GOOD EVIDENCE MATTERS

GEMs of the Week

SPOTLIGHT

Low Back Pain:
Separating the Helpful from the Hype

Back in Action:
The Role of Resistance Training in Chronic Low Back Pain

Insomnia Treatment Showdown:
iCBT vs Psychoeducation

rTMS and Tai Chi Improves Cognition and Sleep in Older Adults

Beyond Insulin:
Can GLP-1 Agonists Transform T1DM Care?

How Low Can You Go:
Intensive LDL Cholesterol Lowering in Secondary Prevention of ASCVD

The Breast Defense

FPIN
Family Physicians Inquiries Network

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Pharmacological Treatments for Low Back Pain in Adults: An Overview of Cochrane Reviews

Cashin AG, Wand BM, O'Connell NE, et al. Pharmacological treatments for low back pain in adults: an overview of Cochrane Reviews. *Cochrane Database Syst Rev*. 2023;4(4):CD013815. Published 2023 Apr 4. doi:10.1002/14651858.CD013815.pub2

KEY TAKEAWAY: Most pharmacologic treatments do not meaningfully improve pain or function in adults with chronic low back pain (LBP) compared to placebo. Non-steroidal anti-inflammatory drugs (NSAIDs) for acute LBP and opioids for chronic LBP provide small improvements in pain and function, while muscle relaxants and opioids increase adverse events. Safety data for other agents remain inconsistent.

STUDY DESIGN: Cochrane review of seven reviews including 103 randomized controlled trials (RCTs) (N=22,238)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: LBP is common around the globe with estimates that up to 38% of people will experience it in their lifetime. Pharmacologic intervention is the most used treatment in LBP. This study aimed to summarize effectiveness and safety of medications used to treat LBP.

PATIENTS: Adults ≥18 years old with nonspecific, chronic LBP

INTERVENTION: Various pharmacologic interventions

CONTROL: Placebo

PRIMARY OUTCOME: Pain, physical function, and safety
Secondary Outcome: Ratings of improvement, health related quality of life (HRQoL)

METHODS (BRIEF DESCRIPTION):

- A search identified Cochrane reviews of RCTs evaluating systemic pharmacologic treatments for adults with non-specific LBP.
  - Chronic LBP defined as pain >12 weeks between the bottom rib and gluteal fold
- Reviews with LBP due to spinal stenosis and other known anatomical defects (fractures, neoplasm) were excluded.
- Interventions included NSAIDs, paracetamol, muscle relaxants, benzodiazepines, opioid analgesics, and antidepressants
- Treatment/intervention dosages were not included. Various routes of administration were used.
- Treatment duration ranged from one injection up to 24 weeks.
- All reviews included placebo comparisons, and two included only intervention versus control comparisons
- Primary outcomes:
  - Pain was measured via the Visual Analogue Scale (VAS), Numerical Rating Scale (NRS), Brief Pain Inventory (BPI), and other validated measures. Scores on the scales range from 0–100 scales, with higher scores indicating worse pain.
  - Physical function was measured via the Roland-Morris Disability Questionnaire (RMDQ) and Oswestry Disability Index (ODI). Scores on the RMDQ range from 0–24, with higher scores indicating worse disability. Scores on the ODI range from 0–100% with higher scores indicating worse disability
  - Safety was measured as withdrawal due to adverse events and reported adverse events.
- Secondary outcomes:
  - Rating of improvement were measured using the Patient Global Impression of Change on a seven-point scale with a score of one being "Very Much Improved."
  - HRQoL was measured vis the 36 Item Short Form Health Survey (SF36). Scores range from 0–100, with higher scores indicating better health.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Variable (1 injection to up to 24 weeks of treatment)

RESULTS:

Primary Outcome –

- NSAIDs, muscle relaxants, and benzodiazepines reduced acute LBP intensity compared to placebo.

