GOOD EVIDENCE MATTERS

GEMs of the Week

SPOTLIGHT

The Cost of Caution: Real-World Complications of Lung Cancer

Don’t D-Lay:

High dose Vitamin D Reduces Disease Activity in Multiple Sclerosis

Tuning Out the Baby Blues:

Does Music Help?

FPIN
Family Physicians Inquiries Network

Volume 6 Issue 13

The Cost of Caution: Real-World Complications of Lung Cancer

Rates of Downstream Procedures and Complications Associated with Lung Cancer Screening in Routine Clinical Practice: A Retrospective Cohort Study

Rendle KA, Saia CA, Vachani A, et al. Rates of Downstream Procedures and Complications Associated with Lung Cancer Screening in Routine Clinical Practice: A Retrospective Cohort Study. *Ann Intern Med*. 2024;177(1):18-28. doi:10.7326/M23-0653

KEY TAKEAWAY: Rates of downstream imaging, invasive procedures and complications from lung cancer screening with low-dose computed tomography (LCS-LDCT) are higher in clinical practice than in trial-based studies.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Lung cancer screening guidelines are largely based on clinical trials which have demonstrated LCS-LDCT yields early lung cancer detection and reduce mortality but carries risks of downstream procedural complications. As real-world data on downstream harms is lacking, this study examined the frequency of LCS-LDCT in clinical practice.

PATIENTS: Adults who completed a baseline LCS-LDCT

INTERVENTION: LCS-LDCT

CONTROL: National Lung Cancer Screening Trial (NLCS)

PRIMARY OUTCOME: Downstream procedures and complications

Secondary Outcome: Accuracy and reliability of LCS-LDCT

METHODS (BRIEF DESCRIPTION):

- Retrospective patient data was gathered from the Population-based Research to Optimize the Screening Process (PROSPR) Lung Consortium across five health care systems in the United States.
- The study analyzed a primary "screening cohort" of adults 55–80 years old who completed a baseline LCS-LDCT between 2014 and 2018.
- A nested "invasive procedures cohort" also identified those who underwent invasive procedures following abnormal screening.
- A matched cohort of non-screened patients was reported in a study supplement.
- PROSPR data was compared to the National Lung Screening Trial (NLST) data.
- Outcomes reported:
  - Screening results
  - Downstream Imaging: Chest CT, LCS-LDCT, positron emission tomography (PET), magnetic resonance imaging (MRI)
  - Downstream invasive procedures: Needle biopsy, bronchoscopy, mediastinoscopy or mediastinotomy, thoracoscopy, thoracotomy, and other pleural procedures
  - Minor, intermediate, or major complications
- Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of LCS-LDCT vs confirmed lung cancer diagnosis were also reported.

INTERVENTION (# IN THE GROUP):

- Screening cohort: 9,266
- Invasive procedures cohort: 180

COMPARISON (# IN THE GROUP):

- Supplemental matched cohort: Not specified in primary study
- NLST participants: 26,309

FOLLOW-UP PERIOD:

- 12 months for downstream outcomes
- 12–24 months for lung cancer confirmation.

RESULTS:

Primary Outcome –

- 32% (95% CI, 31–33) of PROSPR patients underwent downstream imaging.
- 2.8% (95% CI, 2.5–3.1) of PROSPR patients underwent invasive procedures.
- 31% (95% CI, 24–37) of PROSPR patients who underwent invasive procedures experienced complications; 21% (95% CI, 15–27) experienced major complications.
  - Compared to NLST in which 18% experienced complications and 9.4% experienced major complications.

Secondary Outcome –

- 16% of screening cohort had abnormal baseline LCS-LDCT; 9.5% of which received a lung cancer diagnosis within 12 months.
  - Sensitivity 93% (95% CI, 89–97)
  - Specificity 84% (95% CI, 84–85)
  - PPV 9.5% (95% CI, 8.0–11)

- NPV 99.8% (95% CI, 99.7–99.9)

LIMITATIONS:

- The retrospective design had potential underreported data due to coding inaccuracies.
- Indications for procedures and complications were inferred from codes, risking misclassification and limiting causal conclusions.
- Different criteria for abnormal results in this study and the NLST limit direct comparison.
- Findings may not represent all healthcare systems.

Sean George, DO
Community Health Care FMRP
Tacoma, WA

Don't D-Lay: High dose Vitamin D Reduces Disease Activity in Multiple Sclerosis

High-Dose Vitamin D in Clinically Isolated Syndrome Typical of Multiple Sclerosis: The D-Lay MS Randomized Clinical Trial

Thouvenot E, Laplaud D, Lebrun-Frenay C, et al. High-Dose Vitamin D in Clinically Isolated Syndrome Typical of Multiple Sclerosis: The D-Lay MS Randomized Clinical Trial. *JAMA*. 2025;333(16):1413-1422. doi:10.1001/jama.2025.1604

KEY TAKEAWAY: Oral vitamin D at 100,000 IU every two weeks significantly reduced disease activity in early, relapsing remitting multiple sclerosis (MS).

