GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of October 7 - 11, 2024

SPOTLIGHT:
Goals Matter When Deciding Between Exercise vs Diet vs Both for Your Health

Goals Matter When Deciding Between Exercise vs Diet vs Both for Your Health

Combined vs Independent Effects of Exercise Training and Intermittent Fasting on Body Composition and Cardiometabolic Health in Adults: A Systematic Review and Meta-Analysis

Khalafi M, Symonds ME, Maleki AH, Sakhaei MH, Ehsanifar M, Rosenkranz SK. Combined versus independent effects of exercise training and intermittent fasting on body composition and cardiometabolic health in adults: a systematic review and meta-analysis. *Nutr J.* 2024;23(1):7. Published 2024 Jan 6. doi:10.1186/s12937-023-00909-x

KEY TAKEAWAY: Combining exercise with intermittent fasting results in increased weight loss and improves body composition more than intermittent fasting alone, but does not outperform intermittent fasting alone in the improvement of cardiometabolic health markers except for VO_2 max.

STUDY DESIGN: Systematic review and meta-analysis of 11 randomized clinical trials (RCTs) (N=606)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: It is well documented that exercise alone and intermittent fasting alone can improve body composition and cardiometabolic health. This meta-analysis and systematic review attempted to determine if combining exercise with intermittent fasting would have an additive or synergistic effect on the above-listed factors.

PATIENTS: Adults that are overweight, obese or "hidden obese"

INTERVENTION: Exercise program + intermittent fasting

CONTROL: Exercise program alone or intermittent fasting alone

PRIMARY OUTCOME: Changes in body composition and cardiometabolic health

METHODS (BRIEF DESCRIPTION):

- The authors used PubMed, Web of Science, and Scopus as their databases to collect RCTs.
- Patients were individuals 21–45 years old with a BMI ranging from 22–37 kg/m^2.
  - There were no specific characterizations for the determination of “overweight”, “obese”, or “hidden obese” patients.
- Exercise intervention characteristics: HIIT, aerobic or combination exercise that was either supervised or unsupervised for 3–7 sessions a week.
  - The unsupervised sessions had a measurable goal that was to be reached by participants such as the number of steps.
- Dietary intervention characteristics: Varying between fasting vs ad libitum feeding days, usually 2–4 days of fasting in which 25% of daily energy requirement was consumed with ad libitum feeding on non-fasting days.
  - Four studies utilized a model in which participants had ≤10-hour eating window in a 24-hour period in which they could eat ad libitum.
  - One study made use of the diurnal fasting schedule of Ramadan: A dry fast of approximately 16 hours a day.
- Outcomes:
  - Body composition factors were composed of body weight, body mass index (BMI), lean body mass, visceral fat, and waist circumference.
  - Cardiometabolic health outcomes included fasting glucose, insulin, total cholesterol (TC), low-density lipoprotein cholesterol (LDL), triglycerides (TG), high-density lipoprotein cholesterol (HDL), systolic blood pressure (SBP), diastolic blood pressure (DBP), and $VO_{2max/peak}$.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: 4–16 weeks

RESULTS:

Primary Outcome –

- Compared to exercise alone, an exercise program + intermittent fasting resulted in decreased:
  - Body weight (11 studies, N=606; weighted mean difference [WMD] –3.0 kg; 95% CI, –3.4 to –2.5; I^2=0.0)
  - BMI (7 studies, n=403; WMD –1.1 kg/m^2; 95% CI, –1.3 to –0.95; I^2=0.0)
  - Body fat (11 studies, n=606; standard mean difference [SMD] –0.72; 95% CI, –1.2 to –0.21; I^2=79)

- Visceral fat (6 studies, n=344; SMD –0.34; 95% CI, –0.63 to –0.05; I^2=0.0)
- Waist circumference (5 studies, n=252; WMD –2.6 cm; 95% CI, –4.2 to –1.1; I^2=78)