    - NSAIDs (4 studies, n=815; mean difference [MD] −7.29; 95% CI, −11 to −3.6; I^2=0%)
    - Muscle relaxants and benzodiazepines (5 studies, n≈500; risk ratio [RR] 0.62; 95% CI, 0.46–0.85; I^2=not reported)
- Paracetamol did not reduce pain intensity compared to placebo. No Cochrane reviews reported placebo-controlled data for opioids in acute LBP.
- NSAIDs, strong opioids, tramadol, buprenorphine, muscle relaxants, and benzodiazepines reduced chronic LBP intensity compared to placebo.
    - NSAIDs (13 studies, n=1,354; MD −6.9; 95% CI, −11 to −3.2; I^2=65%)
    - Strong opioids (5 studies, n=1,400; standardized mean difference [SMD] −0.43; 95% CI, −0.56 to −0.30; I^2=0%)
    - Tramadol (3 studies, n=900; SMD −0.55; 95% CI, −0.66 to −0.44; I^2=0%)
    - Buprenorphine (2 studies, n;650; SMD −0.40; 95% CI, −0.58 to −0.23; I^2=not reported)
    - Muscle relaxants (3 studies, n=300; RR 0.63; 95% CI, 0.40–0.98; I^2=not reported)
    - Benzodiazepines (2 studies, n=200; RR 0.71; 95% CI, 0.50–0.90; I^2=not reported)
- Antidepressants, tricyclic antidepressants, and SSRIs did not reduce pain intensity compared to placebo.
- NSAIDs, muscle relaxants, and benzodiazepines improved acute LBP disability compared with placebo.
    - NSAIDs (4 studies, n=815; MD −2.0; 95% CI, −2.9 to −1.2; I^2=0%)
    - Muscle relaxants and benzodiazepines (4 studies, n=400; RR 0.60; 95% CI, 0.40−0.80; I^2=not reported)
- Paracetamol did not improve disability compared to placebo.
- Strong opioids, tramadol, buprenorphine, and NSAIDs improved chronic LBP disability compared to placebo.
    - Strong opioids (5 studies, n=1,400; SMD −0.30; 95% CI, −0.37 to −0.20; I^2≈0%)
    - Tramadol (3 studies, n=900; SMD −0.20; 95% CI, −0.30 to −0.10; I^2≈0%)
    - Buprenorphine (2 studies, n=650; SMD −0.10; 95% CI, −0.50 to −0.20; I^2=not reported)
    - NSAIDs (13 studies, n=1,354; MD −0.89; 95% CI, −1.30 to −0.40; I^2≈60%)
- Antidepressants did not improve disability compared to placebo.
- Muscle relaxants, benzodiazepines, and opioids increased adverse events compared to placebo.
    - Muscle relaxants and benzodiazepines (5 studies, n=500; RR 1.5; 95% CI, 1.1−2.0; I^2=not reported)
    - Opioids (11 studies, n=2,500; RR 1.3; 95% CI, 1.1−1.4; I^2=not reported)
- Paracetamol and NSAIDs did not increase adverse events compared to placebo.

Secondary Outcome –

- Muscle relaxants and benzodiazepines increased the likelihood of patient-reported improvement compared to placebo in acute LBP.
    - Muscle relaxants (5 studies, n=500; RR 0.62; 95% CI, 0.46−0.85; I^2=not reported)
    - Benzodiazepines (2 studies, n=200; RR 0.71; 95% CI, 0.50−0.90; I^2=not reported)
- Opioids and antidepressants did not improve HRQoL compared to placebo in chronic LBP.

LIMITATIONS:

- Several authors of the included reviews also authored this review
- Six of seven reviews were published >5 years ago
- Lack of standardized reporting of side effects across intervention limits safety data.

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Back in Action: The Role of Resistance Training in Chronic Low Back Pain

Impact of Isolated Lumbar Extension Strength Training on Reducing Nonspecific Low Back Pain, Disability, and Improving Function: A Systematic Review and Meta-Analysis

Trybulski R, Michał W, Małgorzata S, et al. Impact of isolated lumbar extension strength training on reducing nonspecific low back pain, disability, and improving function: a systematic review and meta-analysis. *Sci Rep*. 2025;15(1):6426. Published 2025 Feb 21. doi:10.1038/s41598-025-90699-5

KEY TAKEAWAY: Isolated lumbar extension (ILEX) strength training reduces pain intensity but does not consistently show improvement in disability or physical function in adults with chronic nonspecific low back pain.

STUDY DESIGN: Systematic review and meta-analysis of eight randomized controlled trials (RCTs) (N=381)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to significant heterogeneity)

BRIEF BACKGROUND INFORMATION: Chronic nonspecific low back pain is a leading cause of disability worldwide, and resistance-based exercise is commonly recommended as part of treatment. Isolated lumbar extension training targets lumbar extensor musculature using pelvic stabilization to strengthen the area that may be causing pain. As its effectiveness relative to other interventions remains unclear, this review aims to evaluate whether isolated lumbar extension training improves pain, disability, and function.

