GOOD EVIDENCE MATTERS

GEMs of the Week

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The Pressure to Pee

Chlorthalidone vs Hydrochlorothiazide and Kidney Outcomes in Patients with Hypertension: A Secondary Analysis of a Randomized Clinical Trial

Ishani A, Hau C, Raju S, et al. Chlorthalidone vs Hydrochlorothiazide and Kidney Outcomes in Patients with Hypertension: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Netw Open*. 2024;7(12):e2449576. Published 2024 Dec 2. doi:10.1001/jamanetworkopen.2024.49576

KEY TAKEAWAY: Chlorthalidone and hydrochlorothiazide (HCTZ) can safely treat hypertension (HTN) in patients with chronic kidney disease (CKD).

STUDY DESIGN: Multicenter, nonblinded randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Thiazide diuretics are a common treatment for HTN. In patients with co-morbid CKD, concern that specific thiazide diuretic, chlorthalidone vs HCTZ, may have an effect of CKD progression exists. To better understand potential harm each medication has on kidney function, this study compared HCTZ to chlorthalidone and the relative risk of CKD progression.

PATIENTS: Hypertensive veterans ≥65 years old on HCTZ

INTERVENTION: Transition of HCTZ to dose equivalent chlorthalidone

CONTROL: Continuation of HCTZ

PRIMARY OUTCOME: CKD progression

Secondary Outcome: Development of CKD, progression of pre-existing CKD, incidence of hypokalemia, hospitalization for acute kidney injury (AKI)

METHODS (BRIEF DESCRIPTION):

- Participants were selected through the Veterans Affairs (VA) patient population with the following inclusion criteria:
  - Participants were ≥65 years old.
  - History of HTN
  - Participants also had a history of HTN with most recent systolic blood pressure ≥120 mmHg
  - Active prescription of HCTZ (25 or 50 mg) for HTN
- There was no exclusion criteria for kidney function.
- The participants were randomized into continuing HCTZ group (25 mg per day or 50 mg per day) or transitioned to 12.5 mg per day chlorthalidone from HCTZ 25 mg per day or 25 mg per day chlorthalidone from HCTZ 50 mg per day.
- Medications were considered ongoing unless a lapse in prescription fills were ≥90 days.
- Electronic health record (EHR) information was used to document date intervention transition, CKD progression, and medication discontinuation.
- Medication was considered discontinued if >90 days between refills were seen on pharmacy fill records.
- The primary outcome of CKD progression was monitored through lab work ordered by PCP.
- Guidelines for repeating blood work were not defined by study protocol.
- CKD progression was defined as doubling of baseline creatinine, decrease to eGFR <15 mL/min, or dialysis initiation.
- Secondary outcomes were monitored through lab work and review of EHRs.
- Development of CKD defined as eGFR <60 mL/min in patients without pre-existing CKD.
- Rate of annual change in eGFR slope monitored through lab work.
- Incidence of hypokalemia was found on lab work.
- Hospitalization for AKI monitored through EHRs.

INTERVENTION (# IN THE GROUP): 6,118

COMPARISON (# IN THE GROUP): 6,147

FOLLOW-UP PERIOD: 3.9 years

RESULTS:

Primary Outcome –

- There was no significant difference in CKD progression between the groups (hazard ratio [HR] 0.94; 95% CI, 0.81–1.1).

Secondary Outcome –

- There was no statistical difference in the new onset incidence of CKD, rate of eGFR decline per year, hypokalemia hospitalization, and AKI hospitalization between the groups.
- Chlorthalidone increased the incidence of hypokalemia compared to HCTZ (6.5% vs 4.8%, respectively; *P*<.001).

