GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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Week of October 2 - 6, 2023

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Shedding Light on Preeclampsia: The Potential of Vitamin D as a Preventative Measure

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Vitamin D Supplementation and Incident Preeclampsia: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

Fogacci S, Fogacci F, Banach M, et al. Vitamin D supplementation and incident preeclampsia: A systematic review and meta-analysis of randomized clinical trials. *Clin Nutr*. 2020;39(6):1742-1752. doi:10.1016/j.clnu.2019.08.015

KEY TAKEAWAY: Supplementing with vitamin D could be beneficial for preventing preeclampsia, especially if supplementation starts before 20 weeks of gestational age.

STUDY DESIGN: Systematic review and meta-analysis of 12 randomized controlled trials

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: The effectiveness of vitamin D supplementation in preventing preeclampsia remains a topic of debate, despite the evidence that its deficiency has been linked to a higher likelihood of preeclampsia.

PATIENTS: Pregnant women, 13–45 years old with no previous vitamin D exposure

INTERVENTION: Vitamin D supplementation

CONTROL: Placebo

PRIMARY OUTCOME: Preeclampsia

Secondary Outcome: Initiation and length of vitamin D supplementation, supplementation with calcium and vitamin D, and vitamin D alone, increasing dose of vitamin D

METHODS (BRIEF DESCRIPTION):

- Inclusion criteria: Prospective RCT, presence of a control group, at least a single dose of vitamin D administered to the intervention group, and only women with no previous vitamin D exposure.
- Exclusion criteria: No appropriate controlled design for supplementation of vitamin D, studies with participants from other studies, population-based cohort studies, reviews/letters/comments.
- The Cochrane criteria risk-of-bias (RoB 2) tool was utilized to conduct a comprehensive evaluation of the potential bias in the studies, however overall studies were at low risk of bias.
- Participants were pregnant females, 13–45 years old, not previously treated with vitamin D, with a low risk for preeclampsia.
- The intervention group received vitamin D supplementation that varied between 1,000–5,000 IU/day and 50,000 IU every two weeks.
- Subgroup analyses were conducted to investigate the timing of supplementation, duration of supplementation, calcium intake, and maternal age.
- A fixed-effect model was used to combine studies' results due to low heterogeneity.

INTERVENTION (# IN THE GROUP): 2,487

COMPARISON (# IN THE GROUP): 2,290

FOLLOW-UP PERIOD: Unavailable

RESULTS:

Primary Outcome –

- Vitamin D supplementation significantly decreased the risk of preeclampsia (12 studies, N=1,676; odds ratio [OR] 0.37; 95% CI, 0.26–0.52).

Secondary Outcome –

- The risk of preeclampsia was significantly lower when supplementation began up to 20 weeks of gestation (5 studies, N=374; OR 0.35; 95% CI, 0.24–0.50), but not when initiated after 20th week (7 studies, N=1,302; OR 0.60; 95% CI, 0.18–2.0).
- The risk of preeclampsia was not affected by the length of supplementation until delivery (3 studies, N=960, OR 0.38; 95% CI, 0.21–0.69), did not supplement until delivery (9 studies, N=716; OR 0.36; 95% CI, 0.23–0.55).
- Calcium plus vitamin D (4 studies, N=820; OR 0.36; 95% CI, 0.20–0.67) did not decrease the risk of preeclampsia more than vitamin D alone (8 studies, N=856; OR 0.37; 95% CI, 0.24–0.56).
- Dosage of vitamin D was inversely associated with the risk of preeclampsia (OR 0.33; 95% CI, 0.18–0.63).
- Preeclampsia risk was not associated with maternal age.

LIMITATIONS:

- Varied timing and pharmaceutical forms of Vitamin D were administered to pregnant women.
- Participants were not selected based on their baseline circulating vitamin D level.

- None of the studies were conducted in the United States.

