GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of July 31 - August 4, 2023

SPOTLIGHT: Is Ethnicity Associated with COVID-19 Severity?

- Are Statins to Blame for Muscle Pain?
- Fall Training for Healthy Elderly
- Does COVID-19 Vaccination Prevent Fetal Death?

Is Ethnicity Associated with COVID-19 Severity?

Association Between Ethnicity and Severe COVID-19 Disease: A Systematic Review and Meta-Analysis

Raharja A, Tamara A, Kok LT. Association Between Ethnicity and Severe COVID-19 Disease: A Systematic Review and Meta-Analysis. *J Racial Ethn Health Disparities*. 2021;8(6):1563-1572. doi:10.1007/s40615-020-00921-5

KEY TAKEAWAY: There is no confirmed association between ethnicity and COVID-19 severity. There may not be an association between race and ethnicity and COVID-19 severity; however, there were significant limitations in this article, which do not accurately reflect the general population.

STUDY DESIGN: Systematic review and meta-analysis of 59 cohort studies and 13 ecological studies (N=17,950,989)

LEVEL OF EVIDENCE: STEP 2 (Downgraded based on study quality and disparities within the data set)

BRIEF BACKGROUND INFORMATION: Several risk factors have been shown to correlate with the severity of COVID-19 disease. This research aimed to identify if ethnicity is one of those risk factors, which could help determine how alarming, fast-acting, or cautious one should be in different ethnicity groups when infected with the virus.

PATIENTS: Patients with COVID-19

INTERVENTION: Non-White race

CONTROL: White race

PRIMARY OUTCOME: All-cause mortality

Secondary Outcome: Hospitalization, advanced respiratory support requirement, critical care admission, extra-corporal membrane oxygen use, acute kidney injury

METHODS (BRIEF DESCRIPTION):

- The patients' selections from the USA and UK were of different ethnicities such as White, Black, Asian, Hispanic, and other (some studies had missing ethnicity data).
  - The comorbidities were not specified.
- The risk of bias was reported to be low with a median Newcastle-Ottawa Scale (NOS) 7 of 9 (with 9 being the maximum bias) (interquartile range 6–8).
- The disease severity of Covid-19 infection was based on hospitalization, kidney failure, respiratory failure, and mortality.
  - Since the studies included cohort and reviewed articles, no treatment was administered.
- Outcome was measured by comparing hazard ratio (HR) and risk ratio (RR). Unadjusted and adjusted comorbidities for each group were included as well.

INTERVENTION (# IN THE GROUP): 1,454,138 (Non-white), 4,596,081 (missing ethnicity data)

COMPARISON (# IN THE GROUP): 11,502,289

FOLLOW-UP PERIOD: A literature search of databases was conducted from database inception to June 15, 2020

RESULTS:

Primary Outcome –

- There was no significant difference in all-cause mortality between the various ethnicities of patients compared to the White population.
  - Compared to the Black population: (HR 0.95; 95% CI; 0.72–1.3)
  - Compared to the Asian population: (HR 1.2; 95% CI; 0.84–1.6)
  - Compared to the Hispanic population: (HR 0.94; 95% CI; 0.63–1.4)

Secondary Outcome –

- Hospitalization: Risk of Black and Asian was markedly higher in the UK.
  - For Black ethnicity: (RR 5.5; 95% CI; 2.5–12) in UK studies vs. RR 1.36 [95% CI: 1.08–1.72] in US studies
- Advanced respiratory support requirement: After adjusting for sex, age, and comorbidities, the associations were attenuated and non-significant in Black, Asian, and Hispanic ethnicity.
- Critical care admission: The risk of ICU admission for the Black ethnicity was non-significant after adjusting for age, sex, and comorbidities.
  - There was inadequate data for meta-analysis for Asian ethnicity.
  - Only two studies reported age-, sex-, and comorbidity-adjusted analysis for Hispanic ethnicity, showing a non-significant association with ICU admission.

- Acute kidney injury: Only two separate studies showed an association that remained significant after adjustment of age, sex, and comorbidities for the Black ethnicity, but the pooled RR was non-significant.
    - Two studies reported a lower unadjusted risk of AKI in Asian ethnicity. One study reported a non-significantly lower adjusted risk of AKI in Asian ethnicity.
    - Two studies did not find an increased unadjusted risk of AKI in Hispanic ethnicity.

