GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

Volume 3 - Issue 48

FPIN
Family Physicians Inquiries Network

What's in this week's issue?

Week of November 27 - December 1, 2023

SPOTLIGHT: Effect of Diet in Reducing Cardiovascular Morbidity and Mortality: Is the Mediterranean Diet as Good as it Seems?

Effect of Diet in Reducing Cardiovascular Morbidity and Mortality: Is the Mediterranean Diet as Good as it Seems?

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Comparison of Seven Popular Structured Dietary Programmes and Risk of Mortality and Major Cardiovascular Events in Patients at Increased Cardiovascular Risk: Systematic Review and Network Meta-Analysis

Karam G, Agarwal A, Sadeghirad B, et al. Comparison of seven popular structured dietary programmes and risk of mortality and major cardiovascular events in patients at increased cardiovascular risk: systematic review and network meta-analysis. *BMJ*. 2023;380:e072003. Published 2023 Mar 29. doi:10.1136/bmj-2022-072003

KEY TAKEAWAY: Among patients with established or increased risk factors for cardiovascular disease, the promotion of Mediterranean and low-fat diets is likely to reduce all-cause mortality and non-fatal MI, regardless of additional interventions.

STUDY DESIGN: Systematic review and network meta-analysis of 40 RCTs (N=35,548)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Several studies suggest the importance of diet in reducing cardiovascular morbidity and mortality but have not quantified this benefit using meta-analysis on high-quality evidence.

PATIENTS: Individuals with or at increased risk of CV disease

INTERVENTION: Structured dietary program

CONTROL: Minimal intervention

PRIMARY OUTCOME: All-cause mortality, cardiovascular mortality

Secondary Outcome: Cardiovascular events (Non-fatal MI, stroke, angina, HF, Afib, peripheral vascular events, unplanned CV interventions)

METHODS (BRIEF DESCRIPTION):

- Adults with a history of CAD, MI, stroke, or PAD or have two or more of the following: HTN, HLD, obesity, and DM were included in the study.
- Structured dietary program interventions:
  - Low fat (16 trials, n=9,243)
  - Very low fat (4 trials, n=987)
  - Combined low fat and low sodium (3 trials, n=2,673)
  - Mediterranean (10 trials, n=8,075)
  - Ornish-fat intake <10% (2 trials, n=125)
  - Pritikin-fat intake 5–10%, increased fiber intake (1 trial, n=26)
- The minimal intervention included usual diet advice or no advice.
- Using the Cochrane risk of bias tool, investigators judged 13 trials as a low risk of bias and 27 as a high risk of bias.

INTERVENTION (# IN THE GROUP): 21,809

COMPARISON (# IN THE GROUP): 13,739

FOLLOW-UP PERIOD: Nine months to seven years

RESULTS:

Primary Outcome –

- Among those at increased CV risk all-cause mortality is lower with:
  - Mediterranean diet (OR 0.72; 95% CI, 0.56–0.92)
  - Low-fat diet (OR 0.84; 95% CI, 0.74–0.95)
- Mediterranean diet alone reduced cardiovascular mortality among those with increased CV risk (OR 0.55; 95% CI, 0.39–0.78).

Secondary Outcome –

- Mediterranean and low-fat diets reduce non-fatal MI among those with increased CV risk.
  - Mediterranean diet (OR 0.48; 95% CI, 0.36–0.65)
  - Low-fat diet (OR 0.77; 95% CI, 0.61–0.96)
- Mediterranean diet reduces the risk of stroke (OR 0.65; 95% CI, 0.46–0.93).

LIMITATIONS:

- Dietary programs were classified by name only (did not look at food or macronutrient composition).
- Unable to control adherence to the dietary program.
- Minimal intervention was classified differently based on what was considered the intervention arm in each study but was always less than the intervention from the same study (minimum/no dietary advice vs. dietary advice with little reinforcement vs optional dietary counseling).
- Did not provide demographics of the study population.

