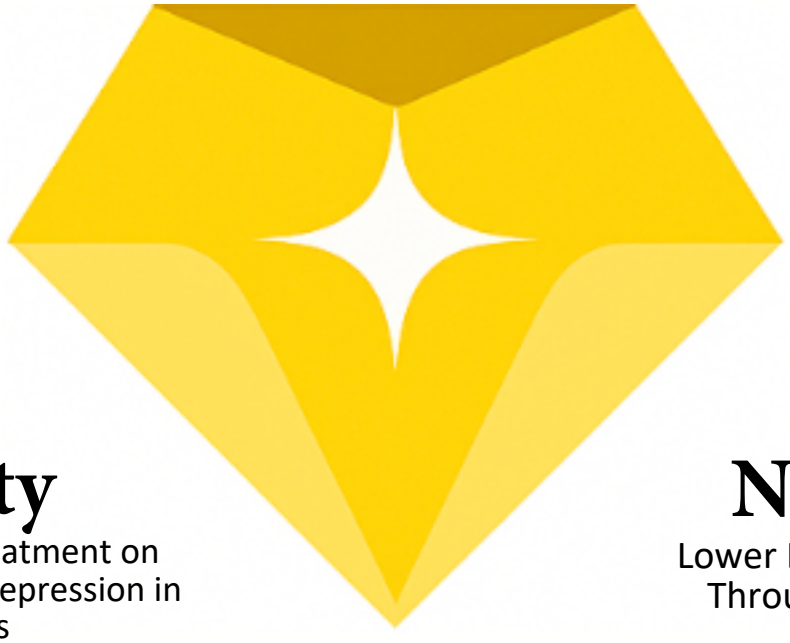
GOOD EVIDENCE MATTERS

GEMs of the Week



Obesity

Effects of Obesity Treatment on Eating Disorders and Depression in Adolescents

Nutrition

Lower Lipid Levels Achieved Through Vegetarian and Vegan Diets

SPOTLIGHT: Menopausal Health

Under Pressure: Hormone Therapy's Impact on Blood Pressure After Menopause

Medical Records

Charting the Right Course: Check the Prompt!

Heart Health

Empagliflozin and EPO: The Added Benefits in Patients with Heart Failure

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Under Pressure: Hormone Therapy's Impact on Blood Pressure After Menopause

Effect of Hormone Therapy on Blood Pressure and Hypertension in Post-Menopausal Women: A Systematic Review and Meta-Analysis

Ferreira Campos L, de Andrade Costa G, Domingues Feitosa M, et al. Effect of hormone therapy on blood pressure and hypertension in postmenopausal women: a systematic review and meta-analysis. *Menopause*. 2024;31(6):556-562.
doi:10.1097/GME.0000000000002359

KEY TAKEAWAY: In postmenopausal women, conjugated equine estrogens (CEE) + progestogen increases systolic blood pressure (SBP), while other hormone therapy formulations, including CEE or estradiol (E2) alone, E2 + progestogen, and tibolone, do not significantly affect SBP or diastolic blood pressure (DBP).

STUDY DESIGN: Systematic review and meta-analysis of 10 randomized controlled trials (RCTs) and one prospective cohort study (N=81,041)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to significant heterogeneity and lack of generalizability)

BRIEF BACKGROUND INFORMATION: Menopause can significantly impact a woman's quality of life in a variety of ways including physically, emotionally, and socially. Hypertension is a significant risk factor for cardiovascular diseases. Menopause hormone therapy (HT) can be used to address many symptoms including vasomotor symptoms that greatly affect a woman's quality of life, but the effect of exogenous HT on blood pressure is still unclear. This study reviewed the evidence regarding the effect of HT on blood pressure in postmenopausal women which can be used when determining risk vs benefit of using HT in practice.

