GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of November 4 - 8, 2024

SPOTLIGHT:
Can SGLT2is Improve Functional Capacity and Quality of Life in Patients with Heart Failure

Can SGLT2is Improve Functional Capacity and Quality of Life in Patients with Heart Failure

SGLT2 Inhibitors, Functional Capacity, and Quality of Life in Patients with Heart Failure: A Systematic Review and Meta-Analysis

Gao M, Bhatia K, Kapoor A, et al. SGLT2 Inhibitors, Functional Capacity, and Quality of Life in Patients With Heart Failure: A Systematic Review and Meta-Analysis. *JAMA Netw Open*. 2024;7(4):e245135. Published 2024 Apr 1. doi:10.1001/jamanetworkopen.2024.5135

KEY TAKEAWAY: Sodium-glucose co-transporter 2 inhibitors (SGLT2is) in patients with heart failure (HF) improve patients' quality of life as demonstrated by exercise capacity and validated patient-reported metrics.

STUDY DESIGN: Systematic review and meta-analysis of 17 randomized placebo-controlled trials (N=23,523)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Multiple studies have demonstrated an association between SGLT2i use and a mortality benefit and reduced hospitalization in patients with heart failure. However, this data does not adequately convey the impact on patients' daily living. Increased exercise tolerance and patient-reported quality measures may provide evidence for improved quality of life.

PATIENTS: Adults diagnosed with HF

INTERVENTION: SGLT2i

CONTROL: No intervention

PRIMARY OUTCOME: Functional capacity and quality of life, 6-minute walking distance (6MWD), and Kansas City Cardiomyopathy Questionnaire-12 (KCCQ-12)

METHODS (BRIEF DESCRIPTION):

- Meta-analysis of 17 randomized placebo-controlled trials, included patients with a mean age of 69 years old, diagnosed with HF with a mean left ventricular ejection fraction of 44%.
  - Studies were selected if they investigated adults with HF and analyzed the effect of SGLT2i use on peak VO_2, 6MWD, or KCCQ-12.
- All studies used SGLT2i as the primary pharmacologic intervention:
  - Empagliflozin (9 studies)
  - Dapagliflozin (6 studies)
  - Canagliflozin (2 studies)
- Outcomes were quantifiable increases in functional capacity via peak VO_2 and 6MWD or patient-reported quality of life via the KCCQ-12.
  - Peak VO_2 was examined in four studies (n=250), 6MWD in seven studies (n=1,457), and KCCQ-12 scores across 10 studies (n=17,643).
- Average peak VO_2 values for a healthy adult range from 30–40 mL/kg/min.
- The KCCQ is scored from 0–100, with higher scores indicating improved health status among patients with heart failure.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Average follow-up ranged from 12–52 weeks

RESULTS:

Primary Outcome –

- SGLT2i treatment improved peak VO_2 compared to no intervention (4 trials, n=250; mean difference [MD] 1.6 mL/kg/min; 95% CI, 0.59–2.6; I^2=27%).
- SGLT2i treatment improved 6MWD compared to no intervention (7 trials, n=1,457; MD 13 m; 95% CI, 1.2–25; I^2=55%).
- SGLT2i treatment improved patient functional capacity and quality of life compared to no intervention.
  - KCCQ-total symptom score (10 trials, n=17,643; MD 2.3; 95% CI, 1.7–2.8; I^2=0%).
  - KCCQ-clinical summary score (9 trials, n=17,538; MD 2.1; 95% CI, 1.5–2.7; I^2=15%).
  - KCCQ-overall summary score (9 trials, n=17,538; MD 1.9; 95% CI, 1.4–2.4; I^2=0%).

LIMITATIONS:

- Data was analyzed at the study level rather than using individual patient data extracted from each study, which would have enabled standardization of outcome measurements (i.e. peak VO_2 and 6MWD).
- Moderate heterogeneity was demonstrated for studies examining 6MWD, showing the need for further study and clarification of the proposed benefits to functional capacity.

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Psychological Therapy Not the Cure for Temporomandibular Pain

Psychological Therapies for Temporomandibular Disorders (TMDs)

Penlington C, Bowes C, Taylor G, et al. Psychological therapies for temporomandibular disorders (TMDs). *Cochrane Database Syst Rev*. 2022;8(8):CD013515. Published 2022 Aug 11. doi:10.1002/14651858.CD013515.pub2

KEY TAKEAWAY: Cognitive behavioral therapy (CBT) does not improve pain intensity at treatment completion compared to standard treatment or no treatment. CBT may slightly improve pain intensity at 6–12 months follow-up compared to standard treatment or no treatment.

