GOOD EVIDENCE MATTERS

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The Significance of Our Daily Steps in Overall Mental Well-being

Daily Step Count and Depression in Adults: A Systematic Review and Meta-Analysis

Bizzozero-Peroni B, Díaz-Goñi V, Jiménez-López E, et al. Daily Step Count and Depression in Adults: A Systematic Review and Meta-Analysis. *JAMA Netw Open*. 2024;7(12):e2451208. Published 2024 Dec 2. doi:10.1001/jamanetworkopen.2024.51208

KEY TAKEAWAY: Higher step counts are associated with lower depressive symptoms among adults.

STUDY DESIGN: Systematic review and meta-analysis of 27 cross-sectional studies and six longitudinal studies (N=96,173)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to quality of studies included and high heterogeneity)

BRIEF BACKGROUND INFORMATION: The benefits of physical activity on physical and cardiovascular health are well established. This study explored the link between physical activity and mental health, with a particular focus on the need for objective, quantifiable measures of activity such as step counts.

PATIENTS: Adults

INTERVENTION: Higher daily step count (active)

CONTROL: Lower step count (sedentary)

PRIMARY OUTCOME: Depression symptoms

METHODS (BRIEF DESCRIPTION):

- Eligible studies included observational studies correlating daily step counts with depression in adults (55% female), ≥18 years old, with a focus on younger adults (18–35 years old), younger adults (18–35 years old), middle-aged adults 36–64 years old) and older adults (≥65 years old).
- Studies were conducted in 13 countries spanning Asia, Europe, North and South America.
- Studies that did not use objective measures of step counts and did not assess depression or depressive symptom as an outcome were excluded.
- Daily step count data were obtained from accelerometers, pedometers, or smartphones for a minimum measurement period of three days to a maximum of 365 days (most studies 7 days).
- Step counts were presented as either a continuous variable (steps/day) or as a categorical variable as follows:
  - Highly active: >10,000 steps
  - Active: >7,500 steps
  - Low step count: <7,500 steps
  - Sedentary: <5,000 steps
- Depression was assessed using validated self-report instruments such as the Patient Health Questionnaire (PHQ-9), the Center for Epidemiologic Studies Depression Scale (CES-D), and the Geriatric Depression Scale (GDS) for older adults.
- Depression was reported either as a diagnosis (categorical variable) or as depressive symptoms (continuous or categorical variable), with harmonization across studies to facilitate meta-analysis.
- Among the included longitudinal cohort studies, participants who reported depression or had mild to severe depressive symptoms at baseline were excluded from analyses to minimize reverse causality and confounding.
- Researchers estimated pooled correlation coefficients (r) with their 95% confidence intervals using Fisher z transformation.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Variable (24 weeks to 2 years)

RESULTS:

Primary Outcome –

- Categories of higher step counts were associated with fewer depressive symptoms compared to the sedentary category of <5,000 steps a day:
  - 10,000 or more steps/day (7 studies, n=3,978; standard mean difference [SMD] −0.26; 95% CI, –0.38 to –0.14; I^2=57%)
  - 7,500 to 9,999 steps/day (7 studies, n=3,541; SMD –0.27; 95% CI, –0.43 to –0.11; I^2=64%)
  - 5,000 to 7,499 steps/day (6 studies, n=3,505; SMD –0.17; 95% CI, –0.30 to –0.04; I^2=0%)
- Daily step counts of ≥7,500 were associated with fewer depressive symptoms compared to daily step counts <7,500 (12 studies, n=9,084; SMD –0.30; 95% CI, –0.44 to –0.16; I^2=65%).
- Analysis of step count as a continuous variable demonstrated an inverse relationship between step counts and depressive symptoms:

    - Cross-sectional studies (19 studies, n=3,994; r –0.12; 95% CI, –0.20 to –0.04; I^2=65%)
    - Longitudinal studies (3 studies, n=700; r –0.17; 95% CI, –0.28 to –0.04; I^2=61%)
- Based on the prospective cohort studies, having increased 1,000 steps per day reduced depression incidence compared to not doing so (2 studies, n=77,729; risk ratio [RR] 0.91; 95% CI, 0.87–0.94; I^2= 48%).
- Based on the prospective cohort studies, adults with ≥7,000 steps per day had a lower risk of depression, compared to their counterparts with<7,000 steps per day (2 studies, n=5,110; RR 0.69; 95% CI, 0.62–0.77; I^2=0%).

