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EVIDENCE-BASED PRACTICE

A Peer-Reviewed Journal of the Family Physicians Inquiries Network

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FPIN
Family Physicians Inquiries Network

FPIN envisions a primary care workforce that thinks critically, communicates expertly, and utilizes the best current evidence to improve the health of patients.

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EVIDENCE-BASED PRACTICE

A PEER-REVIEWED JOURNAL OF THE FAMILY PHYSICIANS INQUIRIES NETWORK

STATEMENT OF PURPOSE

Evidence-Based Practice (EBP) addresses important patient care questions asked by practicing family physicians, using the best sources of evidence in a brief, clinically useful format. Our goal is to instruct our authors on how to write peer-reviewed scholarly research for the medical and scientific community.

EDITORIAL POLICY

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DISCLOSURE

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Vaccination Nation

I used to tell everyone how much I liked vaccines. If there was a vaccine for something—yellow fever, rabies, cholera—I'd sign up for the shot at the first opportunity. I was a travel clinic's dream patient. "Why, yes, I *will* be visiting the rice paddies and staying in a grass hut with no screens or running water. Oh, that qualifies me for another vaccine? Let me roll up my sleeve!"

When SARS-CoV-2 hit town, we were all rooting for a vaccine. I was amazed (and thankful) when two highly effective RNA vaccines arrived about a year later. Who cared if you needed two shots in the primary series? Hepatitis B and rabies prophylaxis (back when I took it) each consisted of three shots, so no big deal. I was in line on the second day of the roll out. I was also down with myalgias the day after that, but it was a small price to pay for the partial return of a normal civic life.

But dang those RNA viruses and their rapid evolution. Now we are coming off the (first?) wave of BA.5 and wondering what letter of the Greek alphabet we might have to learn next. I and many "seniors" are already four vaccines into SARS-CoV2 and about to get our fifth (the omicron version) soon. And just to liven things up, we now have a new virus *de jour*—monkeypox! I thought I was going to get a pass with monkeypox because I was vaccinated for smallpox as a kid. But apparently that will not be good enough.

I share with all America the frustration of needing ever more shots, but the evidence remains—we are better off with them than without them. So, I'll still race you to the front of the line when we essential workers are called. I remain a fan of all shots, though fondness wanes a touch with frequency.

Jon O. Neher

The authors declare no conflicts of interest.

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Olive oil and mortality

Guasch-Ferré M, Li Y, Willett WC, et al. Consumption of Olive Oil and Risk of Total and Cause-Specific Mortality Among U.S. Adults. J Am Coll Cardiol. 2022;79(2):101-112. doi:10.1016/j.jacc.2021.10.041

DOI 10.1097/EBP.0000000000001711

The study was a pooled analysis of two large, ongoing prospective cohort studies: the Nurses Health Study (NHS) and the Health Professionals Follow-up Study (HPFS). The current study investigated the association between olive oil consumption and all-cause and disease-specific mortality. After excluding participants from NHS and HPFS with cancer or cardiovascular disease at baseline, missing data on olive oil consumption, or implausibly high or low values for total energy intake, 92,383 participants (65.6% women) were included in the analysis. Every four years, a validated food frequency questionnaire (FFQ) that included three specific questions on olive oil intake was used to estimate average daily olive oil consumption. Mortality was assessed using state vital statistic records, the National Death Index, and reports by family members. Causes of death were based on physician review of medical records, autopsy reports, and death certificates. Adjusted age-stratified Cox proportional hazards models were fit using the mean olive oil intake from the two most recent FFQs. Sensitivity analyses were conducted using cumulative olive oil intake and a variety of additional factors. Twenty-eight years of follow-up were done, in which 40% of participants died. The pooled results for total mortality—the primary outcome—demonstrated decreasing adjusted hazard ratios (aHRs) for increasing levels of daily olive oil intake compared with no olive oil intake (≤1 tsp aHR 0.88 [95% CI, 0.86–0.90]; 1–1.5 tsp aHR 0.86 [0.82–0.90]; >1.5 tsp aHR 0.81 [0.78–0.84]). Similarly, an inverse association was noted between daily olive oil intake and disease-specific mortality. Results of sensitivity analyses were consistent with the primary analysis. Limitations of the study included the use of self-report measures (ie, FFQ) for categorization of exposures, unclear masking of outcomes assessors for disease-specific mortality determinations, residual confounding, and unclear applicability beyond the predominantly non-Hispanic White population of health professionals enrolled.

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described **here**.

Does this meet PURL criteria?			
Relevant	Yes	Medical care setting	Yes
Valid	Yes	Implementable	Yes
Change in practice	No	Clinically meaningful	Yes

Bottom line: Although increased daily olive oil intake is associated with lower mortality, primary care providers are already accustomed to making dietary recommendations that would increase olive oil intake (eg, Mediterranean diet), and this study would not likely change those already existing practices.

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Does routine in-office fluoride varnish or gel application improve rates of dental caries in children?

EVIDENCE-BASED ANSWER

Fluoride varnish application for children <5 years old decreases childhood dental caries (SOR: **A**, systematic review of randomized controlled trials and observational studies). The United States Preventive Service Task Force and the American Academy of Pediatrics endorse primary care physicians applying fluoride varnish for prevention of childhood caries (SOR: **C**, expert opinion).

DOI 10.1097/EBP.0000000000001703

A 2021 systematic review and meta-analysis evaluated evidence for the prevention of dental caries in children <5 years old.[1] Fifteen trials (N=9,541) evaluated the application of topical fluoride to children <5 years old. The application of topical fluoride was compared with placebo or no intervention. The primary outcomes were the reduction of dental caries progression (recorded as the mean difference in decayed, missing, and filled teeth or surfaces) or the development of new caries at follow-up. Follow-up ranged from 1 to 3 years. As a secondary outcome, harms were also studied. Ten trials were conducted in dental clinics and five took place in day care or preschool settings. Although eight trials were conducted in "first world" countries, all trials except for one studied high-risk children defined by low socioeconomic status, high baseline community rate of caries, or poor dental care literacy. Except for three trials, all study participants also received dental healthcare education.

Topical fluoride application was associated with a reduction of dental caries progression (13 trials, N=5,733; mean difference –0.94; 95% CI, –1.74 to –0.34) and reduction in the development of new caries (12 trials, N=8,177; risk ratio 0.80; 95% CI, 0.66–0.95; absolute risk difference, –7%), with a number needed to treat of 14 to prevent one child with incident caries. No harms were associated with the application of topical fluoride varnish including no increased risk of fluorosis. Limitations of the systematic review and meta-analysis included heterogeneity in fluoride varnish concentration, fluoride type, settings (clinic, school, and day care), application timing, duration of follow-up, sample size, randomization, high attrition, and blinding. Although intuition suggests that the outcomes should be similar regardless of the setting where the application occurs, none of the trials occurred in a primary care clinic.

In 2021, the United States Preventative Services Task Force (USPSTF) updated and did not change its 2014 Grade B recommendation (moderate certainty that the net benefit is moderate) regarding the use of fluoride varnish in pediatric caries prevention.[2] The USPSTF recommendation restated that primary care clinicians should apply fluoride varnish to the primary teeth of all children <5 years old starting at a child's primary tooth eruption.

In 2020, the American Academy of Pediatrics published a clinical report for the prevention of caries in the primary care setting, recommending in-office fluoride application for low- and high-risk children.[3] They stated that varnish should be applied to all children at least every six months and every three months for high-risk children. This consensus-based guideline contained no strength of recommendation or level of evidence indicators applied to key recommendations. The authors of the guideline reported no financial or potential conflicts of interest. EBP

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Is there any utility of using manual blood pressure cuffs in the clinical setting compared with modern automated blood pressure monitors?

EVIDENCE-BASED ANSWER

Maybe. Automated blood pressure office-based monitoring is more closely associated with ambulatory blood pressure monitor compared with non-standardized manual office-based monitoring (SOR: **B**, randomized parallel control trial and a prospective cohort). However, a moderate correlation was observed between office-based automated and manual testing when a standardized manual technique is implemented (SOR: **B**, randomized cross-over study).

DOI 10.1097/EBP.0000000000001743

This clinical question was developed as an HDA through a standardized, systematic methodology (HDA Methods, Supplemental Digital Content).

