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FPIN
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Tocolytics to Delay Preterm Birth: What Really Works?

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Tocolytics for Delaying Preterm Birth: A Network Meta-Analysis (0924)

Wilson A, Hodgetts-Morton VA, Marson EJ, et al. Tocolytics for delaying preterm birth: a network meta-analysis (0924). *Cochrane Database Syst Rev*. 2022;8(8):CD014978. Published 2022 Aug 10. doi:10.1002/14651858.CD014978.pub2

KEY TAKEAWAY: Tocolytics are effective in delaying preterm birth by 48 hours and seven days compared to placebo or no intervention.

STUDY DESIGN: Meta-analysis of 120 randomized controlled trials (RCTs) (N=13,697)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Preterm death is a leading cause of newborn death. This study aimed to identify whether the use of tocolytics can delay preterm birth to improve neonatal morbidity and mortality.

PATIENTS: Pregnant women with threatened preterm birth

INTERVENTION: Tocolytics

CONTROL: No tocolytics

PRIMARY OUTCOME: Delay in birth by 48 hours and seven days, pregnancy prolongation, and cessation due to adverse effects (AEs)

Secondary Outcome: Maternal AEs, neonatal morbidity, low birth weight, gestational age at birth

METHODS (BRIEF DESCRIPTION):

- Pregnant women ranging from 20–36 weeks gestation were included in the study.
  - 71% of studies included women with intact membranes, 6% with ruptured membranes, and 23% of studies did not specify
  - 50% were singleton pregnancies and 50% were mixed or not specified.
  - 55% of studies used tocolytics to suppress contractions and 40% for >48 hours.
- Most studies excluded multiple pregnancies and those in advanced preterm labor.
- Various study interventions were assessed which included tocolytic drugs of any dosage, duration, or regimen, other tocolytic, placebo, or no treatment.
- The primary outcomes measured the delay in birth by 48 hours or seven days, pregnancy prolongation, and cessation due to AEs.
- The secondary outcomes measured maternal AEs, neonatal morbidity, low birth weight, and gestational age at birth.
- Surface under the cumulative ranking curve (SUCRA) scale was used to rank tocolytic classes between each other, with higher percentages indicating a higher ranking.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Variable

RESULTS:

Primary Outcome –

- Tocolytics significantly delayed birth by 48 hours compared to placebo or no intervention (86 trials, N=9,853):
  - Combinations of tocolytics (SUCRA 76%; relative risk [RR] 1.2; 95% CI, 1.1–1.3)
  - Nitric oxide donors (SUCRA 74%; RR 1.2; 95% CI, 1.1–1.3)
  - Calcium channel blockers (SUCRA 72%; RR 1.2; 95% CI, 1.1–1.2)
  - Oxytocin receptor antagonists (SUCRA 78%; RR 1.2; 95% CI, 1.1–1.3)
  - COX inhibitors (SUCRA 42%; RR 1.1; 95% CI, 1.01–1.2)
  - Betamimetics (SUCRA 42; RR 1.1; 95% CI, 1.1–1.2)
- Tocolytics significantly delayed birth by seven days compared to placebo or no intervention (60 trials, N=7,143):
  - Combinations of tocolytics (SUCRA 79%; RR 1.2; 95% CI, 1.1–1.3)
  - Nitric oxide donors (SUCRA 76%; RR 1.2; 95% CI, 1.02–1.4)
  - Calcium channel blockers (SUCRA 61%; RR 1.2; 95% CI, 1.02–1.4)
  - Oxytocin receptor antagonists (SUCRA 50%; RR 1.1; 95% CI, 1.1–1.2)
  - Betamimetics (SUCRA 55%; RR 1.1; 95% CI, 1.03–1.3)

- The only tocolytics that significantly prolonged pregnancy was the following (47 trials, N=5,093):
  - Oxytocin antagonists (mean difference [MD] 9.5 days; 95% CI, 2.4–17)
  - Calcium channel blockers (MD 4.7 days; 95% CI, 0.32–9.1)
- Use of tocolytics did not cause a significant difference in maternal infection or neonatal death before 28 days.
- The tocolytics that required frequent cessation due to AE were:
  - Betamimetics (RR 14; 95% CI, 6.1–34)
  - Calcium channel blockers (RR 3.0; 95% CI, 1.2–7.1
  - Magnesium sulphate (RR 3.9; 95% CI, 1.1–14)
  - Combinations of tocolytics (RR 6.9; 95% CI, 2.1–23)

