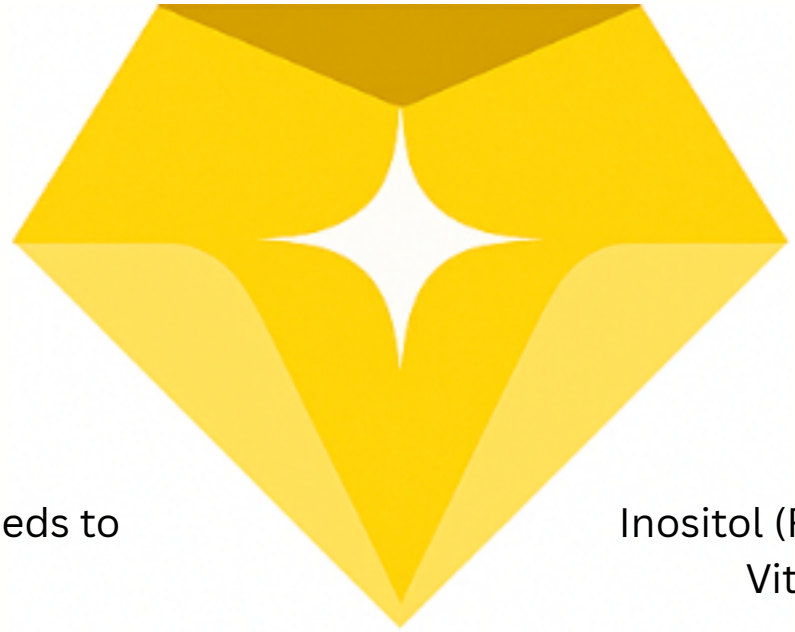
GOOD EVIDENCE MATTERS

GEMs of the Week



HTN

What Goes Up Needs to Come Down

Inositol

Inositol (Formerly Known as Vitamin B8) for PCOS

SPOTLIGHT: HPV

Swab for Change: Do HPV Self-Tests Increase Cervical Screening?

HRT

HRT for Menopause: Does It Increase Risk of Cardiovascular Disease?

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Swab for Change: Do HPV Self-Tests Increase Cervical Screening?

Strategies to Increase Cervical Cancer Screening with Mailed Human Papillomavirus Self-Sampling Kits: A Randomized Clinical Trial

Winer RL, Lin J, Anderson ML, et al. Strategies to Increase Cervical Cancer Screening with Mailed Human Papillomavirus Self-Sampling Kits: A Randomized Clinical Trial. *JAMA*. 2023;330(20):1971-1981. doi:10.1001/jama.2023.21471

KEY TAKEAWAY: For patients due or overdue for cervical cancer screening, direct-mail and opt-in self-sampling increase cervical cancer screening.

STUDY DESIGN: Pragmatic, parallel, single-blind randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: More than half of cervical cancers are diagnosed in patients overdue for screening in the United States. There have been few studies evaluating patient-oriented strategies to improve cervical cancer screening. This study aimed to determine if HPV self-sampling mailing kits increase adherence to cervical cancer screening.

PATIENTS: Females 30–64 years old

INTERVENTION: Direct mail and opt-in

CONTROL: Education alone

PRIMARY OUTCOME: HPV screening within six months

Secondary Outcome: Screening initiation, time from randomization to screening completion

METHODS (BRIEF DESCRIPTION):

- Patients were identified using Kaiser Permanente Washington (KWPA) electronic health records (EHRs) and administrative claims.
- Patients included had KPWA insurance, current female sex, 30–64 years old, intact cervix, and having a KPWA primary care doctor.
- Patients not on a routine screening schedule, previous randomization to the HOME study, opting out of research, current pregnancy, or requirement of language interpreter were excluded from the study.
- Patients were first identified as due for screening (<3 months), overdue for screening, and unknown screening history.
- Patients due to screening were randomized to direct mail or opt-in groups.
    - The direct mail group received usual care, education materials, and mailed a sampling kit.
    - The opt-in group received usual care, education materials, and the option to request a sampling kit.
- Patients overdue for screening were further randomized to usual care, education, or direct mail groups.
- Patients with unknown screening history were further randomized to usual care, education, or opt in groups.
- The primary analysis compared participants who received direct mail or opted in with those randomized to the education group.
- The primary outcome was the completion of HPV screening within six months.
- The secondary outcomes were screening initiation and time from randomization to screening completion.