A 2011 randomized parallel design control trial (n=555) compared the accuracy of manual and automated blood pressure readings in the office using awake 24-hour ambulatory blood pressures as the gold standard[1]. Patients were older than 45 years with untreated hypertension (systolic blood pressure greater than 160 and diastolic blood pressure greater than 95) or treated with systolic blood pressure greater than 140 and diastolic blood pressure greater than 90 without diabetes or evidence of target organ damage. Measurements were taken consecutively, a total of six times every two minutes with no rest periods for both groups. No instruction or standardization of manual blood pressure technique was used to keep the integrity of typically reported measurements to baseline. Systolic/diastolic automated blood pressures showed a stronger correlation with the gold standard (correlation coefficient [r]=0.34/r=0.56) in comparison with the systolic/diastolic manual blood pressure (r=0.10/r=0.40) with the gold standard. This study was limited by excluding patients with comorbidities typically seen with hypertension. Authors noted that use of a standardized manual blood pressure protocol might have yielded a different outcome.

A 2011 prospective, randomized, cross-over study (n=101) compared manual office-based blood pressure cuffs, automated blood pressure, ambulatory blood pressure monitoring, and home self-measurement of blood pressure[2]. Patients were older than 18 years with hypertension and no recent changes or planned changes in medications. Hypertension was defined using the Canadian hypertension education program guidelines, for ambulatory blood pressure monitoring (daytime mean of ≥135/85 or 24 hours mean of ≥130/80, while automated blood pressure: ≥135/85). All patients completed an automated blood measure protocol, a manual measure protocol, and a 24-hour ambulatory blood pressure protocol. Participants were randomized to home or office-based testing first. Office-based testing was completed within a 20-minute period and included two manual measurements one minute and six automated blood pressure measurements taken one minute apart. Home self-measurements consisted of three readings twice a day daily for a maximum of 14 days. Manual office-based reading technique was standardized using the Canadian hypertension education program guidelines. Office-based manual and automated measurements demonstrated a moderate correlation (kappa coefficient [κ] of 0.65, 95% CI, 0.493–0.813) with home-automated measurement demonstrating a fair correlation with 24-hour ambulatory monitoring (κ=0.47, 95% CI, 0.31–0.64). All other measurement techniques demonstrated a fair correlation between measurements to include both office manual (κ=0.27, 95% CI, 0.12–0.43) and office-automated (κ=0.27, 95% CI, 0.12–0.41) measurements to 24-hour ambulatory monitoring. The results were limited because office measures were taken only at one visit; there may have been greater delays between measurements with at home readings.

A 2020 prospective cohort study (n=103) at a single medical center in the United States evaluated and compared blood pressure measurement methods over three days[3]. Patients were 51% female, 29% Black, with a mean age of 57 years old, and all with diagnosed

hypertension (defined as blood pressure ≥140/90). The evaluation involved one-day ambulatory blood pressure monitoring compared with two manual clinic-based blood pressure measurements taken over two office visits spaced two days apart or three unwatched automated office blood pressure measurements spaced two minutes apart in the same office visit. Mean automated blood pressure measurements were no different than ambulatory blood pressure measurements for systolic blood pressure and diastolic blood pressure. Mean manual blood pressure measurements were higher than ambulatory blood pressure monitoring for both systolic blood pressure (137 vs 131, $P=.21$) and diastolic blood pressure (81 vs 78, $P=.62$), although neither finding was statistically significant. Limitations of this study included inconsistency with timing of blood pressure measurements, with manual blood pressures taken two days apart and automated blood pressure measurements taken from one visit only. In addition, manual blood pressures were taken by various healthcare professionals with varying experience and no standardized technique. EBP

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Does clamping the umbilical cord >30 seconds after birth decrease intraventricular hemorrhage in infants born before 37 weeks?

EVIDENCE-BASED ANSWER

Delayed umbilical cord clamping for more than 30 seconds modestly reduces the risk of intraventricular hemorrhage (IVH) in infants born before 37 weeks' gestation with a number needed to treat of 32 to 42 (SOR: **A,** systematic reviews of randomized controlled trials [RCTs]), but likely no difference is observed in risk of severe (grade 3 or 4) IVH (SOR: **B**, systematic reviews of low-quality RCTs). The American College of Obstetrics & Gynecology (ACOG) recommends delaying cord clamping for at least 30 to 60 seconds after birth in preterm infants (SOR: **C,** consensus guideline).

DOI 10.1097/EBP.0000000000001740

This clinical question was developed as an HDA through a standardized, systematic methodology (HDA Methods, Supplemental Digital Content).

A 2019 systematic review and meta-analysis pooled data from 16 randomized controlled trials (RCTs; N=2,423) comparing the effectiveness of delayed (>30 seconds) versus early (<30 seconds) umbilical cord clamping to prevent intraventricular hemorrhage (IVH) in infants born before 37 weeks[1]. The studies were from Asia (6 RCTs, N=411), North America (5 RCTs, N=279), Africa (2 RCTs, N=122), Europe (1 RCT, N=39), and Australia (1 RCT, N=31); one trial (N=1,541) was conducted in multiple continents. Infants were between 22+5/7 and 36+6/7 weeks gestation, and most studies evaluated

neonates born before 34 weeks (12 RCTs, N=2,078). Delayed cord clamping was up to three minutes but was typically between 30 and 60 seconds. Primary outcomes included any IVH, severe IVH (grade 3 or 4 diagnosed by ultrasound), infant periventricular leukomalacia, infant chronic lung disease, and maternal blood loss greater than 500 mL. Delayed cord clamping compared with early cord clamping was associated with a 17% relative risk (RR) reduction in any IVH (15 RCTs, N=2,333; RR 0.83; 95% CI, 0.70–0.99; NNT=32) but did not decrease the risk of severe IVH (10 RCTs, N=2,058; RR 0.94; 95% CI, 0.63–1.4). No increase was observed in potential harms to the infant with delayed versus early cord clamping including the risk of periventricular leukomalacia (4 RCTs, N=1,544, RR 0.58; 95% CI, 0.26–1.3) and chronic lung disease (6 RCTs, N=1,644; RR 1.0, 95% CI, 0.94–1.1), and no difference was observed in maternal blood loss greater than 500 mL (2 RCT, N=180; RR 1.1; 95% CI, 0.07–17.6). Most of the studies were small with unclear risk of bias in the domains of selection bias, detection bias, and reporting bias.

A 2021 systematic review and network meta-analysis identified 25 RCTs (N=3,316) directly comparing the effectiveness of delayed (30–180 seconds) versus immediate (<30 seconds) umbilical cord clamping for the prevention of IVH in preterm infants[2]. Sixteen trials were also in the previously mentioned meta-analysis[1]. Neonates were born before 37 weeks' gestation or had a birthweight less than 2,500 g. The review analyzed IVH and severe IVH (grade 3 or 4) as secondary outcomes. In network meta-analysis, delayed cord clamping was associated with a lower odds of IVH compared with immediate cord clamping (17.8% vs 15.4%, respectively; odds ratio [OR] 0.73; 95% credible interval [CrI], 0.54–0.97; NNT=42); however, no difference was noted in severe IVH (15 RCTs, N=2,469; OR 0.83; 95% CrI, 0.47–1.3) except among infants born younger than 29 weeks' gestation (1 RCT, n=37; OR 0.18; 95% CrI, 0.03–0.99). The major limitation was only 39% of the studies had overall low risk of bias and that potential harms were not evaluated.

A 2020 ACOG Committee Opinion consensus-based guideline recommended delaying cord clamping for at least 30 to 60 seconds after birth in preterm infants (no recommendation rating given)[3]. The recommendation was based on a systemic review of 15 RCTs demonstrating lower risk of IVH with delayed versus immediate umbilical cord clamping in infants born between 24 and 36 weeks' gestation. EBP

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Does continuous glucose monitoring in patients with type 2 diabetes lead to less hypoglycemic events while hospitalized?

EVIDENCE-BASED ANSWER

Perhaps. Hospitalized patients with type 2 diabetes who are monitored with continuous glucose monitoring seem to experience fewer numbers of hypoglycemic events and less time in a hypoglycemic state compared with patients monitored with point of care capillary blood glucose measurements (SOR: **C**, low-quality randomized controlled trials).