- Exercise program + intermittent fasting had greater improvements in $VO_{2\ max/peak}$ compared to intermittent fasting alone (5 studies, n=338; SMD 0.55; 95% CI, 0.14–0.97; I^2=0.0) but not exercise alone (5 studies, n=338; SMD 0.26; 95% CI, –0.1 to 0.63; I^2=0.0).
- Exercise program + intermittent fasting did not improve the following compared to exercise alone:
  - Lean body mass (7 studies, n=370; SMD –0.04; 95% CI, –0.35 to 0.25; I^2=8.3)
  - Cholesterol:
    - TG (7 studies, n=423; WMD 3.2 mg/dl; 95% CI, –7.8 to 14; I^2=0.0)
    - TC (8 studies, n=446; WMD 3.8 mg/dl; 95% CI, –4.4 to 12; I^2=0.0)
    - LDL (7 studies, n=423; WMD –2.2 mg/dl; 95% CI, –11 to 6.4; I^2=0.0)
    - HDL (8 studies, n=446; WMD 0.11 mg/dl; 95% CI, –4.5 to 4.8; I^2=50)
  - Blood Pressure:
    - SBP (5 studies, n=291; WMD –1.7 mmHg; 95% CI, –4.6 to 1.2; I^2=0.0)
    - DBP (5 studies, n=291; WMD –0.21 mmHg; 95% CI, –2.5 to 2.1; I^2=0.0)
  - Blood glucose levels (5 studies, n=308; WMD –1.9 mg/dl; 95% CI, –6.2 to 2.4; I^2=38)
  - Insulin levels (4 studies, n=266; WMD –0.24; 95% CI, –0.58 to 0.10; I^2=0.0)

LIMITATIONS:

- Small sample size.
- Limited studies were able to satisfy inclusion and exclusion criteria.
- A limited number of studies in the analyses included data on blood pressure.
- Statistically significant heterogeneity was found for some but not all outcomes.
- Many of the studies analyzed had short-term follow up.

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Spitting in the Face of Adrenal Insufficiency: Salivary Cortisol Test as a Screening Adjunct

Home Waking Salivary Cortisone to Screen for Adrenal Insufficiency

Debono M, Elder CJ, Lewis J, et al. Home Waking Salivary Cortisone to Screen for Adrenal Insufficiency. *NEJM Evid.* 2023;2(2):EVIDoa2200182. doi:10.1056/EVIDoa2200182

KEY TAKEAWAY: At-home salivary cortisone testing proves a more convenient, comparable screening adjunct to the standard adrenocorticotropic hormone (ACTH) stimulation test usually performed in the hospital.

STUDY DESIGN: Prospective, blinded, comparative diagnostic accuracy test study

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Given the increased use of therapies with adrenal-suppressing side effects in addition to the persistence of conditions such as tuberculosis in developing countries, there stands a risk of undetected adrenal insufficiency in the outpatient setting. Salivary glucocorticoid samples may be how we can effectively and conveniently screen at-risk patients. The study aimed to assess the utility of salivary cortisol as a screening adjunct to the standard in-hospital ACTH stimulation test for adrenal insufficiency.

PATIENTS: Adults at high risk for adrenal insufficiency

INTERVENTION: Waking salivary glucocorticoid testing

CONTROL: Hospital ACTH stimulation test

PRIMARY OUTCOME: Identifying waking salivary cortisone cutoff values to successfully exclude, confirm, or require further testing for adrenal insufficiency

Secondary Outcome: Waking salivary cortisol and baseline serum cortisol levels in the hospital with ACTH stimulation testing to exclude adrenal insufficiency

METHODS (BRIEF DESCRIPTION):

- Adults ≥18 years old with an increased risk for any adrenal insufficiency were included.
- Increased risk was defined as patients on long-term glucocorticoids, patients with pituitary disease, inflammatory diseases, or cranial radiotherapy.
- Patients who were night shift workers, unable to produce sufficient salivary samples, with protein wasting conditions, alcohol use disorder, severe liver disease, uncontrolled active infections, pregnant, or who were taking estrogen were excluded from the study.
- Patients on drugs that impact the hypothalamic-pituitary-adrenal axis were withheld during testing.
- Each individual had designated testing days on which they provided a salivary sample and received the gold-standard ACTH stimulation test with baseline and 30-minute cortisol measurement.
- Those on glucocorticoids were asked to discontinue these medications for one day starting the evening before testing.
- Each patient was also surveyed on their views regarding at-home and in-hospital testing for adrenal insufficiency.
- The area under the receiver-operating characteristic (ROC) curve was used to detect the probability of accurately finding abnormal results.
- Outcomes were validated by liquid chromatography with tandem mass spectrometry (LC-MS-MS) assay.