INTERVENTION (# IN THE GROUP):

- Direct mail: 2,897
- Opt-in: 7,462

COMPARISON (# IN THE GROUP): 8,854

FOLLOW-UP PERIOD: Six months

RESULTS:

Primary Outcome –

- Women due for a screening and received direct mail were more likely to complete an HPV screening at six months compared to education alone (relative risk [RR] 1.3; 95% CI, 1.2–1.4).
- Women due for a screening and assigned to opt-in group were more likely to complete an HPV screening at six months compared to education alone (RR 1.1; 95% CI, 1.02–1.1).
- Women overdue for a screening and received direct mail were more likely to complete an HPV screening at six months compared to education alone (RR 1.9; 95% CI, 1.7–2.2).
- Women with an unknown screening history and assigned to opt-in group were more likely to complete an HPV screening at six months compared to education alone (RR 1.1; 95% CI, 1.03–1.3).

Secondary Outcome –

- Women due for a screening and received direct mail were more likely to initiate HPV screening compared to education alone (RR 1.3; 95% CI, 1.2–1.4).
- Women due for a screening and assigned to opt-in group were more likely to initiate HPV screening compared to education alone (RR 1.1; 95% CI, 1.03–1.1).
- Women overdue for a screening and received direct mail were more likely to initiate HPV screening compared to education alone (RR 1.9; 95% CI, 1.7–2.2).
- Women with an unknown screening history and assigned to opt-in group were more likely to initiate HPV screening compared to education alone (RR 1.2; 95% CI, 1.04–1.2).
- Women due for a screening and received direct mail completed screening quicker compared to education alone (19 vs 70 days, respectively; $p<.001$).
- Women due for a screening and assigned to opt-in group completed screening quicker compared to education alone (39 vs 116 days, respectively; $p<.001$).
- Women overdue for a screening and received direct mail completed screening quicker compared to education alone (18 vs 68 days, respectively; $p<.001$).
- Women with an unknown screening history and assigned to opt-in group compared to education alone was not statistically significant.

LIMITATIONS:

- The study has limited generalizability to non-English speaking patients, as the self-sampling kit instructions were available in English only
- Patients must have KWPA insurance, increase the risk of selection bias and potentially limiting accessibility to patients without insurance.

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HRT for Menopause: Does It Increase Risk of Cardiovascular Disease?

Contemporary Menopausal Hormone Therapy and Risk of Cardiovascular Disease: Swedish Nationwide Register Based Emulated Target Trial

Johansson T, Karlsson T, Bliuc D, et al. Contemporary menopausal hormone therapy and risk of cardiovascular disease: Swedish nationwide register based emulated target trial. *BMJ*. 2024;387:e078784. Published 2024 Nov 27. doi:10.1136/bmj-2023-078784

KEY TAKEAWAY: Several hormone replacement therapy (HRT) regimens including combined continuous, combined sequential, and transdermal combined increase the risk of venous thromboembolism (VTE) compared to non-initators. Tibolone increases the risk of cerebral infarction (CI), myocardial infarction (MI), and ischemic heart disease (IHD).

STUDY DESIGN: Emulated target trial, prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Cardiovascular disease (CVD) is a major cause of death globally, and CVD in women often develops around the time they are undergoing the menopausal transition. There have been conflicting reports on the relationship between menopausal HRT and CVD based on several observational and randomized trials in the late 1990s and early 2000s. In the past two decades, there have been significant changes in the formulations and routes of HRT prescribed to patients. This study aimed to assess the relationship between contemporary forms of HRT and CVD.

PATIENTS: Women 50–58 years old

INTERVENTION: Various HRT regimens

CONTROL: Non-iniators of HRT

PRIMARY OUTCOME: CI, MI, VTE, IHD

METHODS (BRIEF DESCRIPTION):

- Investigators used the Swedish national patient register, to select women 50–58 years old who had not redeemed a prescription for HRT for menopause in the past two years and had no history of IHD, stroke, peripheral vascular disease, peripheral arterial disease, or cancer from 2007–2018.
- The following treatment groups were defined by the HRT regimen initiated by the women:
  - Oral combined continuous therapy (used by over 1/3 of women, ratio of estrogen and progestogen <7)
  - Oral combined sequential therapy (ratio of estrogen and progestogen >7)
  - Oral unopposed estrogen
  - Oral estrogen combined with levonorgestrel intrauterine system
  - Tibolone (not approved in US)
  - Transdermal combined therapy (used by >25% of women)
  - Transdermal unopposed estrogen
- The comparison group included non-initiators who did not start any menopausal hormone therapy during the trial months.
- Investigators reviewed medical records for the outcome diagnoses.
- Using intention to treat, investigators calculated inverse probability weight-adjusted hazard ratios (IPW-aHR) for CI, MI, VTE, and IHD.