DOI 10.1097/EBP.0000000000001665

A 2020 randomized controlled trial (RCT; n=72) compared real-time continuous glucose monitoring

(CGM) with point-of-care (POC) capillary blood glucose measurements in patients with type 2 diabetes (DM-2) to determine the effect on the number of hypoglycemic events.[1] Hospitalized patients with DM-2, an expected stay >72 hours, and risk factors for hypoglycemic events (age >65 years old, body mass index <27 kg/m^2, total insulin ≥0.6 units/kg, history of renal failure, liver failure, cerebrovascular accident, active malignancy, congestive heart failure, systemic infection, or history of hypoglycemia in a recent hospitalization) were included. Patients with severe hyperglycemia requiring insulin infusion or intensive care unit admission were excluded. The researchers compared the number of hypoglycemic (<70 mg/dL) and severe hypoglycemic (<54 mg/dL) events between the treatment group and the control group during their hospitalization. The intervention used was Dexcom G6 CGM versus standard POC capillary blood glucose measurements. Compared with the control group, the treatment group had fewer hypoglycemic events per patient (0.67 vs 1.69; *P*=.0024; number needed to treat [NNT]=10) and fewer severe hypoglycemic events per patient (0.08 vs 0.75; *P*=.003; NNT=15). A decreased percent of time in hypoglycemia was noted between the treatment and control groups (0.4% vs 1.88%; *P*=.002; NNT=67) as well as the time in severe hypoglycemia (0.05% vs 0.82%; *P*=.017; NNT=130). Limitations of the study included small sample size, and only non-ICU patients represented in the study.

A 2020 RCT (n=110) compared real-time CGM with POC capillary glucose measurements in hospitalized patients with DM-2 comparing mean glucose and hypoglycemic events.[2] Adults with DM-2, mean six years old, with at least three POC or serum glucose values >200 mg/dL within 24 hours of admission were included in the study. Patients admitted to the intensive care unit or requiring intravenous insulin were excluded. The intervention used was the Dexcom G6 CGM versus POC blood glucose measurements. Researchers compared the number of hypoglycemic events (hypoglycemia defined similar to previous study) and the average mean glucose between the treatment and control groups. No difference in percentage of time was noted in hypoglycemia between the two groups, which was overall very low. However, among patients who had hypoglycemic events, the median number of events was lower in the CGM group (1.0 vs 2.0 for blood glucose [BG] <70 mg/dL and 1.0 vs 3.5 for BG <54 mg/dL). In addition, the duration of time spent in hypoglycemic events was lower in the CGM group compared with POC group (50 min less for BG <70 mg/dL and 7.41 min less for BG <54 mg/dL). However, *P* values could not be calculated because of the small number of hypoglycemic events in the subanalysis. EBP

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Can intrauterine devices help prevent ovarian cancer in women?

EVIDENCE-BASED ANSWER

Intrauterine device (IUD) is associated with a 33% risk reduction in the incidence of ovarian cancer compared with non-IUD use, and levonorgestrel-containing IUDs equally reduce the risk of ovarian cancer (SOR: **C**, meta-analysis of case–control and cohort studies). There also seems to be an age-related increased risk of ovarian cancer if the first IUD use is after age 25 years old (SOR: **C**, meta-analysis of case–control and cohort studies).

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A 2021 meta-analysis (N=383,796) of five case–control and four cohort studies examined ever-use versus never-use of intrauterine device (IUDs) and the risk of ovarian cancer.[1] Patients were between the ages of 18

and 69 years old. No other patients' demographic information was reported. Patients were included if they had been diagnosed with ovarian cancer compared with their age-matched controls. Across studies, both copper and hormonal IUDs were included. Ever-use of an IUD conferred a significantly lower risk of ovarian cancer compared with never-users (9 trials, N=383,796; odds ratio [OR] 0.67; 95% CI, 0.60–0.74; I^2=71%). This association remained significant when results were restricted to studies evaluating levonorgestrel IUDs alone (2 trials, N=198,161; OR 0.58; 95% CI, 0.47–0.71; I^2=0%). Limitations included that most of the studies did not specify the type of IUD, did not look at the beneficial effect of IUD for various histological subtypes, and did not address the duration of use necessary to observe a risk reduction of ovarian cancer.

A 2021 meta-analysis (N=228,216) of one case–control study (the New England Case Control Study, NEC) and two prospective cohort studies (Nurses' Health Studies I and II, NHS/NHSII) examined the association between IUD use and the risk of ovarian cancer.[2] The NEC and NHS/NHSII data were not included in the study above. The NEC study included 4,662 females 18 to 80 years old between 1984 and 2008 who were diagnosed with epithelial ovarian cancer, whereas the NHS/NHSII study included 223,554 nurses 30 to 55 years old in 1976 and 25 to 42 years old in 1989. IUD type, age at the first IUD use, and duration of IUD use with ovarian cancer risk were measured. Overall, no evidence of an association between IUD use and the risk of epithelial ovarian cancer was noted (3 studies, N=228,216; risk ratio 0.94; 95% CI, 0.81–1.08). However, among ever IUD users, a significant trend of increased ovarian cancer risk with older age was noted at the first IUD use (age at the first IUD use 25 years old or younger: reference, OR 0.98; 95% CI, 0.66–1.46 for 25–29 years; OR 1.19; 95% CI, 0.73–1.46 for 30–34 years; and OR 1.81; 95% CI, 0.95–3.44 for 35 years old or older; *P* trend=.03). Limitations included the inability to assess the association by tumor histotype, susceptibility to recall bias, and the lack of assessment on type of IUD (hormonal vs nonhormonal). EBP

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Do intra-articular steroid injections affect blood glucose levels in diabetic patients?

EVIDENCE-BASED ANSWER

Intra-articular corticosteroid injection at the knee can significantly increase glucose elevations one day post-injection with return of blood glucose levels to baseline by day 8 after injection (SOR: **C**, case–control clinical trial). Peaks in blood glucose levels can occur between 2 and 84 hours postinjection of various joints with a return to baseline levels within 18 to 104 hours (SOR: **C**, systemic review of prospective observational studies).

DOI 10.1097/EBP.0000000000001704

A 2018 case–control clinical trial (n=21) evaluated the impact of intra-articular corticosteroid injection (depot betamethasone) in the knee joint in patients with type 2 diabetes.[1] All patients were adults with painful arthritis of the knee and non–insulin-dependent type 2 diabetes and no changes in their antidiabetic regimen in the last three months (medication, diet, or physical activity). Patients who were on any form of steroid therapy or had received intra-articular injection over the previous three months were excluded. Eleven people were recruited into the treatment group and 10 into the control group. The control group received usual care without systemic or intra-articular steroids. Fasting blood glucose (FBG), insulin resistance (IR), and HbA1c were measured before injection of the intra-articular steroid, and these baseline

values were compared with the readings at day 1 and day 8 postinjection. IR was calculated using the Homeostasis Model Assessment for Insulin Resistance calculator. One day postinjection, the treatment group experienced a significant increase in both IR (21 vs 5.1, $P<.01$) and FBG levels (247 vs 148 mg/dL, $P<.01$) compared with baseline readings. However, readings at day 8 showed no significant difference in either IR (11 vs 5.1, $P=.15$) or FBG levels (142 vs 148 mg/dL, $P=.76$) compared with baseline.

A 2016 systematic review of seven prospective observational studies (N=72) investigated the effects of intra-articular steroid injections on blood glucose levels in patients with diabetes mellitus.[2] All patients had well-controlled diabetes and continued their same diabetic treatment regimens before injection. The studies involved injection of one of three types of steroids (methylprednisolone, triamcinolone, or celestone) into various intra-articular spaces. Timing of the injections varied throughout the day for each of the studies. Because of heterogeneity issues, results were reported on their overall findings and were not pooled together. All seven studies showed a rise in blood glucose compared with baseline after intra-articular steroid injection. Overall, four of the seven studies (57%) showed a statistically significant increase (defined as >2 SD increase from baseline mean) in blood glucose compared with baseline values. Among the four studies with statistical significance, peak blood glucose values ranged from 165 to 500 mg/dL. Time to achieve these peaks ranged from 2 to 84 hours. Furthermore, the time for peak values to return to baseline ranged from 18 to 104 hours. Limitations included heterogeneity of baseline patient characteristics, diabetic treatment regimens, and location of intra-articular injection site. EBP

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Do nasal saline rinses improve severity of acute sinus congestion in adults with seasonal allergies?

