GEMs
GOOD EVIDENCE MATTERS

# GEMs of the Week

Volume 2 - Issue 26

FPIN
Family Physicians Inquiries Network

## What's in this week's issue?

**Week of June 27 - July 1, 2022**

**SPOTLIGHT: Brain Retraining - Using Pain Reprocessing Therapy to Reduce Chronic Back Pain**

# Brain Retraining: Using Pain Reprocessing Therapy to Reduce Chronic Back Pain

**Effect of pain reprocessing therapy vs placebo and usual care for patients with chronic back pain: A randomized clinical trial**

Ashar YK, Gordon A, Schubiner H, et al. Effect of Pain Reprocessing Therapy vs Placebo and Usual Care for Patients With Chronic Back Pain: A Randomized Clinical Trial. *JAMA Psychiatry*. 2022; 79(1):13-23. doi:10.1001/jamapsychiatry.2021.2669



KEY TAKEAWAY: Pain reprocessing therapy (PRT), which aims to change beliefs about causes and threat of pain, reduces self-reported pain and disability due to chronic back pain.

STUDY DESIGN: Randomized control trial, open placebo

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Chronic back pain (CBP) impacts activity, quality of life, and ability to function, but in 85% of cases, a definitive cause cannot be identified. Pain reprocessing therapy (PRT) modifies the brain's response when limited injury is present by shifting pain appraisal and lowering threat perception. This study evaluates the effectiveness of a four-week trial of PRT.

PATIENTS: Patients with chronic low back pain (LBP)

INTERVENTION: Pain reprocessing therapy

CONTROL: Usual care or placebo

OUTCOME: Average pain over previous week

Secondary Outcomes: Disability, depression, anxiety, sleep disturbance

METHODS (BRIEF DESCRIPTION):

- Patients (17-70 years old, mean age 41 years old, 54% female) with CBP for at least 50% of days during previous six months and a one-week average pain intensity score of 4/10 or more were recruited from the community.
- Pain was self-assessed using 10-point pain intensity scale (0=no pain, 10=most pain imaginable).
- Disability self-assessment using Oswestry Disability Index (0-100) with higher scores indicating increased disability.
- Depression and sleep disturbance assessed using PROMIS measures (higher scores indicate greater symptoms).
- Baseline functional magnetic resonance imaging (fMRI) assessed evoked pain-related activity.
- PRT was performed twice weekly for four weeks (eight one-hour visits).
- Patients in placebo cohort viewed a video demonstrating that placebo treatments could relieve pain and subcutaneous saline injections were administered at site of pain.
- No additional treatment provided to usual care patients.
- Pain assessed at one, two, three, six, and 12 months.
- Post-treatment fMRI assessed brain activity during evoked pain at one month after baseline fMRI.

INTERVENTION (# IN THE GROUP): 50

COMPARISON (# IN THE GROUP):

- Open placebo: 51
- Usual care: 50

FOLLOW UP PERIOD: One year

RESULTS:

Primary Outcome –

- PRT decreased pain more than usual care and placebo post-treatment and at one year.
  - PRT reduced pain relative to placebo and relative to usual care (PRT vs placebo: g, -1.1; 95% CI, -1.7 to -0.71; PRT vs usual care: g, -1.7; 95% CI, -2.3 to -1.3).
  - At one year, more PRT patients reported little, or no pain compared to placebo and usual care (PRT vs placebo: g, -0.70, $p$=.001; PRT vs usual care: g, -1.0, $p$<.001).

Secondary Outcomes –

- PRT decreased self-assessed disability more than usual care and placebo at post-treatment and at one year (PRT vs placebo: g, -1.3, $p$<.001; PRT vs usual care: g, -1.7, $p$<.001).
- PRT decreased depression at post-treatment and at one year (PRT vs placebo: g, -0.35, $p$<.099; PRT vs usual care: g, -0.56, $p$<.009).
- PRT decreased sleep disturbances (PRT vs placebo: g, -.41, $p$=.056; PRT vs. usual care: g, -0.63, $p$=.003).
- No adverse events reported.