LIMITATIONS:

- There was a significant number of ethnicity data missing or not included.
- There were minimal articles that adjusted risks in Hispanics and Asians.
- Some studies in this systematic review have a higher White population for comparison.
- There was minimal involvement of the pediatric population.

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Are Statins to Blame for Muscle Pain?

Effect of Statin Therapy on Muscle Symptoms: An Individual Participant Data Meta-Analysis of Large-Scale, Randomised, Double-Blind Trials

Cholesterol Treatment Trialists' Collaboration. Effect of statin therapy on muscle symptoms: an individual participant data meta-analysis of large-scale, randomised, double-blind trials [published correction appears in Lancet. 2022 Oct 8;400(10359):1194]. *Lancet*. 2022;400(10355):832-845. doi:10.1016/S0140-6736(22)01545-8

KEY TAKEAWAY: Although statin therapy caused a slight excess of typically mild muscle pain and weakness in the first year, most reports of pain by patients on statin therapy cannot be attributed to the statin itself. The known cardiovascular benefits outweigh the small risk of muscle pain.

STUDY DESIGN: Meta-analysis of 19 placebo-controlled double-blind studies and four dose comparison double-blind studies

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Atherosclerotic cardiovascular disease is a leading cause of death worldwide, with Low-Density Lipoprotein (LDL) cholesterol being a significant risk factor. Long-term statin use reduces LDL cholesterol and the risk of myocardial infarction and stroke. However, in many observational studies, statin-related muscle pain and weakness suggest that statin therapy is associated with a significant excess risk in musculoskeletal disorders. Prior reviews of randomized controlled trials have shown most of those symptoms to be from non-placebo effects rather than the statins themselves. But, they have included unreliable and underpowered studies. This study seeks to provide more reliable information about the size, severity, and timing of musculoskeletal-related adverse effects caused by various statin regimens.

PATIENTS: Patients with known cardiovascular disease or risk for cardiovascular disease

INTERVENTION: Statin therapy, more intensive statin therapy (secondary)

CONTROL: Placebo, less intensive statin therapy (secondary)

PRIMARY OUTCOME: Reported muscle pain or weakness (stratified via types of muscle pain)

Secondary Outcome: Reports of muscle pain (stratified by time, sex, and statin dose), myopathy

METHODS (BRIEF DESCRIPTION):

- Double-blinded randomized trials of statin therapy that had >1,000 patients with at least two years of follow-up.
- 19 placebo vs statin double-blinded randomized control trials and four double-blinded studies that evaluated intensive vs less intensive statin therapy regimens:
  - Atorvastatin 40–80 mg simvastatin 80 mg OR
  - Rosuvastatin 20–40 mg vs pravastatin 40 mg OR
  - Simvastatin 10–20 mg).
- Statin intensity was defined as <30% LDL reduction (low), 30% to <50% LDL reduction (moderate), and >50% LDL reduction (intense).
- Primary measured outcomes were reported muscle pain and weakness (separated by type).
- Secondary outcomes were reports of pain within the first year vs subsequent years, pain reported in men vs in women, dose relationship of reported pain to statin dose, the intensity of statin therapy effect on reports of muscle pain, and myopathy.

INTERVENTION (# IN THE GROUP): 62,028 (statin therapy), 15,390 (more intense statin therapy)

COMPARISON (# IN THE GROUP): 61,912 (placebo), 12,334 (less intense statin therapy)

FOLLOW-UP PERIOD: At least two years, median follow-up of 4.3 years

RESULTS:

Primary Outcome –

- Reported muscle pain among patients assigned to statin therapy had a 3% relative increase in pain compared to placebo at 27% (RR 1.0; 95% CI, 1.0–1.1).
- The RRs were similar (heterogeneity *P*=.43) for each used to categorize muscle symptoms
  - Myalgia: (RR 1.0; 0·99–1.0)
  - Limb pain: (RR 1.0; 0.92–1.1)
  - Other musculoskeletal pain: (RR 1.0; 0.99–1.1)
- When stratified over time, statin therapy had a 7% increase in muscle pain/weakness (RR 1.1; 95% CI,

1.0–1.1) in the first year compared to placebo, but no increase in subsequent years (RR 0.99; 95% CI, 0.96–1.0).
    - This would be an absolute excess rate of 11 per 1000 persons in the first year, with 1 in 15 reports of muscle symptoms attributable to statin therapy.

