GEMs
GOOD EVIDENCE MATTERS

# GEMs of the Week

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## What's in this week's issue?

**Week of August 16 - 20, 2021**

### SPOTLIGHT: A Healthy Mom Means a Happy Mom!

- Heart Failure Benefits in Patients with Chronic Kidney Disease Taking SGLT-2 Inhibitors
- Are Diet Sodas a Safe Alternative to Regular Sodas? Know the Risks
- Does Time to Think about End-of-Life Care Lead to Care Consistent with Values?

# A Healthy Mom Means a Happy Mom!

**Interventions to Prevent Perinatal Depression: Evidence Report and Systematic Review for the US Preventative Services Task Force**

O'Connor E, Senger CA, Henninger ML, Coppola E, Gaynes BN. Interventions to Prevent Perinatal Depression: Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA*. 2019; 321(6):588–601. doi:10.1001/jama.2018.20865

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KEY TAKEAWAY: In pregnant and post-partum patients at increased risk of perinatal depression, counseling interventions can prevent perinatal depression while other interventions require further studies to determine effectiveness.

STUDY DESIGN: Meta-analysis of 49 RCTs and 1 non-randomized control intervention study

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Perinatal depression is common in primary care and adversely affects the health outcomes of both mother and child. While many interventions are used in clinical settings, their efficacy is not well studied. There are no guidelines for the prevention of perinatal depression.

PATIENTS: Pregnant and post-partum (<1 year) patients without a current diagnosis of depression with at least one risk factor

INTERVENTION: Varied by study

CONTROL: No treatment

OUTCOME: Depression status

Secondary Outcomes: Maternal quality of life, functioning, health outcomes; infant health outcomes; mortality rate; incidence of neglect and abuse

METHODS (BRIEF DESCRIPTION):

- Included studies: Interventions to reduce perinatal depression during pregnancy or first year post-partum; maternal or child health outcomes at least six weeks after intervention
- Depression risk factors:
  - Personal or family history of depression
  - Current depressive symptoms without a diagnosis of depression
  - Current stressors
  - Undesired pregnancy
  - Pre-gestational or gestational diabetes
  - Pregnancy-related health complications
  - History of intimate partner violence
  - History of adverse life events
  - Lack of social support
  - Mental health comorbidities
  - Socioeconomic status
- Included interventions:
  - Counseling, such as cognitive-behavioral therapy and interpersonal therapy (20 studies, N=4,107)
  - Other interventions with limited studies and participants: Physical activity; education alone; pharmacotherapy, such as Nortriptyline and Sertraline; Omega-3 Fatty Acid supplementation; health system interventions; supportive interventions; expressive writing; sleep; yoga; debriefing

INTERVENTION (# IN THE GROUP): Varied by study

COMPARISON (# IN THE GROUP): Varied by study

FOLLOW UP PERIOD: Varied by study

RESULTS:

- Counseling reduced the risk of perinatal depression by 39% compared to no intervention (17 trials, N=3,094; pooled RR 0.61; 95% CI, 0.47–0.78; $I^2$=61%).
- Alternative interventions had a low to insignificant strength of evidence due to limited research and lack of good-quality studies.

LIMITATIONS:

- Small scale studies included, which could increase small studies effect and increase risk of publication bias.
- Lack of generalized screening tools to identify patients who would most benefit from interventions.
- Lack of larger-scale trials on alternative preventative methods.
- Some interventions are not widely available in the United States.
- Not applicable to general low-risk patient populations.

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# Heart Failure Benefit in Patients with Chronic Kidney Disease Taking SGLT-2 Inhibitors

**Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease**

Bhatt DL, Szarek M, Pitt B, et al. Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease. *N Engl J Med*. 2021;384(2):129-139. doi:10.1056/NEJMoa2030186

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KEY TAKEAWAY: Patients with type II diabetes and chronic kidney disease (GFR 25-60) and at least one cardiovascular risk factor benefit from Sotagliflozin to decrease the risk of hospitalizations for heart failure (HF) and urgent visits for HF.
STUDY DESIGN: Multisite, double blind randomized trial
LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: SGLT-2 Inhibitors are becoming a prevalent medication used for diabetic management. Little research has investigated the overall effect on cardiovascular disease (stroke, myocardial infarction [MI]) and HF.