LIMITATIONS:

- Assessment of pain symptoms and disability was subjective.
- Baseline pain and disability was low to moderate.
- Clinicians proficient in PRT may not be readily available.
- Study was performed at one academic setting.

*Karla Hemesath, PhD*
*Department of Family Medicine, University of Iowa*
*Iowa City, IA*

# Is Surgery Beneficial for Patellar Tendinopathy Knee Pain?

**Surgery for patellar tendinopathy (jumper's knee)**

Dan M, Phillips A, Johnston RV, Harris IA. Surgery for patellar tendinopathy (jumper's knee). *Cochrane Database Syst Rev*. 2019; 9(9):CD013034. Published 2019 Sep 23. doi:10.1002/14651858.CD013034.pub2



KEY TAKEAWAY: Open surgery for patellar tendinopathy isn't better compared to exercise, and arthroscopic surgery may be superior to a sclerosing injection.

STUDY DESIGN: Systematic review of two randomized controlled trials (N=94)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to the lower quality studies and inconsistent findings)

BRIEF BACKGROUND INFORMATION: Patellar tendinopathy is a painful knee injury that most often affects athletes. First-line treatment is conservative measures including rest, physical therapy, medications, and/or injections. Surgery is typically reserved for those failing conservative measures.

PATIENTS: Adult athletes with patellar tendinopathy

INTERVENTION: Surgical interventions (open and arthroscopic)

CONTROL: Non-surgical (eccentric exercise or sclerosing injections)

OUTCOME: Pain, function, global assessment of success

METHODS (BRIEF DESCRIPTION):

- The authors searched Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Library, OVID MEDLINE, OVID Embase, clinical trial registries, and the WHO trials portal databases and selected the only two studies that met inclusion criteria.
  - Patients: 92 recreational to elite athletes
  - Majority male: >90%
  - Mean age: 26-31 years old
- Selection criteria:
  - Exercise-induced patella tendon pain for at least three months
  - Affected ability to participate at the same level prior to injury
  - Magnetic Resonance Imaging or Ultrasound findings consistent with tendinopathy
  - Pain persistent after at least three months of rest, analgesia, and physical therapy
- Exclusion criteria:
  - Less than 18 years old
  - Refused surgery
  - Known inflammatory or degenerative joint conditions
  - Acute presentation of pain
- Randomized selection of 46 athletes in surgical group versus 46 athletes in eccentric exercises group or sclerosing injection.
- Outcomes were assessed at six and 12 months, but only reported at 12 months.
- Outcomes included:
  - Knee Pain with standing jump using Visual Analogue Scale (VAS) 0–100
  - Function using Victorian Institute of Sports Assessment (VISA) 0–100 (higher scores indicate better function)
  - Patients' global assessment of treatment on a -5 to +5 scale (improvement of symptoms)
  - Pain level at rest using Visual Analogue Scale (VAS) 0–100
  - Pain level with activity using VAS 0–100

INTERVENTION (# IN THE GROUP):

- Open Surgery: 20
- Arthroscopic Surgery: 24

COMPARISON (# IN THE GROUP):

- Eccentric Exercise Group: 20
- Sclerosing Injection: 26

FOLLOW UP PERIOD: 12 months

RESULTS:

Mixed results:

- Open surgery had no clinical difference compared to eccentric exercise in knee pain.
  - Standing jump: mean difference [MD] 0.4 (95% CI, -1.2 to 0.4)
  - Function: MD 7.2 (95% CI, -4.5 to 19),
  - Global assessment: mean improvement 0.2 points (95% CI, -0.8 to 1.7).
- The surgery improved the following areas more than sclerosing injection:
  - Pain during specific sport activity and rest: MD -28 (95% CI, -42 to -15)
  - Global assessment: mean improvement 34 points (95% CI, 19–49)

LIMITATIONS:

- Only two randomized control trials were compared.
- Small sample size of 92 participates.
- No placebo group present.
- No long-term effects of surgery reported, such

as tendon rupture.
- Studies were not alike using two different surgical techniques and comparator.