INTERVENTION (# IN THE GROUP): 77,512

COMPARISON (# IN THE GROUP): 842,102

FOLLOW-UP PERIOD: Until diagnosis of a CVD outcome, death, emigration, or two years after collecting baseline data, whichever occurred first

RESULTS:

Primary Outcome –

- Tibolone increased the risk of CI compared to non-intiators (IPW-aHR 2.0; 95% CI, 1.02–3.8).
- The other HRT regimens were not associated with an increased risk of CI compared with non-initiators:
  - Combined continuous (IPW-aHR 1.1; 95% CI, 0.73–1.6)
  - Combined sequintal (IPW-aHR 0.49; 95% CI, 0.20–1.2)
  - Oral estrogen (IPW-aHR 1.02; 95% CI, 0.33–3.2)
  - Oral estrogen + intrauterine progestin (IPW-aHR 1.4; 95% CI, 0.51–3.6)
  - Transdermal combined (IPW-aHR 0.64; 95% CI, 0.27–1.6)
  - Transdermal unopposed estrogen (IPW-aHR 0.78; 95% CI, 0.25–2.4)
- Tibolone increased the risk of MI compared to non-initiators (IPW-aHR 1.9; 95% CI, 1.01–3.7).
- The other HRT regimens were not associated with an increased risk of MI compared to non-initiators.
  - Combined continuous (IPW-aHR 1.4; 95% CI, 0.99–1.9)
  - Combined sequential (IPW-aHR 1.2; 95% CI, 0.71–2.1)
  - Oral estrogen (IPW-aHR 0.64; 95% CI, 0.16–2.6)
  - Oral estrogen + intrauterine progestin (IPW-aHR 0.63; 95% CI, 0.15–2.5)
  - Transdermal combined (IPW-aHR 0.50; 95% CI, 0.19–1.4)
  - Transdermal unopposed estrogen (IPW-aHR 1.3; 95% CI, 0.04–1.8)
- Combined continuous HRT increased the risk of VTE compared to non-initiators (IPW-aHR 1.6; 95% CI, 1.3–1.9).
- Combined sequential HRT increased the risk of VTE compared to non-initiators (IPW-aHR 2.0; 95% CI, 1.6–2.5).
- Transdermal combined HRT increased the risk of VTE compared to non-initiators (IPW-aHR 1.5; 95% CI, 1.1–1.9).
- The other HRT regimens were not associated with an increased risk of VTE compared to non-initiators:
  - Oral estrogen (IPW-aHR 1.6; 95% CI, 0.86–3.0)
  - Oral estrogen + intrauterine progestin (IPW-aHR 1.6; 95% CI, 0.91–2.8)
  - Tibolone (IPW-aHR 0.76; 95% CI, 0.38–1.5)
  - Transdermal unopposed estrogen (IPW-aHR 1.1; 95% CI, 0.59–2.0)
- Combined continuous HRT increased the risk of IHD compared to non-initators (IPW-aHR 1.3; 95% CI, 1.01–1.6).
- Tibolone was increased risk of IHD compared to non-initators (IPW-aHR 1.8; 95% CI, 1.1–2.7).
- The other HRT regimens were not associated with an increased risk of IHD compared to non-iniators:
  - Combined sequential (IPW-aHR 1.1; 95% CI, 0.76–1.6)
  - Oral estrogen (IPW-aHR 1.3; 95% CI, 0.70–2.4)
  - Oral estrogen + intrauterine progestin (IPW-aHR 1.1; 95% CI, 0.53–2.1)
  - Transdermal combined (IPW-aHR 0.67; 95% CI, 0.39–1.2)
  - Transdermal unopposed estrogen (IPW-aHR 0.82; 95% CI, 0.48–1.8)

LIMITATIONS:

- Inclusion eligibility was based on age, not specifically menopausal status.
- The study did not account for confounders such as obesity and smoking.
- The study did not confirm that the patients adhered to the medications. Thus, the patients' exposure to the medications could be misclassified.
- Unopposed estrogen is not a standard therapy and inclusion in the study might reflect prescription for women with an intact uterus.
- Variable accuracy of the outcome diagnoses might lead to underrepresentation of HRT risks.
- Investigators could not use pooled logistic regression analysis, potentially leading to selection bias.
- The study used static HRT treatment regimens but using dynamic strategies could adjust HRT individually and mitigate risk.