STUDY DESIGN: Systematic review and meta-analysis of 22 randomized control trials (N=2,001)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION:

Temporomandibular disorders are a group of medical conditions that affect the jaw and the muscles and tissues that manipulate the jaw. The disorders often are associated with intense pain and are often chronic conditions that interfere with quality of life and mood. The study assessed the effects of psychological therapies in people with TMDs lasting ≥3 months.

PATIENTS: Patients with TMDs

INTERVENTION: Psychological therapies

CONTROL: No treatment or standard care

PRIMARY OUTCOME: Pain intensity at treatment completion and pain intensity at follow-up

Secondary Outcome: Disability caused by pain, adverse events, psychological distress

METHODS (BRIEF DESCRIPTION):

- This meta-analysis and systematic review used standard Cochrane methods to decide which studies to include, with CBT being studied in a majority of studies.
- Youth and young adults >12 years old with TMDs that have lasted at least three months were included in the study.
- Individuals participated in a variety of psychological therapies, such as cognitive behavior therapy, behavior therapy, acceptance and commitment therapy, and mindfulness.
- Some studies compared these individuals with psychological interventions to those with no intervention and some studies compared the individuals to the standard care or oral appliance medication and physiotherapy.
- Overall pain intensity was measured with Characteristic Pain Intensity, Single Visual Analogue Scale, or Numerical rating scales. These scales were standardized for analysis.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: 6–12 months

RESULTS:

Primary Outcome –

- CBT or other psychological treatments did not affect pain intensity at the completion of treatment compared to:
  - Alternative treatment (5 trials, n=509; standardized mean difference [SMD] 0.03; 95% CI, –0.21 to 0.28; I^2=44%)
  - Control (6 studies, n=577; SMD –0.09; 95% CI, –0.30 to 0.12)
- CBT demonstrated a small benefit in reducing pain intensity at follow-up compared to:
  - Alternative treatment (5 studies, n=475; SMD –0.29; 95% CI, –0.50 to –0.08)
  - Control (6 studies, n=639; SMD –0.30; 95% CI, –0.51 to –0.09)

Secondary Outcome –

- CBT treatments or psychological treatments did not show any difference in disability due to pain when compared with alternative therapies.
- CBT treatments or psychological treatments did not show any difference in adverse effects when compared with standard treatment, which was only reported in one study.
- CBT treatments or psychological treatments did not show any difference in psychological distress when compared with standard treatment, which was only reported in one study.

LIMITATIONS:

- The included studies had methodological flaws and varied in treatment approaches, limiting the

reliability of the evidence for psychological therapies for TMDs.

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Are There Beneficial Adjuncts to Physiotherapy in Patellofemoral Pain?

Are Adjunct Treatments Effective in Improving Pain and Function when Added to Exercise Therapy in People with Patellofemoral Pain? A Systematic Review with Meta-Analysis and Appraisal of the Quality of Interventions

Souto LR, De Oliveira Silva D, Pazzinatto MF, Siqueira MS, Moreira RFC, Serrão FV. Are adjunct treatments effective in improving pain and function when added to exercise therapy in people with patellofemoral pain? A systematic review with meta-analysis and appraisal of the quality of interventions. *Br J Sports Med.* 2024;58(14):792-804. Published 2024 Jul 1. doi:10.1136/bjsports-2024-108145

KEY TAKEAWAY: Neuromuscular electrical stimulation (NMES) and diathermy may improve pain in patients undergoing physiotherapy for patellofemoral pain syndrome (PFPS). Other adjunct treatments do not appear to offer any benefit.

STUDY DESIGN: Systematic review and meta-analysis of 25 randomized controlled trials (RCTs) (N=1,050)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to high heterogeneity in several adjunct therapies)

BRIEF BACKGROUND INFORMATION: PFPS is a highly prevalent condition with a poor prognosis for full recovery. Exercise therapy is the mainstay for the treatment of PFPS, which is then often supplemented with other adjunct multimodal therapy modalities. This review aimed to investigate supplemental modalities specifically as an adjunct to exercise physiotherapy.

PATIENTS: Patients with PFPS

INTERVENTION: Adjunct treatment + exercise

CONTROL: Exercise alone

PRIMARY OUTCOME: Self-reported pain and function

METHODS (BRIEF DESCRIPTION):

- A literature search of seven databases in November of 2023 with no restrictions on the year of publication or language.
- Included RCTs consisted of exercise therapy compared to exercise therapy with adjunct therapies for patients specifically with PFPS.
- Exercise was defined as strength, stretching, endurance, aerobic or resistance training, and power and proprioception exercises.
- Adjunct therapies performed included:
  - NMES (6 studies, 5 pooled)
  - Monopolar diathermy (2 studies, 2 pooled)
  - Knee taping (9 studies, 8 pooled)
  - Whole body vibration (4 studies, 4 pooled)
  - Knee bracing (2 studies, 2 pooled)
  - Electromagnetic (EMG) biofeedback (2 studies, 2 pooled)
- Outcomes measured self-reported pain or function. Variable study/patient inclusion based on individual study's reported outcome measures.
- Standardized mean differences with 95% confidence intervals were utilized for data pooling.
- Revised Cochrane Risk of Bias two tool and Template for Intervention Description and Replication checklist applied to appraise the quality of literature.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Variable