PATIENTS: Adults with chronic nonspecific low back pain

INTERVENTION: ILEX strength training

CONTROL: No intervention or alternative exercise programs

PRIMARY OUTCOME: Pain intensity, disability, physical function

METHODS (BRIEF DESCRIPTION):

- PubMed Clinical Queries was utilized with the search terms “chronic low back pain AND resistance training” with a therapy filter and broad scope. Articles were then screened for relevance and eligibility.
- Adults (>18 years old) with chronic low back pain participating in resistance training from RCTs, studies with the intervention lasting at least four weeks that included a minimum of one supervised session per week and consisted of a specific lumbar training program utilizing a restraint system designed to facilitate isolated lumbar extension resistance training were included in the study.
- Exclusion criteria:
  - Individuals <18 years old and those with non-chronic low back were excluded.
  - Studies that focused on pain associated with pregnancy, infection, tumors, osteoporosis, fractures, structural deformities (e.g., scoliosis), inflammatory disorders, radicular syndrome, or cauda equina syndrome.
  - Resistance interventions did not include isolated lumbar extension resistance training
  - Assessments that reported only one time point or other health-related outcomes
- The intervention was ILEX training using specialized lumbar extension machines with pelvic stabilization
- Comparisons included no treatment or general exercise programs
- The following were measured as the primary outcomes:
  - Pain intensity was measured using the Visual Analogue Scale (VAS), scored 0–100, the Numerical Rating Scale (NRS), scored 0–100, and the Brief Pain Inventory (BPI), scored 0–100. Higher scores indicate worse pain
  - Disability was measured using the Roland-Morris Questionnaire, scored 0–24 and the Oswestry Disability Index, scored 1–100. Higher scores indicate higher disability
  - Physical function measured:
    - Range of motion using the trunk flexion test. Scores range from 0–5 with higher scores indicating more function
    - Strength levels using the sit to stand test. A numerical value recorded in 30 seconds with higher number indicating higher function
    - Flexibility level using the Thomas Test which was graded as a pass/fail based on visual examination of hip flexor tightness.

- Risk of bias was assessed using RoB 2, and certainty of evidence was evaluated using GRADE

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Varied (ranged from 6–12 weeks)

RESULTS:

Primary Outcome –

- ILEX reduced pain intensity compared to control (4 studies, n=123; effect size [ES] −0.63; 95% CI, −1.1 to −0.20; I^2=19%).
- ILEX did not significantly improve disability compared to control (4 studies, n=111; ES −0.29; 95% CI, −0.73 to 0.14; I^2=20%).
- ILEX did not significantly improve physical function compared to control (4 studies, n=172; ES 0.97; 95% CI, −0.35 to 2.3; I^2=93%).

LIMITATIONS:

- The meta-analysis included a small number of trials.
- Overall, there were small sample sizes across studies.
- There was a moderate risk of bias in several trials due to lack of blinding.
- There was significant heterogeneity (92%) present for the strength outcomes.
- Based on GRADE, there is a very low certainty of evidence.

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Insomnia Treatment Showdown: iCBT vs Psychoeducation

Efficacy of a Self-Guided Internet Intervention with Optional On-Demand Feedback vs Digital Psychoeducation on Sleep Hygiene for University Students with Insomnia: Randomized Controlled Trial

Zarski AC, Bernstein K, Baumeister H, et al. Efficacy of a Self-Guided Internet Intervention With Optional On-Demand Feedback Versus Digital Psychoeducation on Sleep Hygiene for University Students With Insomnia: Randomized Controlled Trial. *J Med Internet Res*. 2025;27:e58024. Published 2025 May 8. doi:10.2196/58024

KEY TAKEAWAY: Self-guided internet based cognitive behavioral therapy (iCBT) improves insomnia severity compared to sleep hygiene education for university students with insomnia after six months.

STUDY DESIGN: Randomized controlled trial (RCT)

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size)

BRIEF BACKGROUND INFORMATION: Insomnia is highly prevalent in university students and is associated with worse mental and physical health and reduced quality of life. Current treatment guidelines recommend CBT as the first-line intervention for insomnia. This study investigated the benefits of iCBT compared to sleep hygiene psychoeducation alone.

PATIENTS: University students ≥18 years old with insomnia

INTERVENTION: Independent CBT

CONTROL: Sleep hygiene psychoeducation

PRIMARY OUTCOME: Insomnia severity

Secondary Outcomes: Insomnia diagnosis, depression, sleep quality, sleep efficiency, worrying, recovery experiences, recovery activities, presenteeism, procrastination, cognitive irritation, recuperation in sleep, user satisfaction

METHODS (BRIEF DESCRIPTION):

