controlled trials (N=38,732)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Stroke occurrence carries high morbidity for patients and increases healthcare costs. Initial observational study reports suggested an increased risk of stroke in COVID-19 with a reported incidence of 0.5–5%. This study was designed to provide a more accurate estimate of the true incidence of stroke during the acute covid infection period.

PATIENTS: COVID-19 serologically confirmed patients

INTERVENTION: Not applicable

CONTROL: Not applicable

PRIMARY OUTCOME: Stroke incidence

METHODS (BRIEF DESCRIPTION):

- Preferred Reporting items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) were applied for the selection of eligible Randomized controlled trials (RCT) published prior to July 30, 2021.
- RCTs inclusion criteria included: reporting of stroke incidence, COVID-19 confirmation among patients, and the study included one or more treatment interventions.
    - Included patients had a mean age of 55 years old and 38% of patients were women.
- Stroke incidence from eligible RCT was extracted for culmination across all eligible studies.
- No restrictions on patient age, clinical setting, etc.

INTERVENTION (# IN THE GROUP): Not applicable

COMPARISON (# IN THE GROUP): Not applicable

FOLLOW-UP PERIOD: 23 ± 13 days

RESULTS:

- Overall population incidence of stroke (77 trials, N=38,732; absolute incidence [AI] 0.168%; cumulative incidence [CUI] 0.001; 95% CI, 0.001–0.002)
- Hospitalized population incidence of stroke (71 trials, N=37,069; AI 0.175%; CUI 0.001; 95% CI, 0.001–0.002)
- Outpatient population incidence of stroke (6 trials, N=1,263; no strokes)
- Studies published later had a higher incidence of stroke compared to earlier studies (0.24% vs 0.08%, respectively; *P*=.001).

LIMITATIONS:

- Study utilized reported adverse events from studies rather than primary data.
- Only population gender and mean age were reported.
- Higher proportion of men in the population than the general public.
- The prospective nature of these trials prevents the risk of reporting bias (which inflates estimates of incidence), but the limitations on entry into the studies could also reduce the estimate.

Andrew Sprader, DO
Dwight David Eisenhower Army Medical Center FMRP
Fort Gordon, GA

The opinions and assertions contained herein are those of the author and are not to be construed as official or as reflecting the views of the US Army Medical Department, the Army at large, or the Department of Defense.

Is Aspirin the New Hip Drug?

Effect of Aspirin vs Enoxaparin on Symptomatic Venous Thromboembolism in Patients Undergoing Hip or Knee Arthroplasty: The CRISTAL Randomized Trial

CRISTAL Study Group, Sidhu VS, Kelly TL, et al. Effect of Aspirin vs Enoxaparin on Symptomatic Venous Thromboembolism in Patients Undergoing Hip or Knee Arthroplasty: The CRISTAL Randomized Trial. *JAMA*. 2022;328(8):719-727. doi:10.1001/jama.2022.13416

KEY TAKEAWAY: Enoxaparin is superior to aspirin monotherapy at preventing symptomatic venous thromboembolism after total hip arthroplasty (THA) or total knee replacement (TKR).

STUDY DESIGN: Cluster-randomized, crossover, noninferiority trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: The use of aspirin for venous thromboembolism (VTE) prophylaxis following total hip or knee arthroplasty has increased in recent years. However, evidence regarding its safety and efficacy, as a sole VTE prophylactic agent is currently limited. This study investigates whether aspirin is noninferior to enoxaparin in preventing symptomatic VTE after THA or TKA for osteoarthritis.