INTERVENTION (# IN THE GROUP): 208

COMPARISON (# IN THE GROUP): 208

FOLLOW-UP PERIOD: Not applicable

RESULTS:

Primary Outcome –

- Waking salivary cortisone testing proved to have similar accuracy in 70% of subjects when confirming and excluding adrenal insufficiency compared with a 30-minute ACTH stimulation test (AuROC 0.95; 95% CI, 0.92–0.97).
  - A cutoff value of ≥612 ng/dL excluded adrenal insufficiency with 97% sensitivity (95% CI, 91–99) and a negative predictive value (NPV) of 96% (95% CI, 90–99).
  - A cutoff value of <251 ng/dL confirmed adrenal insufficiency with 97% specificity (95% CI, 92–99) and a positive predictive value (PPV) of 96% (95% CI, 87–99).

Secondary Outcome –

- Waking salivary cortisol levels and baseline serum cortisol (part of the ACTH testing protocol) were only mildly weaker predictors than the salivary cortisone levels (AuROC 0.89; 95% CI, 0.85–0.94).
  - A cutoff value of ≥180 ng/dL (5 nmol/L) excluded adrenal insufficiency with 95% sensitivity (95% CI, 88–99) and NPV of 94% (95% CI, 85–98).

    - A cutoff value of <35 ng/dL (1 nmol/L) confirmed adrenal insufficiency with 97% specificity (95% CI, 92–100) and PPV of 93% (95% CI, 80–99).
- Baseline serum cortisol levels (AuROC 0.90; 95% CI, 0.86–0.94)
    - A cutoff value of ≥11 µg/dL (310 nmol/L) excluded adrenal insufficiency with 96% sensitivity (95% CI, 90–99) and NPV of 93% (95% CI, 84–98).
    - A cutoff value <5.5 µg/dL (152 nmol/L) confirmed adrenal insufficiency with a specificity of 95% (95% CI, 90–98) and a PPV of 91% (95% CI, 81–97).

LIMITATIONS:

- The study population was largely White with only 10% of the subjects as non-White.
- The study population was comprised of only high-risk patients.
- There are no established, widely accepted, normal cortisol or cortisone levels; cutoffs were determined in relation to the reference range derived from the routine lab immunoassay's data that is purportedly reflective of global clinical care.

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Resist Depression: Can Resistance Training Reduce Depression in Older Adults?

A Systematic Review and Meta-Analysis of Resistance Training on Quality of Life, Depression, Muscle Strength, and Functional Exercise Capacity in Older Adults Aged 60 Years or More

Khodadad Kashi S, Mirzazadeh ZS, Saatchian V. A Systematic Review and Meta-Analysis of Resistance Training on Quality of Life, Depression, Muscle Strength, and Functional Exercise Capacity in Older Adults Aged 60 Years or More. *Biol Res Nurs.* 2023;25(1):88-106. doi:10.1177/10998004221120945

KEY TAKEAWAY: Resistance training interventions targeting adults ≥60 years old decrease depression compared to no training.

STUDY DESIGN: Systematic review and meta-analysis of 21 randomized controlled trials and control trials (N=1,610)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: As individuals age, they are prone to chronic conditions, disability, and overall muscle weakness, leading to decreased quality of life. Resistance training interventions may affect the overall health of the older population by increasing quality of life and decreasing depression. Managing chronic conditions and preventive care is the backbone of primary care. The study aimed to investigate the efficacy of resistance training on depression and overall quality of life.