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New Moves, Plant Foods, Good Moods: A Lifestyle Medicine Approach to Rheumatoid Arthritis

A Multidisciplinary Lifestyle Program for Rheumatoid Arthritis: The 'Plants for Joints' Randomized Controlled Trial

Walrabenstein W, Wagenaar CA, van der Leeden M, et al. A multidisciplinary lifestyle program for rheumatoid arthritis: the 'Plants for Joints' randomized controlled trial. *Rheumatology* (Oxford). 2023;62(8):2683-2691. doi:10.1093/rheumatology/keac693

KEY TAKEAWAY: A multidisciplinary lifestyle program in addition to pharmacologic treatment may decrease disease activity in patients with low-moderate Rheumatoid Arthritis (RA).

STUDY DESIGN: Randomized, single-blind, controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: RA is a chronic systemic inflammatory disease most notable for polyarthritis. Only 20% of patients reach the goal of sustained remission, with most suffering from pain, fatigue, and loss of function. There are no prior studies evaluating the benefits of non-pharmacologic, multidisciplinary lifestyle programs in RA treatment.

PATIENTS: Adult patients with low to moderate RA severity

INTERVENTION: Multidisciplinary lifestyle program

CONTROL: Usual care

PRIMARY OUTCOME: RA Disease activity score (DAS28)
Secondary Outcome: Weight, fat mass, hemoglobin A1c, blood pressure, and patient-reported outcomes of depression, fatigue, pain interference, and physical function.

METHODS (BRIEF DESCRIPTION):

- Study participants included adults (mean age 55 years old, mostly female 92%) with RA diagnosis according to the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2010 criteria.
- Participants were classified as low to moderate RA as identified by DAS28 scores of 2.6–5.1.
  - DAS28 is a measurement of disease activity over time with a possible score range of 0–9.4 (remission <2.6).
  - DAS28 reduction of 0.6 represents a moderate improvement.
  - DAS28 reduction of 1.2 represents a major improvement.
- Inclusion criteria: Stable treatment with disease-modifying anti-rheumatic drugs (DMARDs) or off DMARDs for at least three months.
- Exclusion criteria: Patients already on a plant-based diet, unwilling to quit smoking, or are pregnant.
- Patients were randomized to one of the following:
  - 16-week multidisciplinary lifestyle program called Plants for Joints (PFJ).
  - PFJ group received individualized dietician and physical therapy intake sessions followed by group sessions.
  - PFJ groups of 6–12 participants gathered 10 times for 2–3 hour meetings, 17 participants had all live meetings, and the remaining 23 participants had hybrid (in-person, virtual) due to COVID-19 measures.
  - Meetings included:
    - Weekly meal planning and daily supplements
    - Exercise plans
    - Psychoeducation on the effect of stress on health
    - Coaching on sleep
- The control group received the usual care and was advised not to change lifestyle habits.
- Participants were interviewed by a research nurse blinded to group allocation and participants were asked not to discuss group assignment during DAS28 assessments at baseline, eight, and 16 weeks.
- Participants were weighed at baseline, eight, and 16 weeks.
- Fat mass outcomes were measured by DEXA scan at baseline, eight, and 16 weeks.
- Metabolic outcomes (blood pressure, hemoglobin A1c, and lipids) were assessed by a research nurse.
- Validated Dutch-Flemish Patient Reported Outcomes Measurement Information System (PROMIS) was utilized to quantify patient-reported outcomes for depression, fatigue, pain interference, and physical function at baseline, eight, and 16 weeks.

INTERVENTION (# IN THE GROUP): 41
COMPARISON (# IN THE GROUP): 42

FOLLOW-UP PERIOD: 16 weeks

RESULTS:

Primary Outcome –

- The PFJ group had a statistically significant decrease in disease activity at 16 weeks compared to the control group (mean difference –0.90; 95% CI, –1.3 to –0.41).

Secondary Outcome –

- Loss of weight and loss of fat mass were significantly larger in the PFJ vs control group:
  - Weight loss: between-group difference –3.9 kg (95% CI, –5.2 to –2.6)
  - Fat mass loss: between-group difference –2.8 kg (95% CI, –3.8 to –1.7)
- Metabolic and patient-reported outcomes of depression, fatigue, pain interference, and physical function were not significantly different between the two groups.