Secondary Outcome –

- Betamimetics were associated with an increase in the following:
  - Dyspnea (RR 12; 95% CI, 4.7–31)
  - Palpitations (RR 7.4; 95% CI, 3.8–14)
  - Nausea or vomiting (RR 1.9; 95% CI, 1.2–2.9)
  - Tachycardia (RR 3.0; 95% CI, 1.2–7.7)
- Nitric oxide donors were associated with an increase in the following:
  - Headaches (RR 4.2; 95% CI, 2.1–8.3)
  - Birth weight (MD 430 g; 95% CI, 224–627)
  - Gestational age at birth (MD 1.4 weeks; 95% CI, 0.4–2.3)
- Calcium channel blockers were associated with reduced:
  - Neurodevelopmental morbidity (RR 0.5; 95% CI, 0.3–0.9)
  - Respiratory morbidity (RR 0.7; 95% CI, 0.5–0.9)
- Calcium channel blockers resulted in a birthweight < 2,500 g (RR 0.5; 95% CI, 0.3–0.9)
- Calcium channel blockers resulted in a birthweight < 2,000 g (RR 0.8; 95% CI, 0.7–0.9)

LIMITATIONS:

- Pregnancies were limited to singleton gestation only.
- There was high heterogeneity among studies and data.
- There was variability in duration, dosage, and the type of tocolytics utilized.
- There was low confidence in the data utilized.

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Delicious But Dangerous: Ultra-Processed Food and GI Cancer Risk

Ultra-Processed Food Consumption and Gastrointestinal Cancer Risk: A Systematic Review and Meta-Analysis

Meine GC, Picon RV, Espírito Santo PA, Sander GB. Ultra-Processed Food Consumption and Gastrointestinal Cancer Risk: A Systematic Review and Meta-Analysis. *Am J Gastroenterol*. 2024;119(6):1056-1065. doi:10.14309/ajg.0000000000002826

KEY TAKEAWAY: Higher consumption of ultra-processed foods (UPFs) is associated with an increased risk of colorectal and non-cardia gastric cancers, highlighting the need for dietary modifications and public health interventions to help mitigate these risks.

STUDY DESIGN: Systematic review and meta-analysis of five prospective cohort studies (N=1,128,243)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to design of included studies)

BRIEF BACKGROUND INFORMATION: UPFs are industrially formulated and chemically modified for enhanced flavor, appearance, and shelf stability containing various additive and preservatives. Previous research has linked UPFs to conditions like obesity and cardiovascular diseases, and there is considerable concern about their association with gastrointestinal (GI) cancer risk.

PATIENTS: Adults consuming varying levels of ultra-processed food

INTERVENTION: Highest levels of ultra-processed food consumption

CONTROL: Lowest levels of ultra-processed food consumption

PRIMARY OUTCOME: Incidence of cancer

METHODS (BRIEF DESCRIPTION):

- Adult participants from five prospective cohort studies were included.
- Included studies assessed UPF consumption with Nova classification which categorizes foods based on the extent and type of processing they undergo.
- Foods are placed in categories 1–4, with higher numbers being more processed. GI cancers were also reported by subsite.
- Exclusion criteria included studies before 2009 when the term UPF was introduced.
- Participants were categorized into high and low consumption of NOVA 4 class of food. This was assessed by studies' dietary questionaries.
- Cancer risk was quantified using pooled hazard ratios. A Leave-one-out sensitivity analysis was done (excluding one study at a time from the overall analysis).

INTERVENTION (# IN THE GROUP): 241,201

COMPARISON (# IN THE GROUP): 223,366

FOLLOW-UP PERIOD: Mean 18 years

RESULTS:

Primary Outcome –

- High UPF consumption was associated with increased risks for certain gastrointestinal cancers:
  - Colorectal cancer (4 studies, n=415,434; hazard ratio [HR] 1.1; 95% CI, 1.03–1.2; I^2=31%)
  - Colon cancer (3 studies, n=362,945; HR 1.1; 95% CI, 1.02–1.2; I^2=0%)
  - Non-cardia gastric cancer (2 studies, n=317,566; HR 1.4; 95% CI, 1.02–2.0; I^2=0%)
- No significant associations were found for hepatocellular, esophageal, pancreatic, gastric cardia, or rectal cancers.

