GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of June 6 - 10, 2022

SPOTLIGHT: Lack of Exercise Associated with Increased Risk of Severe COVID-19 Outcomes

- Is Pulsed Low-Intensity Ultrasound an Effective Treatment Modality for Knee Osteoarthritis?
- Colchicine Decreases Future Cardiovascular Events in Patients with Chronic Coronary Disease
- Does Low-Dose Aspirin Prevent Preeclampsia for All?

Lack of Exercise Associated with Increased Risk of Severe COVD-19 Outcomes

Physical inactivity is associated with a higher risk for severe COVID-19 outcomes: a study in 48 440 adult patients

Sallis R, Young DR, Tartof SY, et al. Physical inactivity is associated with a higher risk for severe COVID-19 outcomes: a study in 48 440 adult patients. *Br J Sports Med*. 2021; 55(19):1099–1105. doi:10.1136/bjsports-2021-104080

KEY TAKEAWAY: Physical inactivity is a strong, modifiable risk factor for severe COVID-19 outcomes.
STUDY DESIGN: Retrospective cohort study
LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: The US Centers for Disease Control and Prevention (CDC) has identified risk factors for severe COVID-19 outcomes including age, BMI, and various underlying medical conditions. However, there has been no data on the impact of physical activity on COVID-19 disease outcomes.

PATIENTS: Adults with COVID-19 diagnosis
INTERVENTION: Consistent physical inactivity
CONTROL: Inconsistent or consistent physical activity
OUTCOME: Hospitalization, ICU admission, or death due to COVID-19

METHODS (BRIEF DESCRIPTION):

- Conducted at Kaiser Permanente Southern California (KPSC), an integrated health care system serving more than four million members.
- Members 18 years old and older who tested positive for COVID-19 between January 1, 2020 and October, 21 2020 were included.
- Exercise habits were assessed by "Exercise Vital Sign" (EVS) in the electronic medical record (EMR), which is self-reported minutes of moderate to strenuous exercise per week, categorized into three levels:
  - Consistently Inactive: EVS 0–10 min/week at all assessments
  - Some activity: EVS 11–149 min/week or those with variability in their EVS measures
  - Consistently meeting US Physical Activity guidelines: EVS> 150 min/week at all assessments
- Included patients had to have three or more recorded EVS measurements in the two years prior to March 2020.
- Patient outcomes in terms of hospitalization, ICU admission, and death following COVID-19 diagnosis were assessed via the EMR.
- Statistical analysis used multivariable logistic regression to estimate the effect of physical inactivity on COVID-19 outcomes.

INTERVENTION (# IN THE GROUP):

- 6,984 consistently inactive

COMPARISON (# IN THE GROUP):

- 3,118 consistently active
- 38,338 inconsistently active

FOLLOW UP PERIOD: Unclear

RESULTS:
Consistent physical inactivity was independently associated with increased risk of severe COVID-19 outcomes, compared to those who were consistently active.

- Hospitalization: OR 2.3 (95% CI, 1.8–2.8)
- ICU admission: OR 1.7 (95% CI, 1.2–2.5)
- Death: OR 2.5 (95% CI, 1.3–4.6)

LIMITATIONS:

- Physical activity was self-reported.
- Observational study design precludes ability to infer causality.
- Duration of follow-up for outcomes was unclear.
- Outcomes may have been missed if care was received outside the KPSC system; similarly, COVID-19 diagnoses may have been missed if testing occurred outside the KPSC system.
- Population of KP Southern California may not be fully representative of the general population.

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Is Pulsed Low-Intensity Ultrasound an Effective Treatment Modality for Knee Osteoarthritis?

Effect of Pulsed Low-Intensity Ultrasonography on Symptom Relief and Tibiofemoral Articular Cartilage Thickness Among Veterans Affairs Enrollees with Knee Osteoarthritis: A Randomized Clinical Trial

Sawitzke AD, Jackson CG, Carlson K, et al. Effect of Pulsed Low-Intensity Ultrasonography on Symptom Relief and Tibiofemoral Articular Cartilage Thickness Among Veterans Affairs Enrollees with Knee Osteoarthritis: A Randomized Clinical Trial. *JAMA Netw Open*. 2022;5(3):e220632. doi:10.1001/jamanetworkopen.2022.0632

KEY TAKEAWAY: Pulsed low-intensity ultrasound is not an effective treatment modality for symptomatic relief or cartilage loss in knee osteoarthritis.