LIMITATIONS:

- A small number of participants.
- Short duration of follow-up.
- Limited generalizability since the trial only included low to moderate severity RA and participants were predominantly women.
- Unable to blind participants in the treatment group.
- PFJ group combined multiple lifestyle factors, so this study is unable to determine the impact on individual lifestyle modifications in improving RA.
- PFJ group received intensive intervention which may be difficult to achieve in the community.

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Hep Hep Hooray! Comparisons of Anticoagulation Dosing with Low-Molecular-Weight Heparin in COVID-19 Pneumonia

Effects of Standard-Dose Prophylactics, High-Dose Prophylactic, and Therapeutic Anticoagulation in Patients with Hypoxemic COVID-19 Pneumonia: The ANTICOVID Randomized Clinical Trial

Labbé V, Contou D, Heming N, et al. Effects of Standard-Dose Prophylactic, High-Dose Prophylactic, and Therapeutic Anticoagulation in Patients With Hypoxemic COVID-19 Pneumonia: The ANTICOVID Randomized Clinical Trial. *JAMA Intern Med*. 2023;183(6):520-531. doi:10.1001/jamainternmed.2023.0456

KEY TAKEAWAY: High-dose prophylactic anticoagulation with low-molecular-weight heparin (LMWH) may decrease de novo thrombosis in patients with hypoxemic COVID-19 pneumonia without significantly increasing the risk for a major bleeding event compared to standard dose prophylactic and therapeutic anticoagulation.

STUDY DESIGN: Randomized clinical open-label trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: COVID-19 pneumonia predisposes patients to the development of de novo thrombosis due to systemic inflammation, endothelial dysfunction, and platelet activation. Observational data suggests that between 10–30% of patients with COVID-19 pneumonia receiving standard-dose prophylactic anticoagulation are affected by macrovascular thrombosis, contributing to patient morbidity and mortality. There has been no direct comparison of high-dose prophylactic anticoagulation vs therapeutic anticoagulation vs standard-dose prophylactic anticoagulation, in reducing thromboembolic risk and overall mortality in patients with hypoxemic COVID-19 pneumonia.

PATIENTS: Hospitalized adult patients with hypoxemic COVID-19 pneumonia

INTERVENTION: Anticoagulation with therapeutic dose LMWH, high dose prophylactic LMWH, or standard dose prophylactic LMWH

CONTROL: Not applicable

PRIMARY OUTCOME: Hierarchal criterion of outcomes (ranging from clinical improvement to death) assessed at day 28

Secondary Outcome: Incidence of major bleeding and thrombosis

METHODS (BRIEF DESCRIPTION):

- Adult patients diagnosed with COVID-19 pneumonia with hypoxia and no evidence of preexisting pulmonary artery thrombosis were included in the study.
- Patients were randomly assigned to one of three anticoagulation regimens using LMWH: standard dose prophylactic (3,500 IU/24h), high dose prophylactic (7,000 IU/24h), and therapeutic (175 IU/Kg/24h).
- Treatments were administered by unblinded inpatient providers for 14 days, or until hospital discharge, or until weaning off supplemental oxygen for 48 consecutive hours (whichever came first).
- Primary outcome assessing time to clinical improvement was measured using a seven-category ordinal scale focused on respiratory function.
- Morbidity and mortality were assessed by calculating hospital length of stays, number of oxygen/ventilator-free and vasopressor-free days, and all-cause death.

INTERVENTION (# IN THE GROUP):

- Standard dose prophylactic: 166
- High dose prophylactic: 111
- Therapeutic dose: 112

COMPARISON (# IN THE GROUP): Not applicable

FOLLOW-UP PERIOD: 28 days

RESULTS:

Primary Outcome –

- In the intention-to-treat population, the ranked composite primary outcome through day 28 was not significantly different between the three groups.