PATIENTS: Adults ≥60 years old

INTERVENTION: Resistance training

CONTROL: No resistance training

PRIMARY OUTCOME: Depression severity

Secondary Outcome: Quality of life, muscle strength

METHODS (BRIEF DESCRIPTION):

- The patient population included adults from diverse backgrounds ranging from healthy individuals to those with multiple chronic conditions.
- Exclusion criteria included studies without a control group, resistance training with another intervention, and an active group.
- Individuals participated in a variety of resistance training exercises, which were defined as a regimented program to work muscle groups by using eccentric, concentric, or isometric muscle action.
- Each study compared individuals with resistance training to those with no intervention.
- Depression, quality of life, and muscle strength were measured by physical functioning, social functioning, mental health, general health, and mental component scores, which were standardized between studies.

INTERVENTION (# IN THE GROUP): 876

COMPARISON (# IN THE GROUP): 734

FOLLOW-UP PERIOD: Ranged from two weeks to nine months

RESULTS:

Primary Outcome –

- Resistance training significantly reduced depression compared to no intervention (4 trials, n=347; standardized mean difference [SMD] –1.1; 95% CI, –2.0 to –0.024).

Secondary Outcome –

- Resistance training significantly improved quality of life compared to no intervention (14 studies, n=943; SMD 0.31; 95% CI, 0.05–0.57).
- Resistance training significantly improved social functioning compared to no intervention (8 trials, n=550; SMD 0.25; 95% CI, 0.07–0.42).
- Resistance training increased muscle strength compared to no intervention.
  - Upper body strength (3 trials, n=2,065; mean difference [MD] 15 kg; 95% CI, 5.5–25; I^2=98%)
  - Lower body strength (3 trials, n=2,065; MD 48 kg; 95% CI, 6.5–90; I^2=100%)
  - Handgrip strength (2 trials, n=108; MD 1.4 kg; 95% CI, 0.47–2.2; I^2=0%)

LIMITATIONS:

- The type of resistance training varied greatly.
- The outcomes and how they were measured and interpreted varied greatly across studies.
- Resistance training for two weeks may not have the same outcomes as nine months as two weeks might not be enough time to see changes in depression.

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Continuous or Intermittent β-Lactam in Sepsis: Which is Better?

Continuous vs Intermittent β-Lactam Antibiotic Infusions in Critically Ill Patients with Sepsis: The BLING III Randomized Clinical Trial

Dulhunty JM, Brett SJ, De Waele JJ, et al. Continuous vs Intermittent β-Lactam Antibiotic Infusions in Critically Ill Patients With Sepsis: The BLING III Randomized Clinical Trial. *JAMA*. 2024;332(8):629-637. doi:10.1001/jama.2024.9779

KEY TAKEAWAY: In patients with sepsis, there is no significant difference in 90-day mortality with β-lactam infusion administered continuously or intermittently.

STUDY DESIGN: Randomized, open-label, controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Continuous infusions of β-lactam antibiotics, compared to intermittent administration, have higher concentrations for patients with sepsis. Despite previous randomized controlled trials investigating this, none have definitively shown improved patient-centered outcomes. This study aimed to ascertain whether continuous infusion of piperacillin-tazobactam or meropenem reduces 90-day mortality in septic patients compared to intermittent infusion.

PATIENTS: Adult patients in the ICU with sepsis

INTERVENTION: Continuous infusions of piperacillin-tazobactam or meropenem

CONTROL: Intermittent Infusion of piperacillin-tazobactam or meropenem

PRIMARY OUTCOME: All-cause mortality at day 90

Secondary Outcome: Clinical cure at day 14, new acquisition, colonization, or infection with a multi-drug resistant organism (MRO) or C difficile, all-cause intensive care unit (ICU) mortality, all-cause hospital mortality

METHODS (BRIEF DESCRIPTION):