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Bupropion with Naltrexone Decreases Methamphetamine Use in Methamphetamine Use Disorder

Bupropion and Naltrexone in Methamphetamine Use Disorder

Trivedi MH, Walker R, Ling W, et al. Bupropion and Naltrexone in Methamphetamine Use Disorder. *N Engl J Med*. 2021;384(2):140-153. doi:10.1056/NEJMoa2020214

KEY TAKEAWAY: Bupropion in combination with injectable naltrexone is effective in decreasing methamphetamine use compared to placebo in patients with methamphetamine use disorder.

STUDY DESIGN: Randomized, double-blind, two-stage, placebo-controlled trial with sequential parallel comparison design

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION:

Methamphetamine is the second most common illicit substance used in the US, with more than two million people in 2019 reporting use in the past year. Methamphetamine use is associated with high rates of comorbid psychiatric conditions, cardiovascular disease, polysubstance use, risky behavior, suicidality, and systemic infection. Unfortunately, there is little evidence for medications with significant effectiveness in decreasing methamphetamine use.

PATIENTS: Adults with moderate or severe methamphetamine use disorder

INTERVENTION: Naltrexone injection and bupropion ER tablet

CONTROL: Placebo IM injection and placebo PO tablets

PRIMARY OUTCOME: Response to treatment

Secondary Outcome: Percentage of methamphetamine-negative urine samples, methamphetamine craving severity, depressive symptoms, quality of life

METHODS (BRIEF DESCRIPTION):

- Participants were 18–65 years old (68.7% male, 71.2% white) with moderate to severe methamphetamine use disorder and expressed a desire to quit or reduce methamphetamine use.
- Participants reported methamphetamine use on at least 18 of the past 30 days and had two or more positive urine tests for methamphetamine in the 10 days preceding randomization.
- Participants were excluded if they were using opioids, receiving treatment for a substance use disorder, upcoming opioid therapy was anticipated, or they had a medical contraindication to treatment with bupropion or naltrexone.
- This was a 12-week trial conducted in two, six-week stages:
- Stage 1: Participants were randomized in a 0.26:0.74 ratio (treatment:placebo)
    - Treatment: Naltrexone ER 380 mg IM every three weeks and bupropion ER 150 mg tablets PO daily, titrated up to 450 mg over three days as tolerated.
    - Placebo: IM injection every three weeks and PO daily tablets.
- Stage 2: Participants in the placebo treatment group who did not respond to treatment were re-randomized 1:1 into intervention and placebo groups for a second six-week period.
- Participants visited their clinic twice weekly for urine drug tests and safety monitoring.
- Primary outcome: Treatment responsiveness is defined as three of four methamphetamine-negative urine drug tests in the last two weeks of each six-week stage.
- Secondary outcomes:
    - Overall methamphetamine use defined as the percentage of a patient's 12 urine drug tests negative for methamphetamines.
    - Methamphetamine craving as measured weekly by a 100-point visual analog scale.
    - Depressive symptoms as measured weekly by the Patient Health Questionnaire 9 (PHQ-9) standardized assessment tool.
    - Treatment Effectiveness Assessment (TEA) scores are measured during the last week of each stage.
        - TEA measures the quality of life, health, community, and interpersonal relationships on a scale from 4–40 with increased scores indicating improvement.

INTERVENTION (# IN THE GROUP):

- Stage 1: 109
- Stage 2: 114

COMPARISON (# IN THE GROUP):

- Stage 1: 199
- Stage 2: 111

FOLLOW-UP PERIOD: Twice a week for each six-week stage

RESULTS:

Primary Outcome –

- Treatment with bupropion and naltrexone resulted in an increase in treatment response compared to placebo (between-group difference 11.1%; 95% CI, 6.3; *P*<.001)

Secondary Outcome –

- Bupropion and naltrexone intervention resulted in the following compared to control:
  - Increase in methamphetamine-negative urine samples (weighted average difference of 6.8%; 95% CI, 3.5–10.1)
  - Less severe methamphetamine cravings (between-group difference on the visual analog scale –9.7; 95% CI, –13.8 to –5.6)
  - Fewer depressive symptoms (weighted average between-group PHQ-9 score difference –1.1; 95% CI, –1.9 to –0.2)
  - Improved quality of life, health, and relationships (between-group average TEA score difference 4.0; 95% CI, 2.3–5.7)
  - Increased adverse effects of nausea, vomiting, and dizziness (*P*<.05 for each above-listed adverse event for both stages of the study)