RESULTS:

Primary Outcome –

- NMES + exercise slightly improved self-reported pain compared to exercise therapy alone (5 studies, n=265; standardized mean difference [SMD] –0.27; 95% CI, –0.53 to –0.02; I^2=0%).
- There was no statistically significant difference in self-reported knee function with NMES + exercise compared to exercise therapy alone (4 studies, n=154; SMD –0.44; 95% CI, –1.1 to 0.20; I^2=73%).
- Diathermy + exercise slightly improved self-reported pain compared to exercise alone (2 studies, n=140; SMD –2.6; 95% CI, –4.6 to –0.57; I^2=95%).
- There was no statistically significant difference in self-reported knee function with diathermy + exercise compared to exercise alone (2 studies, n=140; SMD –0.93; 95% CI, –2.1 to –0.26; I^2=91%).
- There was no statistically significant difference in self-reported knee pain with knee taping + exercise compared to exercise alone (8 studies, n=275; SMD 0.17; 95% CI, –0.07 to 0.41; I^2=0%).
- There was no statistically significant difference in self-reported knee function with knee taping + exercise compared to exercise alone (8 studies, n=275; SMD 0.02; 95% CI, –0.22 to 0.26; I^2=0%).

- There was no statistically significant difference in self-reported knee pain with whole body vibration + exercise compared to exercise alone (4 studies, n=144; SMD –1.1; 95% CI, –2.3 to 0.14; I^2=91%).
- There was no statistically significant difference in self-reported knee function with whole body vibration + exercise compared to exercise alone (3 studies, n=120; SMD –0.87; 95% CI, –1.8 to 0.06; I^2=83%).
- There was no statistically significant difference in self-reported knee function with a knee brace + exercise compared to exercise alone (2 studies, n=100; SMD –0.87; 95% CI, –1.8 to 0.06; I^2=89%).
- There was no statistically significant difference in self-reported knee pain with EMG biofeedback + exercise compared to exercise alone (2 studies, n=86; SMD 0.34; 95% CI, –0.08 to 0.77; I^2=0%).

LIMITATIONS:

- Low trial numbers for individual pooled analysis.
- Wide variety in patient populations.
- Heterogeneity of adjunct intervention techniques, as well as poor descriptions of them.
- Lack of placebo for some interventions.

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Does Exercise Improve Depressive Symptoms, Quality of Life, and Muscle Strength?

Effect of Aerobic, Resistance, and Combined Exercise Training on Depressive Symptoms, Quality of Life, and Muscle Strength in Healthy Older Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Mahmoudi A, Amirshaghaghi F, Aminzadeh R, Mohamadi Turkmani E. Effect of Aerobic, Resistance, and Combined Exercise Training on Depressive Symptoms, Quality of Life, and Muscle Strength in Healthy Older Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Biol Res Nurs*. 2022;24(4):541-559. doi:10.1177/10998004221104850

KEY TAKEAWAY: Aerobic and/or resistance training exercise of medium and long-term duration in adults >60 years old significantly improves depression symptoms, certain quality-of-life metrics, overall muscle strength, and body weight.

STUDY DESIGN: Systematic review and meta-analysis of 18 randomized control trials (RCTs) (N=1,354)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to high heterogeneity and small sample size)

BRIEF BACKGROUND INFORMATION: In aging populations, physical activity helps maintain overall health and cognitive functions, but depression presents an obstacle to maintaining these. Exercise has been proposed to help reduce depressive symptoms, while also improving quality of life and muscle strength. This study assesses if healthy, older adults >60 participating in exercise, including aerobic exercise, resistance training, or both then will improve depression symptoms, quality of life, and muscle strength.

PATIENTS: Elderly patients >60 years old

INTERVENTION: Aerobic, resistance, and combined exercise training

CONTROL: Baseline

PRIMARY OUTCOME: Depression symptoms

Secondary Outcome: Quality of life, muscle strength, and body composition

METHODS (BRIEF DESCRIPTION):

- Studies chosen for this meta-analysis included full-text RCTs published in English.
- Healthy, older adult men and women with or without depression and without regular exercise (<150 min per week) before study enrollment were recruited.
- The mean age of those included in the study ranged from 65–85 years old.
- 13 studies included males and females, while three only recruited females and two only recruited males
- The participants were involved in varied exercise interventions (range of 8–36 weeks):
    - Aerobic exercise (7 studies)
    - Resistance training (8 studies)
    - Combined resistance exercises and team sport exercises (1 study)
    - Isolated aerobic, resistance, or functional and combined aerobic plus resistance or functional training (2 studies)
- The duration and intensity of these exercise interventions varied widely across the RCTs.
- The studies measured depression symptoms and quality of life (in 9 studies, 13 arms) with a wide variety of scales, which were standardized for a pooled analysis.
- Strength was assessed in three studies (4 arms), using the chest press test and biceps curl test to evaluate upper strength, and the leg press test, leg extension test, and chair stand test to evaluate lower strength.