- Adult >18 years old ICU patients with suspected sepsis (based on infection suspicion + end-organ damage) receiving either continuous or intermittent, piperacillin-tazobactam or meropenem
- Patients were randomized in an open-label manner to receive 14 g of piperacillin-tazobactam or 3 g of meropenam daily.
- This was given either by:
  - Continuous infusion (over 24 hours)
  - Intermittent infusion (over 30 minutes)
- All-cause mortality at 90 days was measured as the primary outcome and was defined as mortality from any cause in the patients in each group, at least 90 days from the randomization process.
- All-cause mortality at 90 days was adjusted for the following four covariates: Sex, Acute Physiology and Chronic Health Evaluation (APACHE) score, admission source (emergency, elective surgery, other), type of β-lactam before randomization (piperacillin-tazobactam or meropenem).
  - The results of the adjusted analysis for this outcome were also reported.
- The secondary outcomes measured:
  - "New acquisition, colonization, or infection with an MRO or C difficile" was checked until 14 days after the randomization process.
  - Cure on the 14th day of treatment was defined as no need for antibiotic restart within 48 hours of discontinuation.
  - All-cause ICU mortality was defined as death from any cause during the duration of the ICU stay.
  - All-cause hospital mortality was defined as death from any cause during the duration of the hospital stay.

INTERVENTION (# IN THE GROUP): 3,498

COMPARISON (# IN THE GROUP): 3,533

FOLLOW-UP PERIOD: 90 days

RESULTS:

Primary Outcome –

- There was no statistically significant difference between continuous infusion vs intermittent infusion for all-cause mortality at day 90 (absolute difference [AD] –1.9; 95% CI, –4.9 to 1.1).
- There was no statistically significant difference between continuous infusion vs intermittent infusion for the adjusted analysis for all-cause mortality at day 90 (AD –2.2; 95% CI, –5.5 to 1.1).

Secondary Outcome –

- Continuous infusion resulted in higher clinical cure at day 14 compared to intermittent infusion (AD 5.7; 95% CI, 2.4–9.1).

- There was no statistically significant difference for new acquisition, colonization, or infection with MRO or C difficile, all-cause ICU mortality, and hospital mortality for continuous infusion compared to intermittent infusion.

LIMITATIONS:

- There was a possibility of some randomized groups having participants with non-infectious organ dysfunction.
- Antibiotics were not adjusted based on susceptibility patterns.
- The continuous group received intermittent dosing before randomization, this could potentially be a cause for decreased difference.
- The patients were all from high-income ICU settings.

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SPACED-Out: Navigating the Decision-Making Challenges of Mild Cognitive Impairment

Mild Cognitive Impairment is Associated with Poorer Everyday Decision Making

Fenton L, Han SD, DiGuiseppi CG, et al. Mild Cognitive Impairment is Associated with Poorer Everyday Decision Making. *J Alzheimers Dis.* 2023;94(4):1607-1615. doi:10.3233/JAD-230222

KEY TAKEAWAY: Mild cognitive impairment (MCI) in older adults demonstrates poorer decision-making abilities compared to older adults without cognitive impairment.

STUDY DESIGN: Randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Decision-making in older adults can be complex, particularly regarding health care and finances, and may be further complicated by age-related cognitive changes. While dementia's impact on decision-making is well-documented, the effects of MCI are less understood. Exploring how MCI affects everyday decisions is essential for creating interventions that support the autonomy and well-being of older adults. This study aimed to investigate how MCI affects everyday decision-making abilities in older adults.

PATIENTS: Community-dwelling older adults

INTERVENTION: Mild cognitive impairment

CONTROL: No cognitive impairment

PRIMARY OUTCOME: Decision-making ability

METHODS (BRIEF DESCRIPTION):

- Participants were recruited from the AUTO study, which included English-speaking older adults ≥70 years old with a valid driver's license, driving at least once a week, diagnosed with medical conditions affecting driving safety, and scoring ≥21 on a five-minute Montreal Cognitive Assessment (MoCA).
- Participants were categorized into MCI or control groups based on their cognitive assessment scores.
  - For in-person assessments, the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) was used, with scores <85 on the Delayed Memory Index (DMI) indicating MCI.
  - For telephone assessments, the Brief Test of Adult Cognition by Telephone (BTACT) and the Oral Trail Making Test (OTMT) were used, with scores of –1 or lower on three or more tests indicating MCI.
  - All other participants were placed in the control group.
- Decision-making ability was assessed using the Short Portable Assessment of Capacity for Everyday Decision Making (SPACED). Scores range from 0–8, with higher scores indicating better decision-making ability.
- Statistical analysis involved a negative binomial generalized linear model to assess the impact of MCI on SPACED scores, adjusting for covariates such as age, education, sex, and study site.