STUDY DESIGN: Phase 2A, sham-controlled, parallel, double-blind randomized clinical trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Osteoarthritis (OA) commonly causes joint pain and disability in older adults. Around 30% of people 45 years old and older have some radiographic evidence of this disease. Pulsed low-intensity ultrasound (PLIUS) has been used for fracture healing in the past, and animal trials suggest that it may help with cartilage growth.

PATIENTS: Veterans with symptoms of knee osteoarthritis for at least six months and radiographic evidence of osteoarthritis

INTERVENTION: Pulsed low-intensity ultrasound

CONTROL: Sham ultrasound

OUTCOME: Symptom improvement, cartilage preservation

METHODS (BRIEF DESCRIPTION):

- Patients were veterans who were 45 years old and older from San Diego and Salt Lake City.
- Patients had symptoms of knee osteoarthritis for six months or more and radiographic evidence of OA.
- Randomly assigned to PLIUS treatment or sham treatment performed for 20 min daily for 48 weeks total. Treatments were self-administered.
- Evaluation done initially and periodically until 48 weeks.
- Used pain, function, and patient global assessment to measure symptomatic response to treatment.
    - Symptom therapeutic response based upon at least 50% improvement in pain and function on the Outcome Measures in Rheumatology Clinical Trials Osteoarthritis Research Society International Response Rate.
- Used MRI to measure tibiofemoral joint cartilage thickness at baseline and at 48 weeks.

INTERVENTION (# IN THE GROUP): 67

COMPARISON (# IN THE GROUP): 65

FOLLOW UP PERIOD: 48 weeks

RESULTS:

- There was no statistically significant difference in therapeutic PLIUS vs sham treatment on knee osteoporosis symptoms (70% response vs 67% response, respectively; *P*=.84).
- There was no clinically or statistically significant difference in therapeutic PLIUS vs sham treatment on tibiofemoral joint cartilage thickness (74 µm vs 42 µm, respectively; *P*=.44).

LIMITATIONS:

- Participants were all recruited from the VA and cannot represent the general OA population.
- Subgroup analysis of men and women was not done so there can be no differentiation of results between men and women in this study.
- PLIUS parameters for this study were based on successful parameters in fracture healing. These may not be ideal parameters for cartilage repair.

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Colchicine Decreases Future Cardiovascular Events in Patients with Chronic Coronary Disease

Colchicine in Patients with Chronic Coronary Disease

Nidorf SM, Fiolet ATL, Mosterd A, et al. Colchicine in Patients with Chronic Coronary Disease. *N Engl J Med*. 2020; 383(19):1838–1847. doi:10.1056/NEJMoa2021372

KEY TAKEAWAY: 0.5 mg of colchicine daily for six months reduces cardiovascular events in patients with chronic coronary disease.

STUDY DESIGN: Multisite, double-blind, randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: A prior double-blind, randomized control trial (COLOCOT) had shown colchicine was effective in preventing future cardiovascular events among patients who recently suffered a myocardial infarction within the last 30 days. The purpose of this study (LoDoCo 2) is to confirm these results via a multicenter, investigator driven, double-blind, randomized controlled trial.

PATIENTS: Patients diagnosed with coronary atherosclerosis

INTERVENTION: 0.5 mg of colchicine daily

CONTROL: Placebo

OUTCOME: Composite of cardiovascular death, spontaneous (nonprocedural) myocardial infarction, ischemic stroke, and ischemia-driven coronary revascularization

Secondary Outcomes: Composite of cardiovascular death, spontaneous myocardial infarction, ischemic stroke, ischemia-driven coronary revascularization, death from any cause

METHODS (BRIEF DESCRIPTION):

- 6,528 patients between 35–82 years old diagnosed with coronary atherosclerosis, with at least six months of clinical stability were enrolled in the open-label, run-in phase.
  - 1,006 (15%) of them did not complete the study.
- 2,762 patients were randomized to colchicine and 2,760 received placebo.
- Both groups received a one-month colchicine run-in phase.
- Both groups received follow-up assessments at six-month intervals for a trial length of one year.
- Hazard ratios and confidence intervals were calculated using intention-to-treat analysis.

INTERVENTION (# IN THE GROUP): 2,762

COMPARISON (# IN THE GROUP): 2,760

FOLLOW UP PERIOD: 1 year

RESULTS:

- Colchicine treatment reduced the risk for the primary composite outcome compared to placebo (6.8% vs 9.6%, respectively; Hazard Ratio [HR] 0.69; 95% CI, 0.57–0.83; number needed to treat [NNT] = 91).
- Colchicine treatment reduced the risk for the secondary composite outcome compared to placebo (4.2% vs 5.7%, respectively; HR 0.72; 95% CI, 0.57–0.92; NNT = 167).
- Colchicine treatment was associated with higher non-cardiovascular death compared to placebo (HR 1.5; 95% CI, 0.99–2.3; NNT = 500 for 1 year to cause on additional non-cardiovascular death).