LIMITATIONS:

- Low attrition/high adherence limits generalizability among conventional primary care settings with limited capacity for weekly patient follow-up.
- Low representation of female participants, which may impact generalizability to female patients.
- Demographic information does not describe housing security or socioeconomic status, which limits generalizability.
- No follow up was performed beyond 12 weeks.
- Naltrexone was dosed every three weeks, while the FDA-approved dosing interval is every four weeks; payors may not approve the dosing frequency utilized in this study.
- Naltrexone/bupropion combination therapy was only compared to placebo and not naltrexone or bupropion monotherapies.

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Moderate Alcohol Consumption and Liver Disease Progression in NAFLD

Does Moderate Alcohol Consumptions Accelerate the Progression of Liver Disease in NAFLD? A Systematic Review and Narrative Synthesis

Jarvis H, O'Keefe H, Craig D, Stow D, Hanratty B, Anstee QM. Does moderate alcohol consumption accelerate the progression of liver disease in NAFLD? A systematic review and narrative synthesis. *BMJ Open*. 2022;12(1):e049767. Published 2022 Jan 4. doi:10.1136/bmjopen-2021-049767

KEY TAKEAWAY: Any level of alcohol consumption may worsen liver disease in patients with non-alcoholic fatty liver disease (NAFLD); therefore, clinicians should recommend abstinence from alcohol in this patient group.

STUDY DESIGN: Systematic review and narrative synthesis of six cohort studies (N=84,049)

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

BRIEF BACKGROUND INFORMATION: Although the etiology of NAFLD is not alcohol-related, there is limited evidence that can be used to support recommendations on appropriate alcohol consumption among patients with NAFLD. With the increase of metabolic-syndrome-related liver disease, it is critical for clinicians to have good evidence to support their recommendations.

PATIENTS: Adults with NAFLD

INTERVENTION: Moderate alcohol consumption

CONTROL: Abstinence

PRIMARY OUTCOME: Progression of liver disease

METHODS (BRIEF DESCRIPTION):

- Inclusion criteria: Adults with NAFLD, moderate alcohol exposure, and progression of liver disease as a primary outcome
- Other articles were excluded based on inadequate data, incorrect study design, advanced disease, or alcohol-related liver disease at baseline.
- The included studies were conducted in Finland, US, South Korea, Sweden, and Japan.
  - Participants had a mean age of 37.7–53.7 years old and most studies included a majority of male participants.
- "Moderate alcohol consumption" was measured in g/day (except for one US study) and definitions varied widely between studies, with one study having no upper limit.
- Measurement of the primary outcome (progression of liver disease) varied between studies and included: Composite non-fatal and fatal liver disease events, histological progression, fibrosis-4 (Fib4) score, or hepatocellular carcinoma (HCC) on imaging.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: 3.9–13.8 years

RESULTS:

Primary Outcome –

- Alcohol consumption of 10–19 g/week (~14 units per week) was associated with an increased incidence of liver events as compared to abstinence (1 trial, N=8,345; hazard ratio [HR] 2.2; 95% CI, 1.1–4.5).
  - There was no difference between groups with <10 g/day of alcohol consumption.
- As compared to moderate consumption, abstinence was associated with improved rates of NASH resolution (1 trial, N=285; OR 0.32; 95% CI, 0.11–0.92).
- As compared to abstinence, moderate alcohol consumption (10–30 g/day) was associated with an increased risk of progression to advanced fibrosis by Fib4 score (1 trial, N=58,927; HR 1.3; 95% CI, 1.1–1.6).
- Drinking 40–69 g/day was associated with increased rates of HCC (1 trial, N=9,959; HR 2.5; 95% CI, 1.01–6.6) as compared to drinking <20 g/day.

LIMITATIONS:

- Varying methods for measuring NAFLD progression and defining "moderate consumption" prevented any pooling of data between studies.
- Alcohol consumption was measured by a questionnaire, which likely increased the risk of reporter bias.
- Heterogeneity in patient populations across studies makes comparison and generalizability more difficult.
- Abstinence was defined as <20 g/day in one study.

