GEMs of the Week

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GEMs
GOOD EVIDENCE MATTERS

FPIN
Family Physicians Inquiries Network

What's in this week's issue?

Week of January 16 - 20, 2023

SPOTLIGHT: Exercise - Good for Physical Health, Good for Mental Health

Exercise: Good for Physical Health, Good for Mental Health

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Association Between Physical Activity and Risk of Depression: A Systematic Review and Meta-Analysis

Pearce M, Garcia L, Abbas A, et al. Association Between Physical Activity and Risk of Depression: A Systematic Review and Meta-analysis. *JAMA Psychiatry*. 2022;79(6):550–559. doi:10.1001/jamapsychiatry.2022.0609

KEY TAKEAWAY: Physical activity, even at small volumes, is associated with lower risks of depression.

STUDY DESIGN: Systematic review and meta-analysis of 15 prospective cohort studies (N=191,130)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to reverse causality, recall, and publication bias)

BRIEF BACKGROUND INFORMATION: Depression is one of the most common mental health-related diseases and is the leading cause of disability worldwide. Physical activity can help prevent depression, but the dose-response association between physical activity and depression is unknown.

PATIENTS: Adult patients

INTERVENTION: Varying levels of non-occupational physical activity

CONTROL: Lower volumes of physical activity

PRIMARY OUTCOME: Depression incidence

METHODS (BRIEF DESCRIPTION):

- The authors searched PubMed, SCOPUS, Web of Science, and PsychINFO.
- Data extraction was performed by two independent reviewers for eligibility with disagreements resolved by a third reviewer.
- Exclusion criteria included sample size <3,000, studies reporting less than three exposure levels, and less than three years follow up.
- The 15 studies selected occurred almost exclusively in high-income countries (all but one).
- Participants were from 18–93 years old and were mostly women (64%).
- Physical activity level was standardized to marginal metabolic equivalent task hours per week (mMET-hrs/wk) which reflects the energy expended above the resting metabolic rate.
- Outcome measures included incidence of major depression (per self-report of physician diagnosis, registry data, or diagnostic interview) and elevated depression symptoms (established through validated depression screen).

INTERVENTION (# IN THE GROUP): Unavailable

COMPARISON (# IN THE GROUP): Unavailable

FOLLOW UP PERIOD: Three to 27 years

RESULTS:

- Adults accumulating half the recommended volume of physical activity (4.4 mMet-hrs/wk) had a lower risk of depression as compared to no activity (relative risk (RR) 0.82; 95% CI, 0.77–0.87).
- Adults accumulating the recommended volume of physical activity (8.8 mMet-hrs/wk) had a decreased risk of depression as compared to no activity (RR 0.75; 95% CI, 0.68–0.82).
- Adults accumulating more than the recommended volume of physical activity (17.5 mMet-hrs/wk) had a decreased risk of depression as compared to no activity, although there was greater observed uncertainty (RR 0.72; 95% CI, 0.64–0.81).
- The relationship between physical activity and major depression and physical activity and elevated depressive symptoms showed a similar inverse curvilinear dose response; heterogeneity was significant, however (I^2=74%; P<.001).
- Based on estimate of exposure prevalence, if less active adults had followed the current physical activity guidelines, an estimated 12% (95% CI, 7.7%–15%) of depression cases could have been prevented.

LIMITATIONS:

- Findings may be due to reverse causality bias as depression at baseline results in lower physical activity level.
- Self-report of physical activity levels may have resulted in recall bias.
- Data was limited at higher physical activity levels
- Results were not stratified by gender, age, or socio-economic status due to limited data.
- Unpublished literature was not searched, resulting in possible publication bias.

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Ezetimibe: To Add or Not to Add?

Long-Term Efficacy and Safety of Moderate-Intensity Statin with Ezetimibe Combination Therapy versus High-Intensity Statin Monotherapy in Patients with Atherosclerotic Cardiovascular Disease (RACING): A Randomised, Open-label, Non-Inferiority Trial

Kim BK, Hong SJ, Lee YJ, et al. Long-term efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease (RACING): a randomised, open-label, non-inferiority trial. *Lancet*. 2022;400(10349):380- 390. doi:10.1016/S0140-6736(22)00916-3

KEY TAKEAWAY: In patients with established atherosclerotic cardiovascular disease (ASCVD), moderate-intensity statin in combination with ezetimibe is noninferior to high-intensity statin therapy in decreasing major cardiovascular outcomes. Additionally, combination therapy has lower discontinuation rates and improved LDL reduction when compared to high-intensity statin alone.