LIMITATIONS:

- Lack of generalizability to general population, 15% of the patients in the study were women and race/ethnicity demographics were not provided.
- Study was funded by multiple governmental and foundational grants. Multiple authors received a variety of incentives from pharmaceutical companies that do not manufacture colchicine.

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Does Low-Dose Aspirin Prevent Preeclampsia for All?

Low-Dose Aspirin for Preeclampsia Prevention: Efficacy by Ethnicity and Race

Tolcher MC, Sangi-Haghpeykar H, Mendez-Figueroa H, Aagaard KM. Low-dose aspirin for preeclampsia prevention: efficacy by ethnicity and race. *Am J Obstet Gynecol MFM*. 2020; 2(4):100184. doi:10.1016/j.ajogmf.2020.100184

KEY TAKEAWAY: Low-dose aspirin reduces preeclampsia risk in low-risk non-Hispanic White women, but not low-risk Hispanic women or non-Hispanic Black women compared to placebo. Low-dose aspirin was not observed to reduce preeclampsia risk in high-risk women in any of the racial/ethnic groups. However, this study did not account for systemic racism or genetic factors in its analysis.

STUDY DESIGN: A secondary analysis of two RCTs

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Preeclampsia is a preventable and prevalent pregnancy disorder that has important public health consequences for both mother and infant. Studies have shown that low-dose aspirin reduces risk for women at a high-risk of preeclampsia. When stratifying for race/ethnicity, previous studies reported the number of Latinx women experiencing recurrent preeclampsia is lower with aspirin, but higher in non-Hispanic Black women. There is a need to investigate the efficacy of low-dose aspirin in both high and low risk groups of varying race/ethnicity.

PATIENTS: Women at low or high risk for preeclampsia

INTERVENTION: 60 mg ASA PO daily

CONTROL: Placebo

OUTCOME: Preeclampsia occurrence by race/ethnicity

Secondary Outcomes: Placental abruption, SMA, stillbirth, neonatal death, gestational age at delivery & preterm delivery

METHODS (BRIEF DESCRIPTION):

- Secondary analysis of 2 randomized controlled trials previously performed by the Maternal-Fetal Medicine Units (MFMU) Network; the Low-Risk Aspirin (LRA) study and the High-Risk Aspirin (HRA) study.
  - Normotensive, nulliparous women without risk factors for preeclampsia were included in the LRA study.
  - Women with pre-gestational insulin-treated diabetes mellitus, chronic hypertension, multiparous or nulliparous, or a history of preeclampsia were included in the HRA study.
- Participants in both studies were randomized to 60 mg ASA daily or a placebo starting at 13-26 weeks gestation through delivery.
  - Study outcomes measured by multivariate analysis.
    - Adjustments were made for compliance of tablets taken (greater than or equal to tablets taken) as well as gestational age at time of randomization.

INTERVENTION (# IN THE GROUP):

- Low-risk study: 1,018
- High-risk study: 2,539

COMPARISON (# IN THE GROUP): 1,564

FOLLOW UP PERIOD: Through conclusion of pregnancy

RESULTS:

Primary Outcome –

- In low-risk patients, aspirin decreased the risk of preeclampsia in non-Hispanic White women, but not in Hispanic or non-Hispanic Black women (RR 0.19; 95% CI, 0.06–0.63).
- Aspirin did not decrease preeclampsia risk in any of the high-risk groups.

Secondary Outcome –

- In low-risk patients, aspirin increased the risk of placental abruption compared to placebo (RR 5.6; 95% CI, 1.2–25).
- In low-risk patients, aspirin increased the risk of stillbirth in non-Hispanic Black women, but not in other race/ethnic groups (RR 3.6; 95% CI, 1.0-13).
- Other secondary outcomes did not have statistically significant results.

LIMITATIONS:

- Dose of Aspirin used in the study was 60 mg. This is different from the dose available in the U.S. which is 81 mg. Further studies should investigate if varying dosage effects study outcome.
- This study did not account for social, genetic and/or cultural factors contributing to differences in treatment responses between racial/ethnic groups. Future studies examining the effects of systemic racism and genetic contributors to maternal neonatal outcomes in different racial/ethnic groups is needed.

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