PATIENTS: Adults undergoing THA or TKR

INTERVENTION: Aspirin

CONTROL: Enoxaparin

PRIMARY OUTCOME: Symptomatic VTE

Secondary Outcome: Events requiring surgery, major bleeding, death

METHODS (BRIEF DESCRIPTION):

- Hospitals were chosen to participate if they performed 250 THA or TKA procedures annually.
- Patients were randomized to receive aspirin (100 mg/d) or enoxaparin (40 mg/d) for 35 days after THA and for 14 days after TKA starting within 24 hours after surgery
- Patients received a web link via email or text message to complete online data collection at 90 days postoperatively.
- Adverse outcomes reported by the patients, such as VTE (pulmonary embolism and deep venous thrombosis) or major bleeding within 90 days, were confirmed through written documentation from the treating physicians.
- Patients were excluded if they received preoperative anticoagulation (i.e., direct oral anticoagulant, warfarin, or dual antiplatelet therapy) but patients receiving preoperative antiplatelet therapy were eligible for inclusion and received either aspirin according to the study dosage or aspirin according to their usual dose in combination with the study-prescribed enoxaparin.

INTERVENTION (# IN THE GROUP): 5,675

COMPARISON (# IN THE GROUP): 4,036

FOLLOW-UP PERIOD: Within 90 days of THA or TKR

RESULTS:

Primary Outcome –

- Enoxaparin reduced the risk of symptomatic VTE after 90 days compared to aspirin (estimated difference [ED] 2.0; 95% CI, 0.54–3.4).
- Aspirin was noninferior to enoxaparin in preventing pulmonary embolism (ED 0.44; 95% CI, –0.19 to 1.1).
- Aspirin increased the risk for below the knee DVT compared to enoxaparin (ED 1.5; 95% CI, 0.48–2.5).

Secondary Outcome –

- Aspirin was noninferior to enoxaparin in:
  - Death (ED 0.05; 95% CI, –0.05 to 0.15)
  - Major bleeding (ED –0.05; 95% CI, –0.35 to 0.25)
  - Reoperation within six months (ED 0.16; 95% CI, –0.82 to 1.1)

LIMITATIONS:

- 5.2% of patients were lost to follow-up.
- Hospitals were not blinded to treatments.
- The study was limited to patients undergoing knee or hip replacement for osteoarthritis.
- Most of the difference in DVT was caused by below the knee DVT.
- Participants taking aspirin prior to the trial and were randomized to aspirin did not receive additional anticoagulants, while those randomized to enoxaparin continued taking aspirin.

Nikolay Denkov, MD
UAMS Southwest FMR
Texarkana, AR

Does Blood Flow Restriction Enhance Training Adaptations in Adults?

Effects of Blood Flow Restriction Therapy for Muscular Strength, Hypertrophy, and Endurance in Healthy and Special Populations: A Systematic Review and Meta-Analysis

Perera E, Zhu XM, Horner NS, Bedi A, Ayeni OR, Khan M. Effects of Blood Flow Restriction Therapy for Muscular Strength, Hypertrophy, and Endurance in Healthy and Special Populations: A Systematic Review and Meta-Analysis. *Clin J Sport Med*. 2022;32(5):531-545. doi:10.1097/JSM.0000000000000991

KEY TAKEAWAY: Blood flow restriction (BFR) improves performance compared to standard low-intensity resistance training but is inferior to standard high-intensity resistance training.

STUDY DESIGN: Systematic review and meta-analysis of 33 quantitative and 20 qualitative studies (N=1,337)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to high heterogeneity)

BRIEF BACKGROUND INFORMATION: Previously, increasing muscle strength, size, and endurance relied on high-intensity resistance training alone. Now, modalities like blood-flow restriction (proximal occlusion of blood flow to distal muscles) are gaining popularity. Emerging evidence supports enhanced muscle characteristics and possibly improved performance with occasional incorporation of BFR into training regimens.

PATIENTS: Adult patients

INTERVENTION: Blood flow restriction (BFR) during low-intensity training

CONTROL: No BFR; low-intensity and high-intensity resistance training

PRIMARY OUTCOME: Muscle strength, hypertrophy, endurance

METHODS (BRIEF DESCRIPTION):

- The study consisted of 64% male and 36% female participants in Japan and USA with a mean age of 36 years old.
- Participants selected had either a prior exercise training background or no prior training experience.
- "Blood flow restriction" involved limb vessel blood flow occlusion with tourniquet or pneumatic compression cuff during physical activity.
- The control group performed identical exercises without BFR.
    - Exercises: walking, cycling, weight training (upper and lower extremities)
- Overall performance was assessed by measuring:
    - Strength after one repetition of maximum weight (N=358)
    - Torque measured by N-m (N=191)
    - Hypertrophy measured by muscle cross-sectional area (N=314)
    - Endurance measured by oxygen uptake via VO_2 max (N=111)