EVIDENCE-BASED ANSWER

Yes. Nasal saline may yield large improvements in symptom severity compared with no nasal saline in adults with acute allergic rhinitis (SOR: **B**, meta-analysis of small randomized controlled trials). Buffering nasal saline to a pH of 7.2–7.4 may improve overall nasal symptom severity slightly, whereas lower pH (6.2–6.4) and higher pH (8.2–8.4) do not (SOR: **C**, small crossover trial.) The 2018 International Consensus Statement of Allergy and Rhinology recommended nasal saline irrigation along with other pharmacological treatments for allergic rhinitis (SOR: **C**, evidence-based review).

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A 2018 meta-analysis of seven randomized controlled trials (RCTs; N=248) investigated the effects of nasal saline irrigation in patients with allergic rhinitis.[1] The trials included adults with allergic rhinitis symptoms and a positive radioallergosorbent test or skin prick test. Patients were excluded for nasal polyposis, asthma, nasal anatomic abnormalities, previous immunotherapy, and prior topical or oral antihistamines, decongestants, or corticosteroids. Studies were conducted in five countries (Italy, China, Thailand, Turkey, and the United States) in undefined settings. Nasal saline irrigation was delivered by different means, volumes (0.15–500 mL per nostril per application or not stated), tonicity (normal to hypertonic or not stated), and

alkalinity (not stated). Duration of treatment ranged from 7 days to 3 months. The primary outcomes measured were patient-reported disease severity and the adverse effect of epistaxis. Seven studies compared nasal saline with no nasal saline. All studies evaluating symptom severity used different scoring systems, so data were pooled using the standardized mean difference (SMD). Compared with no treatment, adults treated with nasal saline irrigation up to four weeks reported greatly improved symptoms (2 trials, N=85; SMD –2.06; 95% CI, –3.8 to –0.32). No adverse effects were reported, although means of assessment and reporting of epistaxis were inconsistent. Subgroup analyses for volume and tonicity were inconclusive because of heterogeneity. Limitations included variable treatment formulations, delivery methods, and outcome measures.

A 2013 prospective, double-blinded, randomized, three-arm crossover study (n=36) compared the effect of various saline solutions for the treatment of allergic rhinitis.[2] The trial included adult patients with allergic rhinitis confirmed by skin prick test who had not used intranasal corticosteroids for two weeks or oral antihistamines for one week before start of study. Patients with asthma, acute upper or lower respiratory tract infection, nasal polyps, markedly deviated nasal septum, pregnancy, severe underlying diseases, or history of allergen-specific immunotherapy were excluded. Patients were treated with a 10-day course of three isotonic nasal saline irrigations: nonbuffered (pH 6.2–6.4), buffered with mild alkalinity (pH 7.2–7.4), and buffered with alkalinity (pH 8.2–8.4). All patients underwent baseline evaluation of rhinorrhea, nasal blockage, sneezing, itchy nose, and five-day overall nasal symptoms on a 10-point visual analog scale (VAS, 0=no symptoms, 10=very severe symptoms). All patients completed a 10-day course of all three nasal saline irrigations with five-day washout periods between trials. The order in which these were completed was randomized. After the 10th day of each treatment, patients returned to the office to record nasal symptoms on the VAS. After all three irrigation trials were completed, outcomes were compared between baseline and posttreatment and also between the three nasal saline irrigation solutions. For buffered solution irrigation (pH 7.2–7.4), mean VAS score for overall nasal symptoms improved from baseline by 0.4 points (P=.03). After 10 days of buffered solution irrigation (pH 8.2–8.4), mean VAS score for sneezing significantly improved from baseline by 1.25 (P=.04). Side effects were minimal and included nasal burning (36.1% in nonbuffered, 19.4% in buffered [pH 7.2–7.4], and 25% in buffered [pH 8.2-8.4]) and ear fullness/pain (30.6% in nonbuffered, 33.33% in buffered [pH 7.2–7.4], and 25% in buffered [pH 8.2–8.4]). This study was limited by the absence of a control or placebo group.

The 2018 evidence-based International Consensus Statement of Allergy and Rhinology recommended that nasal saline be used as an adjuvant to other pharmacological treatments for allergic rhinitis.[3] This was listed as a "Strong Recommendation" based on "Grade A" evidence: one meta-analysis and 11 well-designed RCTs, showing generally consistent benefits, including nasal symptoms scores and quality of life, and a lack of harm. A key weakness was that most of the research cited was 9 to 17 years old. EBP

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Does adherence to a diet with a low dietary inflammatory index decrease the incidence of depression?

EVIDENCE-BASED ANSWER

Perhaps. Pro-inflammatory diets are associated with an increased likelihood of being diagnosed with depression and an increase in depressive symptoms (SOR: **B**, meta-analysis and systemic review, both with primarily cohort data).

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Methods

The authors developed the clinical question, "Does adherence to a diet with a low dietary inflammatory index decrease the incidence of depression," based on the clinical needs of their practice site. EBP editors approved the question based on its relevance and applicability to practicing primary care clinicians. EBP editors also verified the question does not duplicate other HelpDesk Answers written in the prior three years.

The **TABLE** includes the databases and search terms the authors used to find studies matching the following study inclusion criteria: patients – adult patients; intervention – diet with a high inflammatory index or Mediterranean diet; comparison – a diet with a low dietary inflammatory index; and outcome – incidence of depression or depressive symptoms. Authors selected the most relevant, highest evidence level studies published within the last five years to prepare the HDA manuscript (**Figure**).

A 2018 meta-analysis (4 cross-sectional studies, N=54,530; 7 longitudinal studies, N=47,420) examined an anti-inflammatory diet as a potential intervention for depressive disorders.[1] Patient ages ranged from 16 to 74 years old. Longitudinal studies had a follow-up of 5 to 13 years. Depression or depressed symptoms were identified using a variety of methods including the Patient Health Questionnaire 9, the Center for Epidemiologic Studies Depression Scale (CES-D), expert physician opinion, or antidepressant use. Studies used the dietary inflammatory index to assess the level of dietary inflammation or measured specific inflammatory markers. All included studies used 24-hour dietary recalls or a food frequency questionnaire (FFQ) to assess diet and generate a dietary inflammatory index with a range between 10 and 39 different food parameters. Patients with a pro-inflammatory diet were more likely to be diagnosed with depression or present with depressed symptoms compared with those with an anti-inflammatory diet (odds ratio 1.40; 95% CI, 1.21–1.62;

TABLE. HDA search strategy

Search engine	Search term or combination of search terms	Total number of records identified
PubMed Clinical Queries	a) Depression, "Anti-Inflammatory Diet" category: [therapy] scope: [broad] b) Depression, "Dietary Inflammatory Index" category: [therapy] scope: [broad]	a) 6 results, 2 relevant b) 45 results, 7 relevant
Trip Database	a) Depression, "Dietary Inflammatory Index"	a) 1 results, 0 relevant
Cochrane Library	a) Depression, "Dietary Inflammatory Index" b) Depression, "Anti-Inflammatory Diet:"	a) 11 results, 0 relevant b) 7 results, 0 relevant
Google Scholar	a) Depression, "Anti-Inflammatory Diet" b) Depression, "Dietary Inflammatory Index" (In title) c) "Depressive Symptoms", "Dietary Inflammatory Index" (In title) d) Mediterranean diet inflammation (In title)	a) 1 result, not useable b) 9 results, 4 relevant c) 5 results, 2 relevant d) 4 results, 1 relevant

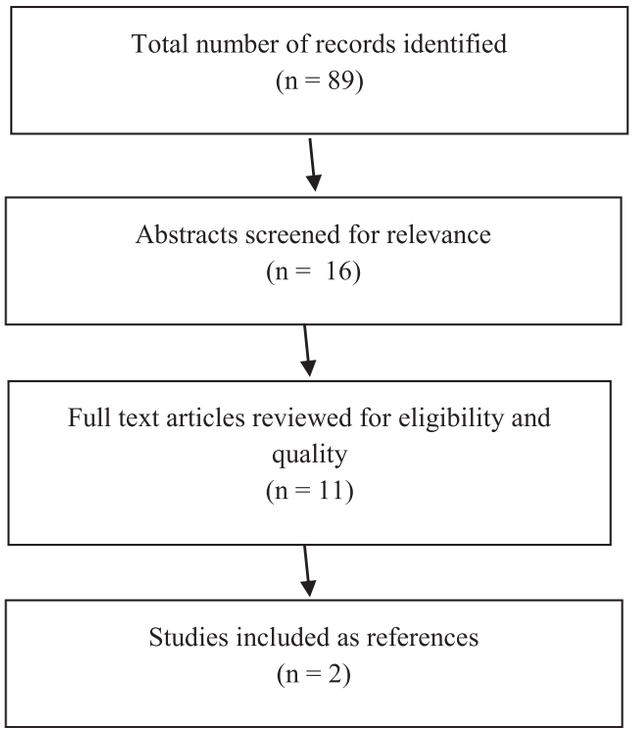

Figure.
Literature search flow diagram.