Secondary Outcome –

- The composite of thrombotic events was significantly reduced in the following groups:
  - High dose prophylactic vs. standard dose prophylactic (absolute difference –14.8; *P*= .001)
  - Therapeutic dose vs. standard dose prophylactic groups (absolute difference –14.7; *P*=.001).
- No significant difference in thrombotic events was found between the high-dose prophylactic and therapeutic dose groups.

- There was no significant difference in the incidence of major bleeding between the three groups.

LIMITATIONS:

- This was an open-label trial utilizing outcome measurements that can be subjective, predisposing the study to performance bias.
- Detection bias may have also led to increased screening for potential events (including asymptomatic thrombotic events) in patients in the standard-dose prophylactic compared to the high-dose prophylactic or therapeutic dose groups.
- Given the relatively small number of randomized patients, the effect size regarding secondary outcomes is limited.

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Does Testosterone-Replacement Therapy Increase Cardiovascular Risk in Men with Age-Related Hypogonadism?

Cardiovascular Safety of Testosterone-Replacement Therapy

Lincoff AM, Bhasin S, Flevaris P, et al. Cardiovascular Safety of Testosterone-Replacement Therapy. *N Engl J Med.* 2023;389(2):107-117. doi:10.1056/NEJMoa2215025

KEY TAKEAWAY: For men 45–80 years old, with symptomatic hypogonadism and preexisting cardiac disease or cardiovascular risk factors, testosterone replacement therapy was non-inferior to placebo for major adverse cardiac events.

STUDY DESIGN: Multicenter randomized double-blind, placebo-controlled non-inferiority trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: The cardiovascular risk profile of testosterone-replacement therapy in hypogonadal middle-aged men is not well established. This randomized controlled trial was conducted by AbbVie and other makers of testosterone-replacement therapies in response to the Food and Drug Administration's (FDA) guidance requiring manufacturers to conduct clinical trials to determine the effect of testosterone-replacement therapy on cardiovascular outcomes.

PATIENTS: Men 45–80 years old with hypogonadism and pre-existing or high risk of cardiovascular disease

INTERVENTION: Testosterone replacement therapy

CONTROL: Placebo

PRIMARY OUTCOME: First occurrence of any major adverse cardiac events (death from cardiovascular causes, non-fatal MI, or nonfatal stroke)

METHODS (BRIEF DESCRIPTION):

- Phase four, randomized, double-blind, placebo-controlled, non-inferiority, event-driven.
- 316 clinical trial sites in the US.
- Men 45–80 years old with low serum testosterone (<300 ng/dL) who exhibit hypogonadal symptoms (non-congenital acquired, not severe) and have evidence of cardiovascular disease or are at increased risk of cardiovascular disease were included.
- Excluded men with congenital or severe acquired hypogonadism, men with prostate-specific antigen >3.0 ng/mL, men treated with testosterone in the past 6 months, and men for whom testosterone therapy was contraindicated.
- The treatment group received daily transdermal 1.62% testosterone gel and the placebo group received daily matching placebo gel.
- Dose adjustments were made to maintain testosterone levels 350–750 ng/dL, or sham adjustments if placebo.
- Discontinued testosterone or placebo if testosterone >750 ng/dL or hematocrit >54%, new diagnosis of prostate cancer, or at risk for suicide.
- Used Cox proportional-hazards regression model for statistical analysis.
- The full-analysis population included all patients who had undergone randomization.
- The safety population included all patients who had undergone randomization and received at least one dose of testosterone or placebo.

INTERVENTION (# IN THE GROUP): 2,601

COMPARISON (# IN THE GROUP): 2,603

FOLLOW-UP PERIOD:

- Mean duration of treatment:
  - Testosterone: 21.8 +/- 14.2 months
  - Placebo: 21.6 +/- 14.0 months
- Mean duration of follow up:
  - Testosterone: 3.1 +/- 12.1 months
  - Placebo: 32.9 +/- 12.1 months

RESULTS:

Primary Outcome –

- In the safety population, a combined primary cardiovascular endpoint occurred in 182 patients (7.0%) in the testosterone group and in 190 patients (7.3%) in the placebo group.
- Testosterone did not reduce the risk of a combined primary cardiovascular endpoint compared to placebo (HR 0.96; 95% CI, 0.78–1.2).