- Narrative analysis included one study with a high risk of bias.

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Does Nutritional Quality of Energy-Restricted Diet Affect Weight Loss and Cardiovascular Health?

Diverging Metabolic Effects of 2 Energy Restricted Diets Differing in Nutrient Quality: A 12-Week Randomized Controlled Trial in Subjects with Abdominal Obesity

Schutte S, Esser D, Siebelink E, et al. Diverging metabolic effects of 2 energy-restricted diets differing in nutrient quality: a 12-week randomized controlled trial in subjects with abdominal obesity. *Am J Clin Nutr*. 2022;116(1):132-150. doi:10.1093/ajcn/nqac025

KEY TAKEAWAY: Higher-quality diets produce more weight loss and beneficial cardiovascular risk profile than low-quality diets with the same energy restriction/calorie deficit.

STUDY DESIGN: Single-site, parallel-designed, randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Obesity is a growing health issue worldwide associated with chronic diseases and poor health outcomes. Energy restriction is known to be an essential component of weight loss, but the ideal nutritional composition of the diet is unknown.

PATIENTS: Adults with abdominal obesity

INTERVENTION: Energy-restricted diet with high-nutrient or low-nutrient qualities

CONTROL: Habitual diet (no changes or energy restriction)

PRIMARY OUTCOME: Weight, intrahepatic lipids, body fat distribution, fasting and postprandial response, vascular measurements

METHODS (BRIEF DESCRIPTION):

- Participants 40–70 years old were selected from eligible candidates in the Netherlands with a BMI >27 or waist circumference >88 cm (women) or >102 cm (men) without diabetes, smoking, heavy alcohol use, or other long-term medical conditions.
- The estimated energy requirement (EER) for each participant was calculated using size and reported physical activity levels.
- Weight and metabolic markers were measured via MRIs, blood draws, and meal challenges prior to starting the study.
- A diet including 25% fewer calories than the EER was calculated and provided to each participant.
- The high-nutrition diet had a higher percentage of calories from mono-unsaturated fatty acids, Omega-3 fatty acids, fiber, plant protein, and less from fructose than the low-nutrition diet.
- The high-nutrition diet had a capsule of 400 mg EPA and 300 mg DHA to supplement the Omega-3 fatty acids.
- Weekly meetings with a dietician to review diet, leftovers were deducted from the amount provided.
- Measurements were repeated after the 12-week trial period.

INTERVENTION (# IN THE GROUP):

- High-quality nutrients: 40
- Low-quality nutrients: 40

COMPARISON (# IN THE GROUP): 30

FOLLOW-UP PERIOD: 12 weeks

RESULTS:

Primary Outcome –

- High-nutrient 25% energy-restricted diet induced more weight loss than low nutrient 25% energy-restricted diet (–8.4 vs –6.3, respectively; *P*=.007).

Secondary Outcome –

- High-nutrient-quality also reduced the following compared to low-nutrient-quality diet:
  - Serum total cholesterol (–0.5 vs –0.2, respectively; *P*=.013)
  - Triglycerides (–0.4 vs –0.2, respectively; *P*<.001)
- The difference in weight loss between energy-restricted diets was seen in insulin-sensitive individuals (high-quality –9.8 kg vs low-quality –5.9 kg; *P*<.007)

LIMITATIONS:

- Results were measured after 12 weeks.
- The study was not blinded.
- Self-reporting of diet leaves room for inaccuracy.
- Participants were not representative of the population at large.
- Cardiovascular health improvements extrapolated from measurements.
- Food and dietary counseling were provided to participants and did not represent typical dieting.

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Impact of 24-Hour Ambulatory Blood Pressure Readings on Mortality

Relationship Between Clinic and Ambulatory Blood Pressure and Mortality: An Observational Cohort Study in 59,124 Patients

Staplin N, de la Sierra A, Ruilope LM, et al. Relationship between clinic and ambulatory blood pressure and mortality: an observational cohort study in 59 124 patients. *Lancet*. 2023;401(10393):2041-2050. doi:10.1016/S0140-6736(23)00733-X

KEY TAKEAWAY: 24-hour blood pressure monitoring, especially night-time recordings, is more strongly associated with the risk of all-cause death than clinic blood pressure.