I^2=63%). This systemic review was limited by significant heterogeneity of study designs.

A 2019 systematic review (6 randomized controlled trials, N=4,585; 7 cross-sectional, N=11,357; 13 longitudinal, N=131,477) looked at the Mediterranean dietary pattern (MedDiet) and depression risk.[2] Patients were 18 to 102 years old. Most of the studies used FFQs to assess diet, and CES-D was the most commonly used to assess for depression. Although a meta-analysis was not possible, 85% of the observational studies support the evidence that Mediterranean dietary pattern was associated with a -reduced incidence of depression or improvement in depressive symptoms (11 cross-sectional, N=10,487; 6 longitudinal, N=124,744). This review was limited by the heterogeneity of Mediterranean Diet definitions and measurements of depressed symptoms. EBP

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What is the most accurate screening tool for detecting opioid use disorder in pregnancy?

EVIDENCE-BASED ANSWER

No single screening tool has all the desired test characteristics for detecting opioid use in pregnancy. Of available tools, the 4 Ps Plus (parents, partner, past, pregnancy) is higher in sensitivity, the National Institute on Drug Use (NIDA) Quick Screen is higher in specificity, and the NIDA Quick Screen-ASSIST is higher for negative predictive value (SOR: **B**, 2 prospective cross-sectional studies). However, both 5 Ps (4 Ps Plus+peers) and NIDA Quick Screen show poor overall accuracy (SOR: **C**, large prospective cross-sectional studies).

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A 2019 prospective cross-sectional study of pregnant women (n=453) compared the validity (ie, sensitivity, specificity, positive and negative predictive value [PPV, NPV]), and reliability (ie, test-retest reliability) of three screening instruments for the detection of substance use in pregnancy.[1] Patients were 70% African Americans, with a mean age of 27.8 years old across the three trimesters from two US prenatal clinics. Inclusion criteria

were pregnant at the time of enrollment, 18 years old or older, and natural hair length of at least 3 cm (for drug testing). Of three screening instruments used in the study, two screening instruments included opioid use: 4 Ps Plus (parents, partner, past, pregnancy) and National Institute on Drug Use (NIDA) Quick Screen-ASSIST (modified alcohol, smoking, and substance involvement screening test). Urine and hair drug test results were used as reference standard for both recent and past (0–90 days) drug use, including both prescription and nonprescription opioids. Screening tests were repeated in one week to assess test-retest reliability. The primary outcomes were sensitivity, specificity, PPV, NPV, and test-retest reliability of each of the two screening tests. For the 4 Ps Plus, sensitivity was 90%, specificity 30%, PPV 44%, and NPV 83%. For the NIDA Quick Screen-ASSIST, sensitivity was 80%, specificity 83%, PPV 74%, and NPV 87%. Test-retest (phi) correlation coefficient was 0.84 for 4 Ps Plus and 0.77 for NIDA Quick Screen-ASSIST. This study was limited by selection bias, because women who were willing to enroll may have had higher baseline use, and by possible false positives and false negatives in biological testing of hair and urine.

A 2019 prospective cross-sectional study (n=1,220) compared the accuracy of five screening instruments for substance use in pregnancy, including opioids, against a reference standard (positive urine drug screening or 30 calendar-day positive self-report recall).[2] Patients were pregnant women with a mean age of 29 years old from four US prenatal clinics, and 40.1% were non-Hispanic African American, 37.1% non-Hispanic White, and 15.9% Hispanic. Patients were excluded if they were cognitively impaired, were currently hospitalized, or were considering pregnancy termination or adoption. Of five screening instruments used in the study, two instruments: 5 Ps questionnaire (parents, peers, partner, pregnancy, past) and the NIDA Quick Screen sought to identify opioid use. Primary outcomes were sensitivity, specificity, and area under the curve (AUC; <0.70 of AUC was considered to have poor accuracy). In addition, overall accuracy was defined as true positives plus true negatives divided by the full sample. The 5 Ps showed 81% sensitivity, 35% specificity, 37% overall accuracy, and AUC of 0.58. The NIDA Quick Screen showed 16% sensitivity, 99% specificity, 96% overall accuracy, and an AUC of 0.57. This study was limited by a self-selected sample of patients. In addition, the reference standard of a urine drug screen was limited by a short window of detection. EBP

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Is intralesional *Candida* therapy more effective than cryotherapy in treatment of warts?

EVIDENCE-BASED ANSWER

It may be. Intralesional *Candida* seems more effective than cryotherapy in complete remission of warts with a number needed to treat of 3 to 5, including complete resolution of distant noninjected warts (SOR: **B**, 2 small randomized controlled trials).

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A 2017 randomized controlled trial (RCT; n=60) examined the effectiveness of intralesional *Candida* compared with cryotherapy in treatment of warts.[1] This study included patients older than 15 years old (mean age 26) who were referred to a dermatology clinic in Iran for either plantar warts or verruca vulgaris, with most of the patients (>80%) with 6 to 8 warts and average total surface area of 3.8 cm^2. Patients with immunodeficiency, pregnancy, skin allergies, asthma, facial or genital warts, and previous wart treatment in the last month were

excluded. The intervention group received intralesional *Candida* with dose determined by induration diameter of an intradermal test dose (0.3 mL of 1/1,000 solution for diameter of 5–20 mm, 0.2 mL for 20–40 mm, and 0.1 mL for >40 mm). Injections were administered in three-week intervals for up to a maximum of three injections or complete resolution warts, treating only the largest surface area wart in cases of multiple warts. The control group received once weekly two-cycle cryotherapy with liquid nitrogen using cotton probes with a freeze margin of 1 to 2 mm until complete clearance or a maximum of 10 sessions. Outcomes included percent reduction in wart surface area after one-third, two-thirds, and all treatment sessions; number of patients with complete resolution of warts; and number of sessions needed for complete resolution. Reduction in wart surface area was not significantly different between intralesional *Candida* and cryotherapy after one-third of sessions (25% vs 45%, $P=.098$) or two-thirds of sessions (78% vs 61%, $P=.17$), but intralesional *Candida* was significantly better after all sessions (89% vs 64%; $P=.023$). Patients treated with intralesional *Candida* were more likely to have complete resolution after full treatment course (77% vs 57%; $P=.023$; number needed to treat [NNT]=5), and complete remission of untreated distant warts was observed in 77% with remission rates of untreated warts not reported for the cryotherapy group. No difference was observed in number of sessions needed for complete resolution (2.2 for Candida vs 3.8 for cryotherapy; $P=.051$). Side effects included pain in all patients, blistering (50%), itching (17%), and infection (7%) in the cryotherapy group and pain in all patients, local erythema (17%), and flu-like syndrome (3%) in the intralesional *Candida* group. This RCT was limited by lack of blinding and allocation concealment, lack of predefined primary and secondary outcomes, and lack of long-term follow-up.

