GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

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Can Multivitamins Improve Memory in Older Adults?

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Multivitamin Supplementation Improves Memory in Older Adults: A Randomized Clinical Trial

Yeung LK, Alschuler DM, Wall M, et al. Multivitamin Supplementation Improves Memory in Older Adults: A Randomized Clinical Trial. *Am J Clin Nutr.* 2023;118(1):273-282. doi:10.1016/j.ajcnut.2023.05.011

KEY TAKEAWAY: Daily multivitamin supplementation improves recall memory in older adults compared to placebo.

STUDY DESIGN: Randomized, double-blind, controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Cognitive decline is a major concern for many older adults and their caregivers. Multivitamin use is common in adults; however, little evidence exists regarding their cognitive benefits. This study sought to evaluate the effects of multivitamin supplementation on hippocampus-mediated cognition.

PATIENTS: Older adults

INTERVENTION: Daily multivitamin

CONTROL: Placebo

PRIMARY OUTCOME: Episodic memory (immediate recall memory)

Secondary Outcome: Episodic memory (recall memory) over three-year follow-up in participants with cardiovascular disease history

METHODS (BRIEF DESCRIPTION):

- This is an ancillary study of the COSMOS trial which studied daily cocoa extract and multivitamin use.
- This study enrolled women >65 years old or men >60 years old without a history of myocardial infarction or stroke in the previous two years.
- Participants were required to access an internet-connected computer.
- Participants were randomized to daily Centrum Silver® supplementation or placebo.
  - Baseline demographics were similar between the groups.
- Missed pills were assessed every six months.
- Participants completed a baseline COSMOS-Web cognitive assessment and then annually for three years.
- Self-administered COSMOS-Web assessments were completed in the participant's home.
- COSMOS-Web assessments included ModRey (a listening test measuring immediate recall), ModBent (an object recognition test), and Flanker (a test of executive control or prefrontal cortex function where patients are shown a series of arrows).
  - Participants with a history of CVD started with lower baseline scores.

INTERVENTION (# IN THE GROUP): 1,758

COMPARISON (# IN THE GROUP): 1,804

FOLLOW-UP PERIOD: Three years

RESULTS:

Primary Outcome –

- Participants assigned to the multivitamin intervention had significant improvement in ModRey immediate recall memory when year one results were compared to baseline testing (t[5889]=2.3; P=.025).

Secondary Outcome –

- Ongoing improvement in years two and three was insignificant compared to placebo.
- The effect of daily multivitamin use on recall memory as measured with the ModRey showed significant improvement compared to participants taking a placebo reporting a history of CVD compared with participants with no history of CVD (t[5885]=2.6; P=.009).

LIMITATIONS:

- Participants were mostly White, educated, and required to have home computer access which can limit the applicability of results to the overall population.
- The testing was developed for this study and has not been validated independently.
- This trial was funded by Pfizer, the maker of Centrum Silver® and Mars Edge, potentially creating bias.

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Should the Initiation of Dual Antiplatelet Therapy Be Extended to 72 Hours Post-Ischemic Event?

Dual Antiplatelet Treatment up to 72 Hours After Ischemic Stroke

Gao Y, Chen W, Pan Y, et al. Dual Antiplatelet Treatment up to 72 Hours after Ischemic Stroke. *N Engl J Med*. 2023;389(26):2413-2424. doi:10.1056/NEJMoa2309137

KEY TAKEAWAY: Dual antiplatelet (DAP) therapy within 72 hours of a mild ischemic stroke/high-risk transient ischemic attack (TIA) can reduce the incidence of new stroke within 90 days when compared to aspirin alone. However, the incidence of a moderate to severe bleed may increase.

STUDY DESIGN: Double-blind, randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: DAP therapy initiated within 24 hours of the onset of the stroke is a well-understood standard of care, however, initiation of treatment within 72 hours of stroke diagnosis is not well-studied.

PATIENTS: Adults with mild ischemic stroke/high-risk TIA

INTERVENTION: Aspirin/clopidogrel within 72 hours of diagnosis

CONTROL: Aspirin only within 72 hours of diagnosis

PRIMARY OUTCOME: Reduction of a new stroke at 90 days, incidence of hemorrhage

METHODS (BRIEF DESCRIPTION):

- Patients were identified as eligible for inclusion 24–72 hours after symptom onset and were diagnosed with a mild ischemic stroke (National Institute of Health Stroke Scale score <5) or high-risk TIA (age, blood pressure, clinical features, duration score >4).
- Further imaging was required to document 50% stenosis of a major intracranial or extracranial artery or multiple infarcts found on CT or MRI.
- Participants were randomized in a 1:1 ratio to receive:
  - DAP therapy: 3 mg of clopidogrel on day one, followed by 75 mg daily on days 2–90, and aspirin 100–300 mg on day one followed by 100 mg daily on days 2–21, then aspirin placebo for days 22–90.
  - Aspirin alone: Clopidogrel placebo for 90 days plus aspirin 100–300 mg on day one, then aspirin 100 mg daily for days 2–90.
- Patients were monitored for new stroke within 90 days of initial symptom onset.
- The incidence of hemorrhage was recorded in patients assigned to the dual antiplatelet group vs aspirin-only group.