---

*Tiffany Bujak, DO, MAJ, MC, USA*
*Dwight D. Eisenhower FMR*
*Fort Gordon, GA*

*The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Army Medical Department, the Army at large, or the Department of Defense.*

# Effect of COVID-19 on Maternal and Neonatal Morbidity and Mortality

**Maternal and Neonatal Morbidity and Mortality Among Pregnant Women With and Without COVID-19 Infection: The INTERCOVID Multinational Cohort Study**

Villar J, Ariff S, Gunier RB, et al. Maternal and Neonatal Morbidity and Mortality Among Pregnant Women With and Without COVID-19 Infection: The INTERCOVID Multinational Cohort Study [published correction appears in *JAMA Pediatr.* 2022 Jan 1;176(1):104]. *JAMA Pediatr*. 2021; 175(8):817–826. doi:10.1001/jamapediatrics.2021.1050



KEY TAKEAWAY: There is an association between COVID-19 during pregnancy and an increase in maternal and neonatal adverse outcomes.

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Early in the pandemic there was little evidence on the effect of COVID-19 on pregnant individuals and newborns. This cohort study presents a large amount of data from multiple institutions with a comparison group that reduces selection bias. Knowledge of the risks of COVID-19 during pregnancy can help physicians better take care of obstetric patients and their newborns.

PATIENTS: Pregnant adult women during any stage of pregnancy or delivery

INTERVENTION: Diagnosis of COVID-19 via laboratory, radiographic, or symptomatic findings

CONTROL: Women without a COVID-19 diagnosis

OUTCOME: Maternal morbidity, neonatal morbidity, severe neonatal conditions

METHODS (BRIEF DESCRIPTION):

- Patients were enrolled over an eight-month period starting on March 2, 2020, across 43 institutions and 18 countries; criteria included women 18 years old and older during any stage of pregnancy or delivery that had a diagnosis of COVID-19.
- The definition of a COVID-19 diagnosis included laboratory confirmation, pulmonary findings on radiograph consistent with COVID-19, or having at least two or more pre-defined symptoms of COVID-19.
- For the comparison group, two pregnant women not meeting the diagnostic criteria for COVID-19 were enrolled at the same time and from the same population as the women with COVID-19.
- A centrally coordinated data management system that was developed for the INTERGROWTH-21st Project was used to collect data. The outcomes (MMMI, SNMI, SPMMI) were measured via clinical observation during the antenatal and post-partum periods.
- MMMI is a standardized index that includes at least one pregnancy-related morbidity such as preeclampsia, preterm labor, or infections requiring antibiotics, among several other complications.
- SNMI is a standardized index that includes at least three severe neonatal complications including bronchopulmonary dysplasia, hypoxic-ischemic encephalopathy, and sepsis, among several other complications.
- SPMMI is a standardized index that includes at least one severe neonatal condition listed in the SNMI, admission to the neonatal ICU for seven days or longer, or neonatal death before hospital discharge.

INTERVENTION (# IN THE GROUP): 706

COMPARISON (# IN THE GROUP): 1,420

FOLLOW UP PERIOD: Eight Months

RESULTS:

- COVID-19 infection increased maternal morbidity and mortality compared to those without infection (relative risk [RR] 1.5; 95% CI, 1.3–1.8).
- Patients with COVID-19 during pregnancy also had a higher neonatal morbidity and mortality risk than those without a COVID-19 diagnosis (RR 2.7; 95% CI, 1.7–4.2).
- Severe neonatal conditions were also significantly higher in patients with COVID-19 than those without (RR 2.1; 95% CI, 1.7–2.8).
- Women with a COVID-19 diagnosis had a greater risk of ICU admission (RR 5.0; 95% CI, 3.1–8.1) and stayed an average of 3.7 days longer than women without COVID-19 (95% CI, 2.4–5.9).
- There were 11 deaths in the group of women with a COVID-19 diagnosis compared to one death in the group without (RR 22; 95% CI, 2.9–172).
- Asymptomatic women with COVID-19 had no statistically significant increased risk of the primary outcomes.
    - However, presence of any symptoms, especially fever and shortness of breath, did significantly increase the risk for adverse outcomes.
        - Maternal morbidity and mortality (RR 2.6; 95% CI, 1.9–3.4)
        - Neonatal morbidity and mortality (RR 5.0; 95%