Secondary Outcome –

- No evidence supported a clear dose relationship or difference of RR among different statins.
- Compared with placebo, high-intensity regimens had a higher RR (1.1; 95% CI, 1.0–1.1) compared to less intensive, moderate intensity, and high-intensity statins (RR 1.0; 95% CI, 1.0–1.1) within the first year, with no difference for either after the first year.
- Muscle pain reported was greater in women (RR 1.1; 95% CI, 1.0–1.2) than in men (RR 1.0; 95%CI 0.97–1.0).

LIMITATIONS:

- Only a single trial provided data on treatment adherence vs reported muscle symptoms.
- Some trials used simvastatin 80 mg per day which is no longer approved.
- There was considerable heterogeneity in the methodology to determine muscle symptoms between trials, with some data missing.

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Fall Training for Healthy Elderly

Effect of Treadmill Perturbation-Based Balance Training on Fall Rates in Community-Dwelling Older Adults: A Randomized Clinical Trial

Nørgaard JE, Andersen S, Ryg J, et al. Effect of Treadmill Perturbation-Based Balance Training on Fall Rates in Community-Dwelling Older Adults: A Randomized Clinical Trial. *JAMA Netw Open*. 2023;6(4):e238422. Published 2023 Apr 3. doi:10.1001/jamanetworkopen.2023.8422

KEY TAKEAWAY: Perturbation-based training (PBT) does not change fall risk.

STUDY DESIGN: Assessor-blinded randomized controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to lack of participant blinding)

BRIEF BACKGROUND INFORMATION: Studies show that the cost of treatment and rehabilitation caused by falls among community-dwelling older adults is substantial. The impact of perturbation-based balance training (PBT) has been shown to help with reactive balance control. This study examines the effects of perturbation-based balance training on fall rates in community-dwelling adults.

PATIENTS: Adults ≥ 65 years

INTERVENTION: PBT

CONTROL: Treadmill walking at preferred speed

PRIMARY OUTCOME: Daily life fall rates

Secondary Outcome: Lab setting fall rates

METHODS (BRIEF DESCRIPTION):

- Community-dwelling adults aged 65 and older able to walk without a walking aide were recruited using radio and television advertisements in Denmark.
- Patients with osteoporosis, insufficient walking ability, and neurologic disease were excluded. The mean age was 72 years, and 56% were women.
  - Frailty median score was 2, and 40% had a fall within the last year.
- Treatment group received 4 PBT sessions (20 min sessions including 40 perturbations, 20 to each leg).
  - Sessions occurred twice on day one, once after one week, and once at six months.
  - Comparison group received the same sessions at 20 minutes at their preferred walking speed.
- Daily video records and fall calendars measured the rate of falls per person-years of follow-up.
  - A blinded research assistant reviewed fall calendars, and falls were validated over the phone with patients for 12 months after their third training session.
- Laboratory fall assessments included exposure to level-1 perturbations with fall criteria including a slow-motion video evaluation and the safety harness needed to stop the patient's motion conducted at pre-post assessments and 6 and 12 months.

INTERVENTION (# IN THE GROUP): 70

COMPARISON (# IN THE GROUP): 70

FOLLOW-UP PERIOD: 12 months

RESULTS:

Primary Outcome –

- Patients who received PBT had lower rates of falls, but this was not statistically different compared to those who received preferred walking speed sessions.
  - Incidence rate ratio (IRR) 0.78; 95% CI, 0.48–1.3.
- No significance between group differences in any secondary daily life fall outcomes.
- Patients who received PBT had lower laboratory fall rates than those who participated in preferred walking speed sessions at six, 12, and 24 months.
  - IRR 0.20; 95% CI, 0.10–0.41
  - IRR 0.47; 95% CI, 0.26–0.86
  - IRR 0.37 95% CI, 0.19–0.72 respectively

LIMITATIONS:

- Participants were unblinded.
- No established dose-response association between perturbation balance training and daily life falls.
- Lab falls were evaluated by video inspection instead of by any weight placed on the safety harness and may not have caught more minor falls.

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Does COVID-19 Vaccination Prevent Fetal Death?