STUDY DESIGN: Multi-site double blind randomized phase three trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to disease-oriented outcome)

BRIEF BACKGROUND INFORMATION: In patients with MS, lower vitamin D is associated with higher risk of relapse, magnetic resonance imaging (MRI) lesions, and functional disability. Vitamin D is often used as an adjunctive therapy for MS. This study investigated the use of monotherapy vitamin D for MS relapse.

PATIENTS: Adults with clinically isolated syndrome (CIS) consistent with MS

INTERVENTION: Vitamin D supplementation

CONTROL: Placebo

PRIMARY OUTCOME: Time to relapse or first MRI detected activity.

Secondary Outcome: MRI activity, clinical outcomes

METHODS (BRIEF DESCRIPTION):

- The multicenter phase three placebo-controlled trial randomized adults with CIS consistent with MS over two years to receive vitamin D or placebo and followed for relapse of MS.
- Patients 18–55 years old were recruited from 36 MS centers in France.
- Patients with CIS by the 2010 McDonald criteria were included (with MRI findings of T2/FLAIR and T1 gadolinium weighted imaging regardless of spinal cord MRI demonstrated dissemination in space or 2 MRI lesions consistent with MS and cerebrospinal fluid with two unique oligoclonal bands).
- The McDonald guidelines (2017) were updated during the study period and patients were re-categorized as MS vs prior CIS and included as a subgroup for analysis.
- Patients already treated with Disease Modifying Antirheumatic Drugs (DMARDS) and vitamin D levels >100 nmol/L were excluded.
- Patients had a mean age of 35 years old, most were women (66% in vitamin D group vs 73% in placebo group), and average vitamin D was <50 nmol in both groups.
- The treatment group received 100,000 IU of oral Vitamin D3 every two weeks.
- The comparison group received an oral placebo.
- The primary outcome was time to disease activity (defined as first relapse or first detected MRI activity) which was determined by neurologists at regularly scheduled medical visits.
- Relapses were determined by type of neurological finding, defined as multi or monofocal, and date of onset of symptoms.
- Medical visits included spinal and brain MRI and a battery of disability scales and patient questionnaires.
- These were measured at baseline, three, 12, 24 months, and at relapse.
- The secondary outcomes were new and contrast-enhancing lesions as identified on MRI. Disability was measured using the Expanded Disability Status Scale (EDSS). Scores range from 0–10, with higher scores indicating more disability.

INTERVENTION (# IN THE GROUP): 156

COMPARISON (# IN THE GROUP): 147

FOLLOW-UP PERIOD: 24 months

RESULTS:

Primary Outcome –

- Patients in the Vitamin D group had longer time to disease activity compared to placebo (432 days vs 224 days, respectively; log rank test p=.003).
- Patients in the Vitamin D group had less disease activity at 24 months compared to placebo (94 events vs 109 events, respectively; adjusted hazard ratio [aHR] 0.65; 95% CI, 0.49–0.87; NNT=8).

Secondary Outcome –

- Patients had similar rates of relapse in the Vitamin D group compared to placebo (28 events vs 32 events, respectively; HR 0.69; 95% CI, 0.42–1.2).
- Patients in the vitamin D group had less MRI activity compared to placebo (89 events vs 96; HR 0.72; 95% CI, 0.53–0.97).
- Patients had fewer enlarging or new lesions in vitamin D group compared to placebo (72 vs 87, respectively; HR 0.62; 95% CI, 0.44–0.86).
- Patients had no significant difference in disability in the vitamin D group compared to placebo.

LIMITATIONS:

- The time from MRI findings to clinical symptoms can be up to five years and may affect ability to detect outcomes.
- The study was conducted in France and lacks generalizability.
- MRI was done on fixed time which means some lesions may have started or may be missed in real time occurrence.
- The study was not funded to measure vitamin D blood levels at each visit.
- The McDonald criteria changed during the study and many patients reclassified with MS would have been started on DMARDS making the results difficult to interpret for future CIS patients.

Brian Renner, MD, MS
Alaska Family Medicine Residency
Anchorage, AK

Tuning Out the Baby Blues: Does Music Help?

Effect of Music Intervention on Perinatal Depressive Symptoms: A Meta-Analysis

Sun X, Wang R, Cong S, et al. Effect of Music Intervention on Perinatal Depressive Symptoms: A Meta-analysis. *J Psychiatr Res*. 2024;178:78-87. doi:10.1016/j.jpsychires.2024.08.004

KEY TAKEAWAY: Music interventions can reduce short-term perinatal depressive symptoms compared to control, particularly in low/middle income countries.