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: One to 12 weeks

RESULTS:

Primary Outcome –

- High intensity resistance training (HIRT) was more effective for muscle strength than low intensity-blood flow restriction (LI-BFR) (MD 5.3 kg; 95% CI, 2.6–8.1; I^2=93%).
- LI-BFR was more effective compared to equal routines of non-occluded low intensity resistance training (LIRT):
    - Torque: MD 9.9 N-m (95% CI, 5.4–14; I^2=58%)
    - Muscle hypertrophy: MD 1.1 cm^2 (95% CI, 0.14–2.0; I^2=13%)
- LI-BFR did not improve endurance training compared to endurance training alone (MD 0.37 mL/kg/min; 95% CI, –0.97 to 3.2).

LIMITATIONS:

- There was high heterogeneity among studies chosen due to a large variety of protocols, equipment used, and results reporting.
- There was a difference in muscle composition and health status that was not accounted for.
- There was a high potential for bias due to an absence of "blinding" of participants or researchers.
- BFR efficacy in high-risk/older populations was not adequately addressed due to limited available data on this specific population.

Kellen Mandehr, DO
Samaritan Health Services FMRP
Corvallis, OR

Lecanemab: Initial Evidence of a Delaying Agent in Early Alzheimer's Disease

Lecanemab in Early Alzheimer's Disease

van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in Early Alzheimer's Disease [published online ahead of print, 2022 Nov 29]. *N Engl J Med*. 2022;10.1056/NEJMoa2212948. doi:10.1056/NEJMoa2212948

KEY TAKEAWAY: Lecanemab may reduce cognitive and functional decline in adults with Alzheimer's disease; however, this reduction is not clinically meaningful.

STUDY DESIGN: Randomized, double-blind, placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Alzheimer's disease is the most common form of neurodegenerative dementia and affects over six million Americans. Current FDA-approved disease-modifying treatments are limited in efficacy. This paper examines a potential new disease-modifying treatment with lecanemab–a humanized monoclonal antibody targeting soluble amyloid-beta protofibrils.

PATIENTS: 50–90-year-old patients with mild cognitive impairment or dementia from Alzheimer's disease

INTERVENTION: Lecanemab

CONTROL: Placebo

PRIMARY OUTCOME: Cognition and function

METHODS (BRIEF DESCRIPTION):

- Patient demographics: majority White adults 50–90 years old across North America, Europe, and Asia with mild cognitive impairment (62%) or mild dementia from Alzheimer's disease as determined by the National Institute on Aging–Alzheimer's Association criteria (CDR-SB score) and evidence of amyloid on PET scan or CSF testing.
- Patients were required to have impairment in episodic memory one standard deviation lower than the age-adjusted mean on the Wechsler Memory Scale.
- Patients were randomized in a 1:1 fashion to lecanemab IV 10 mg/kg every two weeks or placebo.
- Patients underwent serial blood testing for Alzheimer's biomarkers and could opt into monitoring with PET scans and CSF markers.
- Primary endpoint was measured by the change in cognition and function score on the Clinical Dementia Rating (CDR) sum of boxes at baseline and 18 months with interval scores measured every three months.
  - CDR scores range from 0 to 18 with higher numbers indicating worsening Alzheimer's disease.
  - Scores from 0.5 to 6 indicate early Alzheimer's disease with this trial averaging a baseline of 3.17.
  - The minimal clinically important difference for CDR is a 1–2 point increase.

INTERVENTION (# IN THE GROUP): 898 (354 participated in the sub-study of PET amyloid)

COMPARISON (# IN THE GROUP): 874 (344 participated in the sub-study of PET amyloid)

FOLLOW-UP PERIOD: 18 months

RESULTS:

- Patients in the lecanemab group had significantly, but not clinically meaningful, lower rate of cognitive and functional decline than the placebo group (mean change 1.2 vs 1.7, respectively; mean difference –0.45; 95% CI, –0.67 to –0.23).