A 2021 RCT (n=105) published only as a research letter examined the effectiveness of intralesional *Candida*, intralesional bivalent human papilloma virus (HPV) vaccine, and cryotherapy for wart treatment compared with placebo.[2] Patients (mean age 31 years old) were selected if they had multiple common warts, with most having five or more warts. The groups received either 0.2 mL of 1/1,000 solution intralesional *Candida* (n=30), 0.2 mL of intralesional bivalent HPV vaccine (n=30), cryotherapy (n=30), or 0.2 mL of intralesional saline (n=15) every two weeks until complete clearance or a maximum of five sessions. The primary outcome was complete clearance of warts and secondary outcome was resolution of distant noninjected warts. Complete remission of warts was seen in 63% of *Candida* group versus 20% of cryotherapy group ($P=.001$; NNT=3). Complete resolution of distant noninjected warts was 71% with intralesional *Candida* (results not reported for cryotherapy). Side effect rates were not reported but included injection site edema, induration and flu-like symptoms with intralesional *Candida*, and blistering and dyspigmentation in the cryotherapy group. This RCT was limited by lack of reporting of inclusion/exclusion criteria, lack of blinding and allocation concealment, unclear randomization process, undefined cryotherapy dosing, and lack of long-term follow-up. EBP

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Does SSRI use increase bleeding risk in patients taking anticoagulants?

EVIDENCE-BASED ANSWER

Not clear. In patients taking any form of anticoagulation for atrial fibrillation, no significant increase was noted in clinically relevant bleeding when co-medicated with selective serotonin reuptake inhibitors (SSRIs); SOR: **B**, large randomized controlled trial. No significant difference in hemorrhage was noted between SSRIs and other antidepressants when combined with anticoagulation (SOR: **B**, large retrospective cohort study). However, hospitalized bleeding events were observed frequently among patients taking SSRI and anticoagulation (SOR: **C**, nested case–control study).

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A 2018 randomized controlled trial (RCT; n=1,474) compared bleeding risk between selective serotonin reuptake inhibitor (SSRI) users concomitantly with oral anticoagulation such as warfarin and non-vitamin K oral anticoagulants (NOACs) and non-SSRI users.[1] SSRI patients had a mean age of 75 years old and were 53% female and 91% white, whereas non-SSRI patients had a mean age of 73 years old and were 39% female and 83% white. Average $CHADS_2$ score (a tool used for estimation of stroke risk in atrial fibrillation [AF]) for both groups was 3.5, indicative of a 5.9% risk of thromboembolic event per year. Patients who took a serotonin-noradrenaline reuptake inhibitor (SNRI) without an SSRI, took both an SNRI and an SSRI in which the SNRI was started first, took trazadone without an SSRI, or took both trazadone and an SSRI in which trazadone was started first were excluded. Patients were taking an SSRI (no data regarding doses provided) for at least 14 days (n=737) and were 1:1 propensity score matched to patients not taking SSRIs (n=737) in demographics (eg, age, race) and comorbidity variables (eg, HTN, diabetes). The primary outcome was a composite of major clinically relevant bleeding events and nonmajor clinically relevant bleeding (NMCR). Major bleeding was defined as fatal outcome (death), involvement of critical anatomic site (intracranial, spinal, ocular, pericardial, articular, retroperitoneal, or intramuscular with compartment syndrome), a decrease in hemoglobin (>2 g/dL), transfusion of packed red blood cells (>2 units), and permanent disability. NMCR was defined as overt bleeding not meeting criteria for major bleeding but requiring clinical intervention, unscheduled contact with a physician, temporary interruption in treatment with study drug, pain, or impairment of daily activities. Bleeding rates were reported in events/100 patient-years. At a mean of 1.6 years of follow-up, no significant difference was noted in the rate of major/nonmajor clinically relevant bleeding between SSRI users and non-SSRI users (users, 18.57 events/100 patient-years vs nonusers, 16.84 events/100 patient-years, adjusted hazard ratio 1.16; 95% CI, 0.95–1.43).

A 2019 retrospective, nationwide cohort study (n=81,504) compared the risk of SSRI and other antidepressant co-medication with oral anticoagulations: NOACs such as apixaban versus vitamin K antagonists (VKAs) such as warfarin for bleeding.[2] Data were extracted from 13 different health insurance records in Austria from 2010 to 2015. Patients were 63% female with an average age of 76 years old. Patients were included if they had prescriptions for anticoagulation therapy in combination with SSRI or other anti-depressants or they filled an anticoagulation and anti-depressant medication from day one of the study. Hospital discharge diagnoses of gastrointestinal (GI) bleeding and cerebral hemorrhage were measured using international classification of diseases-10 codes. Differences in bleeding between NOACs and VKAs were also assessed. Significant differences were noted in bleeding risk (risk ratio [RR] 1.21; 95% CI, 1.05–1.40) and GI bleeding (RR 1.53; 95% CI, 1.28–1.84) between co-medication of SSRI with NOACs and VKAs, but no significant difference was noted in hemorrhage between SSRI versus other antidepressants. Limitations included that the study did not account for medication adherence, severity of bleeding, or population demographics and comorbidities.

A 2020 nested case–control study (n=28,704) compared risk of bleeding events between patients who were taking concomitant nonsteroidal anti-inflammatory drugs (NSAIDs) or SSRIs with NOACs versus no use.[3] Patients in the case arm had an average age of 76 years old, were 53.9% female, and had average CHA_2DS_2-VASc and HAS-BLED scores of 4.64 (4.8–7.2% stroke risk per year) and 3.48 (5.8–8.9% risk of major bleeding), respectively. The control group was quasi-identical to the case arm

(average age 76.6 years old, 53.9% female, average CHA_2DS_2-VASc and HAS-BLED scores of 4.35 and 2.85 [4.1–5.8% risk of major bleeding], respectively). All patients had AF, were prescribed an NOAC between 2013 and 2017, and had no bleeding history. Patients with a cancer diagnosis or switched from an NOAC to warfarin were excluded. Patients were placed into case groups (n=1,233): NSAIDs plus NOAC (n=556), SSRIs plus NOAC (n=95), NOAC only (n=632), NSAIDs only (n=506), SSRIs only (n=45), and NOAC plus NSAIDs with SSRIs (n=50). For each case, up to 20 controls at risk for the bleeding event were randomly selected by age, sex, episode status, and duration from diagnosis of AF to prescription of NOACs. Subanalysis of covariates included proton pump inhibitor prophylaxis, indices of comorbidities (CHA_2DS_2-VASc), and bleeding risk (HAS-BLED). Patients with concomitant NSAIDs (adjusted odds ratio [aOR] 1.41; 95% CI, 1.24–1.61) or SSRIs (aOR 1.92; 95% CI, 1.52–2.42) had significantly higher bleeding risk compared with controls (no use of either drug). SSRIs with NOAC had an increased risk for intracranial bleeding (aOR 2.69; 95% CI, 1.57–4.59) when compared with NSAIDs plus NOAC, or NOAC alone. Limitations included that medication adherence was unknown because of the study using claim data. In addition, over-the-counter medications and smoking status were not assessed. EBP

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What is the optimal duration of skin-to-skin to produce improved breastfeeding outcomes?

EVIDENCE-BASED ANSWER

The evidence is not clear on optimal duration of skin-to-skin contact (SSC) to improve breastfeeding. SSC of any duration may increase the number of patients breastfeeding at 1 to 4 months and increase the duration of breastfeeding by 60 days compared with no SSC (SOR: **B**, meta-analysis of randomized controlled trials). A threshold of at least 20 minutes of SCC may result in an increase in breastfeeding duration as compared with no SCC (SOR: **C**, low-quality cohort trial). SSC is associated with exclusive breastfeeding before initial discharge in a dose-dependent fashion (SOR: **B**, cohort trial).

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A 2016 meta-analysis analyzed data from 38 randomized controlled trials, which included 3,472 mother–infant pairs, evaluating various outcomes related to skin-to-skin contact (SSC), including differences in breastfeeding and neonatal outcomes.[1] All studies compared high duration of SSC (>60 minutes) with low duration of SSC (<60 minutes). The breastfeeding outcomes reviewed included the number of patients breastfeeding at 1 to 4 months post birth and the duration of breastfeeding in days. Compared with no SSC, the number of patients breastfeeding at 1 to 4 months was higher in both low duration of SSC (10 trials; N=724; risk ratio [RR] 1.2; 95% CI, 1.0–1.5) and high duration of SCC (5 trials; N=298; RR 1.2; 95% CI, 1.1–1.4). A statistically significant difference was not noted between the two duration groups (P=.96). In a subgroup analysis, compared with no SSC, both low duration of SSC (3 trials; N=148; mean difference [MD] 65 days; 95% CI, 26–206) and high duration of SSC (3 trials; N=116; MD 62 days; 95% CI, 29–96) showed a significant increase in the

duration of breastfeeding in days but did not show a statistically significant difference between the two duration groups ($P=.89$). A key limitation of this study was an inadequate number of trials to evaluate a dose–response effect.