LIMITATIONS:

- Intention-to-treat analysis may be biased in favor of non-inferiority, authors attempted to combat this by performing on-treatment sensitivity analyses.
- The authors used the safety population to determine the primary outcome, not the intention to treat the population.

- Adherence and retention were lower in this study than in most cardiovascular outcome studies, albeit like other testosterone or estrogen therapy studies for symptomatic conditions such as hypogonadism and post-menopausal symptoms.
- Difficult to study the effects on patients who discontinued testosterone therapy before the trial concluded.
- The trial was funded by AbbVie and other companies that make testosterone therapy drugs for hypogonadism.

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Motor Control Strength Exercises vs Education Alone for Rotator Cuff Related Pain

Does the Addition of Motor Control of Strengthening Exercises to Education Result in Better Outcomes for Rotator Cuff-Related Shoulder Pain? A Multi-Arm Randomized Controlled Trial

Dubé MO, Desmeules F, Lewis JS, Roy JS. Does the addition of motor control or strengthening exercises to education result in better outcomes for rotator cuff-related shoulder pain? A multiarm randomized controlled trial. *Br J Sports Med*. 2023;57(8):457-463. doi:10.1136/bjsports-2021-105027

KEY TAKEAWAY: In patients with rotator cuff-related shoulder pain, adding motor control or strength exercises did not show a clinically significant difference compared to education alone, in the improvement of symptoms.

STUDY DESIGN: Multi-arm randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: 70% of shoulder pain visits are related to rotator cuff pain. It is associated with reduced function and performance. Education on pain management, strengthening exercises, and motor control exercises are common treatment components.

PATIENTS: Adults with rotator cuff-related shoulder pain

INTERVENTION: Education and motor control exercises or education and strengthening exercises

CONTROL: Education alone

PRIMARY OUTCOME: Pain reduction, function, symptoms

METHODS (BRIEF DESCRIPTION):

- 123 adults 18–75 years old with symptoms of rotator cuff associated shoulder pain were blindly divided into three groups: Education group, strengthening exercises group, and motor control exercises group.
- Symptoms and function were measured at baseline, three weeks, six weeks, 12 weeks, and 24 weeks using questionnaire called QuickDASH (disability of ARM shoulder, and hand questionnaire) and the Western Ontario rotator cuff (WORC) index.
- Pain-related fear and catastrophizing were evaluated using the Tampa Scale of Kinesiophobia (TSK) and the Pain Catastrophizing Scale (PCS), respectively.
    - The TSK is a Likert scale of 1–4 from strongly disagree to strongly disagree with questions about pain. The maximum score is 60.
    - PCS scoring is a similar Likert scale with scores of 0–4 from "not at all" to "all the time" answering questions regarding pain. The maximum score is 52.
- Linear mixed modeling was used to compare the effects of the three programs.

INTERVENTION (# IN THE GROUP):

- Education and motor control exercises: 41
- Education and strengthening exercises: 41

COMPARISON (# IN THE GROUP): 41

FOLLOW-UP PERIOD: 24 weeks

RESULTS:

Primary Outcome –

- Education and motor control exercises nor education and strengthening exercises improved pain compared to education alone.

Secondary Outcome –

- Participants presented with an overall mean weekly improvement in pain of 0.8 and 1.2 points on the PCS and TSK questionnaires over the 24-week treatment duration.
    - The overall mean weekly improvement at the 12-week mark was 1.3 and 2.1.
- There was no significant difference in group-by-time interaction for the following measures: Acromiohumeral distance; brief pain inventory; pain catastrophizing; Tampa Scale of Kinesiophobia

LIMITATIONS:

- Patient sample with a convenient sample of volunteers.
- Patients may have believed that the interventions tested in this study may help their symptoms and bias them to enroll.
- Since there was no true control group, the study cannot confirm that improvement in symptoms is a result of the educational videos.