LIMITATIONS:

- Adverse effects were not a primary or secondary outcome and the data on adverse effects were not reported with confidence intervals or p-values.
  - 14% of the lecanemab group experienced serious adverse effects and 26% had infusion-related reactions.

Tobias Rumschlag, MD
Indiana University Arnett FMRP
Lafayette, IN

Can Targeted Prostate Biopsy Improve Population-Based Prostate Cancer Screening?

Prostate Cancer Screening with PSA and MRI Followed by Targeted Biopsy Only

Hugosson J, Månsson M, Wallström J, et al. Prostate Cancer Screening with PSA and MRI Followed by Targeted Biopsy Only. *N Engl J Med*. 2022;387(23):2126-2137. doi:10.1056/NEJMoa2209454

KEY TAKEAWAY: Utilization of MRI-targeted biopsy of suspicious prostate lesions may reduce the detection of clinically insignificant prostate cancer by half as compared to traditional systematic biopsy.

STUDY DESIGN: Single-center, prospective, population-based, randomized controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to primarily disease-oriented endpoints)

BRIEF BACKGROUND INFORMATION: Prostate cancer is a leading cause of cancer death, but optimal screening protocols remain unclear. While some studies have shown prostate-specific antigen (PSA)-based screening may reduce death from prostate cancer, it is associated with significant harms related to overdiagnosis and subsequent treatment complications. This study evaluated if screening with PSA, followed by MRI with lesion-directed biopsy reduced prostate cancer overdiagnosis.

PATIENTS: Men 50–60 years old

INTERVENTION: MRI-targeted biopsy of suspicious prostate lesions

CONTROL: Systematic prostate biopsy

PRIMARY OUTCOME: Clinically insignificant prostate cancer detection

Secondary Outcome: Clinically significant prostate cancer, safety, adverse events

METHODS (BRIEF DESCRIPTION):

- Investigators invited 37,887 Swedish men for prostate cancer screening.
- Those agreeable to screening were included, while those with prostate cancer or who emigrated or died before randomization were excluded.
- Participants had a median age of 56 years, a median PSA level of 0.8 ng/mL, and 1% had a previous prostate biopsy.
- All participants underwent PSA testing.
- Men in the intervention arm with PSA ≥3 ng/mL had prostate MRI, and MRI-targeted biopsy only for lesions of Prostate Imaging-Reporting and Data System (PI-RADS) score 3– 5 unless PSA ≥10 ng/ml.
    - Men in the intervention arm with Gleason 3+3 findings on targeted biopsy were offered systematic biopsy.
- Men in the control arm with PSA ≥3 ng/mL had prostate MRI, and systematic (10–12 core samples) and targeted (if applicable) biopsies.
- Clinically insignificant prostate cancer was defined as a Gleason score of 3+3; clinically significant prostate cancer was defined as a Gleason score of 3+4 or higher.

INTERVENTION (# IN THE GROUP): 11,986

COMPARISON (# IN THE GROUP): 5,994

FOLLOW-UP PERIOD: 30 days post-biopsy

RESULTS:

Primary Outcome –

- MRI-targeted biopsies detected clinically insignificant prostate cancer less often than systematic biopsies (relative risk [RR] 0.46; 95% CI, 0.33–0.64).

Secondary Outcome –

- MRI-targeted biopsies were non-inferior when detecting clinically significant prostate cancer compared to systematic biopsies (RR 0.81; 95% CI, 0.60–1.1).
- Ten patients had clinically significant prostate cancer diagnosed solely by systematic biopsy with negative MRI results.
- Within 30 days after the biopsy, 0.1% of men in the control group required antibiotics compared to 0.03% in the intervention group, and hospitalization rates after the biopsy were 0.07% in the control arm and 0.008% in the intervention arm.
- No deaths were reported.