- University students from Germany, Austria, and Switzerland >18 years old with an Insomnia severity index (ISI) score ≥10 who had internet access were included in the study. Patients were screened with the ISI score through a phone call by a clinical professional.
- Patients were randomized 1:1 to iCBT-I or active control.
- The intervention group consisted of six weekly online sessions of iCBT-I including information about recovery and sleep hygiene, stimulus control and sleep restriction techniques, improvement of sleep efficiency via reviewing their sleep restriction, addressing negative thinking, metacognitive therapy, and relapse prevention
- The control group received one digital psychoeducation session without interactive exercises
- Primary outcome was insomnia severity measure using the German version of the Insomnia Severity Index (ISI), a 7-item scale with scores ranging from 0–28, with higher scores indicating a more severe disease insomnia. Minimal clinically important difference (MCID) was 4.7 points.
- Secondary outcomes were measured as follows:
  - Depression presence using DSM-5 diagnosis criteria
  - Sleep quality was measured using Pittsburgh Sleep Quality Index. Scores range from 0–3, with higher scores indicating worse sleep quality.
  - Sleep efficiency was quantified by sleep time/hours in bed, a higher percentage (>85%) indicates efficient sleep
  - Worrying was measured using the Penn State Worry Questionnaire. Scores range from 0–18, with higher scores indicating more worrying.
  - Recovery experiences were measured using a 16-item Recovery Experience Questionnaire. Scores range from 16–80, with higher scores indicating greater recovery experiences.
  - Recovery activities were measured using a 21-item Recreation Experience and Activity Questionnaire. Scores range from 21–105, with higher scores indicating more engagement.
  - Presenteeism was measured using a 10-item survey to measure work impairment. Scores range from 20–100, with higher scores indicating lower presenteeism.
  - Procrastination was measured using a seven-item scale. Scores range from 7–35, with higher

scores indicating increased procrastination present.
    - Cognitive irritation was measured using a three-item Irritation Scale. Scores range from 3–21, with higher scored indicating more irritation.
    - Recuperation in sleep was measured using an eight-item sleep questionnaire. Scores range from 8–40, with higher scores indicating more sleep recuperation.
    - User satisfaction was measured using an eight-item Client Satisfaction Questionnaire. Scores range from 8–32, with higher scores indicating more satisfaction.
- The primary and secondary outcomes were analyzed using analysis of covariance (ANCOVA) with intention-to-treat principle. Effect sizes between the groups were calculated with Cohen's d with 95% CI.

INTERVENTION (# IN THE GROUP): 45

COMPARISON (# IN THE GROUP): 45

FOLLOW-UP PERIOD: Eight weeks and six months

RESULTS:

Primary Outcome –

- iCBT-I did not reduce insomnia severity more than the sleep hygiene psychoeducation at eight weeks (mean score 11 vs 12, respectively; *P*=.29; cohen d –0.26; 95% CI, –0.68 to 0.17).
- iCBT-I reduced insomnia severity more than the sleep hygiene psychoeducation at six months (mean score 9.4 vs 12, respectively; *P*=.03; cohen d –0.57; 95% CI, –1.1 to –0.06).

Secondary Outcome –

- There were no significant differences in any of the secondary outcomes between iCBT and aCG groups at eight weeks or six months.

LIMITATIONS:

- The findings may lack clinical significance, as the mean difference in the primary outcome does not meet the MCID threshold.
- The study did not include a nontreatment control group.
- Participants may have been highly motivated students, which is not representative of other unmotivated patients.
- Women were overrepresented in the study, but this may reflect the higher prevalence of insomnia among women.
- The study included only participants with heightened insomnia severity and did not evaluate milder cases of insomnia.
- The small sample size may have limited the study's statistical power.
- Participants may have known their group intervention due to difference in intervention lengths (not double blinded).
- Circadian rhythm sleep disorders were not excluded or documented.

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rTMS and Tai Chi Improves Cognition and Sleep in Older Adults

Repetitive Transcranial Magnetic Stimulation and Tai Chi Chuan for Older Adults with Sleep Disorders and Mild Cognitive Impairment: A Randomized Clinical Trial

Liu Z, Zhang L, Bai L, et al. Repetitive Transcranial Magnetic Stimulation and Tai Chi Chuan for Older Adults with Sleep Disorders and Mild Cognitive Impairment: A Randomized Clinical Trial. *JAMA Netw Open*. 2025;8(1):e2454307. Published 2025 Jan 2. doi:10.1001/jamanetworkopen.2024.54307

KEY TAKEAWAY: Repetitive transcranial magnetic stimulation (rTMS) targeting the right dorsolateral prefrontal cortex improved the benefits of Tai Chi Chuan (TC) for sleep and cognitive performance in older adults compared to sham rTMS.