INTERVENTION (# IN THE GROUP): 795

COMPARISON (# IN THE GROUP): 559

FOLLOW-UP PERIOD: 8–36 weeks

RESULTS:

Primary Outcome –

- Exercise training improved depression symptoms compared to baseline (18 trials, n=1,354; standardized mean difference [SMD] –0.52; 95% CI, –0.76 to –0.28; I^2 =74%).
- Aerobic-only exercise improved depression symptoms compared to baseline (7 trials, n= 630; SMD –0.42; 95% CI, –0.60 to –0.24; I^2=8%).
- Resistance training only exercise improved depression symptoms compared to baseline (9 trials, n= 482; SMD –0.73; 95% CI, –1.2 to –0.25; I^2=82%).
- Combined aerobic exercise and resistance training did not improve depression symptoms compared to

baseline (2 trials, n= 242; SMD –0.20; 95% CI, –0.59 to 0.19; I^2=0%).

- Medium-term exercise interventions improved depression symptoms compared to baseline (10 trials, n= 626; SMD –0.37; 95% CI, –0.63 to –0.11; I^2=53%).
- Long-term exercise interventions improved depression symptoms compared to baseline (7 trials, n= 728; SMD –0.66; 95% CI, –1.1 to –0.24; I^2=80%).

Secondary Outcome –

- Quality of Life:
  - Exercise training improved mental health compared to baseline (3 trials, n= 143; SMD 1.4; 95% CI, 0.99–1.7).
  - Exercise training improved bodily pain compared to baseline (4 trials, n= 249; SMD –0.50; 95% CI, –0.92 to –0.08).
  - Exercise training improved physical functioning compared to baseline (5 trials, n= 348; SMD 0.34, 95% CI, 0.11–0.57).
  - Exercise training improved general health compared to baseline (4 trials, n=187; SMD 0.56; 95% CI, 0.25–0.87).
  - Exercise did not improve social functioning, vitality, and overall quality of life compared to baseline.
- Muscle Strength:
  - Exercise training improved upper body strength compared to baseline (4 trials, n= 327; SMD 4.4 kg; 95% CI, 1.9–6.9).
  - Exercise training improved lower body strength compared to baseline (4 trials, n=327; SMD 4.6 kg; 95% CI, 2.2–7.0).
- Body Composition:
  - Exercise training increased body mass compared to baseline (5 trials, n=168; mean difference [MD] 0.34 kg; 95% CI, 0.10–0.59).
  - Exercise did not improve BMI and body fat percentage compared to baseline.

LIMITATIONS:

- Heterogeneity of RCTs makes results less generalizable.
- Small sample sizes in RCTs make results less conclusive.
- Certain *p* values between comparators, or 95% confidence intervals, were not readily available.
- The best risk of a bias assessment tool for exercise-training programs is unclear: PEDro scale vs the Cochrane tool.
- Inability to blind therapists and participants, though this is inevitable
- This study was not registered with the PROSPERO registration platform as a systematic review and/or meta-analysis.
- Difficulty distinguishing impacts of exercise interventions that vary in dose, type, and frequency and amongst gender populations

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Does Meditation Reduce Blood Pressure in Patients at High Risk for Cardiovascular Events?

Meditation for the Primary and Secondary Prevention of Cardiovascular Disease

Rees K, Takeda A, Court R, Kudrna L, Hartley L, Ernst E. Meditation for the primary and secondary prevention of cardiovascular disease. *Cochrane Database Syst Rev.* 2024;2(2):CD013358. Published 2024 Feb 15. doi:10.1002/14651858.CD013358.pub2

KEY TAKEAWAY: Mindfulness-based interventions (MBI) and transcendental meditation (TM) improved systolic and diastolic blood pressure compared to inactive treatments in adults at high risk for cardiovascular disease (CVD).

STUDY DESIGN: Systematic review and meta-analysis of 81 randomized control trials (N=6,971)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to significant heterogeneity and bias)

BRIEF BACKGROUND INFORMATION: Meditation has been used for generations to reduce stress, depression, and anxiety and to improve overall quality of life. This review aimed to identify if MBI or TM are effective in reducing systolic and diastolic blood pressure.