LIMITATIONS:

- As a single-center study, broad applicability may be limited.
- The primary outcome is disease-oriented, as the evolution of detected cancers is uncertain.
- Additional biopsy techniques were not evaluated.

- Risk stratification using urine or serum biomarkers, and age-based PSA level cut-offs may guide future screening.

Christine E LeRoy, MD, PhD
St. Joseph's Health Department of Family Medicine
Paterson, NJ

Does Prolonged Breastfeeding Help to Reduce Mortality of CVD and Cancer?

Breastfeeding Duration and Subsequent Risk of Mortality Among US Women: A Prospective Cohort Study

Wang YX, Arvizu M, Rich-Edwards JW, et al. Breastfeeding duration and subsequent risk of mortality among US women: A prospective cohort study. *EClinicalMedicine*. 2022;54:101693. Published 2022 Oct 13. doi:10.1016/j.eclinm.2022.101693

KEY TAKEAWAY: Prolonged breastfeeding may reduce the risk for all-cause mortality, including mortality from CVD and cancer.

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 3 (downgraded due to lack of generalizability)

BRIEF BACKGROUND INFORMATION: Breastfeeding exclusively is recommended by multiple national and international organizations to help both mother and child health. There have been multiple studies showing the benefit for children and for maternal morbidity. However, there have been no large studies looking at breastfeeding's impact on mortality, namely the two largest causes of death in America, cardiovascular disease and cancer.

PATIENTS: Parous nurses involved in the Nurse's Health Study who breastfed for any length of time

INTERVENTION: >4 months of breastfeeding

CONTROL: 0–4 months of breastfeeding

PRIMARY OUTCOME: All-cause mortality

Secondary Outcome: Cancer- and CVD-related mortality

METHODS (BRIEF DESCRIPTION):

- Questionnaires were mailed to nurses who were part of the NHS 1 and NHS 2 studies to collect data about background lifestyles and length of breastfeeding in their lifetime.
- Data was collected on mortality and cause of death.
- A hazard ratio was calculated stratifying the length of breastfeeding over their life versus the risk of CVD and cancer.
- Confounders were adjusted for using a multivariable cox model: smoking status, length of smoking habit, eating habits, alcohol use, exercise load, location of birth, length of time varying parity, breastfeeding length per parity, pregnancy complications

INTERVENTION (# IN THE GROUP): 72,589

COMPARISON (# IN THE GROUP): 94,119

FOLLOW-UP PERIOD: At least 30 years

RESULTS:

Primary Outcome –

- Compared to those who breastfed for less than four months, prolonged breastfeeding decreased all-cause mortality.
  - 4–6 months of breastfeeding: hazard ratio [HR] 0.95 (95% CI, 0.92–0.98)
  - 7–11 months of breastfeeding: HR 0.94 (95% CI, 0.91–0.98)
  - 12–23 months of breastfeeding: HR 0.93 (95% CI, 0.90–0.97)
  - >24 months of breastfeeding: HR 0.93 (95% CI, 0.89–0.97).

Secondary Outcome –

- Compared to those who breastfed for less than three months, prolonged breastfeeding decreased the risk of death from cancer.
  - 4–11 months of breastfeeding: HR 0.90 (95% CI, 0.86–0.95)
  - 12–23 months of breastfeeding: HR 0.85 (95% CI, 0.80–0.91)
  - >24 months of breastfeeding: HR 0.87 (95% CI, 0.80–0.94)
- Compared to those who breastfed for less than three months, prolonged breastfeeding decreased the risk of death from CVD.
  - 4–11 months of breastfeeding: HR 0.87 (95% CI, 0.82–0.93)
  - 11–23 months of breastfeeding: HR 0.87 (95% CI, 0.81–0.94)
  - >24 months of breastfeeding: HR 0.87 (95% CI, 0.79–0.96)

LIMITATIONS:

- The survey was self-reported.
- Data was primarily from a homogenous pool of females who were all nurses with a similar education level and socioeconomic status compared to the general population; therefore, generalizability is limited.

Austin Gold, MD
LewisGale Medical Center Family Medicine Residency

Roanoke, VA

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