STUDY DESIGN: Randomized, open-label, non-inferiority trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Current guidelines recommend the use of high-intensity statin therapy in patients with established ASCVD to lower LDL concentrations and mitigate cardiovascular risk. Studies have been performed comparing the addition of ezetimibe to same dose statin therapy; however, there have been no studies on the addition of ezetimibe to lower-dose statin therapy as an alternative to high-dose statin use.

PATIENTS: Patients with established ASCVD who requiring high-intensity statin

INTERVENTION: Moderate-intensity statin + ezetimibe

CONTROL: High-intensity statin

PRIMARY OUTCOME: Cardiovascular death, major cardiovascular events, non-fatal stroke

Secondary Outcomes: LDL goal of <70 mg/dL, discontinuation or reduction of dose

METHODS (BRIEF DESCRIPTION):

- Participants included South Koreans with established ASCVD and a goal LDL concentration of <70 mg/dL.
- Established ASCVD was defined by having at least one of the following: myocardial Infarction, history of Acute Coronary Syndrome, history of coronary or arterial revascularization, history of ischemic stroke or Peripheral Arterial Disease.
- The average participant was 64 years old, 25% were female, the average BMI was 25.0 kg/m^2, and 37% had diabetes.
- Patients were randomized to either:
  - Rosuvastatin 10 mg in combination with ezetimibe 10 mg
  - Rosuvastatin 20 mg
- Neither patient nor treating physician were blinded.
- At the end of three years, cardiovascular end points including cardiovascular death, major cardiovascular events, and non-fatal stroke were evaluated.
- LDL concentration was checked at one, two, and three years.
- Post-hoc analysis to investigate a goal concentration of <55 mg/dL in keeping with changing guidelines was performed at one, two, and three years.
- Discontinuation or lower doses of medication was assessed at the end of three years.

INTERVENTION (# IN THE GROUP): 1,894

COMPARISON (# IN THE GROUP): 1,886

FOLLOW UP PERIOD: Three years

RESULTS:

Primary Outcomes –

- Moderate intensity statin in combination with ezetimibe showed no difference in cardiovascular outcomes compared to high intensity statin alone (9.1% vs 9.9%, respectively; absolute difference –0.78; 90% CI, –2.4 to 0.83).

Secondary Outcomes –

- Compared to high intensity statin, moderate intensity statin in combination with ezetimibe resulted in:
  - 18% lower LDL at one year (95% CI, 14–21)
  - 15% lower LDL at two years (95% CI, 12–18)
  - 15% lower LDL at three years (95% CI, 11–18)
- Moderate intensity statin in combination with ezetimibe resulted in less discontinuation or dose lowering compared to high intensity statin alone (4.8% vs 8.2%, respectively; absolute difference –3.4; 95% CI, –5.1 to –1.1).

LIMITATIONS:

- The patient population was homogenous with an entirely South Korean demographic and a normal BMI, which is not consistent with the population of the United States.
- A small number of cardiovascular events may have led to a larger than expected confidence interval.

Therefore, even though the study met its noninferiority margin, this is based on a small sample size of cardiovascular events.

- Open label trial contributes to potential biases.

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Are We Over Diagnosing Gestational Diabetes?

Lower versus Higher Glycemic Criteria for Diagnosis of Gestational Diabetes

Crowther CA, Samuel D, McCowan LME, et al. Lower versus Higher Glycemic Criteria for Diagnosis of Gestational Diabetes. *N Engl J Med*. 2022;387(7):587-598. doi:10.1056/NEJMoa2204091

KEY TAKEAWAY: Lower versus higher glycemic criteria are not associated with the incidence of large-for-gestational age infants (LGA). However, mothers in the lower glycemic criteria group have significantly more hypoglycemic infants and utilization of diabetes services or treatments than their counterparts.

STUDY DESIGN: Double-blinded randomized comparison trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Gestational diabetes (GDM) is a known risk factor for both perinatal and later cardiometabolic conditions. However, there is no consensus on the optimal gestational diabetes diagnostic criteria to reduce infant complications without compromising maternal outcomes.