INTERVENTION (# IN THE GROUP): 28

COMPARISON (# IN THE GROUP): 269

FOLLOW-UP PERIOD: Not available

RESULTS:

Primary Outcome –

- Participants with MCI demonstrated significantly poorer decision-making abilities compared to participants without cognitive impairment (mean ratio 2.2; 95% CI, 1.0–4.6).

LIMITATIONS:

- The study sample was predominantly White (95%) and non-Hispanic (99%), which limits the generalizability of the findings to more diverse populations.
- Participants were assessed using different cognitive measures due to a protocol change from in-person to telephone-based assessments during the COVID-19 pandemic. This variation may introduce inconsistencies in the classification of cognitive status.
- The small sample size for participants classified with MCI (n=28) may limit the statistical power and generalizability of the findings.

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Lifting Your Mood: Can Resistance Training Improve Depression Symptoms in Older Adults?

Can Resistance Training Improve Mental Health Outcomes in Older Adults? A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Cunha PM, Werneck AO, Santos LD, et al. Can resistance training improve mental health outcomes in older adults? A systematic review and meta-analysis of randomized controlled trials. *Psychiatry Res.* 2024;333:115746. doi:10.1016/j.psychres.2024.115746

KEY TAKEAWAY: Resistance training in adults ≥60 years old effectively reduces depressive symptoms in those with and without mental health conditions.

STUDY DESIGN: Systematic review of 27 randomized controlled trials (RCTs) and meta-analysis of 21 RCTs (N=968)

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

BRIEF BACKGROUND INFORMATION: Resistance training for older adults is associated with multiple health benefits. However, study results on mental health parameters have been inconsistent. One reason could be due to various types of training. This study sought to compare different variables of resistance training and their effects on depression symptoms.

PATIENTS: Adults ≥60 years old with and without a mental health diagnosis

INTERVENTION: Resistance training

CONTROL: Inactive intervention

PRIMARY OUTCOME: Depressive and anxiety symptoms

Secondary Outcome: Type of resistance training (traditional vs alternative), number of exercises, number of sets, weekly frequency, duration of intervention

METHODS (BRIEF DESCRIPTION):

- Adults ≥60 years old were included but individual studies varied from 60 to ≥80 years old and some studies included only women, only men, or mixed genders. Some studies included healthy patients, but other studies included those with Parkinson's, diabetes, stroke, or depression.
- Patients who participated in resistance training were categorized as traditional or alternative, though this was not well defined.
- Control groups were present but it was unclear if they used no intervention or a non-active intervention.
- Symptoms were reported pre and post-intervention on 12 different rating scales among the studies such as the Geriatric Depression Scale (GDS) and the Beck Depression Inventory (BDI). These tests were standardized for statistical analysis.

INTERVENTION (# IN THE GROUP): 538

COMPARISON (# IN THE GROUP): 430

FOLLOW-UP PERIOD: Variable (8 weeks to 12 months)

RESULTS:

Primary Outcome –

- Exercise reduced depressive symptoms compared to non-active controls (20 trials, n=933; mean effect –0.94; 95% CI, –1.5 to –0.43; I^2=93%).
- Exercise reduced anxiety symptoms compared to non-active controls (11 trials, n=361; mean effect –1.3; 95% CI, –2.1 to –0.56; I^2=92%).

Secondary Outcome –

- Older adults without any mental disorders had a small reduction in anxiety and depression symptoms with resistance training (15 trials, n=744; mean effect –0.51; 95% CI, –0.67 to –0.35; I^2=37%).
- Older adults with a mental disorder demonstrated a reduction in anxiety and depression symptoms with resistance training (6 trials, n=224; effect size –2.2; 95% CI, –3.0 to –1.3; I^2=92%).

LIMITATIONS:

- High heterogeneity among the resistance training interventions made comparison difficult.
- There was great variation in the scales used for assessing depressive symptoms limiting comparison among studies.
- Results were reported as standardized mean differences of pre and post-test without a MCID making it difficult to determine whether these results were clinically important.
- Sample sizes among all the included studies were small.
- Study definitions of "traditional" vs "alternative" exercise were not well defined.
- Control groups were not well defined and likely varied.