PATIENTS: Postmenopausal women

INTERVENTION: Various formulations of menopause HT

CONTROL: Placebo or nonuse of HT

PRIMARY OUTCOME: SBP and DBP

METHODS (BRIEF DESCRIPTION):

- Participants included menopausal women.
- Women with surgical menopause or premature ovarian failure were excluded from the review.
- Studies were excluded if they included women using anti-hypertensive therapy, medications that effect blood pressure (BP), non-hormonal menopausal symptom control, or preclinical studies.
- Time since menopause ranged from one year to ≥ 15 years.
- The age of the women ranged from 45–65 years, with only one study including women >70 years old.
- HT formulations included estrogen alone, estrogen combined with progestogens, progestogens alone, or tibolone.
- Most studies reviewed oral HT, two reviewed transdermal, and one reviewed any self-reported route.
- Control groups received placebo or no HT.
- The intervention duration ranged from three months to 13 years
- Blood pressure was measured or self-reported as the outcome with hypertension defined as SBP ≥140 and/or DBP ≥90.

INTERVENTION (# IN THE GROUP): 1,157

COMPARISON (# IN THE GROUP): 561

FOLLOW-UP PERIOD: Varied (mean 2.9 years)

RESULTS:

Primary Outcome –

- Tibolone did not significantly impact SBP compared to control (2 trials, n=124; standardized mean difference [SMD] –0.90; 95% CI, –8.9 to 7.1; I^2=83%)
- Tibolone did not significantly impact DBP compared to control (2 trials, n=124; SMD –1.4; 95% CI, –20 to 17; I^2=95%).
- CEE + progestogen increased SBP compared to control (3 trials, n= 630; SMD 0.60 mmHg; 95% CI, 0.19–1.0; I^2=0%).
- CEE + progestogen did not significantly impact DBP compared to control (3 trials, n=630; SMD 0.05 mmHg; 95% CI, −2.6 to 2.8; I^2=86%).
- E2 + progestogen did not significantly impact SBP compared to control (5 trials, n=1,217; SMD –2.0 mmHg; 95% CI, –7.3 to 3.3; I^2=92%).
- E2 + progestogen did not significantly impact DBP compared to control (5 trials, n=1,217; SMD –0.02 mmHg; 95% CI, –0.74 to 0.71; I^2=31%).
- CEE alone did not show significant effect on SBP compared to control (1 trial, n=29; SMD –1.6 mmHg; 95% CI, –2.4 to –0.71).

- CEE alone did not show significant effect on DBP compared to control (1 trial, n=29; SMD 0 mmHg; 95% CI, –0.73 to 0.73).
- E2 alone did not demonstrate any significant effect on SBP compared to control (2 trials, n=67; SMD –0.72 mmHg; 95% CI, –17 to 16; I^2=37%).
- E2 alone did not show significant effect on DBP compared to control (2 trials, n=67; SMD 1.1 mmHg; 95% CI, –12 to 14; I^2=53%).

LIMITATIONS:

- Significant heterogeneity was present in the included studies.
- A small number of studies met inclusion criteria for the systematic review and three studies were excluded from the meta-analysis, limiting generalizability.
- Two of the studies left out of the meta-analysis were the largest studies, further limiting generalizability.

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Effects of Obesity Treatment on Eating Disorders and Depression in Adolescents

Symptoms of Depression, Eating Disorders, and Binge Eating in Adolescents with Obesity: The Fast Track to Health Randomized Clinical Trial

Jebeile H, Baur LA, Kwok C, et al. Symptoms of Depression, Eating Disorders, and Binge Eating in Adolescents With Obesity: The Fast Track to Health Randomized Clinical Trial. *JAMA Pediatr*. 2024;178(10):996-1005. doi:10.1001/jamapediatrics.2024.2851

KEY TAKEAWAY: Intermittent energy restriction (IER) and continuous energy restriction (CER) result in similar symptoms of depression, disordered eating, and binge eating in adolescents with obesity after 52 weeks.