LIMITATIONS:

- The included studies demonstrated moderate heterogeneity, which may impact the consistency of the findings.
- There was a variation in how food consumption was measured across studies.
- Potential confounding factors were not fully addressed.

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Rethinking the Dialogue: Motivational Interviewing in Pediatric Obesity

Outcome of BMI2+: Motivational Interviewing to Reduce BMI Through Primary Care AAP PROS Practices
Resnicow K, Delacroix E, Sonneville KR, et al. Outcome of BMI2+: Motivational Interviewing to Reduce BMI Through Primary Care AAP PROS Practices. *Pediatrics*. 2024; 153(2):e2023062462

KEY TAKEAWAY: Motivational interviewing does not significantly impact body mass index (BMI) compared to usual care for pediatric patients with obesity.

STUDY DESIGN: Multicenter, nonblinded cluster randomized controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to inconsistency between studies and small sample size)

BRIEF BACKGROUND INFORMATION: Pediatric obesity in the United States continues to rise, leading to increased risk of adult obesity and associated health complications. Motivational interviewing addressing nutrition and physical activity in the pediatric population has shown positive effects in two prior studies and mixed effects in others. This study explored the effectiveness of motivational interviewing on BMI for non-adolescent children with obesity.

PATIENTS: Children with obesity

INTERVENTION: Motivational interviewing and reminder/behavioral messages

CONTROL: Usual care

PRIMARY OUTCOME: BMI

METHODS (BRIEF DESCRIPTION):

- Eligible participants were children 3–11 years old with a BMI >85th percentile who had at least one health supervision visit within the past two years.
- Exclusion criteria included diabetes, medications affecting growth or mood, severe medical conditions, sibling enrollment, or recommendation not to participate by clinician.
- Participants were sorted 3:1, with three participants in the usual care/control group for every one participant in the intervention group.
- The intervention group received in-person and telehealth motivational interviewing by a pediatrician and registered dietician, tailored text messages, and a study portal.
    - 12 providers from the nine intervention practices received two-day motivational interviewing training.
    - The intervention included four billed interview sessions by pediatricians and six free sessions by dieticians.
    - The intervention targeted behaviors related to diet, physical activity, and screen time.
- The usual care group received care by their clinicians who received training on recommendations for weight management.
- The primary outcome measured the child's BMI as a percent of the 95th percentile age and sex using mixed effects linear regression.

INTERVENTION (# IN THE GROUP): 280

COMPARISON (# IN THE GROUP): 840

FOLLOW-UP PERIOD: 24 months

RESULTS:

Primary Outcome –

- Motivational interviewing did not significantly change BMI compared to usual care (adjusted estimate 0.60; 95% CI, –1.4 to 2.6).

LIMITATIONS:

- Clinicians and registered dieticians had limited intervention abilities with the two-day course, especially since the course was optional for clinicians.
- This study was conducted during the COVID-19 pandemic, including the lockdown period, where there was reduced access to healthy foods and options for physical activity. Throughout the United States, Black and Hispanic youth gained more weight than other racial groups during the pandemic.
- Racially concordant counselors were not available for Black children.
- Intervention group participants needed to actively enroll while usual care participants were passively enrolled, increasing the risk of selection bias.

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Good Fat, Bad Fat: The Mortality Divide Between Plants and Animal Sources

Association Between Plant and Animal Protein Intake and Overall and Cause-Specific Mortality

Huang J, Liao LM, Weinstein SJ, Sinha R, Graubard BI, Albanes D. Association Between Plant and Animal Protein Intake and Overall and Cause-Specific Mortality. *JAMA Intern Med*. 2020;180(9):1173-1184. doi:10.1001/jamainternmed.2020.2790

KEY TAKEAWAY: A higher intake of animal fat slightly increases the risk of cardiovascular and overall mortality, while a higher intake of plant-based fat slightly reduces the risk of cardiovascular and overall mortality.

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: There are inconsistencies in data regarding fat intake and mortality. Older studies demonstrate benefits of lower fat intake, though newer studies have failed to corroborate this. This study aimed to examine how the intake of different dietary fats, from plants or animals, is associated with mortality.