LIMITATIONS:

- Reverse causality is possible (i.e., depression may lead to lower step counts).
- There was heterogeneity in age, sex, and step counting devices.
- Quality was variable among studies, questioning the certainty and reliability of pooled results.
- Using step counts as a proxy for overall physical activity does not account for other forms of physical activity that can impact depression.
- Publication bias may have influenced pooled associations.
- Short duration of step counting in majority of studies.

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Shedding Light on PCOS: Is Vitamin D the Missing Link?

Effects of Vitamin D3 Treatment on Polycystic Ovary Symptoms: A Prospective Double-Blind Two-Phase Randomized Controlled Clinical Trial

Tóth BE, Takács I, Valkusz Z, et al. Effects of Vitamin D3 Treatment on Polycystic Ovary Symptoms: A Prospective Double-Blind Two-Phase Randomized Controlled Clinical Trial. *Nutrients*. 2025;17(7):1246. Published 2025 Apr 2. doi:10.3390/nu17071246

KEY TAKEAWAY: Vitamin D3 supplementation improves regularity of menstrual cycle, ovarian morphology, and ovulation rate compared to placebo tablet in women with polycystic ovary syndrome (PCOS).

STUDY DESIGN: Prospective, randomized, two-phase, parallel design, placebo-controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to limited external generalizability)

BRIEF BACKGROUND INFORMATION: Vitamin D deficiency is often associated with PCOS, but studies on whether vitamin D supplementation improves PCOS symptoms have reported mixed results. This study investigated the effects of vitamin D3 supplementation on hormonal and metabolic parameters in women with PCOS.

PATIENTS: Women with PCOS and vitamin D insufficiency

INTERVENTION: Oral vitamin D3

CONTROL: Baseline

PRIMARY OUTCOME: Ovarian morphology, regularity of menstrual cycle, and ovulation rate

Secondary Outcome: Estradiol, follicle-stimulating hormone (FSH), luteinizing hormone (LH), parathyroid hormone (PTH), testosterone, androstenedione, sex hormone-binding globulin (SHBG)

METHODS (BRIEF DESCRIPTION):

- 44 premenopausal women (>18 years old) with PCOS, vitamin D3 level 10–30 ng/mL, and body mass index (BMI) <36 were included in the study.
- The study also included a vitamin D-repleted group (n=40) to examine effects of additional supplementation in sufficient participants, but this appraisal focuses on vitamin D-depleted within-group comparison.
- The study participants received calcium and a placebo for the first 12 weeks and then calcium and vitamin D3 for the second 12 weeks.
  - Vitamin D3 dosage: 30,000 IU/week
- The participants were blinded during the first 12 weeks of the study (placebo-controlled lead-in) and were unblinded during the subsequent 12-week vitamin D3 supplementation phase.
- Assessments were completed at baseline, 12 weeks, and 24 weeks.
- The following were measured as the primary outcomes:
  - Regularity of the menstrual cycle was measured via patient-reported menstrual cycle length data.
  - Ovarian morphology was determined using transvaginal ultrasound (findings categorized into “normal”, “polycystic”, or “unilateral partial” with improvement defined as change from polycystic to normal or partial and partial to normal.
  - Ovulation rate was calculated by post-ovulatory progesterone levels using a 10 ng/mL cut-off.
- The following were measured as the secondary outcomes:
  - Labs were collected at baseline, 12 weeks, and 24 weeks that included: Estradiol, FSH, LH, PTH, testosterone, androstenedione, and SHBG.