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To Hear or Not to Hear

Effectiveness of an Over-the-Counter Self-Fitting Hearing Aid Compared with an Audiologist-Fitted Hearing Aid: A Randomized Clinical Trial

De Sousa KC, Manchaiah V, Moore DR, Graham MA, Swanepoel W. Effectiveness of an Over-the-Counter Self-fitting Hearing Aid Compared With an Audiologist-Fitted Hearing Aid: A Randomized Clinical Trial. *JAMA Otolaryngol Head Neck Surg*. 2023;149(6):522-530. doi:10.1001/jamaoto.2023.0376

KEY TAKEAWAY: Self-fitted hearing aids are non-inferior to audiologist-fitted hearing aids and could be an acceptable alternative.

STUDY DESIGN: Single-site randomized trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to unblind research participants)

BRIEF BACKGROUND INFORMATION: Historically, hearing aids have only been accessible to those with a consultation and prescription. This study addresses whether over-the-counter hearing aids would address the accessibility gap.

PATIENTS: Adults with hearing loss

INTERVENTION: Self-fitted hearing aids

CONTROL: Audiologist-fitted hearing aids

PRIMARY OUTCOME: Perceived communication difficulties

Secondary Outcome: Speech recognition and noise

METHODS (BRIEF DESCRIPTION):

- Patients 18 years old and older were recruited via advertisements from the University of Pretoria with self-reported hearing loss.
- Participants had mild to moderate hearing loss, good English proficiency, and access or possession of a smart phone.
- Patients were excluded with normal hearing based (<20 decibels at all frequencies), possible middle ear pathology/air bone gaps, or severe hearing loss defined as >80 decibel hearing loss at two or more frequencies.
- Participants had a mean age of 63.6 years old, 51.6% men, and 73.4% were new users of hearing aids.
- The treatment group received the self-fitting OTC hearing aids and was required to download the Lexie smartphone app for fitting instructions.
  - For the first two weeks, no adjustments were allowed, followed by four weeks with instructions to contact remote services for adjustment or troubleshooting.
- The comparison group received an audiologist appointment for fitting the hearing aids.
  - No adjustments by the audiologist were allowed in the first two weeks, then fine-tuning was completed upon request at two weeks and the following four weeks.
- The primary outcome of self-rated communication difficulties was measured via the Abbreviated Profile of Hearing Aid Benefit (APHAB; scaled 1–99%, with a higher score indicating greater communication difficulty) at baseline, two, and six weeks.
- At two weeks and six weeks, a global benefit score was calculated using APHAB minus unaided baseline with higher scores indicating better hearing outcomes.
- Secondary outcomes of speech in noise were measured via QuickSIN (scaled –25.5 to +25.5, higher scores indicating better hearing) and digits in noise were measured via digits in noise (DIN scaled –22.5 to +22.5, higher scores with better hearing).
- Clinical meaningful difference between groups was established if the effect size was medium or large (Cohen d ≥0.5).

INTERVENTION (# IN THE GROUP): 35

COMPARISON (# IN THE GROUP): 33

FOLLOW-UP PERIOD: Six weeks

RESULTS:

Primary Outcome –

- The overall communication benefit was greater in the self-fitted as compared to the audiologist-fitted hearing aid group at two weeks (APHAB MD, 10.3; 95%, CI 0.1–20.5; Cohen d value –0.5).
- The overall communication benefit was similar in the self-fitted as compared to audiologist-fitted hearing aids at 6 weeks (APHAB MD, 8.7; Cohen d

value –0.4; 95% CI, –0.9 to 0.1) indicating no clinically meaningful differences.

Secondary Outcome –

- QuickSIN scores were not meaningfully different at two weeks or six weeks.
- DIN scores were not meaningfully different at two weeks or six weeks.

LIMITATIONS:

- Over-the-counter availability and options of hearing aids would likely be different in South Africa compared to the United States.
- The study did not specify between sensory versus conductive hearing loss.
- The sample size was relatively small with baseline differences between the two groups including slightly older age and more men in the audiologist-fitted group.