STUDY DESIGN: Prospective observational cohort

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: 24-hour ambulatory blood pressure monitoring (ABPM) and night-time blood pressure monitoring have been previously shown to better predict health outcomes than conventional clinic blood pressure measurements, but prior studies were limited in terms of sample size and clinical outcomes assessed. Similarly, prior studies have been limited on the effects of white coat and masked hypertension on mortality. This study, substantially better powered than prior studies, sought to validate existing associations between ABPM and nighttime blood pressure monitoring and mortality and to further define the impact of masked and white coat hypertension on mortality.

PATIENTS: Adults with hypertension

INTERVENTION: Ambulatory blood pressure monitoring

CONTROL: Clinic blood pressure

PRIMARY OUTCOME: All-cause mortality, cardiovascular mortality

Secondary Outcome: White coat, masked, sustained hypertension

METHODS (BRIEF DESCRIPTION):

- The study enrolled adults 18 years old and older from the Spanish Ambulatory Blood Pressure Registry, which included 223 primary care centers from the Spanish National Health System.
- Inclusion criteria for the registry were suspicion to have white coat hypertension (HTN), refractory or resistant HTN, assessment of drug treatment efficacy, high-risk HTN, labile or borderline HTN, and the study of circadian blood pressure pattern.
- The average age of participants was 57.8 years, 47% were women, 40% had obesity, 15% were currently smoking, 19% had diabetes, 41% had dyslipidemia, and 9.5% had a previous cardiovascular disease.
- The mean of two clinic blood pressure readings were collected on each patient after being seated for five minutes prior.
- 24-hour ambulatory blood pressures were recorded at 20-minute intervals during the day and 30-minute intervals at night.
- The Spanish vital registry was searched to obtain the date and cause of death for the participant; cardiovascular death was determined per ICD code.
- All participants were separated into five quintiles based on each blood pressure measurement among those who died, and Cox regression hazard models were used to compare the top four-fifths of blood pressure measurements to the lowest one-fifth of blood pressure measurements.
- Different HTN variables were categorized and defined as normal, white coat HTN, masked HTN, and sustained HTN. These categories were used to estimate the risk of death using the Cox regression analysis.

INTERVENTION (# IN THE GROUP): 59,124

COMPARISON (# IN THE GROUP): 59,124

FOLLOW-UP PERIOD: Median of 9.7 years

RESULTS:

Primary Outcome –

- After adjusting for confounders, 24-hour systolic blood pressure was found to be strongly associated with all-cause death (adjusted hazard ratio [aHR] 1.30; 95% CI, 1.26–1.34) as compared to clinic blood pressure (aHR 1.08; 95% CI, 1.04–1.11).
- Night-time systolic blood pressure was found to be the most strongly associated with all-cause death (HR 1.36; 95% CI, 1.32–1.40).
- After adjusting for confounders, white coat hypertension was associated with a reduced risk of all-cause death and equivalent for cardiovascular death as compared to the normal range of blood pressure (aHR 0.90; 95% CI, 0.84–0.97).

- An increased risk of all-cause mortality and cardiovascular death was seen for masked hypertension:
  - All-cause mortality (aHR 1.24; 95% CI, 1.12–1.37)
  - Cardiovascular death (aHR 1.37; 95 CI, 1.15–1.63)
- An increased risk of all-cause mortality and cardiovascular death was seen for sustained hypertension:
  - All-cause mortality (aHR 1.24; 95% CI, 1.15–1.32)
  - Cardiovascular death (aHR 1.38; 95% CI, 1.22–1.55)

LIMITATIONS:

- Mean clinic blood pressures may have been overestimated since only two readings were collected.
- Selection bias may have occurred due to the inclusion criteria requiring referral for ambulatory blood pressure monitoring, which was based on indications for this procedure in clinical guidelines at the time of the study.
- This observational study can show correlation but not causality.
- The cohort was mostly White, and as such these findings may not be generalizable to other populations.