INTERVENTION (# IN THE GROUP): 44

COMPARISON (# IN THE GROUP): The same 44 patients

FOLLOW-UP PERIOD: 24 weeks

RESULTS:

Primary Outcome –

- Oral vitamin D3 increased normal ovarian morphology compared to baseline (20% vs 4.6%, respectively; *p*=.0156).
- Oral vitamin D3 decreased menstrual cycle length compared to baseline (40 vs 51 days, respectively; *p*=.031).
- Oral vitamin D3 increased number of ovulations compared to baseline (59–65% vs 40%, respectively; *p*=.044).

Secondary Outcome –

- There was no statistical difference in estradiol, FSH, LH, PTH, testosterone, androstenedione, and SHBG between the groups.

LIMITATIONS:

- The study was conducted only in Hungary, limiting generalizability to other populations.
- The sample size was moderate and may not detect small or rare effects.
- Participants were limited to those with BMI <36, reducing applicability to all PCOS patients.
- The study focused on surrogate outcomes rather than long-term clinical outcomes like fertility.
- The second phase was open label, which may introduce bias.
- Menstrual cycle was self-reported and may be prone to recall bias.

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When Clots Play Hide and Seek

Endovascular Treatment for Stroke Due to Occlusion of Medium or Distal Vessels

Psychogios M, Brehm A, Ribo M, et al. Endovascular Treatment for Stroke Due to Occlusion of Medium or Distal Vessels. *N Engl J Med*. 2025;392(14):1374-1384. doi:10.1056/NEJMoa2408954

KEY TAKEAWAY: In patients with distal or medium vessel occlusion there is no significant difference in disability score with endovascular treatment (EVT) compared to usual care.

STUDY DESIGN: Multi-site, randomized open labeled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to lack of blinding)

BRIEF BACKGROUND INFORMATION: Studies on EVT demonstrate benefit to patients with occlusion dominant, middle cerebral artery however occlusion on medium and distal vessels is lacking. This study investigates EVT in medium and distal vessel occlusion.

PATIENTS: Patients with acute ischemic stroke

INTERVENTION: EVT + usual care

CONTROL: Usual care

PRIMARY OUTCOME: Level of disability at 90 days

Secondary Outcome: Symptomatic hemorrhage, mortality

METHODS (BRIEF DESCRIPTION):

- Authors conducted a single-blind randomized trial at 55 hospitals across 11 European countries and recruited patients ≥18 years with an acute ischemic stroke of isolated medium or distal vessel.
- Patient ≥18 years were included after diagnosis of acute ischemic stroke by computed tomography angiography or magnetic resonance imaging angiography, National Institutes of Health Stroke Scale (NIHSS) score of ≥4 (with lower scores allowed if symptoms disabling, score range 0–42 with higher score indicating more severe symptoms).
- Patients with dominant m2 branch were excluded.
- The mean age was 77 years old in the EVT group and 78 years old in the best medical treatment group. Fewer than half of participants in each group were women (43% in EVT vs 45% in best medical care). The NIHSS median score was six in both groups at admission, and rate of thrombolysis was >60% in both groups.
- The treatment group received EVT + best medical treatment, including thrombolysis when indicated, admission to a stroke unit and intensive care unit treatment according to guidelines.
- The comparison group received best medical treatment.
- The primary outcome was the level of disability assessed 90 days post-stroke by modified Rankin scale. Scores range from 0–6, with higher scores indicating more disability and a score of six indicating death.
- Secondary outcomes of all-cause mortality and symptomatic intracranial hemorrhage were assessed at 90 days during clinic visits or telephonic interviews and reported in a binary fashion.

INTERVENTION (# IN THE GROUP): 271

COMPARISON (# IN THE GROUP): 272

FOLLOW-UP PERIOD: 90 days

RESULTS:

Primary Outcome –

- Patients who underwent EVT had no significant difference in levels of disability at 90 days compared to usual care (odds ratio OR 0.90; 95% CI, 0.67–1.2).

Secondary Outcome –

- Patients who underwent EVT had no significant difference in overall mortality compared to best medical treatment group.
- Patients who underwent EVT had no significant difference in symptomatic intracranial hemorrhage at 24 hours compared to those with usual care.