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Use of Hair Straighteners is Associated with Increased Incidence of Uterine Cancer

Use of Straighteners and Other Hair Products and Incident Uterine Cancer

Chang CJ, O'Brien KM, Keil AP, et al. Use of Straighteners and Other Hair Products and Incident Uterine Cancer. *J Natl Cancer Inst*. 2022;114(12):1636-1645. doi:10.1093/jnci/djac165

KEY TAKEAWAY: Using chemical hair straighteners is associated with an increased risk of uterine cancer.

STUDY DESIGN: Prospective cohort

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Uterine cancer is one of the most common gynecologic cancers, and increased exposure to unopposed estrogen is a well-established risk factor. Studies found that endocrine-disrupting chemicals have estrogenic effects in chemical relaxers, hair dyes, and other hair products. This study was the first epidemiologic study to evaluate any association between chemical hair straighteners and uterine cancer.

PATIENTS: Adult women with no history of breast cancer

INTERVENTION: Use of hair products including dyes, chemical straighteners, and permanents

CONTROL: No use of hair products

PRIMARY OUTCOME: Incidence of uterine cancer

METHODS (BRIEF DESCRIPTION):

- The study population was the sister study of a prospective cohort of 50,884 women enrolled in 2003–2009 in the United States.
- Inclusion criteria: Women 35–74 years old, breast cancer-free, with one sister diagnosed with breast cancer.
- Exclusion criteria: Participants who withdrew, self-reported uterine cancer diagnosis before enrollment or uncertain uterine cancer history, hysterectomy before enrollment, who did not answer the questions on hair product use, and who did not contribute any follow-up time.
- The intervention was self-reported use in the past 12 months of one of the following seven hair products: Permanent, semi-permanent, and temporary hair dyes; bleach; highlights; straighteners, relaxers or pressing products; hair permanents or body waves.
- Use frequency was categorized as 1–2 times per year; every 3–4 months; every 5–8 weeks; one time per month; and more than one time a month.
- Outcomes: Development of uterine cancers including endometrial cancer, uterine sarcoma, or other types of uterine cancers diagnosed after enrollment.
- Adjusted hazard ratios were calculated using the Cox proportional hazards model.
- Analysis adjusted for race/ethnicity, education, BMI, physical activity, menopausal status, parity, smoking status, alcohol use, oral contraceptive use, hormone replacement therapy use, and age at menarche.

INTERVENTION (# IN THE GROUP): 3,091

COMPARISON (# IN THE GROUP): 30,757

FOLLOW-UP PERIOD: Mean 10.9 years

RESULTS:

Primary Outcome –

- Ever use of hair straightening products was associated with a higher incidence of uterine cancer compared to never users (HR 1.8; 95% CI, 1.2–2.9).
- The association was stronger with frequent users, more than four times in a year, compared to never users (HR 2.6; 95% CI, 1.5–4.5).
- There was no statistically significant association between the use of the six other types of hair products and uterine cancer risk.
- Uterine cancer cases were most strongly associated with older age, earlier menarche, elevated BMI, and lower physical activity.

LIMITATIONS:

- Exposures were self-reported.
- There is variability in hair product formulations, especially over time and not all hair products within the same class may confer the same risk.
- Sisters study population may limit generalizability given the demographic with possible higher genetic risk for cancer.
- A cohort study cannot prove causation.
- Younger black women, with elevated BMI and lower physical activity, were more likely to use hair straightening products; therefore, limiting generalizability.

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Could Following Blood Pressure Trajectory in Early Pregnancy Predict Hypertensive Disorders Later in Pregnancy?

Early Pregnancy Blood Pressure Patterns Identify Risk of Hypertensive Disorders of Pregnancy Among Racial and Ethnic Groups

Gunderson EP, Greenberg M, Nguyen-Huynh MN, et al. Early Pregnancy Blood Pressure Patterns Identify Risk of Hypertensive Disorders of Pregnancy Among Racial and Ethnic Groups. *Hypertension*. 2022;79(3):599-613. doi:10.1161/HYPERTENSIONAHA.121.18568

KEY TAKEAWAY: Following the trajectory of blood pressure in early pregnancy is an inexpensive and effective way to evaluate and improve the risk stratification of developing hypertensive disorders during pregnancy.