STUDY DESIGN: Single site randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: TC has previously been shown to improve neural plasticity. rTMS has also been documented to alleviate sleep disturbances. A previous small-scale study in 2024 showed a synergistic effect of combining rTMS with TC to improve sleep.

PATIENTS: Adults with sleep disorders and mild cognitive impairment

INTERVENTION: rTMS with TC

CONTROL: Sham rTMS with TC

PRIMARY OUTCOME: Sleep quality and cognition

Secondary Outcome: Memory, time to task completion, mood

METHODS (BRIEF DESCRIPTION):

- Study participants were recruited from community centers in China with a clinical diagnosis of a sleep disorder and experiencing mild cognitive impairment (MCI) without dementia for evaluation of TC augmentation with rTMS.
- Adults 60–75 years old with a clinically diagnosed sleep disorder, mild cognitive impairment, and not currently participating in moderate intensity exercise were included.
- Patients with depression, use of antipsychotics, or conditions causing secondary sleep disorders were excluded.
- The mean age was 68 years old, most were female (62%), and most never smoked (98% in treatment group, 87% in control) or used alcohol (95% in treatment group, 93% in control).
- For six weeks, participants received either rTMS (20 minutes 5 times per week) and TC (60 minutes 5 times per week), or sham rTMS (20 minutes 5 times per week) and TC (60 minutes times per week).
- Sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI). Scores range from 0–21, with lower scores indicating better sleep quality.
- Cognition was measured using the Montreal Cognitive Assessment (MoCA). Scores range from 0–30, with higher scores indicating better cognition.
- The following were measured as the secondary outcomes:
  - Memory was measured using the Wechsler Scale-Revised. Scores range from 40–160, with higher scores indicating stronger memory.
  - Task completion was measured using the Trail Making Test Part B measured by time to complete the assigned task.
  - Mood was measured using the Hamilton depression scale. Scores range from 0–52, with higher scores indicating more severe depression.
- The primary and secondary outcomes were measured at a six and 12 week visit.

INTERVENTION (# IN THE GROUP): 55

COMPARISON (# IN THE GROUP): 55

FOLLOW-UP PERIOD: Six and 12 weeks

RESULTS:

Primary Outcome –

- Patients who received rTMS in addition to TC had improved sleep compared to those receiving only TC at six and 12 weeks:
  - Six weeks (mean difference [MD] −3.1; 95% CI, −4.2 to −2.1)
  - 12 weeks (MD −2.1; 95% CI, −3.1 to −0.1)
- Patients who received rTMS in addition to TC had improved cognition compared to those receiving only TC at six and 12 weeks:
  - Six weeks (MD 1.4; 95% CI, 0.7–2.1)
  - 12 weeks (MD 0.9; 95% CI, 0.1–1.6)

Secondary Outcome –

- Patients who received rTMS in addition to TC had improved memory compared to those only receiving TC at six and 12 weeks:
  - Six weeks (MD 8.8; 95% CI, 5.0–13)
  - 12 weeks MD 7.0; 95% CI, 3.0–11)
- Patients who received rTMS in addition to TC had improved depression compared to those only receiving TC at six and 12 weeks:
  - Six weeks (MD −1.7; 95% CI, −2.5 to −1.0)
  - 12 weeks (MD –1.3; 95% CI, −2.0 to −0.5)
- Patients who received rTMS in addition to TC had similar task completion time at six weeks but had improved task completion time at 12 weeks compared to those receiving only TC (MD −20 seconds; 95% CI, −35 to −5.2).

LIMITATIONS:

- There was no wrist actigraphy for objective sleep data.
- Participants were limited to community centers in China.
- There was no preset determination on clinical significance for the measurement and the small mean differences reported may not be clinically meaningful.

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Beyond Insulin: Can GLP-1 Agonists Transform T1DM Care?

The Effects of GLP-1 Agonists on HbA1c and Insulin Dose Among Patients with Type 1 Diabetes

Alhowiti A, Mirghani H. The effects of GLP-1 agonists on HbA1c and insulin dose among patients with type 1 diabetes. *Front Endocrinol (Lausanne)*. 2025;16:1550938. Published 2025 Aug 7. doi:10.3389/fendo.2025.1550938

KEY TAKEAWAY: Glucogan-like-peptide-1 (GLP-1) agonists effectively decrease HbA1c and total daily insulin dose compared to placebo in patients with type 1 diabetes mellitus (T1DM).