PATIENTS: Pregnant women

INTERVENTION: Lower diagnostic glycemic criteria

CONTROL: Higher diagnostic glycemic criteria

PRIMARY OUTCOME: Birth of a LGA infant

Secondary Outcomes: Infant and maternal outcomes

METHODS (BRIEF DESCRIPTION):

- The study was conducted at two New Zealand health districts which provided primary to tertiary maternity care.
- Participants underwent routine screening with a 75 g oral glucose tolerance test at 24–32 weeks gestational age and subsequently randomly allocated to either a low or high glycemic group.
- The diagnostic criteria for GDM was as follows:
  - Lower glycemic criteria: fasting plasma glucose level of ≥92 mg/dL, 1hr ≥180 mg/dL, or 2hr ≥153 mg/dL
  - Higher glycemic criteria: fasting plasma glucose level of ≥99 mg/dL or 2hr ≥162 mg/dL
- Exclusion criteria included diabetes mellitus or history of GDM.
- The primary outcome was measured by infant birthweight (LGA was defined as >90%ile using the Fenton WHO standards).
- Secondary infant outcomes were measured with anthropometric measurements including weight/length/head circumference, gestational age at birth, blood glucose levels, and serious health outcomes (i.e., stillbirth, death of a live-born infant before discharge, birth trauma, and/or shoulder dystocia).
- Secondary maternal outcomes were measured by the number of individuals who utilized health services, underwent induction of labor, required pharmacological treatment for GDM, and developed a serious health outcome (e.g., maternal death, acute pulmonary edema, eclampsia, etc.).

INTERVENTION (# IN THE GROUP): 2,019

COMPARISON (# IN THE GROUP): 2,031

FOLLOW UP PERIOD: Through hospital discharge

RESULTS:

Primary Outcome –

- The higher vs lower diagnostic glycemic criteria in mothers were not related to the incidence of LGA infants (lower 8.8% vs higher 8.9%, relative risk [RR] 0.99, 95% CI 0.81– 1.2).

Secondary Outcomes –

- Mothers in the lower glycemic criteria group were significantly more likely to experience the following, compared to mothers in the higher glycemic group:
  - Hypoglycemic infants, requiring treatment after birth (11% vs 8.4%; RR 1.3; 95% CI, 1.1–1.5)
  - Utilize diabetes service visits (0.6 vs 0.2; RR 2.6; 95% CI, 1.9–3.5)
  - Need pharmacologic treatment for GDM (11% vs 4.6%; RR 2.4, 95% CI, 1.9–3.0)
  - Induced labor (34% vs 30%; RR 1.1, 95% CI 1.0–1.2).
- Serious maternal/infant health outcomes did not differ between the two groups.

LIMITATIONS:

- This study did not mention if there was any tracking of blood sugars or specific blood sugar goals amongst women who met criteria and treated for gestational diabetes.
- The generalizability of the study was limited, as it was conducted within only two health districts of New Zealand.

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Cardiac Effects of SARS-CoV-2 in Young Competitive Athletes

SARS-CoV-2 Cardiac Involvement in Young Competitive Athletes

Moulson N, Petek BJ, Drezner JA, et al. SARS-CoV-2 Cardiac Involvement in Young Competitive Athletes. *Circulation*. 2021;144(4):256-266. doi:10.1161/CIRCULATIONAHA.121.054824

KEY TAKEAWAY: The prevalence of SARS-CoV-2 infection-related cardiac involvement in NCAA college athletes is low. Asymptomatic or mildly symptomatic young athletes are at low risk of cardiac events; therefore, the need for testing beyond standard pre-participation cardiac screens may not be warranted.

STUDY DESIGN: Prospective, multicenter, observational cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Severe COVID-19 symptoms are associated with adverse cardiac events such as myocarditis but the prevalence of these in young and otherwise healthy athletes are unknown. Guidelines for cardiac screening and clearance in athletes with SARS-CoV-2 infection before return to play may be warranted.

PATIENTS: Collegiate level athletes testing positive for SARS-CoV-2

INTERVENTION: SARS-CoV-2 related cardiac involvement

CONTROL: Absence of SARS-CoV-2 related cardiac involvement

PRIMARY OUTCOME: Occurrence of cardiac involvement from SARS-CoV-2 infection

Secondary Outcome: Need for additional cardiac testing based on symptoms

METHODS (BRIEF DESCRIPTION):

- SARS-CoV-2 testing was completed on 19,378 collegiate NCAA athletes from September 1 to December 31, 2020.
- 2,820 athletes tested positive and underwent at least one element of cardiac triad testing (12-lead ECG, troponin, transthoracic echocardiography).
- Athletes with cardiac screens that yielded abnormal results then completed a cardiac MRI. If abnormal, further classified the athlete as either with definite, probable, or possible cardiac involvement.
- Classification as an abnormal cardiac imaging result was based on benchmarks from the modified Updated Lake Louise Imaging Criteria of assessing cardiac MRI.
- Firth penalized logistic regression approach evaluated links between SARS-CoV-2 infection and cardiac sequalae. A Firth logistic regression model was constructed to isolate clinical predictors of cardiac involvement.
- Short term follow up was completed to monitor for any cardiac sequalae.