PATIENTS: Adults at high risk for CVD

INTERVENTION: MBI or TM

CONTROL: Active comparators or non-active comparators

PRIMARY OUTCOME: CVD clinical events, systolic and diastolic blood pressure, psychological stress, and adverse events

Secondary Outcome: Individual CVD risk factors, quality of life, and self-efficacy

METHODS (BRIEF DESCRIPTION):

- Populations included patients ≥18 years old, who were overweight or obese, smokers, had type 2 diabetes (T2DM) diabetes or prediabetes and hypertension, stroke survivors, had a known history of CVD, or who were at high risk of CVD.
- Studies compared the effects of MBIs and TM for the reduction of cardiovascular risk over a minimum of 12 weeks with up to five-year follow-up.
- MBI included multiple modalities, and active comparators included weight management, dietary interventions, smoking cessation, and more.
- TM included a standard TM protocol, conscious resting meditation, or mantra-based meditation.
- Non-active comparators included treatment, no treatment, or waitlist as well as non-MBI and TM interventions.
- Outcomes were recorded as a reduction in both systolic and diastolic blood pressure and improvements in anxiety, depression, perceived stress, well-being, and CVD events.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Varied (12 months to 5 years)

RESULTS:

Primary Outcome –

- Mindfulness-based interventions improved the following compared to other active comparators.
  - Perceived stress (6 trials, n=357; standard mean difference [SMD] –0.24; 95% CI, –0.45 to –0.03; I^2=0%)
- Mindfulness-based interventions did not affect the following compared to other active comparators.
  - Systolic blood pressure (6 trials, n=388; SMD –6.1 mmHg; 95% CI, –13 to 0.63; I^2=88%)
  - Diastolic blood pressure (6 trials, n=388; SMD –5.2 mmHg; 95% CI, –10 to 0.29; I^2=91%)
  - Anxiety (9 trials, n=438; SMD –0.06; 95% CI, –0.25 to 0.13; I^2=0%)
  - Depression (11 trials, n=595; SMD 0.08; 95% CI, –0.08 to 0.24; I^2=0%)
  - Well-being (1 trial, n=63; SMD –0.18; 95% CI, –0.67 to 0.32; I^2= not applicable)
- Mindfulness-based interventions improved the following compared to inactive comparators.
  - Systolic blood pressure (9 trials, n=388; SMD –6.6 mmHg; 95% CI, –13 to –0.10; I^2=87%)
  - Diastolic blood pressure (9 trials, n=379; SMD –3.4 mmHg; 95% CI, –5.9 to –0.85; I^2=61%)
  - Anxiety (9 trials, n=533; SMD –0.78; 95% CI, –1.1 to –0.47; I^2=61%)
  - Depression (15 trials, n=912; SMD –0.66; 95% CI, –0.91 to –0.41; I^2=67%)
  - Perceived stress (11 trials, n=708; SMD –0.59; 95% CI, –0.89 to –0.29; I^2=70%)

- Well-being (2 trials, n=198; SMD 0.50; 95% CI, 0.09–0.91; I^2=47%)

- Transcendental meditation improved the following compared to other active comparators.
  - Systolic blood pressure (9 trials, n=774; SMD –2.3; 95% CI, –4.0 to –0.68; I^2=2%)
- Transcendental meditation did not affect the following compared to other active comparators.
  - Diastolic blood pressure (9 trials, n=774; SMD –1.2; 95% CI, –2.9 to 0.55; I^2=53%)
  - Anxiety (3 trials, n=200; SMD 0.06; 95% CI, –0.22 to 0.33; I^2=0%)
  - Depression (5 trials, n=421; SMD –0.12; 95% CI, –0.31 to 0.07; I^2=0%)
  - Perceived stress (3 trials, n=194; SMD 0.04; 95% CI, –0.49 to 0.57; I^2=70%)
- Transcendental meditation improved the following compared to inactive comparators.
  - Systolic blood pressure (2 trials, n=139; SMD –6.3; 95% CI, –9.9 to –2.8; I^2=0%)
  - Diastolic blood pressure (2 trials, n=139; SMD –5.1; 95% CI, –9.1 to –1.2; I^2=18%)

Secondary Outcome –

- Mindfulness-based interventions did not affect the following compared to other active comparators:
  - Total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, hemoglobin A1C (HbA1c), body mass index (BMI), smoking cessation, quality of life, and self-efficacy
- Mindfulness-based interventions reduced fasting blood glucose (2 trials, n=200; mean difference [MD] –0.41 mml/L; 95% CI, –0.56 to –0.25; I^2=0%).

LIMITATIONS:

- There was high heterogenicity among studies which resulted in inconsistent results.
- Some studies did show improvement in both systolic and diastolic blood pressures, other studies showed little or no difference, especially as the studies continued.
- There was a high risk for bias.