CI, 2.1–12)
    - Severe neonatal conditions (RR 5.0; 95% CI, 3.3–7.9)
- Obesity increased the risk for all outcomes for those with COVID-19 compared to non-obese people with COVID-19.
    - Maternal morbidity and mortality (RR 1.8; 95% CI, 1.5–2.2)
    - Neonatal morbidity and mortality (RR 4.2; 95% CI, 2.2–8.0)
    - Severe neonatal conditions (RR 2.4; 95% CI, 1.7–3.5)

LIMITATIONS:

- COVID-19 positive population included individuals that did not have laboratory confirmed COVID-19.
- Potential reporting bias as individuals with a COVID-19 diagnosis may have had closer evaluations and more events reported than those without a diagnosis.

*Paige Macky, MD*
*Eisenhower Army Medical Center FMRP*
*Fort Gordon, GA*

*The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Army Medical Department, the Army at large, or the Department of Defense.*

# Increased Incidence of Anal Carcinoma in HIV Positive Population: Risk Factors from a Longitudinal Cohort Study

**The Risk of Anal Carcinoma After Anogenital Warts in Adults Living With HIV**

Arnold JD, Byrne ME, Monroe AK, Abbott SE; District of Columbia Cohort Executive Committee. The Risk of Anal Carcinoma After Anogenital Warts in Adults Living With HIV. *JAMA Dermatol.* 2021; 157(3):283–289. doi:10.1001/jamadermatol.2020.5252



KEY TAKEAWAY: Patients with HIV who have a history of anogenital warts or a CD4 <200/µL have a higher risk of anal carcinoma compared to those without history of anogenital warts or CD4 ≥200/µL.

STUDY DESIGN: Longitudinal cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: HPV exposure is high among sexually active individuals and is associated with anogenital warts (low-risk types) and anogenital carcinoma (high-risk types). Despite the prevalence of HPV, there are few screening guidelines for anal cancer in the face of increasing incidence and mortality. This study sought to identify the strength of association between a history of anogenital warts and subsequent diagnosis of anorectal squamous cell carcinoma.

PATIENTS: Adults with HIV

INTERVENTION: Diagnosis of anogenital warts

CONTROL: No anogenital warts

OUTCOME: Anal carcinoma

METHODS (BRIEF DESCRIPTION):

- Participants were identified from the District of Columbia Cohort Longitudinal HIV study using searches of ICD-9 and ICD-10 codes, anogenital physical exams, referrals to specialists, and pathology results.
- Exclusion criteria included anal carcinoma before diagnosis of anogenital warts, less than 18 years old, and less than 18 months of follow up.
- Age, gender, HIV transmission risk, length of HIV diagnosis, tobacco use, and CD4 count were collected from participants and the comparison group at the time of enrollment or from the database.
- Statistical analyses were used to compare clinical and demographic variables between the two populations.

INTERVENTION (# IN THE GROUP): 383

COMPARISON (# IN THE GROUP): 6,132

FOLLOW UP PERIOD: At least 18 months, with average follow up of four years

RESULTS:

- The odds of anal carcinoma were 13 times higher in participants with previous diagnosis of anogenital warts compared to those without anogenital warts (OR 13; 95% CI, 6.2–26).
- Odds of anal carcinoma were 5.7 times higher in participants with a CD4 <200/µL compared to those with CD4 ≥200/µL, regardless of anogenital warts (OR 5.7; 95% CI, 2.2–15).
- MSM (men who have sex with men), IV drug use, high-risk heterosexual contact, and smoking history did not have an association with diagnosis of anal carcinoma.

LIMITATIONS:

- As a cohort study, only an association between anogenital warts and anal cancer can be drawn, but not direct causality.
- Participant's HPV genotype and HPV vaccination status were unknown.
- Results had wide confidence intervals.
- There was a possibility of surveillance bias as not all patients were universally screened for warts or anal cancer.
- The mortality risk of anorectal cancer in the study population is unknown, limiting the patient-oriented applicability of the results.
- Female enrollment was low and correlation with cervical HPV was not determined.
- Participants were primarily enrolled based on ICD codes from past clinical visits. A significant number of patients could have been missed if findings were not coded or included in authors' search.