STUDY DESIGN: Retrospective longitudinal cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Gestational hypertensive disorders in pregnancy (HDP), including preeclampsia, eclampsia, and gestational hypertension (HTN), are considered complications of pregnancy and can be life-threatening to both mother and fetus. There is currently no validated predictive tool for estimating a pregnant woman's risk of developing HDP.

PATIENTS: Pregnant women without prior hypertensive history or preeclampsia

INTERVENTION: Blood pressure trajectories

CONTROL: "Ultra-low-declining" BP trajectory group

PRIMARY OUTCOME: Incidence of hypertensive disorders by early BP trajectory group

METHODS (BRIEF DESCRIPTION):

- Exclusion criteria: No prenatal care prior to 14 weeks gestation, patients with a history of prior serious medical condition or chronic HTN or gestational HTN, previous diagnosis of pre-eclampsia/eclampsia.
  - Patients with a history of prior serious medical conditions.
- Electronic health records were used to obtain data points.
- Using BP measurements from outpatient prenatal visits prior to 20 weeks gestation (average 4.1 measurements per subject), six BP trajectory groups were developed based on mean systolic BP:
  - Elevated-stable: 128.7 mmHg, decreased by 2.8 mmHg
  - Moderate-stable: 120.4 mmHg, decreased by 2.6 mmHg
  - Moderate-fast-decline: 20.9 mmHg, decreased by 11.9 mmHg
  - Low-increasing: 109.8 mmHg, increased by 2.2 mmHg
  - Low-declining: 107.4 mmHg, decreased by 5.2 mmHg
  - Ultra-low-declining: 100 mmHg, decreased by 6 mmHg
- Preeclampsia, eclampsia, and gestational HTN after 20 weeks were identified using ICD-9/10 codes.
- The rate of incidence of HDP was estimated in the separate groups.
- The ultra-low-declining group was used as the referent group for the other trajectories for determining the risk of HDP.

INTERVENTION (# IN THE GROUP):

- Elevated-stable: 1,416
- Moderate-stable: 3,275
- Low-Increasing: 1,436
- Moderate-Fast-Decline: 735
- Low-declining: 1,343

COMPARISON (# IN THE GROUP): 137 in ultra-low declining group

FOLLOW-UP PERIOD: Up to one year post delivery

RESULTS:

Primary Outcome –

- When compared to the ultra-low-declining group, the adjusted odds ratio (aOR) for the development of preeclampsia/eclampsia was significantly higher in every group:
  - 9.2 (95% CI, 7.7–11) in the elevated-stable group
  - 5.3 (95% CI, 4.5–6.3) in the moderate-stable group
  - 3.3 (95% CI, 2.7–3.9) in the low-increasing group
  - 2.7 (95% CI, 2.3–3.3) in the moderate-fast-decline group
  - 1.8 (95% CI, 1.5–2.2) in the low-declining group

- When compared to the ultra-low-declining group, the aOR for the development of gestational HTN was also significantly higher in every group:
  - 30 (95% CI, 23–39) in the elevated-stable group
  - 14 (95% CI, 11–18) in the moderate-stable group
  - 6.4 (95% CI, 4.9–8.3) in the low-increasing group
  - 5.4 (95% CI, 4.1–7.1) in the moderate-fast-decline group
  - 2.6 (95% CI 2.0–3.5) in the low-declining group

LIMITATIONS:

- Data collection was limited to previous births in the chosen health system and the potential of missing history of hypertensive disorders of pregnancy in some included patients.
- Some social determinants of health were not corrected for in this study including education, economic resources, health care barriers, discrimination, and nativity. The risk of development of HDP may have been increased had these details been included.
- Preeclampsia, eclampsia, and gestational hypertensive disorders were identified via ICD-9/10 codes. This method of data collection may have missed some diagnoses and outcomes.

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