INTERVENTION (# IN THE GROUP): 21

COMPARISON (# IN THE GROUP): 2,997

FOLLOW UP PERIOD: 113 to 130 days

RESULTS:

Primary Outcome –

- Cardiac involvement was detected in 0.7% of athletes testing positive for SARS-CoV-2 (95% CI, 0.4–1.1).

Secondary Outcome –

- When adjusted for race and sex, the most meaningful indicators of SARS-CoV-2 cardiac involvement included:
  - Cardiopulmonary symptoms such as chest pain and shortness of breath (OR 3.1; 95% CI, 1.2–7.7)
  - One or more abnormality on 12-lead ECG, TTE or troponin result (OR 37; 95% CI, 13–105)
- During follow-up, one athlete experienced sudden cardiac arrest (successfully resuscitated) but was not part of the 21 with SARS-CoV-2 cardiac involvement.

LIMITATIONS:

- Potential element of observer bias as the data for the TTE and cardiac MRI results were gathered using only the clinical reports submitted by each institution; the actual images were not available for interpretation by study investigators.
- Each testing institution selected their own cardiac testing modalities for the screening protocol; thus the occurrence of each cardiac test was not evenly distributed.
- Limited by short duration of follow up.

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Safety of DOACs in Pregnancy

Safety of Direct Oral Anticoagulant Exposure During Pregnancy: A Retrospective Cohort Study

Beyer-Westendorf J, Tittl L, Bistervels I, et al. Safety of direct oral anticoagulant exposure during pregnancy: a retrospective cohort study. *Lancet Haematol* 2020;7(12):e884-e891.

KEY TAKEAWAY: Limited observational data do not suggest that exposure to DOACs during pregnancy carries a significant risk of fetal anomalies or pregnancy loss.

STUDY DESIGN: Case series

LEVEL OF EVIDENCE: STEP 4

BRIEF BACKGROUND INFORMATION: Direct acting oral anticoagulants (DOACs) are the standard of care for many women of childbearing age requiring anticoagulation. There have been cases of pregnancy in women taking DOACs, but little is known about potential embryotoxicity. This is the first study to identify outcomes of many pregnancies affected by DOAC exposure.

PATIENTS: Pregnant women requiring anticoagulation

INTERVENTION: Daily DOAC usage

CONTROL: No comparison group

PRIMARY OUTCOME: Pregnancy outcomes and fetal anomalies

METHODS (BRIEF DESCRIPTION):

- Case reports were obtained from providers directly, pharmaceutical manufacturers, a literature search, and database searches of the European Medicines Agency (EMA), the German Drug Authority (GDA), and the Federal Drug Administration (FDA) yielding 1,193 reports of DOAC exposure during pregnancy.
  - Cases of DOAC exposure were from between February 1, 2007 and July 9, 2020.
- After individual case reports were reviewed and potential duplicates were removed, a total of 614 unique cases of DOAC exposure in pregnancy were identified.
  - 45% of the 614 cases were missing pregnancy outcome data, resulting in 366 pregnancies with known outcomes.
- No inclusion or exclusion criteria were listed.
- All data was reviewed by two independent physicians.
- The data was inputted into a study database where missing values were left blank.
- No statistical analysis was done.

INTERVENTION (# IN THE GROUP): 614

COMPARISON (# IN THE GROUP): Not applicable

FOLLOW UP PERIOD: Not applicable

RESULTS:

- Case reports were mostly women on a DOAC before pregnancy and the medication was stopped early in the first trimester (median duration of exposure 5.3 weeks; N=614).
  - 82% on rivaroxaban, 6% on dabigatran, 8% on apixaban, 4% on edoxaban
- Of the 366 pregnancies with known outcomes:
  - 56% had live births (n=188).
  - 22% had miscarriages (n=74).
  - 22% had elective pregnancy terminations (n=74).
  - The observed miscarriage rate was noted to be similar to the general population.
  - 6% had fetal abnormalities (n=21).
  - 4% had fetal abnormalities considered possibly related to DOAC exposure (n=12).
    - Abnormalities included cardiac, renal, pulmonary, and neurologic (many were unspecified).
    - The overall risk of congenital abnormalities in this study possibly associated with DOAC exposure was lower than the risk of fetal abnormalities associated with Vitamin K antagonist use from prior studies (6–7%).

LIMITATIONS:

- Many case reports had incomplete data on the details of DOAC exposure and pregnancy outcomes.
- There was no direct comparison group in this study. Rates of miscarriage and fetal abnormalities were only compared to rates from prior literature.
- Case reporting was incomplete. Exposure to DOAC may have been missed if not reported to providers, pharmaceutical companies, or drug agencies.
- A majority of cases (82%) were patients exposed to rivaroxaban, limiting generalizability to other DOACs.

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