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What Goes Up Needs to Come Down

Long-Term Cardiovascular Outcomes in Children and Adolescents with Hypertension

Robinson CH, Hussain J, Jeyakumar N, et al. Long-Term Cardiovascular Outcomes in Children and Adolescents With Hypertension [published correction appears in JAMA Pediatr. 2024 Oct 1;178(10):1086. doi: 10.1001/jamapediatrics.2024.3393.]. *JAMA Pediatr*. 2024;178(7):688-698. doi:10.1001/jamapediatrics.2024.1543

KEY TAKEAWAY: Children with hypertension (HTN) are at higher long-term risk of major adverse cardiovascular events (MACE) compared with non-hypertensive controls.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: HTN affects 6% of all children, and its prevalence is increasing. Although pediatric HTN persists into adulthood, there is limited evidence evaluating the relationship of pediatric HTN with long-term cardiovascular outcomes. This study investigated whether pediatric HTN is associated with a higher risk of MACE.

PATIENTS: Children 3–18 years old

INTERVENTION: Children with HTN

CONTROL: Non-hypertensive controls

PRIMARY OUTCOME: MACE

Secondary Outcome: Individual MACE components, congestive heart failure (CHF), other cardiovascular diagnoses, cardiovascular procedures

METHODS (BRIEF DESCRIPTION):

- Children 3–18 years old (median 15 years old) selected from the healthcare database, with a diagnosis of HTN based on outpatient billing claims or discharge diagnosis from the hospital, were included in this study.
- Children with a kidney replacement and a previous diagnosis of HTN before the study were excluded.
- Children with HTN were matched with a control group of children without a diagnosis of HTN and paralleled based on weight at birth, prior comorbidities, age, maternal gestational HTN, sex, and propensity to develop the HTN measurement.
    - HTN propensity scores were utilized to compare the intervention vs control group.
    - The median age of participants at the last follow-up was 27 years old.
- The primary outcome assessed MACE, a composite of cardiovascular death, stroke, hospitalization for acute myocardial infarction (MI) or unstable angina, and coronary intervention.
- The following were measured for the secondary outcomes:
    - Individual MACE components
    - CHF
    - Other cardiovascular diagnoses included angina, atherosclerotic and ischemic heart disease, atrial/ventricular arrhythmias, and peripheral vascular disease
    - Cardiovascular procedures included cardiac surgery, vascular surgery, and pacemaker or defibrillator placement

INTERVENTION (# IN THE GROUP): 25,605

COMPARISON (# IN THE GROUP): 128,025

FOLLOW-UP PERIOD: Median 14 years

RESULTS:

Primary Outcome –

- Children with HTN had a significantly higher risk of MACE compared to those without HTN (hazard ratio [HR] 2.1; 95% CI, 1.9–2.2).

Secondary Outcome –

- Compared to non-hypertensive children, those with HTN had an increased risk of:
    - Stroke (HR 2.7; 95% CI, 2.4–2.9)
    - CHF (HR 2.6; 95% CI, 2.4–2.9)
    - Hospitalization for MI or unstable angina (HR 1.8; 95% CI, 1.7–2.0)
    - Coronary intervention (HR 4.1; 95% CI, 3.2–5.3)
    - Other cardiovascular diagnoses (HR 1.7; 95% CI, 1.6–1.8)
    - Cardiovascular procedures (HR 2.6; 95% CI, 2.3–2.8)
- There was no significant difference in cardiovascular deaths between the two groups.

LIMITATIONS:

- The control group included children without HTN; however, there is a possibility the group included undiagnosed HTN.
- Blood pressure diagnosis was not based on actual readings but on listing of HTN as diagnosis in physician or hospital records.
- The methods for obtaining blood pressure measurements were not known.