STUDY DESIGN: Parallel, multicenter, randomized clinical trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Symptoms of depression and eating disorders increase during the adolescent period. Patients in this age group with obesity are at higher risk of developing physical and psychological health problems. Studies have shown that lifestyle interventions improve binge eating and depression symptoms. This study aimed to evaluate self-reported symptoms during intensive behavioral intervention.

PATIENTS: Adolescents with obesity

INTERVENTION: IER

CONTROL: CER

PRIMARY OUTCOME: Self-reported symptoms for depression, eating disorders, and binge eating

METHODS (BRIEF DESCRIPTION):

- Adolescents were recruited through social media (Facebook).
- Adolescents 13–17 years old with obesity (BMI ≥30) and ≥1 cardiometabolic complication including prediabetes, insulin resistance, presence of acanthosis nigricans, hypertension (HTN), low high-density lipoprotein (HDL), elevated triglycerides, transaminitis, or polycystic ovary syndrome (PCOS) were included in the study.
- Patients were randomized 1:1 via computer-generated schedule to either IER or CER.
- The trial included three phases.
    - Weeks 0–4: Very low energy diet (800 kcal per day)
    - Weeks 5–16: IER or CER
        - IER: Three energy restricted days (600–700 kcal per day) and four days per week of eating without restriction (healthy eating guidelines)
        - CER: Energy prescription based on age (13–14 years old, 1,430–1,670 kcal per day; 15–17 years old, 1,670–1,900 kcal per day)
        - Participants had dietician support at follow up.
    - Weeks 17–52: Continued intervention with less support.
        - Had dietician support at 18, 24, 28, 42, 48 and 52 weeks.
- Participants were screened for depression and eating disorders via self-reported questionnaires at baseline and follow up using the following tools:
    - Center for Epidemiologic Studies Depression Scale (CESDR-10): Scores range from 0–30, with scores of ≥8 indicating symptoms of depression.
    - Eating Disorder Examination Questionnaire (EDE-Q): Scores range from 0–6, with a score of ≥2.7 indicating the presence of disordered eating.
    - Binge-Eating Scale (BES): Scores range from 0–46, with scores of ≤17 indicates no binge eating, a score of 18–26 indicates mild/moderate binge symptoms, and a score ≥27 indicates severe binge eating.

INTERVENTION (# IN THE GROUP): 71

COMPARISON (# IN THE GROUP): 70

FOLLOW-UP PERIOD: 52 weeks

RESULTS:

Primary Outcome –

- There was no significant difference in depression symptoms between groups at 52 weeks (mean difference [MD] 0.8; 95% CI, –1.9 to 3.4).
- There was no significant difference in disordered eating symptoms between groups at 52 weeks (MD 0.02; 95% CI, –0.4 to 0.5).
- IER reduced binge eating symptoms at four weeks compared to CER (MD –4.4; 95% CI, –5.9 to –2.8),

and maintained at 52 weeks (MD –3.7; 95% CI, –6.2 to –1.2).
- There was no significant difference in binge eating symptoms between groups at 52 weeks (MD –2.9; 95% CI, –5.9 to 0.05).

LIMITATIONS:

- Eating disorders can take years to develop, so the length of study may have been too short.
- A large portion of the study was done during COVID-19 pandemic, which could be a confounding variable that increased adolescent depression and disordered eating in the study.
- The data analyzed was self-reported and some adolescents reported misunderstanding questions.
- EDE-Q does not include questions about rigidity and fixation on numerical changes (i.e. calories and weight) that could indicate disordered eating.

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Lower Lipid Levels Achieved Through Vegetarian and Vegan Diets

Vegetarian or Vegan Diets and Blood Lipids: A Meta-Analysis of Randomized Trials

Koch CA, Kjeldsen EW, Frikke-Schmidt R. Vegetarian or vegan diets and blood lipids: a meta-analysis of randomized trials. *Eur Heart J*. 2023;44(28):2609-2622. doi:10.1093/eurheartj/ehad211

KEY TAKEAWAY: Vegan and vegetarian diets are associated with reduction in total cholesterol, low-density lipoprotein (LDL) and apolipoprotein B (apoB) compared to an omnivorous diet in non-pregnant adults.