A prospective cohort study examining duration of SSC on breastfeeding rates (n=1,125) evaluated data from a national survey of maternity hospital practices in Poland in January 1995 and a three-year follow-up survey performed in January 1998 to examine the effect of early SSC and duration of breastfeeding.[2] Duration of SSC was separated into three categories: lack of SSC (n=208), short contact of 1 to 19 minutes (n=845), and extensive contact of greater than 20 minutes (n=72). The breastfeeding outcomes assessed included exclusive breastfeeding in months and overall breastfeeding duration in months. The study found no significant difference in overall breastfeeding ($P=.054$) or exclusive breastfeeding ($P=.095$) between the lack of contact group and the short contact group. Exclusive breastfeeding was significantly prolonged in the extensive (>20 min) contact group compared with the lack of contact group (3.8 vs 2.5 months; $P=.013$). Overall duration of breastfeeding was also prolonged in the extensive contact group compared with the lack of contract group (9.1 vs 7.0 months; $P<.001$). Between the short contact and extensive contact groups, a statistically significant difference was noted in how long patients exclusive breastfeed favoring extensive contact (2.8 vs 3.8 months; $P<.001$), but no significant difference was noted in overall duration of breastfeeding. A key limitat.

A large 2010 prospective cohort study (n=21,842) examined the effectiveness of SSC on breastfeeding using data from 19 hospitals in San Bernardino and Riverside counties in California and included mothers from a variety of racial, ethnic, and educational backgrounds.[3] This study used data from a quality assurance program aimed to develop practices at participating hospitals that promoted maternal–infant bonding in support of infant development. Staff at participating hospitals were trained on various practices that promoted this bonding in the first three hours of life, one of which was early SSC. Duration of SSC was subdivided into four duration ranges, and the breastfeeding outcome evaluated was exclusive breastfeeding during hospital stay. Compared with no SSC (n=4,872), odds of exclusive breastfeeding was higher in all four groups: 1 to 15 minutes (n=1,068; odds ratio [OR] 1.5; 95% CI, 1.4–1,8), 16 to 30 minutes (n=1,469; OR 1.8; 95% CI, 1.6–2.1), 31 to 59 minutes (n=1,212; OR 2.6; 95% CI, 2.3–2.9), and 1 to 3 hours (n=13,126; OR 3.0; 95% CI, 2.8–3.2). When adjusted for maternal infant-feeding method intention, type of delivery, age, race/ethnicity, primary language, education, smoking status, maternal intrapartum analgesia, and hospital of birth, a multivariable analysis revealed a statistically significant dose–response in the odds for exclusive breastfeeding during hospital stay ($P<.001$ for dose–response relationship). A limitation of this study was that no long-term follow-up was done and no outcomes were evaluated after the hospital stay. EBP

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Does prediabetes increase the risk of all-cause mortality and cardiovascular disease?

EVIDENCE-BASED ANSWER

Prediabetes in the general population and in patients with history of atherosclerotic heart disease is associated with an increase in all-cause mortality when using impaired fasting glucose (100–125 mg/dL) to define prediabetes and is associated with an increase in composite cardiovascular disease when using any of the three American Diabetes Association definitions for prediabetes (SOR: **A**, systematic reviews with meta-analyses).

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In 2021, a systematic review and meta-analysis of 106 prospective studies (N=1,847,523) investigated the association of prediabetes with all-cause mortality and incident cardiovascular disease.[1] The review included studies with patients from the general population at least 18 years old with or without previous cardiovascular disease. Study patients included those diagnosed with American Diabetes Association (ADA) criteria for prediabetes defined as impaired fasting glucose of 100 to 125 mg/dL, impaired glucose tolerance (2-hour glucose of 140–199 mg/dL), or HbA1c of 5.7–6.4%. Control patients were those with normoglycemia (fasting glucose <100 mg/dL, 2-hour glucose <140 mg/dL, or HbA1c <5.7%). Primary outcomes included all-cause mortality and cardiovascular disease events, defined as the occurrence of more than one cardiovascular event. Median follow-up period was 9.6 years. Prediabetes was associated with an increase in all-cause mortality when prediabetes was defined as impaired fasting glucose or impaired glucose tolerance but not when prediabetes was defined as HbA1c 5.7–6.4%. Prediabetes was associated with an increase in cardiovascular events for all ADA definitions of prediabetes (**TABLE**). Limitations included heterogeneity in the study populations, outcome definitions, and follow-up times.

In addition to the previous study,[1] a 2020 meta-analysis of 129 prospective cohort studies and post-hoc analysis of clinical trials (N=10,069,955) also evaluated the associations between prediabetes and the risk of all-cause mortality and incident cardiovascular disease in the general population and found similar results.[2] However, unlike the systematic review above, this meta-analysis also evaluated patients with a known history of atherosclerotic cardiovascular disease. Included patients were adults (mean ages ranged from 37 to 79 years old), and studies compared outcomes for those with prediabetes versus normoglycemic patients, using the same ADA definitions as the above systematic review.[1] The

TABLE. Risk of all-cause mortality and composite cardiovascular disease events in patients with prediabetes per American Diabetes Association (ADA) criteria in the general population and in those with known atherosclerotic heart disease, compared with normoglycemic persons

General population									
	All-cause mortality				Composite cardiovascular disease events				
Definition (ADA) of prediabetes	Trials (N)	Patients (N)	HR/RR	95% CI	Trials (N)	Patients (N)	HR/RR	95% CI	Ref. No.
IFG	25	591,626	**1.1**	**1.0–1.2**	17	387,920	**1.2**	**1.1–1.3**	1
	20	7,055,874	**1.1**	**1.0–1.1**	24	1,340,313	**1.1**	**1.0–1.2**	2
IGT	25	576,026	**1.2**	**1.2–1.2**	24	253,001	**1.2**	**1.1–1.3**	1
	15	258,741	**1.3**	**1.2–1.3**	20	268,748	**1.2**	**1.1–1.3**	2
HbA1c	14	600,852	1.1	0.97–1.2	13	313,827	**1.2**	**1.0–1.3**	1
	8	321,455	1.1	0.96–1.2	11	330,435	**1.2**	**1.0–1.3**	2
With atherosclerotic heart disease									

TABLE. Risk of all-cause mortality and composite cardiovascular disease events in patients with prediabetes per American Diabetes Association (ADA) criteria in the general population and in those with known atherosclerotic heart disease, compared with normoglycemic persons *(Continued)*

General population									
All-cause mortality					Composite cardiovascular disease events				
Definition (ADA) of prediabetes	Trials (N)	Patients (N)	HR/RR	95% CI	Trials (N)	Patients (N)	HR/RR	95% CI	Ref. No.
All-cause mortality					Composite cardiovascular disease events				
IFG	5	7,640	**1.6**	**1.2–2.2**	6	11,253	**1.3**	**1.0–1.8**	2
IGT	3	4,440	1.3	0.94–1.9	6	9,478	**1.5**	**1.3–1.9**	2
HbA1c	2	2,116	2.3	0.6–9.4	4	11,093	**1.2**	**1.1–1.5**	2

Statistically significant results are in bold font. Data from systematic reviews and meta-analyses of prospective cohort studies and post-hoc analysis of clinical trials.[1,2] HbA1c=glycosylated hemoglobin of 5.7–6.4%; HR=hazard ratio (reference number 1); IFG=impaired fasting plasma glucose (100–125 mg/dL); IGT=impaired glucose tolerance (plasma glucose 140–199 mg/dL, measured 2 hours after an oral glucose tolerance test); RR=relative risk (reference number 2).

primary outcomes were all-cause mortality and composite cardiovascular events. The median follow-up time was 8.8 years, and 79 of the trials (N=1,737,739) were included in the above systematic review.[1] In the general population, prediabetes was associated with an increased risk of all-cause mortality for all definitions of prediabetes except HbA1c and was associated with an increase in composite cardiovascular disease events for all prediabetes definitions. Among patients with a history of atherosclerotic heart disease, prediabetes was associated with an increase in all-cause mortality only when using the impaired fasting glucose definition but was associated with an increase in composite cardiovascular disease events for all prediabetes definitions (**TABLE**). Limitations included significant heterogeneity in the general population group for the risk of all outcomes (I^2>50%, $P \leq .05$) except for coronary heart disease (I^2=23%, P=.24), for the different definitions of prediabetes. EBP

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Is there evidence to start colorectal cancer screening in African Americans before the standard guideline age?