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How Effective are Intranasal Corticosteroids in Pediatric Chronic Rhinosinusitis?

Effect of an Intranasal Corticosteroid on Quality of Life and Local Microbiome in Young Children with Chronic Rhinosinusitis: A Randomized Clinical Trial

Latek M, Lacwik P, Molinska K, et al. Effect of an Intranasal Corticosteroid on Quality of Life and Local Microbiome in Young Children with Chronic Rhinosinusitis: A Randomized Clinical Trial. *JAMA Pediatr.* 2023;177(4):345-352. doi:10.1001/jamapediatrics.2022.6172

KEY TAKEAWAY: Intranasal corticosteroids can relieve chronic rhinosinusitis symptoms and may improve sinonasal biodiversity in children 4–8 years old.

STUDY DESIGN: Unblinded, open-label, randomized controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size and open-label design)

BRIEF BACKGROUND INFORMATION: There is a lack of evidence supporting the efficacy of intranasal corticosteroids in pediatric patients with chronic rhinosinusitis despite being a first-line treatment. It is also unclear if the sinonasal microbiome plays a role in chronic rhinosinusitis and how it is affected by intranasal corticosteroids.

PATIENTS: Children 4–8 years old with chronic rhinosinusitis

INTERVENTION: Intranasal mometasone and NaCl 0.9% solution nasal nebulizer

CONTROL: NaCl 0.9% solution nasal nebulizer

PRIMARY OUTCOME: Sinus and nasal quality of life, nasopharynx microbiome analysis, nasal mucosa sampling for nasal occurrence of innate lymphoid cells

METHODS (BRIEF DESCRIPTION):

- Subjects were children 4–8 years old with a diagnosis of chronic rhinosinusitis defined as at least 12 weeks of two or more rhinosinusal symptoms.
  - 63 children completed the study (mean age 6.1 years)
- Exclusion criteria: Patients who had active upper respiratory tract infection within two weeks, intranasal or systemic corticosteroid within four weeks, food allergy, exposure to tobacco, immunodeficiency, obesity, or any contraindication to nasal endoscopy or nasal mucosa biopsy.
- Subjects were randomized into two groups at a ratio of 2:1 to minimize the number of children who would go without anti-inflammatory treatment due to ethical reasons.
  - Intervention: 12-week course of intranasal mometasone and supplemental 3 mL NaCl 0.9% solution nasal nebulizer
  - Control: 12-week course of 3mL NaCl 0.9% solution nasal nebulizer
- Subjects were examined at the beginning and at the end of the treatment.
- Primary outcome: Sinus and Nasal Quality of Life Survey (SN-5) includes five symptoms evaluated on a seven-point scale (sinus infection, nasal obstruction, allergic symptoms, emotional distress, activity limitation). Clinically significant improvement was defined as a decrease of 0.5 points or more.
- Secondary outcome: Measures of nasal mucosal microbiome and innate lymphoid cells were performed before and after treatment by next-generation sequencing (16S rRNA sequencing libraries) and flow cytometry.

INTERVENTION (# IN THE GROUP): 44

COMPARISON (# IN THE GROUP): 22

FOLLOW-UP PERIOD: 12 weeks

RESULTS:

Primary Outcome –

- Mometasone intranasal spray improved sinonasal symptoms compared to control (mean between-group difference –0.58; 95% CI, –1.3 to –0.19).
- Mometasone also resulted in a higher likelihood of significant clinical improvement (OR 3.3; 95% CI, 1.1–10).

Secondary Outcome –

- Mometasone significantly increased the richness of the nasopharynx microbiome in the treatment group compared to the control group (OR 4.6; 95% CI, 1.1–20), which correlated with clinically improved sinonasal symptoms.
- No significant changes were observed in the abundance of taxa in the nasopharyngeal microbiome.

LIMITATIONS:

- Open-label design and primary outcome based on parental subjective report increases susceptibility to bias.
- Unclear if secondary outcome assessments were performed blinded.
- Longer-term risks or adverse effects of chronic topical corticosteroid use in pediatrics are unknown, given this study was performed for 12 weeks.
- Small sample size.

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