STUDY DESIGN: Meta-analysis of 30 randomized controlled trials (RCTs) (N=2,372)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to lack of blinding and information on randomization)

BRIEF BACKGROUND INFORMATION: Hyperlipidemia is a known risk factor for atherosclerotic cardiovascular disease (ASCVD), the leading cause of death worldwide. This study aimed to evaluate the lipid and lipoprotein-lowering effect of a vegan or vegetarian diet.

PATIENTS: Non-pregnant adults

INTERVENTION: Vegan or vegetarian diets

CONTROL: Omnivorous diet

PRIMARY OUTCOME: Total blood cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and apoB levels

METHODS (BRIEF DESCRIPTION):

- RCTs were found through literature search conducted from September 2021 to October 2022 in PubMed and Embase for studies published between 1980–2022.
- Studies were excluded if they lacked sufficient data needed for meta-analysis, were unpublished or duplicates.
- Included studies were mostly from the United States (18 studies), with the other countries being Sweden, Finland, South Korea, Australia, Brazil, Czech Republic, Italy, Iran, and New Zealand.
- The RCTs had sample sizes ranging from 11–291 (mean 79), mean body mass index (BMI) ranging from 22–35 kg/m^2 and a mean age between 20–67 years old.
- Intervention included the following:
  - Lacto-vegetarian diet (3 studies, n=106)
  - Lacto-ovo-vegetarian diet (12 studies, n=945)
  - Vegan diet (15 studies, n=1,321)
- Control involved low-fat, high-fat, or low-calories omnivorous diets.
- Each trial's blood lipid and lipoprotein levels were extracted at baseline, and post-intervention in both intervention and control groups.
- For trials with multiple time measurements, only the last point was used for analysis.
- Estimates of lipid and lipoprotein level differences were indicated as means with 95% confidence interval (CI).
- The metanalysis extracted the mean and standard deviations of blood lipid and lipoprotein concentrations at baseline, and post-intervention from each trial in both intervention and control groups.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Varied (mean 29 weeks)

RESULTS:

Primary Outcome –

- A vegan or vegetarian diet reduced TC compared to an omnivorous diet (mean difference [MD] –0.34 mmol/L; 95% CI, −0.44 to −0.23; I^2=69%).
- A vegan or vegetarian diet reduced LDL-C compared to an omnivorous diet (MD –0.30 mmol/L; 95% CI, −0.40 to −0.19; I^2=74%).
- A vegan or vegetarian diet did not significantly impact TG levels compared to an omnivorous diet (MD 0.06 mmol/L; 95% CI, −0.01 to 0.13; I^2=54%).
- A vegan or vegetarian diet reduced apoB levels compared to an omnivorous diet (MD –13 mg/dL; 95% CI, −23 to −3.2; I^2=72%).

LIMITATIONS:

- The RCTs had different vegetarian diets so the intervention with the most benefit in reducing TC remained unknown.
- Most of the RCTs were limited by lack of blinding and detailed information on their randomization so conclusions about their effects on TC should be cautiously interpreted.
- The individual RTCs had small sample sizes (11−291 participants, mean=79) and most trials were less than one year, so extrapolation of results to large

scale and long-term effects should be made with caution.

- Crossover trials had a high risk of bias due to carryover as well as period effect and some trials did not have washout period which could mean that the true effects may be even greater than measured in the study.
- Adherence to intervention was self-reported, if adherence was over or under reported, the true effects of the vegan or vegetarian diet may be greater or lesser than seen in this study.
- Although all studies provided adequate TG data, three did not include LDL data, and six had insufficient data on apoB levels.