EVIDENCE-BASED ANSWER

Early-onset colorectal cancer is up to 4% higher in African Americans than White Americans and 6% more likely to be in an advanced stage (SOR: **C**, retrospective cohort study). African Americans are more likely to have right-sided colon cancer than rectal cancer and with overall lower survival compared with non-African Americans with left-sided colon cancer (SOR: **C**, retrospective cohort study). If colorectal cancer is identified at an earlier stage (I–III), the disparity in survival with cancer sidedness is decreased (SOR: **C**, retrospective cohort study).

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A 2021 retrospective cohort study of 16,545 patients from a surveillance database evaluated the characteristics and cancer-specific survival between different

racial groups with early-onset colorectal cancer.[1] Patients identified as non-Hispanic Black (NHB) (n=2,553), non-Hispanic White (NHW) (n=11,320), or Hispanic (n=2,672). Those with recurrent colorectal cancer or additional primary cancers were excluded. Early-onset colorectal cancer was defined as cases diagnosed in patients younger than 50 years old. Early-onset colorectal cancer occurred more frequently in NHB than NHW (13% vs 8.7%, $P<.01$) with a higher prevalence of right-sided tumors (odds ratio 1.8; 95% CI, 1.6–1.9). When compared with NHW, NHB patients had a lower concentration of patients with stage I to III cancer (76% vs 71%, $P<.01$) but had a larger percentage of patients with advanced stage IV cancer (29% vs 24%, $P<.01$). Larger differences for five-year survival were seen between NHB compared with NHW at stage II (81% vs 91%), stage III (69% vs 80%), and stage IV (12% vs 22%); no *P* values were given for these percentages.

A 2018 retrospective cohort study of 109 patients from a single medical center examined the clinical characteristics of African Americans with early-onset colorectal cancer (younger than 50 years old).[2] Patients with recurrent colorectal cancer were excluded while patients with hereditary nonpolyposis colorectal cancer, familial adenomatous polyposis, and inflammatory bowel disease were included. Ethnicity data were based on self-report in congruence with the US Census definitions and included 75 African Americans and 34 non-African Americans. Clinical demographics, symptom presentation, and tumor location were recorded. When compared with non-African Americans, African Americans had more frequent right sided and transverse cancer (15% vs 39%, $P=.003$) and were more likely to present with weight loss (21% vs 3.0%, $P=.01$) and lower hemoglobin (10.5 vs 12.7 g/dL, $P<.001$). No difference was observed in age, sex, body mass index, cigarette smoking, or alcohol use between the two groups.

A 2019 retrospective cohort study of 26,908 patients with colorectal adenocarcinoma assessed records from the Mayo Clinic and colon registry to measure the impact of tumor location on overall survival.[3] Colorectal cancer was classified by sidedness (right or left) and location (right, left, or rectum) with transverse and rectosigmoid colon cancers excluded. Tumor characteristics were evaluated using a Kaplan–Meier survival, log-rank test, and Cox proportional hazards regression model. Overall survival since diagnosis at five, 10, 15, 25, and 35 years was estimated. When evaluating stage IV cancer, right-sided tumors had significantly less median survival time compared with left-sided tumors (77 vs 93 months, $P<.001$). No difference was observed in location when evaluating stage I to III cancer. Survival was significantly less likely in right-sided versus left-sided when restricted to patients with stage IV (hazard ratio 0.73; 95% CI, 0.67–0.80). No difference was observed in stages I to III. EBP

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Does insomnia treatment decrease the risk of delirium in hospitalized elderly patients?

EVIDENCE-BASED ANSWER

Treatment with suvorexant, melatonin, or ramelteon is associated with a decrease in incidence of delirium in hospitalized elderly patients compared with placebo, no treatment, or other sleep inducers, with a number needed to treat of about three. (SOR **A**, 2 meta-analyses of randomized controlled trials and case-controlled studies and 1 prospective, observational study with consistent findings).[3]

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This clinical question was developed as an HDA through a standardized, systematic methodology (HDA Methods, Supplemental Digital Content).

A 2020 meta-analysis of seven studies (3 randomized controlled trials, 4 retrospective case-control studies; N=402) examined the use of suvorexant for the prevention of delirium.[1] The studies enrolled patients older than 62 years old (older than 20 years old in 1 study) who were hospitalized (intensive care unit [ICU] and non-ICU) with risk factors for delirium (heterogeneously defined). Exclusion criteria generally included patients unable to take oral medications, contraindications to suvorexant (eg, strong CYP3A inhibitors), and active delirium. All studies were conducted in Japan. The studied intervention was oral suvorexant 15 or 20 mg nightly. Duration of treatment was generally 3 to 7 days, but several studies had an unclear treatment duration. Comparison groups received placebo or other sleep inducers (including zolpidem, brotizolam, trazodone, ramelteon, rilmazafone, flunitrazepam, and diazepam). The primary outcome was the incidence of delirium, diagnosed during hospitalization using a validated assessment tool. Secondary outcomes included length of hospital stay, time on a ventilator, drug-related adverse events, and mortality. Suvorexant treatment was associated significantly less delirium than control therapy (odds ratio [OR], 0.30; 95% CI, 0.15–0.42). Secondary outcomes were not significantly different among patients treated with suvorexant compared with controls. Limitations included unclear treatment durations, small sample sizes, no age exclusion criteria, randomizations methods not clearly identified, and inclusion of medications in the control groups which could potentially precipitate delirium (eg, benzodiazepines).

A 2019 meta-analysis (6 studies, N=1,155) investigated the use of melatonin or ramelteon for prevention of delirium in postoperative patients.[2] Included patients were postoperative (from procedures including cardiac surgery, hip fracture surgery, pulmonary resection, liver resection, hip and knee arthroplasty), hospitalized in both ICU and non-ICU settings. Not all studies had inclusion criteria for age, although the mean age for all the studies was at least 56 years old. Exclusion criteria were heterogeneous across studies and included severe infections, acute intracranial events, acute coronary syndromes, and patients taking several classes of psychoactive medications. The intervention was melatonin or ramelteon 2 to 8 mg given nightly for 1 to 7 days, starting on the evening before or the evening of surgery. Control groups varied between no treatment and placebo. The primary outcome was incidence of delirium, diagnosed by validated instruments. Perioperative treatment with melatonin or ramelteon was associated with a decreased incidence of delirium (OR 0.63; 95% CI, 0.46–0.87). Limitations included some studies being insufficiently powered to detect differences, heterogeneity of types of surgeries, and varying dose of medications.

A 2020 prospective observational study (n=526) investigated the effectiveness of ramelteon and suvorexant on delirium prevention.[3] Researchers enrolled patients 65 years or older, who were hospitalized because of either acute illness or elective surgery, with risk factors for delirium (dementia, mild cognitive impairment, concurrent hip fractures, severe illness, history of delirium or insomnia, delirium on the night before enrollment). Exclusion criteria comprised inability to tolerate oral medications and treatment with antipsychotic medications. Patients in the intervention group received ramelteon 8 mg or suvorexant 15 mg per day, to be taken at 7:00 PM or 9:00 PM at the patient's discretion after consultation with a psychiatrist. The comparison group did not receive either treatment. The primary outcome was incidence of delirium during the first seven days of treatment, diagnosed

by psychiatrists using the *DSM-5* criteria. Secondary outcomes included reoccurrence of delirium in patients with the diagnosis on admission. The use of suvorexant or ramelteon was associated with a decreased incidence of delirium (40% vs 66%; risk ratio 0.60; 95% CI, 0.50–0.74; number needed to treat=3.8). Given concerns about baseline group differences, researchers performed logistical regression analysis and found that the association between the intervention and decreased incidence of delirium remained (OR 0.48; 95% CI, 0.29-0.80). Of note, subgroup analysis demonstrated the incidence of delirium was lower when medications were taken at 7:00 PM compared with 9:00 PM (14% vs 53% for ramelteon and 27% vs 42% for suvorexant, CIs not provided by authors). Limitations included heterogeneity in medication administration (taken at patient's discretion). EBP

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