STUDY DESIGN: Systematic review and meta-analysis of 10 randomized clinical trials (RCTs) (N=2,699)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to high heterogeneity of the primary outcome results)

BRIEF BACKGROUND INFORMATION: T1DM accounts for roughly 2–5% of all diabetes cases, and insulin remains the primary treatment strategy. However, insulin therapy is associated with potential drawbacks, including weight gain, risk of hypoglycemia, and no established cardiovascular benefit. In contrast, GLP-1 receptor agonists have been shown to promote weight loss and provide renal and cardiovascular protective effects. As a result, GLP-1 receptor agonists may represent a useful adjunct to insulin therapy in patients with T1DM.

PATIENTS: Individuals diagnosed with T1DM

INTERVENTION: Treatment with a GLP-1 receptor agonist

CONTROL: Placebo

PRIMARY OUTCOME: Change in HbA1c and total daily insulin requirement

METHODS (BRIEF DESCRIPTION):

- A systematic search of Google Scholar, PubMed, and the Cochrane Library was performed by the authors to identify RCTs conducted in human subjects.
- Eligible studies were required to be published in English, have a minimum follow-up period of four weeks, and report outcomes related to HbA1c and total daily insulin requirements.
- Non-randomized designs, opinion articles, and study protocols were excluded. Studies involving patients with type 2 diabetes were omitted, as were trials comparing GLP-1 receptor agonists with other pharmacologic classes such as DPP-4 inhibitors, SGLT-2 inhibitors, or monoclonal antibody therapies. Animal studies and trials with durations shorter than four weeks were excluded from review.
- Participants included individuals diagnosed with T1DM, without restrictions based on age or disease duration.
- Intervention arms consisted of GLP-1 receptor agonists administered alongside insulin therapy, including liraglutide (0.6–1.8 mg daily), exenatide (10 mcg every 8 hours or 2 mg weekly), and albiglutide (50 mg daily).
- Control groups received insulin therapy without the addition of a GLP-1 receptor agonist and were categorized as placebo comparators.
- The primary outcomes assessed were changes in HbA1c and total daily insulin dose.
- Risk of bias was assessed across standard RCT domains, including randomization, blinding, attrition, and reporting, with overall moderate risk and notable heterogeneity.
- Data was analyzed using meta-analysis with standardized mean difference and 95% CI, with statistical significance determined by Z-scores and p-values. Heterogeneity was evaluated using chi-square and I^2.

INTERVENTION (# IN THE GROUP): 2,718

COMPARISON (# IN THE GROUP): 811

FOLLOW-UP PERIOD: Varied (ranged from 4–52 weeks)

RESULTS:

Primary Outcome –

- GLP-1 receptor agonists reduced HbA1c compared to placebo (11 studies, N=2,699; standardized mean difference [SMD] 0.23; 95% CI, 0.1–0.32; I^2=44%).
- Higher dose liraglutide 1.2 mg reduced HbA1c compared to lower dose liraglutide 0.6 mg (3 studies, n=1,147; SMD −0.87; 95% CI, −0.60 to −0.13; I^2=96%).
- Similarly, higher dose liraglutide 1.8 mg improved HbA1c compared to lower dose liraglutide 0.6 mg (3 studies, n=1,147; SMD −0.79; 95% CI, −1.2 to −0.41; I^2=88%).
- GLP-1 receptor agonists reduced total daily insulin requirements compared to placebo (6 studies, n=341; SMD 2.21; 95% CI, 0.43–3.98; I^2=97%).

LIMITATIONS:

- There was high heterogeneity among studies in the insulin dose arm.
- The authors did not include long-acting GLP-1 agonists (semaglutide and dulaglutide) due to few studies assessing role in T1DM.

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How Low Can You Go: Intensive LDL Cholesterol Lowering in Secondary Prevention of ASCVD

Intensive LDL Cholesterol Targeting in Atherosclerotic Cardiovascular Disease

Lee YJ, Lee SJ, Kim JW, et al. Intensive LDL Cholesterol Targeting in Atherosclerotic Cardiovascular Disease. *N Engl J Med*. 2026;394(14):1365-1375. doi:10.1056/NEJMoa2600283

KEY TAKEAWAY: In patients with a history of atherosclerotic cardiovascular disease (ASCVD), intensive lowering of low-density lipoprotein (LDL) cholesterol to a target of <55 mg/dL is associated with a lower three-year risk of death from major atherosclerotic cardiovascular events compared to a conventional LDL target of <70 mg/dL.

STUDY DESIGN: Multi-center, open-label, randomized superiority trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: The most recent 2026 AHA/ACC dyslipidemia guidelines recommend an LDL target of <70 mg/dL for secondary prevention in patients with ASCVD not at very high risk and an LDL target of <55 mg/dL for patients at very high risk for future cardiovascular events. However, the evidence behind these targets is limited, as no study has defined a specific LDL cholesterol target.