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Stewardship Prompts to Improve Antibiotic Selection for Urinary Tract Infection: The INSPIRE Randomized Clinical Trial

Gohil SK, Septimus E, Kleinman K, et al. Stewardship Prompts to Improve Antibiotic Selection for Urinary Tract Infection: The INSPIRE Randomized Clinical Trial. *JAMA*. 2024;331(23):2018-2028. doi:10.1001/jama.2024.6259

KEY TAKEAWAY: Computerized provider order entry (CPOE) prompts decrease the use of extended spectrum antibiotics for patients with low multidrug resistant organism (MDRO) risk compared with routine stewardship in non-critically ill adults admitted with urinary tract infection (UTI).

STUDY DESIGN: Randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: UTI is the second most common infection causing hospitalization, often associated with gram negative MDROs. Over prescription of broad-spectrum antibiotics to patients who do not warrant it is associated with increasing rates of antibiotic resistance, altered gut and urinary microbiomes, risk for *Clostridiodes difficile* infection and overall poor antibiotic stewardship. This study aimed to determine whether utilization of CPOE prompts compared to regular antibiotic stewardship without system prompting, results in fewer total days of empiric extended-spectrum antibiotic use.

PATIENTS: Non-critically ill patients hospitalized with UTI

INTERVENTION: Computerized provider order entry prompts used when ordering empiric antibiotics

CONTROL: Routine, provider driven stewardship without computer prompting

PRIMARY OUTCOME: Days of empiric extended-spectrum antibiotic therapy

Secondary Outcome: Empiric vancomycin and antipseudomonal days of therapy, hospital length of stay, intensive care unit (ICU) transfers, patients requiring antibiotic escalation

METHODS (BRIEF DESCRIPTION):

- Non-critically ill, hospitalized adults with a UTI at private community hospitals in the US were included in the study.
- Patients transferred to the ICU within two days of admission were excluded from the study.
- The CPOE algorithm and prompts were activated when extended-spectrum antibiotics were ordered in a non-ICU location for an indication of UTI within 72 hours of admission.
- The system then required documented indication for all antibiotic orders.
- If the risk was <10% for MDRO infection, the prompt would trigger and recommend standard-spectrum antibiotics
- The control group was the absence of CPOE prompts as listed above.
- Both groups had standard clinical education emphasizing national standards for empiric antibiotic treatment for cystitis and pyelonephritis, including treatment of extended spectrum beta lactamases (ESBLs) and avoiding antibiotics for asymptomatic bacteriuria in both study groups.
- Both groups also received coaching calls and educational materials.
- The primary outcomes measured were extended-spectrum days of therapy in the first three calendar days of hospitalization calculated as the summed number of different extended-spectrum antibiotics received per patient each calendar day in a non-ICU location beginning at the time of admission. This was simplified as empiric period and empiric days that were calculated.
- If two different extended-spectrum antibiotics were used at least once during each of the first three days, this would equal an extended-spectrum days of therapy of six days.
- Secondary outcomes included vancomycin and antipseudomonal days of therapy and safety outcomes of the following:
  - Days of antibiotic escalation defined as hospital days from standard-spectrum antibiotic
  - Days to ICU transfer defined as days from admission until ICU transfer
  - Hospital length of stay in days.

INTERVENTION (# IN THE GROUP): 55,412

COMPARISON (# IN THE GROUP): 71,991

FOLLOW-UP PERIOD: 15 months

RESULTS:

Primary Outcome –

- CPOE prompts decreased the rate of empiric extended spectrum days of therapy compared to routine stewardship (rate ratio [RR] 0.83; 95% CI, 0.77–0.89).

Secondary Outcome –

- CPOE prompts decreased vancomycin days of therapy compared to routine stewardship (RR 0.89; 95% CI, 0.82–0.96).
- CPOE prompts decreased antipseudomonal days of therapy compared to routine stewardship (RR 0.79; 95% CI, 0.72–0.87).
- There were no significant differences in days to ICU transfer, hospital length of stay, or number of patients requiring antibiotic escalation between the two groups.