LIMITATIONS:

- Participant selection was conducted through the VA with an age requirement which may be associated with higher rates of co-morbid conditions and effect generality to younger populations.
- Predominance of males compared to women may limit generalizability of findings.
- A protocol for lab work and clinical follow-up to monitor CKD progression did not exist.
- Participants were on HCTZ prior to the start of experiment which could have reduced adverse effects associated with the medication initiation compared to chlorthalidone.
- Patients who transitioned from HCTZ to chlorthalidone were more likely to transition back to HCTZ due to self-reported side effects which could have influenced tolerability outcomes.
- Doses of hydrochlorothiazide and chlorthalidone were relatively low which may not correlate to side effects associated with higher doses.

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Brain Gains: Creatine Improves Memory in Healthy Adults

Effects of Creatine Supplementation on Memory in Healthy Individuals: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Prokopidis K, Giannos P, Triantafyllidis KK, Kechagias KS, Forbes SC, Candow DG. Effects of Creatine Supplementation on Memory in Healthy Individuals: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Nutr Rev*. 2023;81(4):416-427. doi:10.1093/nutrit/nuac064

KEY TAKEAWAY: Creatine supplementation may improve memory performance in healthy adults, with more pronounced effects in older adults.

STUDY DESIGN: Systematic review of 10 randomized controlled trials (RCTs), eight of which were included in the meta-analysis (N=240)

LEVEL OF EVIDENCE: STEP 3 (downgraded due to significant heterogeneity small sample size, incomplete reporting of data, and high risk of bias)

BRIEF BACKGROUND INFORMATION: Creatine is known to play a key role in brain bioenergetics, but its effects on memory in healthy patients is unclear due to conflicting study results. This systematic review and meta-analysis aimed to clarify the effects of creatinine supplementation on memory performance in healthy individuals.

PATIENTS: Healthy adults

INTERVENTION: Creatine supplementation

CONTROL: Placebo

PRIMARY OUTCOME: Memory performance

METHODS (BRIEF DESCRIPTION):

- Researchers searched PubMed, Scopus, Web of Science, and the Cochrane library from inception through September 2021 for RCTs using the search terms “creatine or creatine monohydrate” and “cogn* or memory.”
- Included studies enrolled healthy adults (67% female, 33% male) from the United Kingdom, Brazil, New Zealand, and the United States and compared creatine to placebo for effects on memory outcomes.
- Studies were excluded if participants had dietary restrictions or comorbidities, a full text was unavailable, or if they were not RCTs.
- Intervention duration ranged from five days to 24 weeks, with daily creatine doses from approximately 2.2 grams to 20 grams.
- Memory was assessed using various tools, including:
  - The Rey Auditory Verbal Learning Test (RAVLT) measures episodic verbal memory and delayed recall. Scores range from 0–75, with higher scores indicating normal cognition.
  - The digit span tests evaluate working memory and attention through repetition of number sequences. Scores range from 0–30. with higher scores indicating strong working memory.
  - The Corsi block test evaluates short-term working memory involving the recall of sequences of tapped blocks. Scores range from 0–9, with a higher score indicating better short-term memory.
- Study quality and bias risk were assessed using the Cochrane risk-of-bias 2 tool for RCTs and evaluated by three independent reviewers.
- I^2 values of >49% classified data with moderate to high heterogeneity.

INTERVENTION (# IN THE GROUP): 122

COMPARISON (# IN THE GROUP): 118

FOLLOW-UP PERIOD: Variable (5 days to 24 weeks)

RESULTS:

Primary Outcome –

- Creatine supplementation improved memory performance compared to placebo (8 trials, N=240; standardized mean difference [SMD] 0.29; 95% CI, 0.04–0.53; I^2=66%).
- Memory improvement was significant in older adults 66–76 years old (2 trials, n=57; SMD 0.88; 95% CI, 0.22–1.6; I^2=83%) but not in younger adults.
- Creatine supplementation in powder form showed significant memory improvement (number of trials and patients not reported; SMD 0.35; 95% CI, 0.05–0.66; I^2=73%) while the encapsulated form did not.
- There was no significant difference in memory improvement based on creatine dosage, treatment duration, or sex.