LIMITATIONS:

- There was heterogeneity in vessel size and occlusion site.
- Interventionist judgement was used to determine if a lesion was medium or distal vessel and could allow for selection bias.
- The study was conducted in specialized stroke centers, limiting applicability to less experienced settings.
- The imaging to detect vascular lesion was slightly outside goal time which could have led to decreased

incidence of successful reperfusion leading to overall no difference between the two groups.

- The time needed for consent led to a delay between imaging and randomization which might have led to difficulty in detecting vascular occlusion.
- Rate of hemorrhage was reported at 24 hours and not at 90 days.
- This trial was not blinded to investigators.

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Beyond Ondansetron: Emerging Therapies for Adolescent Cannabinoid Hyperemesis Syndrome

Acute Treatment of Adolescent Cannabinoid Hyperemesis Syndrome with Haloperidol, Lorazepam, and/or Capsaicin: A Single Institution Case Series

Brown JM, Wilsey MJ, Dhana L, Lonsdale H. Acute Treatment of Adolescent Cannabinoid Hyperemesis Syndrome with Haloperidol, Lorazepam, and/or Capsaicin: A Single Institution Case Series. *J Psychiatr Pract*. 2023;29(5):354-358. Published 2023 Sep 1. doi:10.1097/PRA.0000000000000732

KEY TAKEAWAY: The use of haloperidol, lorazepam, and/or capsaicin may improve cannabinoid hyperemesis symptoms (CHS) in adolescent patients in this limited case series.

STUDY DESIGN: Singe case series

LEVEL OF EVIDENCE: STEP 4

BRIEF BACKGROUND INFORMATION: CHS is a syndrome that stems from cannabis use, particularly chronic use, and involves nausea, vomiting, and abdominal pain. Traditional antiemetics such as ondansetron and metoclopramide are often ineffective. There is currently limited data on effective treatment for acute symptoms of adolescent CHS. Haloperidol is an emerging treatment for CHS in adults. This study aimed to assess the relationship between using haloperidol, lorazepam, and capsaicin and reduction/resolution of acute CHS symptoms in the adolescent population.

PATIENTS: Adolescents 16–19 years old with CHS

INTERVENTION: IV haloperidol + IV lorazepam; IV lorazepam + topical capsaicin; or topical capsaicin alone

CONTROL: None

PRIMARY OUTCOME: Nausea, vomiting, and/or abdominal pain

METHODS (BRIEF DESCRIPTION):

- Retrospective case series of six adolescents, 16–19 years old (5 female, 1 male) presenting to a single institution over a four-month period.
- An extensive workup was performed to rule out other causes to properly diagnose CHS.
- All patients received IV hydration. Specific antiemetic regimens included:
  - IV haloperidol 5 mg + IV lorazepam 2 mg (n=4)
  - IV lorazepam 2 mg + topical capsaicin (0.025%) (n=1)
  - Topical capsaicin alone (0.025%) (n=1)
- Outcomes were measured based on patient self-reported reduction in CHS symptoms of nausea, vomiting, and abdominal pain.

INTERVENTION (# IN THE GROUP): 6

COMPARISON (# IN THE GROUP): Not applicable

FOLLOW-UP PERIOD: No follow-up period beyond the emergency room visit

RESULTS:

Primary Outcome –

- Haloperidol + lorazepam (n=4): 100% of patients reported complete resolution of symptoms. No side effects were reported.
- Lorazepam + capsaicin (n=1): Patient reported complete resolution of symptoms without side effects.
- Capsaicin alone (n=1): Patient reported only partial improvement of nausea.

LIMITATIONS:

- A small sample size, of 6 patients, limits generalizability and restricts power.
- 50% of patients were reported as White patients and only from a single emergency room could have caused selection bias and may not represent a diverse population.
- Only 50% documented quantitative use which limits dose-response relationship or compare outcomes among patients so this can weaken conclusions.
- Although there was a urine drug test involved, there was no detailed documentation on other illicit substances for any of the patients so there may be confounding factors if other substances are involved.
- Lack of control group limits causal inference, therefore unable to determine how this treatment compares to standard treatment.

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The views expressed herein are those of the author and do not necessarily reflect the official policy of the Department of the Army, Defense Health Agency, Department of Defense, or the U.S. Government.