PATIENTS: Adults with type II diabetes, chronic kidney failure, and risk for cardiovascular disease
INTERVENTION: Sotagliflozin
CONTROL: Placebo
OUTCOME: Total deaths from cardiovascular causes, hospitalizations, urgent visits for HF

METHODS (BRIEF DESCRIPTION):

- 19,188 patients were screened, 10,584 were included in the study after meeting criteria for CKD (GFR 25-60) and type 2 diabetes (A1c >7%).
- Patients were split 1:1 to receive Sotagliflozin vs placebo.
- Patients were followed for a median of 16 months prior to discontinuation of trial due to funding.
- Patient demographics were similar for each group.
- Patients were monitored for cardiovascular events including deaths from cardiovascular causes, hospitalizations due to heart failure, and urgent visits for heart failure.

INTERVENTION (# IN THE GROUP): 5,292
COMPARISON (# IN THE GROUP): 5,292

FOLLOW UP PERIOD: Median of 16 months

RESULTS:

- The Sotagliflozin group experienced less cardiovascular events than the placebo group (5.6 vs 7.5 events respectively; HR 0.7; 95% CI, 0.6–0.8).
- The Sotagliflozin group experienced less hospitalizations and urgent visits for HF than the placebo group (3.5 vs 5.1 respectively; HR 0.7; 95% CI, 0.6–0.8).
- There were no significant differences in cardiovascular deaths between the two groups (HR 0.9; 95% CI, 0.7–1.1).

LIMITATIONS:

- Length of trial: Loss of funding and number of events limited ability to qualify all outcomes, therefore, the primary outcome changed during the study to preserve statistical power .
  - This may have biased the findings toward benefit of the trial drug.
- Industry funded

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# Are Diet Sodas a Safe Alternative to Regular Sodas? Know the Risks

**Association between Soft Drink Consumption and Mortality in 10 European Countries**

Mullee A, Romaguera D, Pearson-Stuttard J, et al. Association Between Soft Drink Consumption and Mortality in 10 European Countries. *JAMA Intern Med*. 2019; doi:10.1001/jamainternmed.2019.2478

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KEY TAKEAWAY: Soft drink consumption, both sugar-sweetened and artificially sweetened, is associated with higher all-cause mortality.
STUDY DESIGN: Population-based prospective cohort
LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: It is understood that sugar-sweetened soft drinks lead to poor health. It has not previously been understood whether this translated to increased mortality risk. Furthermore, it has not been demonstrated that artificially sweetened soft drinks pose the same risks as sugar-sweetened soft drinks, especially regarding all-cause mortality.

PATIENTS: Voluntary participants from 10 European countries; mean age of 50.8 years; 28.9% men and 71.1% women
INTERVENTION: Diary recordings of monthly, weekly, or daily consumption of soft drinks either sugar-sweetened or artificially sweetened
CONTROL: Low consumption of soft drinks, defined as <1 glass per month
OUTCOME: All-cause mortality associated with soft drink consumption
Secondary Outcomes: Cause-specific mortality associated with soft drink consumption including cardiovascular disease, cancer, digestive diseases, Parkinson's and Alzheimer's disease

METHODS (BRIEF DESCRIPTION):

- Participants from European Prospective Investigation into Cancer and Nutrition (EPIC). Cohort population reported overall dietary intake and specific soft drink consumption at a baseline enrollment visit, by country-specific methods including self-administered questionnaires, personal interviews, and dietary diary. Participants that reported cancer, heart disease, stroke, or diabetes at baseline; those with inconsistent dietary data; and those with missing soft drink consumptions or follow-up information were excluded.
- At follow-up, deaths of participants were determined through registries and ICD-10 codes used to classify underlying cause of death.
- Association between total soft drink consumption per day, week, and month during the study period of 16.2 years, further divided into sugar-sweetened and artificially sweetened drinks of participants and all-cause mortality was assessed.

INTERVENTION (# IN THE GROUP): 451,743
COMPARISON (# IN THE GROUP): N/A

FOLLOW UP PERIOD: Baseline enrollment visit occurred 1992–2000. Follow-up of participants occurred 2009–2013.

RESULTS:

- Compared to consumption of <1 soft drink per month, all-cause mortality was higher with:
  - Consumption of 2 or more glasses of soft drinks per day (HR 1.2; 95% CI, 1.1–1.2)
  - Sugar-sweetened soft drinks (HR 1.1; 95% CI, 1.0–1.2)
  - Artificially sweetened soft drinks (HR 1.3; 95% CI, 1.2–1.4)
- Compared to consumption of <1 soft drink per month, ischemic disease and cerebrovascular disease mortality risk was higher with:
  - Consuming 2 or more glasses per day of total soft drinks (HR 1.3; 95% CI, 1.1–1.4)
  - Artificially sweetened soft drinks (HR 1.5; 95% CI, 1.3–1.8)
  - No increase with sugar-sweetened soft drinks (HR 1.1; 95% CI, 0.95–1.3)
- Higher gastrointestinal cancer mortality risk including liver, gallbladder, pancreas, esophagus, stomach, and intestines is associated with consuming 1 or more glasses per day of total soft drinks and sugar-sweetened soft drinks (HR 1.6; 95% CI, 1.2–2.1) but not artificially sweetened soft drinks.
- Total soft drink consumption is associated with a higher risk of mortality in participants with Parkinson's disease (HR 1.6; 95% CI, 1.1–2.4).
- Colorectal cancer mortality risk was associated with total soft drink consumption (≥1 glass per day vs <1 glass per month) (HR 1.3; 95% CI, 1.1–1.5).