PATIENTS: Patients with documented ASCVD

INTERVENTION: LDL cholesterol target of <55 mg/dL (intensive)

CONTROL: LDL cholesterol target of <70 mg/dL (conventional)

PRIMARY OUTCOME: A composite of death from cardiovascular causes, nonfatal myocardial infarction (MI), nonfatal stroke, revascularization, or hospitalization for unstable angina at three years after randomization

Secondary Outcome: Individual components of the primary outcome, new-onset diabetes, worsening glycemic control, statin-associated muscle symptoms, cancer diagnosis, cataract surgery, and elevation in liver-associated enzymes or creatinine kinase

METHODS (BRIEF DESCRIPTION):

- From January 2021 through July 2022, patients at 17 sites in South Korea were randomly assigned 1:1 to the intensive or conventional group.
- Mean age of patients was 64±9 years, and 21% were women.
- The median LDL cholesterol level was 76 mg/dL.
- Patients in each group were further randomly assigned 1:1 to either statin monotherapy or statin plus ezetimibe.
- The statin monotherapy group was further randomized to either rosuvastatin or atorvastatin treatment.
- Patients were followed up at one month, one, two, and three years with repeat lipid panel, assessment for occurrence of primary end points and adverse events, as well as medication adherence.
- During follow-up, medications were adjusted as needed to reach specified LDL target with the recommendation to increase statin dose and add ezetimibe prior to initiation of PCSK9 inhibitors.
- Survival status was validated by the Korean National Health Insurance database.

INTERVENTION (# IN THE GROUP): 1,526

COMPARISON (# IN THE GROUP): 1,522

FOLLOW-UP PERIOD: Three years

RESULTS:

Primary Outcome –

- The intensive group had a lower risk of death from cardiovascular causes, nonfatal MI, nonfatal stroke, revascularization, or hospitalization for unstable angina compared to the conventional group (hazard ratio [HR] 0.7; 95% CI, 0.5–0.9).

Secondary Outcome –

- The intensive group had a lower risk of the following compared to the conventional group:
  - Nonfatal MI (HR 0.5; 95% CI, 0.2–0.9)
  - Any revascularization (HR 0.6; 95% CI, 0.5–0.8)
- The intensive group had a lower risk of composite of death from any cause or any primary outcome event compared to the conventional group (HR 0.7; 95%CI, 0.6–0.9).
- There was no significant difference in death from cardiovascular causes, new-onset diabetes, non-fatal stroke, hospitalization for unstable angina, worsening glycemic control, statin-associated muscle

symptoms, elevation in liver-associated enzymes or creatinine kinase between the two groups.
- The intensive group had a lower incidence of creatinine elevation compared to the conventional group (1.2% vs 2.7%, respectively; difference –1.5%; 95% CI, –2.5 to –0.5).

LIMITATIONS:

- Trial was open-label and unblinded.
- Only 61% of patients in the intensive group achieved the LDL target cholesterol at three years, with low use of PCSK9 inhibitors in both groups.
- Other agents used in the United States (bempedoic acid and inclisiran) were unavailable for use in South Korea.
- The follow-up of three years may have been too limited to fully assess long-term effects of more intensive LDL lowering.
- Only East Asian patients were included, which may limit its generalizability.

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Breastfeeding and Health Outcomes for Infants and Children: A Systematic Review

Patnode CD, Henrikson NB, Webber EM, Blasi PR, Senger CA, Guirguis-Blake JM. Breastfeeding and Health Outcomes for Infants and Children: A Systematic Review. *Pediatrics*. 2025;156(1):e2025071516. doi:10.1542/peds.2025-071516

KEY TAKEAWAY: Breastfeeding is associated with significant reductions in infant mortality, sudden infant death syndrome (SIDS), otitis media, gastrointestinal (GI) infections, and obesity, supporting strong promotion of breastfeeding in clinical practice.

STUDY DESIGN: Systematic review of 145 observational and 29 randomized controlled studies (RCTs) (N=not reported)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to the risk of confounding variables and lack of generalizability)

BRIEF BACKGROUND INFORMATION: Breastfeeding is widely recommended by major health organizations, yet rates remain below national targets. Furthermore, while widely recommended, the specifics regarding duration, frequency, and their specific health outcomes are less well known. This review aimed to update the latest evidence of breastfeeding's impact on infant and child health outcomes to inform clinical recommendations for breastfeeding promotion.