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COVID-19 Vaccination in Pregnant Individuals Reveals No Increased Adverse Effects

Neonatal Outcomes After COVID-19 Vaccination in Pregnancy

Norman M, Magnus MC, Söderling J, et al. Neonatal Outcomes After COVID-19 Vaccination in Pregnancy. *JAMA*. 2024;331(5):396-407. doi:10.1001/jama.2023.26945

KEY TAKEAWAY: Vaccination of pregnant individuals with mRNA COVID-19 vaccines is not associated with increased risks of neonatal adverse events in their infants; in fact, vaccination is associated with lower odds of several adverse neonatal outcomes including neonatal mortality.

STUDY DESIGN: Population-based cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: The rates of COVID-19 vaccinations during pregnancy were reduced due to concerns about adverse effects on the fetus and neonate. The study aimed to investigate the safety profile of the mRNA COVID-19 vaccination on the fetus and neonate.

PATIENTS: Liveborn infants

INTERVENTION: In-utero exposure to any COVID-19 mRNA vaccine

CONTROL: No in-utero exposure to any COVID-19 mRNA vaccine

PRIMARY OUTCOME: Broad range of neonatal outcomes

METHODS (BRIEF DESCRIPTION):

- Pregnant individuals were enrolled from national registries in Sweden and Norway. Outcomes for their liveborn infants were prospectively collected.
- The majority of vaccinated pregnant individuals were between 30–34 years old, nulliparous, and had a 12th-grade or higher education.
- Vaccination during pregnancy was defined as any time between conception and delivery.
- Liveborn infants at 22+ weeks gestational age were evaluated for a broad range of neonatal outcomes.
  - No single primary outcome was predefined.
  - Outcomes included disorders of bleeding/thrombosis, infection, as well as central nervous system, circulatory, respiratory, and gastrointestinal disorders.
- All outcomes were assessed for at least the first four weeks of life.
- The statistical analysis was conducted separately for Sweden and Norway and subsequently meta-analyzed.
  - The I^2 statistic was calculated to estimate the heterogeneity between the two countries.
  - *P*<.05 or 95% CIs not including one considered statistically significant.

INTERVENTION (# IN THE GROUP): 94,303

COMPARISON (# IN THE GROUP): 102,167

FOLLOW-UP PERIOD: First four weeks of life or longer if extended hospitalization

RESULTS:

Primary Outcome –

- Infants with in-utero exposure to a COVID-19 mRNA vaccine compared to those without exposure were less likely to have:
  - Preterm delivery (5.8% vs 6.5%; *P*<.001)
  - Small for gestational age (8.8 vs 10.3%; *P*<.001)
  - Apgar score <7 (1.6% vs 1.8%; *P*<.001)
  - Apgar score <4 (0.26% vs 0.34%; *P*<.001)
  - Neonatal nontraumatic intracranial hemorrhage (adjusted odds ratio [aOR] 0.78; 95% CI, 0.61–0.99)
  - Hypoxic-ischemic encephalopathy (aOR 0.73; 95% CI, 0.55–0.96)
  - Neonatal mortality (aOR 0.68; 95% CI, 0.50–0.91)

LIMITATIONS:

- Inadequate power to identify group differences in rare outcomes.
- Misclassification of some register data cannot be excluded, although the data sources are valid.
- No information was available on lifestyle factors, breastfeeding rates, or outcomes beyond the neonatal period.
- Study populations were comprised of residents of Sweden and Norway, limiting generalizability.

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The (Non)Cutting Edge: No-Biopsy Diagnosis for Celiac Disease

Accuracy of the No-Biopsy Approach for the Diagnosis of Celiac Disease in Adults: A Systematic Review and Meta-Analysis

Shiha MG, Nandi N, Raju SA, et al. Accuracy of the No-Biopsy Approach for the Diagnosis of Celiac Disease in Adults: A Systematic Review and Meta-Analysis. *Gastroenterology.* 2024;166(4):620-630. doi:10.1053/j.gastro.2023.12.023

KEY TAKEAWAY: IgA-tTG levels >10xULN result in few false positives but a moderate number of false negatives when diagnosing celiac disease in patients with moderate to high pretest probability compared to the gold standard.

STUDY DESIGN: Systematic review and meta-analysis of 18 retrospective and prospective cohort studies (N=12,103)

LEVEL OF EVIDENCE: STEP 3 (downgraded due to the design of included studies)

BRIEF BACKGROUND INFORMATION: Villous atrophy, crypt hyperplasia, and increased intraepithelial lymphocytic infiltration identified by histology is the mainstay for diagnosing celiac disease. However, diagnostic endoscopy is invasive and can be technically difficult and cause morbidity from complications of the procedure itself or poor fitness for undergoing the procedure. Positive serological testing for immunoglobulin A autoantibodies for tissue transglutaminase is known to be supportive of a diagnosis of celiac disease. This study aimed to investigate whether the diagnosis of celiac disease can be confidently made via serology, which is less invasive than diagnostic endoscopy, thus contributing to good diagnostic stewardship without compromising appropriate patient care.