*Danny Flautero, MD & William Gallagher, MD*
*MedStar Health/Georgetown- Washington Hospital Center FMRP*
*Washington, DC*

# Does Fish Intake Decrease Risk of Major Cardiovascular Disease and Mortality?

**Associations of Fish Consumption With Risk of Cardiovascular Disease and Mortality Among Individuals With or Without Vascular Disease From 58 Countries**

Mohan D, Mente A, Dehghan M, et al. Associations of Fish Consumption With Risk of Cardiovascular Disease and Mortality Among Individuals With or Without Vascular Disease From 58 Countries [published correction appears in *JAMA Intern Med*. 2021 May 1; 181(5):727]. *JAMA Intern Med*. 2021; 181(5):631-649. doi:10.1001/jamainternmed.2021.0036



KEY TAKEAWAY: Two servings (175 g) of fish per week may be associated with a lower risk for major cardiovascular disease in those with prior cardiovascular disease, but not in the general population.

STUDY DESIGN: Pooled analysis of individual participant data from four cohort studies, including 58 countries on six continents

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Fish consumption improves some cardiovascular markers such as triglycerides and blood pressure. However, while dietary guidelines recommend two servings of fish per week, data are inconsistent regarding whether fish consumption reduces CVD and mortality risk, and whether differences in risk reduction exist between those with and without prior CVD.

PATIENTS: Adults with and without CVD

INTERVENTION: Fish consumption

CONTROL: Not applicable

OUTCOME: Major cardiovascular disease (CVD), mortality, or composite of mortality or major CVD

METHODS (BRIEF DESCRIPTION):

- This pooled analysis included individual participant data from four cohort studies:
  - PURE study: N = 147,645 adults (139,827 without CVD and 7,818 with CVD)
  - ONTARGET trial & TRANSCEND trial: N = 31,491 adults with CVD
  - ORIGIN trial: N = 12,422 adults with cardiovascular risk factors and diabetes or impaired fasting glucose
- Baseline data regarding lifestyle, medical history, medication, and vital signs were obtained.
- Exposure was patient-reported fish intake, recorded using validated food frequency questionnaires.
  - ORIGIN trial also gathered information specifying type of fish consumed (high or moderate omega-3 fish, low omega-3 fish, shellfish).
- Association between fish intake (≤50 g/month, 50 g/month to <175 g/week, 175 to <350 g/week, ≥350 g/week) and outcomes were assessed in each cohort individually; followed by pooled cohort data in random-effects meta-analysis.

INTERVENTION (# IN THE GROUP): 191,558

COMPARISON (# IN THE GROUP): Not applicable

FOLLOW UP PERIOD: Median 7.5 years (interquartile range 4.9–9.4 years)

RESULTS:

Primary Outcome –

- Patients with existing CVD who consumed minimal fish intake of 175 g/week (or approximately 2 servings/week) compared with ≤50 g/month had significantly reduced risk of:
  - Major CVD (HR 0.84; 95% CI, 0.77–0.92)
  - Total mortality (HR 0.83; 95% CI, 0.75–0.91)
  - Composite of mortality or CVD (HR 0.86; 95% CI, 0.80–0.92)
- No association was found between fish consumption and CVD, mortality, or composite of mortality or major CVD in patients without existing CVD.
- ORIGIN trial showed high/moderate omega-3 fish consumption in patients with cardiovascular risk factors was strongly associated with lower risk of:
  - Major CVD (HR 0.94; 95% CI, 0.92–0.97 per 5-gram increment of intake)
  - Sudden cardiac death (HR 0.91; 95% CI, 0.86–0.96)

LIMITATIONS:

- Diet was self-reported in studies.
- Possibility of significant heterogeneity in the fish consumed (e.g., differences in cooking methods, differences in contaminants).
- Observational studies included in the analysis may have contained additional confounding factors.
- Only one study (ORIGIN trial; N = 12,422) investigated whether the specific type of fish consumed had effect on outcomes.

*Scott T. Larson, MD*
*University of Iowa FMRP*
*Iowa City, IA*