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Inositol (Formerly Known as Vitamin B8) for PCOS

Inositol Is an Effective and Safe Treatment in Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Greff D, Juhász AE, Váncsa S, et al. Inositol is an effective and safe treatment in polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. *Reprod Biol Endocrinol*. 2023;21(1):10. Published 2023 Jan 26. doi:10.1186/s12958-023-01055-z

KEY TAKEAWAY: Inositol shows non-inferiority to metformin in the treatment of polycystic ovarian syndrome (PCOS) and should be considered in the treatment of patients who cannot tolerate metformin.

STUDY DESIGN: Systematic review of 26 randomized controlled trials (RCTs) with meta-analysis of subsets of 24 RCTs (N=1,691).

LEVEL OF EVIDENCE: STEP 3 (downgraded due to very low level of evidence in the included studies)

BRIEF BACKGROUND INFORMATION: PCOS is a common disorder strongly associated with insulin resistance among females of reproductive age and is primarily treated with lifestyle modification and metformin. However, metformin occasionally has severe gastrointestinal (GI) side effects that limit its use. Inositol, formerly called vitamin B8, is an insulin sensitizer without GI side effects that combat insulin resistance. This study investigated if inositol may be effective in treating PCOS.

PATIENTS: Women with PCOS

INTERVENTION: Inositol

CONTROL: Diet, placebo, or metformin

PRIMARY OUTCOME: Ovarian cycle normalization

Secondary Outcome: Pregnancy rate, body mass index (BMI), carbohydrate metabolism, clinical/laboratory hyperandrogenism, side effects

METHODS (BRIEF DESCRIPTION):

- The review and analysis used the PRISMA 2020 guidelines and the Cochran Handbook.
- MEDLINE, Embase, and CENTRAL databases were used to identify the RTCs comparing the efficacy of inositols vs placebo or metformin.
- Fertile adult women from India, Italy, Iran, Venezuela, and Bosnia with at least two of three criteria for PCOS including ovulatory dysfunction, hyperandrogenism, and PCOS morphology on imaging, were included in the study.
- Inosotols utilized in the studies were myoinositol or D-chiro-inositol at various dosages and durations.
- The controls were either diet, placebo, and or metformin.
- The primary outcome assessed cycle normalization.
- The secondary outcomes of the study assessed pregnancy rate, BMI, carbohydrate metabolism, hyperandrogenism, and side effects.

INTERVENTION (# IN THE GROUP): 830

COMPARISON (# IN THE GROUP): 861

FOLLOW-UP PERIOD: 7–24 weeks

RESULTS:

Primary Outcome –

- Inositol was more effective in normalizing ovarian cycles (2 trials, n=118; risk ratio [RR] 1.8; 95% CI, 1.1–2.9; I^2=0%).
- Myoinositol normalized ovarian cycles similarly to metformin (6 trials, n=424; RR 1.4; 95% CI, 0.8–2.5; I^2=74%).

Secondary Outcome –

- Inositol decreased BMI compared to placebo (8 trials, n=420; mean difference [MD] –0.45 kg/m^2; 95% CI, –0.89 to –0.02; I^2=18%).
- Myoinositol significantly reduced blood glucose compared to placebo (3 trials, n=200; MD –4.0 mg/dl; 95% CI, –6.6 to –1.5; I^2=0%).
- Inositols improved several laboratory markers of hyperandrogenism compared to placebo:
  - Total testosterone decreased (6 trials, n=284; MD –20.39 ng/dL; 95% CI, –40 to –0.66; I^2=73%).
  - Free testosterone decreased (4 trials, n=152; MD –0.41 ng/dL; 95% CI, –0.69 to –0.13; I^2=68%).

- Inositol resulted in fewer side effects than metformin. 7% of participants reported bloating, nausea, and weakness in the inositol group vs 53% in the metformin group (4 trials, n=360; RR 0.16; 95% CI, 0.09–0.28; I^2=11%).
    - No side effects were reported for inositol compared to placebo.

LIMITATIONS:

- A small number of studies with small sample sizes in many of the included meta-analyses with high heterogeneity (I^2>50% indicates a large likelihood of confounders).
- Some of the meta-analyses had as few as two RCTs.
- 12 of the 24 studies did not report a study period or follow-up.
- There were varying medication dosages and duration of the included studies.
- The outcomes studied were not uniform.
- Significant heterogeneity was present in several of the included studies.

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