- Other types of cancer mortality were not associated with soft drink consumption.

LIMITATIONS:

- Inability to establish causality between frequency or volume of soft drink consumption and all-cause or disease specific mortality.
- Soft drink consumption was self-reported, with no direct statistical comparison between sugar sweetened and artificially sweetened drinks.
- Potential bias in observed association due to residual confounding.

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# Does Time to Think About End-of-Life Care Lead to Care Consistent with Values?

**Intuitive vs Deliberative Approaches to Making Decisions About Life Support: A Randomized Clinical Trial**

Rubin EB, Buehler AE, Cooney E, Gabler NB, Mante AA, Halpern SD. Intuitive vs Deliberative Approaches to Making Decisions About Life Support: A Randomized Clinical Trial. *JAMA Netw Open*. 2019; 2(1):e187851. doi:10.1001/jamanetworkopen.2018.7851

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KEY TAKEAWAY: Encouraging hospitalized patients with serious illnesses to deliberate on end-of-life decisions did not change the content or improve the quality of these decisions.
STUDY DESIGN: Single-site, randomized clinical trial
LEVEL OF EVIDENCE: STEP 3 (downgraded due to small effect size)

BRIEF BACKGROUND INFORMATION: Patients with serious illnesses or end-stage disease are expected to decide what level of medical care they wish to receive in the form of advance directives. Often, care options are presented to patients with the expectation they will make decisions about end-of-life care that align with their personal values and respond to the care team after some thought. However, there is another view that asking for an immediate decision would provide better alignment of a patient's values with what care is provided. There is previous work that finds some evidence that both methods are effective, but there are few studies that compare the two.

PATIENTS: Hospitalized patients with severe illness
INTERVENTION: Giving patients time to make end-of-life decisions
CONTROL: Asking patients to provide immediate decisions
OUTCOME: Concordance of patients' decisions regarding life support with previously polled evaluations of health states (e.g. was being on a ventilator with a longer life better than an early death without it)

METHODS (BRIEF DESCRIPTION):

- Patients >60 years old with serious cardiac, pulmonary and renal disease hospitalized in a large urban hospital consented for interviews.
- Participants in the study were given information about various end-of-life interventions like feeding tubes, endotracheal intubation, and tracheostomy.
- Participants were randomized into two groups:
  - The intuitive group was asked 5 questions regarding end-of-life interventions while given a cognitive load (asked to remember a 5 digit number to help limit deliberation).
  - The deliberative group was asked to think about the questions for 1 minute prior to answering and to explain their answers.
- After completing the questions participants were assessed for decisional uncertainty using the Decisional Conflict Scale.
- Without any cognitive load or instructions for deliberation, all participants between both groups were asked to rate physical and cognitive disability on a 5-point scale from worse than death, neither better nor worse, slightly better, somewhat better or much better than death.

INTERVENTION (# IN THE GROUP): 102
COMPARISON (# IN THE GROUP): 98 (97 used in primary analysis, one participant revoked consent after randomization)

FOLLOW UP PERIOD: N/A

RESULTS: There was no statistical difference between deliberative vs intuitive groups when it came to making value-consistent decisions regarding end of life care.

- 16% intuitive patients vs 22% deliberative patients would accept a tracheostomy though they believed requiring a breathing machine would be a fate equal to or worse than death (–6% difference; 95% CI, –26 to 14).
- 15% of intuitive patients vs 30% of deliberative patients would accept a feeding tube though they believed requiring one would be a fate equal to or worse than death (–15% difference; 95% CI, –30 to 2).
- Decisional uncertainty was low for all decisions and did not differ by group.

LIMITATIONS:

- Patient population was predominantly white, male, and married/partnered from a single center, which may affect generalizability.

- It is possible that patients who declined participation may have had vastly different preferences than those who accepted.
- It is possible patients misinterpreted scenarios explained to them by the investigating team.

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