LIMITATIONS:

- Patients identified in the study were risk stratified to have a ≤10% risk of having an MDRO but raising that threshold to ≤20% may have been more effective for CPOE stewardship.
- Patients in this study were admitted to private community hospitals, which may not be generalizable to public or critical access hospitals.
- CPOE prompts were implemented at the same hospitals for patients admitted with pneumonia, which may have contributed to decreased adoption through alarm fatigue.

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Empagliflozin and EPO: The Added Benefits in Patients with Heart Failure

Effects of Empagliflozin on Erythropoiesis in Heart Failure: Data from the Empire HF Trial

Fuchs Andersen C, Omar M, Glenthøj A, et al. Effects of empagliflozin on erythropoiesis in heart failure: data from the Empire HF trial. *Eur J Heart Fail*. 2023;25(2):226-234. doi:10.1002/ejhf.2735

KEY TAKEAWAY: Empagliflozin increases erythropoietin (EPO) levels and decreases hepcidin in adults with heart failure with reduced ejection fraction (HFrEF), but it does not significantly affect the hepcidin/ferritin ratio or erythroferrone levels.

STUDY DESIGN: Post-hoc analysis of a randomized double-blind placebo-controlled trial

LEVEL OF EVIDENCE: STEP 4

BRIEF BACKGROUND INFORMATION: Increases in hematocrit have been observed in heart failure (HF) populations on sodium-glucose cotransporter 2 inhibitors (SGLT2s) and this study aimed to evaluate if it was due to hemoconcentration from the diuretic effect or increased erythropoiesis.

PATIENTS: Adults with HFrEF on guideline directed medical therapy

INTERVENTION: Empagliflozin 10 mg

CONTROL: Placebo

PRIMARY OUTCOME: Serum EPO levels, plasma hepcidin levels, hepcidin/ferritin ratio, and plasma erythroferrone levels

METHODS (BRIEF DESCRIPTION):

- Post-hoc analysis of data collected from the Empire HF trial a double blind, placebo-controlled trial.
- Investigators stated an Intention to treat analysis was used based on initial trial assignments.
- From the initial study of 697 patients, 211 patients were screened, and 190 patients were included.
- Of 95 patients in each group, 90 in the empagliflozin and 89 in the placebo group had complete data for analysis which included alanine transaminase, EPO, glycated hemoglobin (HbA1c), mean corpuscular hemoglobin concentration, and mean corpuscular volume.
- Changes were evaluated with analysis of covariates with 0.05 two-sided significance testing and 95% confidence intervals were used to evaluate effect sizes.

INTERVENTION (# IN THE GROUP): 95

COMPARISON (# IN THE GROUP): 95

FOLLOW-UP PERIOD: 12 weeks

RESULTS:

Primary Outcome –

- Empagliflozin increased EPO levels compared to placebo (adjusted mean difference [aMD] 2.6 IU/L; 95% CI, 0.8–4.4)
- Empagliflozin decreased hepcidin levels compared to placebo (adjusted ratio of change [aRC] 0.76; 95% CI, 0.59–0.97).
- Empagliflozin did not significantly change the hepcidin/ferritin ratio compared to placebo (aRC 1.0; 95% CI, 0.80–1.2).
- Empagliflozin did not significantly change erythroferrone levels compared to placebo (aRC 1.2; 95% CI, 0.86–1.6).
- A subgroup analysis of patients with and without type 2 diabetes mellitus (T2DM), anemia, or chronic kidney disease showed no significant differences in effects.

LIMITATIONS:

- The post-hoc design limits evidence for causality and is predominately exploratory; further prospective studies are needed for confirmation of effects.
- Included patients had stable heart failure with reduced ejection fraction in Denmark. Findings may not be generalizable to those with more severe disease or in other countries.
- The study included few patients with T2DM.
- The study included few patients who had well controlled HbA1c.
- No treatment effect was seen in plasma erythroferrone.

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