PATIENTS: Patients with suspected celiac disease

INTERVENTION: IgA-tTG levels

CONTROL: Gold-standard diagnostic endoscopy

PRIMARY OUTCOME: Diagnostic accuracy

METHODS (BRIEF DESCRIPTION):

- Databases were searched for full-text studies between 1998–2023 in which patient populations were ≥16 years old, IgA-tTG cutoff levels were ≥10 times the upper limit of normal, and celiac disease was defined histologically as having a Marsh score of stage ≥2.
- All studies occurred in secondary or tertiary care settings.
- Patients with known celiac disease or those following a gluten-free diet were excluded.
- These studies were then screened for potential bias based largely on whether they reported consecutive or random sampling, details about the IgA-tTG assay, and timing in between biopsy and serological results.

INTERVENTION (# IN THE GROUP): 12,103

COMPARISON (# IN THE GROUP): Not applicable

FOLLOW-UP PERIOD: Not applicable

RESULTS:

Primary Outcome –

- IgA-tTG >10xULN results in a moderate number of false negatives (18 trials, n=12,103; sensitivity 51%; 95% CI, 42–60).
- IgA-tTG > 10xULN resulted in a minimal number of false positives when diagnosing celiac disease compared to the gold standard (18 trials, n=12,103; specificity 100%; 95% CI, 98–100).

LIMITATIONS:

- All studies were conducted in secondary and tertiary care centers, meaning the statistical validity may be compromised in a primary care setting.
- Additionally, the applicability of this data in primary care settings is limited since the more robust PPVs apply to populations with significant IBS and positive family histories of celiac disease.
- Most included studies were conducted in Europe, which has the highest global prevalence of celiac disease.
- Pathology methods in the 18 studies were not discussed, nor was consensus resolution of discordant histologic diagnosis not discussed. There can be considerable interobserver variability, and we do not know if the studies included accounted for this.

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How the Timing and Type of Smartphone Use Can Affect Sleep Onset and Quality in Adolescents

Daily Links Between Objective Smartphone Use and Sleep Among Adolescents

Burnell K, Garrett SL, Nelson BW, Prinstein MJ, Telzer EH. Daily links between objective smartphone use and sleep among adolescents. *J Adolesc.* 2024;96(6):1171-1181. doi:10.1002/jad.12326

KEY TAKEAWAY: Increased screen time, nighttime phone pickups, and nighttime notifications may be associated with later sleep onset in adolescents.

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Increased digital technology usage is linked to poorer sleep. Adolescents are thought to be particularly vulnerable to this influence. Historically, research in this area has lacked objective evidence, largely depending on cross-sectional and self-reported data. This study used objective measures to evaluate the association between screen time and its effect on sleep in the adolescent population.

PATIENTS: Ethnically diverse US adolescents

INTERVENTION: More screen time

CONTROL: Less screen time

PRIMARY OUTCOME: Sleep quality and sleep onset

METHODS (BRIEF DESCRIPTION):

- 71 ethnically diverse adolescents from the southeastern United States, 15–18 years old, were recruited from a longitudinal study examining digital technology use in adolescents in 2021.
- From an initial sample size of 103 adolescents, individuals were excluded based on Android usage, not completing the 14-day ecological momentary assessment (EMA) period, or iOS usage without available smartphone use data.
- Smartphone use was measured through participants providing screenshots once per day of the iOS Screen Time app which detailed screen time, pickups, and notifications.
- This study reported both between-person associations and within-person associations.
- Sleep onset and sleep quality were measured using self-reporting and Fitbit data.
- Subjective sleep quality was scored using a scale of 1–4 with a score of four being worse sleep quality.
- Subjective sleep onset was scored using a scale of 1–9 with a score of nine being the latest sleep onset.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: None

RESULTS:

Primary Outcome –

- Within-person associations:
  - Later self-reported sleep onset was associated with:
    - More total screen time (0.002; 95% CI, 0.00–0.003)
    - More nighttime screen time (0.006; 95% CI, 0.005–0.007)
    - More nighttime phone pick-ups (0.02; 95% CI, 0.01–0.02)
    - More nighttime notifications (0.01; 95% CI, 0.002–0.01)
  - Self-reported sleep onset was not associated with daytime screentime, pickups, and notifications or total pickups and notifications.
  - Self-reported sleep quality was not associated with nighttime pickups, screen time, or notifications; daytime screen time, pickups, and notifications; or total screen time, pickups, and notifications.
  - Later Fitbit-measured sleep onset was associated with:
    - More nighttime screen time (0.41; 95% CI, 0.26–0.27)
    - More nighttime phone pickups (1.3; 95% CI, 0.50–2.2)
  - Later Fitbit-measured sleep onset was not associated with nighttime notifications, daytime screentime, pickups, and notifications or total screentime, pickups, and notifications.
  - Worse Fitbit-measured sleep quality was not associated with nighttime screentime, pickups, or notifications; daytime screentime, pickups, and notifications; or total screentime, pickups, and notifications.
- There were no associations in the between-person analysis.