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From Rave to Relief: MDMA-Assisted Therapy for PTSD

MDMA-Assisted Therapy for Moderate to Severe PTSD: A Randomized, Placebo-Controlled Phase 3 Trial

Mitchell JM, Ot'alora G M, van der Kolk B, et al. MDMA-assisted therapy for moderate to severe PTSD: a randomized, placebo-controlled phase 3 trial. *Nat Med.* 2023;29(10):2473-2480. doi:10.1038/s41591-023-02565-4

KEY TAKEAWAY: 3,4-methylenedioxymethamphetamine-assisted therapy (MDMA-AT) significantly reduces post-traumatic stress disorder (PTSD) symptoms and clinician-rated functional impairment compared to placebo therapy.

STUDY DESIGN: Randomized, double-blind, placebo-controlled phase three trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Moderate to severe PTSD remains a significant public health challenge, particularly for individuals with high treatment resistance and comorbid conditions. Traditional treatments, such as trauma-focused psychotherapy and SSRIs, have often shown high dropout rates and limited efficacy, creating a pressing need for more effective therapeutic options. This research explored MDMA-assisted therapy, aimed to address these limitations and improve treatment outcomes for those affected by PTSD.

PATIENTS: Adults with PTSD

INTERVENTION: MDMA-AT

CONTROL: Placebo

PRIMARY OUTCOME: Change in PTSD severity

Secondary Outcome: Change in disability from PTSD, adverse effects

METHODS (BRIEF DESCRIPTION):

- Adults ≥18 years old with moderate to severe PTSD of at least six months duration were enrolled across 13 clinical sites.
- PTSD severity was based on the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) of ≥28.
  - CAPS-5 total severity scores range from asymptomatic (0–10), mild (11–22), moderate (23–34), severe (35–46) and extreme (≥47).
- Individuals with primary psychotic disorder, bipolar I disorder, dissociative identity disorder, eating disorder, depression with psychotic features, severe alcohol or cannabis use disorder, active substance use disorder, imminent suicide risk, or cardiovascular disease which could make taking MDMA harmful were excluded from the study.
- Participants had a mean age of 39 years old, 34% identified as other than White, 27% identified as Hispanic, and 71% were assigned female sex at birth, with a higher proportion in the placebo group.
- The mean PTSD duration was 16 years and the mean baseline CAPS-5 score was 39.
- Before treatment, participants had all psychiatric medications tapered off.
- Participants were randomized 1:1 ratio to receive 120–180 mg of MDMA-AT or placebo with identical therapy across three, eight-hour sessions each about one month apart.
- Improvement in PTSD was measured by a reduction in CAPS-5 total severity score and a reduction in the Sheehan Disability Scale (SDS).
  - SDS assesses functional disability across work, social, and family life. Scores range from 0–30, with higher scores indicating greater disability.

INTERVENTION (# IN THE GROUP): 53

COMPARISON (# IN THE GROUP): 51

FOLLOW-UP PERIOD: 18 weeks

RESULTS:

Primary Outcome –

- MDMA-AT significantly reduced PTSD symptom severity compared to placebo (least squares mean [LSM] difference –8.9; 95% CI, –14 to –4.1).

Secondary Outcome –

- MDMA-AT significantly reduced clinician-rated functional impairment compared to placebo (LSM difference –1.2; 95% CI, –2.3 to –0.14).
  - Improvements were observed across all domains including family, social, and work life.
- Treatment-emergent adverse events (TEAE) were common among participants (102/104, 98%) but most were mild.
  - The most frequently reported adverse events were more common in participants treated with MDMA and included muscle tightness, nausea, decreased appetite, and hyperhidrosis.

- Increases in blood pressure and pulse were observed in a dose-dependent manner with MDMA treatment. Tachycardia and palpitations were experienced by eight participants and vascular adverse events, including flushing, peripheral coldness, hot flashes, and moderate hypertension were experienced by nine participants, more commonly occurring in the MDMA-AT group.