Pregnancy Outcomes in Patients After Completion of the mRNA Coronavirus Disease 2019 (COVID-19) Vaccination Series Compared with Unvaccinated Patients

Morgan JA, Biggio JR Jr, Martin JK, et al. Pregnancy Outcomes in Patients After Completion of the mRNA Coronavirus Disease 2019 (COVID-19) Vaccination Series Compared With Unvaccinated Patients. *Obstet Gynecol*. 2023;141(3):555-562.
doi:10.1097/AOG.0000000000005072

KEY TAKEAWAY: Vaccination with two doses of an mRNA vaccine against COVID-19 was associated with a lower perinatal death rate. This rate did not remain significant after propensity score matching.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: The COVID-19 vaccination is recommended in pregnancy by the Centers for Disease Control, the Society for Maternal-Fetal Medicine, and the American College of Obstetrics and Gynecologists, but vaccine rates in this group are lower than other high-risk groups. There is a clear maternal benefit to vaccination against COVID-19 in pregnancy, but there is limited data about its association with the frequency of perinatal death.

PATIENTS: Pregnant persons

INTERVENTION: mRNA Covid-19 vaccination

CONTROL: Unvaccinated pregnant persons

PRIMARY OUTCOME: Perinatal death

Secondary Outcome: Neonatal and maternal complications

METHODS (BRIEF DESCRIPTION):

- The retrospective cohort study included pregnant patients with singleton or twin gestations who delivered after 20 weeks at Ochsner Health System between 1/1/21 and 12/31/21.
  - Patients were identified for inclusion using a delivery contact serial number within the electronic medical record (EMR).
- Patients were divided into two groups: those who had received two doses of an mRNA COVID-19 vaccine (either Pfizer-BioNTech or Moderna) before delivery and those who were unvaccinated.
  - Patients were excluded if they received only one vaccine dose or a viral vector vaccine (Johnson & Johnson/Janssen), had higher-order multiple gestations, or had significant congenital anomalies.
- The vaccinated group had an average age of 31.6 years and an average BMI of 27.9.
  - 25% identified as Black
  - 43.7% were nulliparous
  - 2.5% reported current tobacco use
- The unvaccinated group had an average age of 27.8 years and an average BMI of 29.3.
  - 38.2% identified as Black
  - 36% were nulliparous
  - 9.8% reported current tobacco use
- Patient information was collected from the EMR, and vaccination status was confirmed with the Louisiana Immunization Network (LINK) in the EMR.
  - All patients were tested for SARS-CoV-2 on admission in the timeframe.
- Results were analyzed with covariates including maternal age at delivery, Medicaid insurance, pre-pregnancy BMI, current smoking status, maternal medical comorbidities (diabetes, hypertension), and twin gestation.
- The primary outcome was perinatal death, including stillbirth and neonatal death.
- The secondary neonatal outcomes were preterm delivery, very low birth weight (less than 1500 g), and NICU care admissions.
  - The maternal outcomes were SARS-CoV-2 infection during pregnancy.
- Propensity score matching was performed to balance cohorts based on vaccination status.

INTERVENTION (# IN THE GROUP): 2,069

COMPARISON (# IN THE GROUP): 13,769

FOLLOW-UP PERIOD: 28 days after birth

RESULTS:

Primary Outcome –

- Vaccination was associated with a 44% relative risk reduction in perinatal death (0.5% vs 0.8%, adjusted odds ratio (aOR) 0.2; 95% CI, 0.05–0.88).

- In the cohort of singleton gestations, vaccination was associated with a reduction in perinatal death (aOR 0.1; 95% CI, 0.01–0.75).
- With propensity score matching, the reduction in perinatal death did not remain statistically significant.
- A secondary analysis of a cohort of patients with COVID-19 found no difference in perinatal death rates between the two groups.

Secondary Outcome –

- Preterm delivery before 37 weeks gestation (aOR 0.63; 95% CI, 0.48–0.82)
- Very low birth weight neonates (aOR 0.35; 95% CI, 0.15–0.84)
- NICU care admission (aOR 0.66; 95% CI, 0.52–0.85) as compared to unvaccinated patients
- Maternal outcomes of vaccinated patients associated with lower odds of:
    - SARS-CoV-2 infection during pregnancy (aOR 0.17; 95% CI, 0.09–0.33) compared to unvaccinated patients.

LIMITATIONS:

- The study's retrospective nature may introduce bias through errors in data entry by medical practitioners.
- A lack of pre-pregnancy BMIs for 68.3% of the patients limited propensity score matching.
- Patients included in the study may have been vaccinated outside of Ochsner Health Facility, and the record was not uploaded to the LINKS system.
- The authors could not draw conclusions on boosters due to the timing of the study, and they could not expand results to new viral mutations or new vaccine versions.

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