STUDY DESIGN: Systematic review and meta-analysis of 10 randomized controlled trials (RCTs) (N=988)

LEVEL OF EVIDENCE: STEP 3 (downgraded due to high risk of bias, significant heterogeneity, very-low GRADE rating, short effect duration)

BRIEF BACKGROUND INFORMATION: Perinatal depression is a common complication during pregnancy and the postpartum period, with significant adverse effects on women, their children, and society. While treatments like psychotherapy and medication exist, they have limitations such as high costs, stigma, and potential side effects. This study evaluated music intervention as an inexpensive, non-invasive alternative and explores which specific features of the intervention are most effective.

PATIENTS: Pregnant or postpartum women (up to 12 months after childbirth)

INTERVENTION: Music interventions

CONTROL: Routine care, waitlist control, or sitting quietly

PRIMARY OUTCOME: Depressive symptoms

METHODS (BRIEF DESCRIPTION):

- Systematic review of 2,445 records; 10 RCTs (published 2008–2024) met inclusion criteria.
- RCTs of pregnant or postpartum women (up to 12 months post-birth) utilizing music interventions were included in the review.
  - Six studies in low-/middle-income countries (China, Turkey, Brazil); four in high-income countries (Germany, UK)
- Non-English, no full text, duplicates, combined interventions, or studies related to drug abuse/history of mental illness were excluded from the review.
- The music interventions included:
  - Music medicine (listening to lullabies/folk/classical prescribed by clinicians)
  - Music therapy (sessions led by trained music therapists who led singing/songwriting).
- Intervention frequency ranged from weekly to twice weekly daily with session durations of 10–60 minutes.
- The control included routine care, no intervention waitlist, or quiet sitting.
- The primary outcome assessed depressive symptoms using various validated scales including Edinburgh Postnatal Depression Scale (EPDS), Beck Depression Inventory (BDI), or Hamilton Depression Scale (HAMD).
- A subgroup analysis was completed for the following criteria: Perinatal state, perinatal complication, country income level, intervention site, type of intervention, and total length of interventions.

INTERVENTION (# IN THE GROUP): 531

COMPARISON (# IN THE GROUP): 457

FOLLOW-UP PERIOD: Varied (immediately after the intervention, 8 days to 12 weeks postpartum)

RESULTS:

Primary Outcome –

- Music interventions reduced depressive symptoms compared to control (10 studies, n = 978; standardized mean difference [SMD] −0.61; 95% CI, −0.91 to −0.32; I^2=78%).

Secondary Outcome –

- Music interventions reduced depressive symptoms during pregnancy (6 studies; SMD −0.51; 95% CI, −0.80 to −0.22; I^2=67%) and postpartum (4 studies; SMD −0.75; 95% CI, −1.5 to −0.03; I^2=87%).
- Music interventions reduced depressive symptom for patients with complications (4 studies; SMD −0.81; 95% CI, −1.1 to −0.52; I^2=0%) and without (6 studies; SMD −0.53; 95% CI, −0.93 to −0.14; I^2=85%).
- Music interventions reduced depressive symptom for patients in low-/middle-income countries (6 studies; SMD −0.79; 95% CI, −1.2 to −0.42; I^2=75%); music interventions had no significant effect in high-income countries.

- Music interventions reduced depressive symptoms in hospital (4 studies; SMD −0.86, 95% CI, −1.4 to −0.31; I^2=78%) and home settings (4 studies; SMD −0.66; 95% CI, −0.94 to −0.37; I^2=34%); no significant effect when hospital + home were combined.
- Music medicine reduced depressive symptoms (6 studies; SMD –0.82; 95% CI, –1.2 to –0.47; I^2=74%). Music therapy did not reduce depressive symptoms.
- Interventions evaluated <6 weeks reduced depressive symptoms (5 studies; SMD –0.85, 95% CI, –1.3 to –0.45; I^2=79%). Interventions ≥6 weeks did not reduce depressive symptoms compared to control group.

LIMITATIONS:

- There was high heterogeneity across included trials, limiting precision and pooling confidence.
- Six of the 10 included trials rated high overall risk of bias.
- Most studies assessed only immediate post-intervention with few short follow-ups.
- Intervention variability (type, frequency, duration, setting) and measurement tools (EPDS, BDI, HAMD) contribute to inconsistency.
- GRADE certainly is very low, so results should be interpreted with caution and confirmed by higher-quality RCTs.
- Although statistical significance was reported, the minimal clinical important difference (MCID) was not mentioned or evaluated.

Jenish Patel, MD
Froedtert & Medical College of Wisconsin FMRP
Menomonee Falls, WI