LIMITATIONS:

- Heterogeneity was high across studies, likely due to varied memory assessment tools and study populations.
- The quality of the studies included was moderate, with a high risk of bias found in six of the eight trials included in the meta-analysis.
- Baseline brain or serum creatine levels were not assessed, making it difficult to determine if responsiveness was related to initial creatine status.
- Most studies did not assess dietary creatine intake, which would be a confounding factor.

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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 Navy, Defense Health Agency, Department of Defense, or the U.S. Government.

Beyond the Skin Surface: The Global Epidemiologic Footprint of Hidradenitis Suppurativa

Prevalence of Hidradenitis Suppurativa: A Meta-Analysis of Global Hidradenitis Suppurativa Atlas Studies

Bouazzi D, Nielsen SM, Hagan PG, et al. Prevalence of Hidradenitis Suppurativa: A Meta-Analysis of Global Hidradenitis Suppurativa Atlas Studies. *JAMA Dermatol*. Published online August 27, 2025. doi:10.1001/jamadermatol.2025.2373

KEY TAKEAWAY: The global prevalence of hidradenitis suppurativa (HS) in healthy adults is estimated to be 0.99%, and the only risk factor with significant association to HS prevalence is female sex.

STUDY DESIGN: Meta-analysis of 25 cross sectional studies (N=22,743)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to high heterogeneity of prevalence estimates, wide confidence integrals, and overall low data quality)

BRIEF BACKGROUND INFORMATION: Hidradenitis suppurativa is a chronic, inflammatory skin condition which is thought to be caused by an overactive immune response to hair follicles. It can have a significant negative impact on quality of life due to its painful, reoccurring nature and known associations of increased mortality, psychosocial strain, and comorbidities. Previous studies have estimated HS prevalence, however due to study differences and limited data there is need for further analysis. This study evaluated the global HS prevalence among different populations of varying risk factors using the Global Hidradenitis Suppurativa Atlas (GHiSA) data.

PATIENTS: Healthy adults accompanying a patient to non-dermatology clinic appointments

INTERVENTION: Presence of HS

CONTROL: Not available

PRIMARY OUTCOME: Prevalence of HS

Secondary Outcome: Association between prevalence of HS and factors such as gender, age, geographical location, body mass index (BMI), smoking, gross domestic product (GDP), Human Development Index (HDI)

METHODS (BRIEF DESCRIPTION):

- Healthy adults accompanying a patient to an outpatient visit, excluding dermatology, were invited to complete a screening questionnaire and if positive were examined by a physician for verification of HS diagnosis.
- Data collected from GHiSA studies prior to May 19, 2023, was utilized, and included 23 countries across six continents.
- From the initial 74 countries, 51 of them were excluded due to lack of response, nonadherence to the protocol, and failure to initiate, obtain ethical approval, or finalize the study.
- The primary outcome was global point prevalence of HS.
- Secondary outcomes were measured by utilizing a standardized form of data extraction to review information on age, sex, geographical location, median BMI, BMI>30, smoking status, HDI, and GDP.
- Heterogeneity of studies was measured using I^2 statistic and t^2 as well as 95% prediction intervals.
- A random-effects model was used to complete this meta-analysis of the 25 studies.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Not available

RESULTS:

Primary Outcome –

- 247 HS patients were identified, with an overall global prevalence of 0.99% (95% CI, 0.67–1.5).

Secondary Outcome –

- There were large variations in prevalence estimates (0.13–4.07%; 95% prediction interval, 0.18–5.4; I^2>75%; t^2=0.75).
- There was no statistically significant difference in continent, region, smoking status, BMI, demographics, and prevalence.
- There was a significant association between female sex and HS (β 1.0; 95% CI, 1.0–1.0).

LIMITATIONS:

- There were innate difficulties of large multicountry studies such as language, cultural, and healthcare system differences as well as ecological fallacy.
- Disease severity was not assessed.
- There is a likely degree of selection bias due to lack of stratified sampling.

- There were inconsistencies of data quality in the study characteristics with studies not listing smoking status or BMI data.
- Since only 23 countries were included, there is an extensive amount of global data missing.

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