PATIENTS: Adults

INTERVENTION: Higher quintiles of dietary fat intake

CONTROL: Lowest quintiles of dietary fat intake

PRIMARY OUTCOME: Overall mortality, cardiovascular disease (CVD) mortality

METHODS (BRIEF DESCRIPTION):

- The authors conducted a large prospective cohort study from 1995–2019, with participants from six different states and two metropolitan areas.
- Of 617,119 people enrolled in the National Institute of Health American Association of Retired Persons (NIH-AARP) Diet and Health Study, 566,398 completed the National Cancer Institute Diet History Questionnaire (DHQ), based on a previously validated 1994–1996 United States Department of Agriculture (USDA) food intake survey.
- Participants were excluded if they had pre-existing cancer, renal failure, self-reported CVD or cerebrovascular accident (CVA), completion by proxy of the questionnaire, extremely high calorie intake, and drop-outs of participants.
- The final cohort consisted of 407,531 participants, 57% of whom were female and 90% self-identified as non-Hispanic White.
- Animal fat sources quantified included red meat, white meat, eggs, fish, and dairy.
- Plant fat sources quantified included grain, nuts, beans/legumes, and vegetable oils.
- Patients were divided into quintiles from lowest to highest intake of each fat source in average daily grams
  - Quintile 1 (lowest intake) was used as a comparison group, with increasing fat intake in each subsequent quintile.
- Three statistical models were used to adjust for covariates:
  - Model 1 adjusted for age and sex only.
  - Model 2 additionally adjusted for BMI, race/ethnicity, smoking status, physical activity, education, marital status, diabetes, health status, vitamin/supplement use, total intake of protein, carbohydrates, fiber, trans fatty acids, cholesterol, and alcohol consumption.
  - Model 3 additionally adjusted for intake of food sources and dietary fat sources.
- Patient deaths and causes of death were collected using the Social Security Administration Death Master File.
- Proportional hazard ratios were adjusted in each model based upon underlying potential confounders.
- Follow-up time was from study start to date of death or end of study.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: 24 years

RESULTS:

Primary Outcome –

- Highest quintile of plant fat intake decreased overall mortality compared to the lowest quintile (absolute risk difference [ARD] −1.1; 95% CI, −1.6 to −0.64).
- Highest quintile of plant fat intake decreased CVD mortality compared to the lowest quintile (ARD −0.73; 95% CI −1.1 to −0.4).

- Highest quintile of animal fat intake slightly increased overall mortality compared to the lowest quintile (ARD 0.78; 95% CI, 0.12–1.8).
- Highest quintile of animal fat intake slightly increased CVD mortality compared to the lowest quintile (ARD 0.32; 95% CI, 0.05–1.1).
- After adjusting for all confounders, higher quintiles of plant fat intake reduced mortality compared to the lowest quintile:
  - Quintile 2 (hazard radio [HR] 0.95; 95% CI, 0.94–0.97)
  - Quintile 3 (HR 0.93; 95% CI, 0.91–0.95)
  - Quintile 4 (HR 0.91; 95% CI, 0.90–0.93)
  - Quintile 5 (HR 0.91; 95% CI, 0.89–0.93)
- After adjusting for all confounders, higher quintiles of animal fat intake slightly increased overall mortality compared to the lowest quintile:
  - Quintile 2 (HR 1.03; 95% CI, 1.01–1.1)
  - Quintile 3 (HR 1.1; 95% CI, 1.05–1.1)
  - Quintile 4 (HR 1.1; 95% CI, 1.07–1.1)
  - Quintile 5 (HR 1.2; 95% CI, 1.1–1.2)

LIMITATIONS:

- As there was a large proportion of non-Hispanic White participants in the study, results may not be generalizable to a more diverse patient population.
- Data was collected with a dietary questionnaire, which is prone to inaccuracies and recall bias.
- Outcomes are based solely on baseline dietary intake so does not account for dietary changes that subjects may have made over time.
- There is a possibility of residual or unknown confounders that were not included in the adjusted model.