LIMITATIONS:

- The exclusion of participants with high suicide risk, comorbid personality disorders, and underlying cardiovascular diseases, may limit the generalizability of the findings.
- MDMA-AT was not compared to selective serotonin reuptake inhibitor (SSRI) therapy, the current standard of care for PTSD.
- Despite a relatively low dropout rate and a diverse group of participants, the sample size might still be insufficient to fully establish the efficacy of MDMA-AT across all demographics and comorbid conditions.
- Evaluations were limited to two months after therapy and provided no assessment of MDMA-AT long-term efficacy.
- Potential treatment expectancy effects from participants were not measured, the effects of which can be particularly challenging in psychiatric clinical trials.
- The efficacy of blinding is unclear, as 94% and 75% of participants in the MDMA-AT and placebo groups respectively correctly identified their treatment group at the termination of the study.

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A Closer Look at Testosterone Replacement Therapy and Heart Health

Testosterone Replacement Therapy is Not Associated with Increased Prostate Cancer Incidence, Prostate Cancer-Specific, or Cardiovascular Disease-Specific Mortality in Finnish Men

Siltari A, Murtola TJ, Kausz J, et al. Testosterone replacement therapy is not associated with increased prostate cancer incidence, prostate cancer-specific, or cardiovascular disease-specific mortality in Finnish men. *Acta Oncol.* 2023;62(12):1898-1904. doi:10.1080/0284186X.2023.2278189

KEY TAKEAWAY: Testosterone replacement therapy likely does not increase the risk of prostate cancer, prostate-related mortality, cardiovascular mortality, and all-cause mortality when compared to no testosterone use. Testosterone use may be associated with a decreased risk for prostate cancer.

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: The safety of testosterone replacement therapy (TRT) in men has been controversial due to concern for increased risk of prostate cancer or cardiovascular disease (CVD). Previous studies have addressed the risks but with no definitive results. This study aimed to further stratify the risk of prostate cancer and CVD among men with hypogonadism treated with TRT vs men without hypogonadism and TRT use.

PATIENTS: Finnish men with no previous diagnosis of prostate cancer

INTERVENTION: TRT

CONTROL: No TRT use

PRIMARY OUTCOME: Incidence of prostate cancer
Secondary Outcome: Prostate cancer-specific, cardiovascular, and all-cause mortality

METHODS (BRIEF DESCRIPTION):

- Men 55–67 years old from the Finnish Randomized Study of Screening for Prostate Cancer were followed for 18 years.
- Men were divided into ever, previous, or active TRT use.
- TRT use was further divided into intensity, duration of use, and cumulative daily dose amount.
- Analyses of prostate cancer risk, cancer, grade, and stage were performed using a Cox proportional hazards regression model with variables adjusted for age, TRT use, other medication use, and other comorbidities.
- Subgroup analyses of prostate cancer, cardiovascular, and all-cause mortality were compared using hazard ratios and 95% confidence intervals with time-dependent TRT use for each year.

INTERVENTION (# IN THE GROUP): 2,919

COMPARISON (# IN THE GROUP): 75,696

FOLLOW-UP PERIOD: 18 years

RESULTS:

Primary Outcome –

- TRT use was associated with decreased prostate cancer risk compared to no TRT use (HR 0.58; 95% CI, 0.44–0.77).

Secondary Outcome –

- Active TRT use was associated with decreased prostate-specific mortality risk compared to no TRT use (HR 0.56; 95% CI, 0.46–0.68).
- Active TRT use was associated with decreased CVD mortality risk compared to no TRT use (HR 0.7; 95% CI, 0.5–0.99).
- Active TRT use was associated with decreased all-cause mortality compared to no TRT use (HR 0.56; 95% CI, 0.46–0.68).

LIMITATIONS:

- There was a lack of a comparison group of men with hypogonadism and no TRT use.
- Information regarding whether or not the patient purchased TRT was available but its frequency, dosage, or if it was used at all was unknown.
- No information on patients' serum testosterone levels or the severity of men with testosterone deficiency was available.
- The study was limited to Finnish men.

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