PATIENTS: Infants and children in developed countries

INTERVENTION: Any breastfeeding (exclusive or partial)

CONTROL: No breastfeeding

PRIMARY OUTCOME: Infant and child health outcomes

METHODS (BRIEF DESCRIPTION):

- Search was conducted for English-language studies published between 2006 and 2024 within MEDLINE, Embase, and CINAHL databases supplemented by additional studies by expert recommendations, excluding studies that were assessed as credibly low using the AMSTAR 2 tool.
- Included studies assessed outcomes for term infants born to women without complications to breastfeeding within "very high" developed countries as defined by the 2021 Human Development Index.
- The intervention and comparison of breastfeeding was defined largely as ever vs never breastfeeding; however, inherent heterogeneity was recognized throughout the studies.
- Exposure was further categorized into ever vs never breastfed, exclusively vs non-exclusively breastfed, duration of breastfeeding as defined as if continuing to breastfeed at three vs six vs 18 months, duration of exclusive breastfeeding at similar time intervals, mode meaning direct or expressed breast milk, and source of breastfeeding meaning from the parent vs a donor
- Data on breastfeeding was gathered in most of these studies via maternal report in surveys or interviews
- Results on outcomes were collected throughout the subject's life in some cases, depending on the outcome assessed.
- Outcomes assessed included the incidence of otitis media, respiratory infections, GI infections, dental caries; the development of conditions such as asthma, obesity, cancer as defined as childhood leukemia, allergic rhinitis, malocclusion, inflammatory bowel disease (IBD), type 1 or type 2 diabetes, infant mortality, atopic dermatitis, celiac disease, and/or food allergies; or the impact on cognitive development measured through the Bayley scales of infant development on a scale of 40–160 across five developmental domains with 160 being higher functioning and the Wechsler Intelligence Scale for Children Revised (WISC-R) also assessing 5 developmental domains with a score of 45–155 with a higher score showing higher intellectual ability, cardiovascular outcomes such as systolic blood pressure (SBP), diastolic blood pressure (DBP), and cholesterols, and the rate of growth and weight gain measured at medical appointments.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Varied by outcome (ranged from infant through childhood up to age 18 years old)

RESULTS:

Primary Outcome –

- Breastfeeding significantly reduced the risk of developing acute otitis media compared to less breastfeeding (12 studies, n=not available; odds ratio [OR] 0.67; 95% CI, 0.59–0.76).
- Breastfeeding significantly reduced the risk of developing asthma compared to less breastfeeding (36 studies, n=not available; OR 0.76; 95% CI, 0.68–0.85).
- Breastfeeding significantly reduced the risk of developing obesity compared to less breastfeeding (159 studies, n=not available; OR 0.74; 95% CI, 0.70–0.78).
- Breastfeeding significantly reduced the risk of leukemia compared to less breastfeeding (19 studies, n=not available; risk ratio [RR] 0.90; 95% CI, 0.85–0.95).
- Breastfeeding for >12 months significantly increased the risk of dental caries compared to less breastfeeding (31 studies, n=not available; RR 1.5; 95% CI, 1.2–2.0).
- Breastfeeding was associated with significant reductions in the following:
    - Infant mortality (2 systemic reviews [k=18]; potential reduction in infant mortality; patient number not reported in review)
    - SIDS (included within infant mortality evidence; patient number not reported in review)
    - Otitis media (12 studies; n=not available; OR 0.67; 95% CI, 0.59–0.76)
    - GI infections (8 studies; potential reduction; pooled OR and patient number not reported in review)
    - Lower respiratory tract infections (16 studies; potential reduction; pooled OR and patient number not reported in review)
    - Childhood obesity (159 studies; n=not available; OR 0.74; 95% CI, 0.70–0.78)
    - Longer and exclusive breastfeeding showed stronger protective effects.
- Breastfeeding showed an association, but no significant correlation compared to less breastfeeding for respiratory and GI infections, type 1 diabetes, allergic rhinitis, malocclusion, IBD, rapid weight gain and growth, SBP, DBP, and infant mortality.
- Breastfeeding showed no significant correlation compared to less breastfeeding in the incidence of atopic dermatitis, celiac disease, cognitive ability, food allergies, or type 2 diabetes.

LIMITATIONS:

- Most of the included studies were observational, making it difficult to fully control for confounding variables (e.g., socioeconomic status, maternal education, smoking exposure, daycare attendance, etc.). Observational studies also raise concerns about reverse causation, selection bias, and missing data.
- Randomization of breastfeeding was not feasible.
- Heterogeneity in breastfeeding definitions and differences in duration of breastfeeding across studies limits comparability and makes studying specific impacts more difficult.
- Findings may not generalize to resource-limited settings given barriers such as support given to breastfeed.

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