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It's Not a Stretch! Yoga Can Help with Post-Surgical Anxiety After Coronary Bypass

Effects of Yoga on Anxiety, Pain, Inflammatory and Stress Biomarkers in Patients Undergoing Cardiac Surgery: A Systematic Review and Meta-Analysis

Chandrababu R, Ramesh J, Jagadeesh NS, Guo P, Reddy GG, Hayter M. Effects of yoga on anxiety, pain, inflammatory and stress biomarkers in patients undergoing cardiac surgery: A systematic review and meta-analysis. *Complement Ther Clin Pract*. 2023;53:101798. doi:10.1016/j.ctcp.2023.101798

KEY TAKEAWAY: Yoga therapy may reduce anxiety in adults who have recently undergone cardiac surgery compared to usual care, but the effects on pain, stress biomarkers, and inflammatory biomarkers remain unclear due to limited data.

STUDY DESIGN: Systematic review and meta-analysis (MA) of 10 randomized controlled trails (RCTs), three before and after intervention trials, two non-randomized controlled trials, two case studies (N=1,227)

LEVEL OF EVIDENCE: STEP 4 (downgraded due to significant heterogeneity and bias)

BRIEF BACKGROUND INFORMATION: Anxiety is commonly experienced and managed in patients after a coronary artery bypass grafting (CABG) procedure. Yoga has been studied to be safe and effective for use for a wide range of acute and chronic illnesses. This study sought to evaluate if structured yoga therapy improves patient and/or disease-oriented outcomes in the immediate post-surgical period.

PATIENTS: Adults undergoing CABG surgery

INTERVENTION: Yoga therapy

CONTROL: Usual/standard care

PRIMARY OUTCOME: Self-reported pain and anxiety, inflammatory and stress biomarkers

METHODS (BRIEF DESCRIPTION):

- PUBMED, EMBASE, CINAHL, Scopus, Cochrane CENTRAL, and Web of Science databases were searched, and 17 studies were included in the review.
- Included participants were 48–66 years old and 74% were male.
- Studies from the United States, India, United Kingdom, and China were included.
- Studies were excluded if they did not include yoga therapy as primary intervention or did not involve CABG surgery.
- Various yoga therapies were studied which included breathing, meditation or postures.
- The control was either standard or usual care.
- Self-reported pain was measured using the Visual Analog Scale-Pain. Scores range from 1–100, with higher scores indication worse pain.
- Self-reported anxiety was measured using the following:
  - Beck Anxiety Inventory: Scores range from 0–63. With higher scores indicating worse anxiety symptoms.
  - State Anxiety Inventory: Scores range from 0–120, with higher scores indicating worse anxiety symptoms.
  - Hospital Anxiety Depression Scale: Score range from 0–42, with higher scores indicating worse anxiety and/or depression symptoms.
- Biomarkers IL-6 and C-reactive protein (CRP) were measured to assess inflammation.
- Biomarkers serum cortisol, salivary cortisol, and alpha amylase were measured to assess stress.
- Seven of the 10 RCTs were assessed for bias with the Cochrane risk of bias tool, and four of the seven non-RCT's bias was assessed using the Risk of Bias in Nonrandomized studies of interventions tool.

INTERVENTION (# IN THE GROUP):

- Anxiety: 252
- Pain: 105
- Cortisol: 83
- IL-6/CRP: 10

COMPARISON (# IN THE GROUP):

- Anxiety: 245
- Pain: 75
- Cortisol: 84
- IL-6/CRP: 10

FOLLOW-UP PERIOD: Varied

RESULTS:

Primary Outcome –

- Yoga reduced anxiety compared to usual care (4 trials; standard mean difference [SMD] –1.9; 95% CI, –3.5 to –0.24; I^2>50%).

- There was no MA completed for pain outcome and not enough statistical detail was provided to comment on this outcome.
- There was no MA completed for stress and inflammatory biomarkers and not enough statistical detail was provided to comment on these outcomes.

LIMITATIONS:

- Many included studies were non-randomized controlled trials, meaning meta-analysis was not performed.
- There was significant heterogeneity between the included yoga interventions.
- Several studies assessed intervention up to 6–12 months, however long-term conclusions cannot be made based on this systemic review and meta-analysis.
- Many studies were underpowered for true statistical significance and are not generalizable.
- Only one of the four RCTs in this MA for anxiety were assessed with the Cochrane risk of Bias tool. This RCT was assessed as moderate risk of bias. There were three other RCT's that assessed anxiety but were not included in the MA.

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