LIMITATIONS:

- Study participants provided screenshots that may have affected usage patterns.
- Objective data relied on Apple algorithms which are of questionable reliability.
- There is an unknown impact of notification type whether visual or audible.
- Fitbit devices are limited in the sleep information they provide and are less useful than gold-standard polysomnography.

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Do Dietary and Exercise Changes Impact Knee Osteoarthritis?

Alternative Models to Support Weight Loss in Chronic Musculoskeletal Conditions: Effectiveness of a Physiotherapist-Delivered Intensive Diet Programme for Knee Osteoarthritis, the POWER Randomized Controlled Trial

Allison K, Jones S, Hinman RS, et al. Alternative models to support weight loss in chronic musculoskeletal conditions: effectiveness of a physiotherapist-delivered intensive diet programme for knee osteoarthritis, the POWER randomised controlled trial. *Br J Sports Med.* 2024;58(10):538-547. Published 2024 May 2. doi:10.1136/bjsports-2023-107793

KEY TAKEAWAY: Incorporating a very low-energy diet (VLED) in addition to exercise may help patients with osteoarthritis (OA) lose weight and subsequently improve symptoms of osteoarthritis.

STUDY DESIGN: Randomized controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size limiting generalizability)

BRIEF BACKGROUND INFORMATION: Being overweight or obese can increase the risk for the development of knee osteoarthritis. Knee osteoarthritis is reported to be a common cause of debilitating pain and disability. This study aimed to expand on the dietary recommendations for weight loss in the setting of knee osteoarthritis with goals for symptomatic improvement.

PATIENTS: Overweight adults with osteoarthritis

INTERVENTION: VLED + exercise

CONTROL: Exercise alone

PRIMARY OUTCOME: Body weight

Secondary Outcome: BMI, waist circumference, waist-to-hip ratio, self-reported pain, improvement in knee problems, physical function and performance examinations, pain, function, quality of life, physical activity, performance, or weight self-stigma

METHODS (BRIEF DESCRIPTION):

- Adults ≥45 years old with a diagnosis of OA based on NIH and Care Excellence clinical OA criteria and BMI ≥27 were included.
- Patients were randomized to one of the following groups:
  - VLED + exercise
    - Six consultations with the first one being 75-minutes (30 minutes for exercise and 45 for diet) and subsequent ones 45-minutes (30 for diet and 15 minutes for exercise)
  - Exercise alone
    - Six consultations with the first one being 30-minutes and subsequent ones 20-minutes; 5–6 strengthening exercises assigned for three days/week
- Treatment was provided by physiotherapists in both the intervention and control groups.
  - Physiotherapists and participants were not blinded during this trial.
- Participants weighed at the start of the study and the end (6 months later) using the same scale, bare feet, and light clothing.
- A positive result favors VLED + exercise when results differed between groups.

INTERVENTION (# IN THE GROUP): 42

COMPARISON (# IN THE GROUP): 46

FOLLOW-UP PERIOD: Six months

RESULTS:

Primary Outcome –

- VLED + exercise reduced the percent of body weight lost more than exercise alone at six months (mean difference [MD] 7.2%; 95% CI, 5.1–9.3).

Secondary Outcome –

- VLED + exercise reduced BMI more than exercise alone (MD 2.4 kg/m^2; 95% CI, 1.7–3.0).
- VLED + exercise reduced waist circumference compared to exercise alone (MD 5.8 cm; 95% CI, 2.9–8.7).
- VLED + exercise increased the incidence of 5% body weight loss more than exercise alone (risk difference [RD] 0.6; 95% CI, 0.5–0.8).
- VLED and exercise increased the incidence of 10% body weight loss more than exercise alone (RD 0.4; 95% CI, 0.2–0.5).
- There were no significant differences in waist-to-hip ratio, improvement in knee problems, pain, function, quality of life, physical activity, performance, or weight self-stigma between the two groups.

LIMITATIONS:

- A small sample size (n=88) limits the ability to generalize the results as the study is underpowered.
- Due to the nature of the intervention being a very low-energy diet, it was not possible to blind the participants or the physiotherapists.
- The follow-up period was only six months post-intervention initiation. There was no follow-up after these dates to monitor for continued weight loss.

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