INTERVENTION (# IN THE GROUP): 3,050

COMPARISON (# IN THE GROUP): 3,050

FOLLOW-UP PERIOD: 90 days

RESULTS:

Primary Outcome –

- The incidence of new stroke at 90 days was lower in the dual antiplatelet therapy group compared to the aspirin-only group (7.3% vs 9.2%, respectively; hazard ratio [HR] 0.79; 95% CI, 0.66–0.94).
- The primary safety outcome identified the incidence of moderate to severe bleeding was higher in the dual platelet therapy group vs the aspirin group alone (0.9% vs 0.4%, respectively; HR 2.1; 95% CI, 1.1–4.0).

LIMITATIONS:

- The study did not take into account the use of high-intensity statin therapy in conjunction with DAP therapy.
- There are variations in aspirin dosages on day one from 100–300 mg tablet daily depending on the initial provider who managed the patient.
- The study included data from patients with only mild strokes/high-risk TIAs and it is unclear whether the results can be applied to more severe ischemic events to prevent recurrence.

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For Reducing Dementia Risk in Elderly Patients, Will the Use of Antiplatelet Therapy Help?

Antiplatelet Therapy and Incident Cognitive Impairment or Dementia- A Systematic Review and Meta-Analysis of Randomized Clinical Trials

Kitt K, Murphy R, Clarke A, et al. Antiplatelet therapy and incident cognitive impairment or dementia-a systematic review and meta-analysis of randomized clinical trials. *Age Ageing.* 2023;52(10):afad197. doi:10.1093/ageing/afad197

KEY TAKEAWAY: There is no association with prescribing antiplatelet therapy to elderly patients with reducing dementia or cognitive impairment.

STUDY DESIGN: A systematic review and meta-analysis of 11 randomized clinical trials (N=109,860)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: In vascular dementia, cognitive impairment can be worsened by subsequent vascular incidents. Antiplatelet therapy is given to patients with a known cerebral vascular accident (CVA) history. This study assessed if antiplatelet therapy prevents worsening dementia or cognitive impairment.

PATIENTS: Patients with cognitive impairment or dementia

INTERVENTION: Single or dual antiplatelet therapy

CONTROL: Placebo

PRIMARY OUTCOME: Cognitive impairment

METHODS (BRIEF DESCRIPTION):

- Meta-analysis and systematic review of articles derived from PubMed, EMBASE, and CENTRAL from 2008 to February 2023 with search terms of dementia, cognitive impairment, cognitive testing, randomized trials, and antiplatelet therapy.
- The included trials were randomized, compared treatment with control, and had at least one year of follow-up.
- Patients in the intervention group were treated with single (aspirin) or dual anti-platelet therapy (DAPT; aspirin and clopidogrel or ticagrelor).
- Patients in the control group were treated with a placebo or aspirin + placebo over 70 months (or 6 years) on average.
- The outcome was the measurement of worsening cognitive impairment or dementia based on the International Classification of Diseases (ICD) and the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria.
- Measurements of worsening cognitive abilities were based on cognitive scoring such as the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MOCA), Telephone Interview for Cognitive Status (TICS), Mill Hill vocabulary scale score, or global cognitive scoring by z score.
    - These scores were standardized into an MMSE equivalent score and compared to each other by pooled mean difference.
    - Odds ratios and 95% confidence intervals were used to detect the presence or absence of cognitive impairment or dementia for each trial.

INTERVENTION (# IN THE GROUP):

- Aspirin alone: 1,510
- DAPT: 530

COMPARISON (# IN THE GROUP):

- Aspirin alone: 1,606
- DAPT: 545

FOLLOW-UP PERIOD: 70 months or 5.8 years with yearly follow-up

RESULTS:

Primary Outcome –

- Antiplatelet therapy was not significantly associated with a reduction in cognitive impairment or dementia compared to control (odds ratio [OR] 0.94; 95% CI, 0.88–1.0).
    - Cognitive score (standardized mean difference –0.04; 95% CI, –0.04 to 0.01; P-value for heterogeneity=.18)
    - MMSE score (standardized mean difference 0.0; 95% CI, –0.01 to 0.0)

LIMITATIONS:

- There was high heterogeneity in scoring systems for worsening cognitive impairment.
- Different dosing of antiplatelet therapy and classes of antiplatelet drugs were used in the study.
- The number of patients with dementia in the population group was low. The power to detect dementia patients may be insufficient.

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Sugar Isn't So Sweet: Impact of Beverage Choice Among Adults with Type 2 Diabetes

Beverage Consumption and Mortality Among Adults with Type 2 Diabetes: Prospective Cohort Study

Ma L, Hu Y, Alperet DJ, et al. Beverage consumption and mortality among adults with type 2 diabetes: prospective cohort study. *BMJ*. 2023;381:e073406. Published 2023 Apr 19. doi:10.1136/bmj-2022-073406

KEY TAKEAWAY: Adults with type 2 diabetes (T2DM) who consume coffee, plain water, and low-fat milk may have a lower risk of mortality as compared to those who consume sugar-sweetened beverages (SSBs).

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Intake of beverages with low energy density (water, low-fat milk, coffee) is associated with decreased incidence of obesity, T2DM, and cardiovascular disease (CVD) in the general population. However, limited evidence exists on the impact of beverage choice in those with already-established T2DM, who have altered carbohydrate and macronutrient metabolism.

PATIENTS: Adults with T2DM

INTERVENTION: Consuming SSBs, artificially sweetened beverages (ASBs), coffee, tea, plain water, low-fat milk

CONTROL: Not consuming SSBs, ASBs, coffee, tea, plain water, low-fat milk

PRIMARY OUTCOME: All-cause mortality, CVD, CVD mortality

METHODS (BRIEF DESCRIPTION):

- Participants included US women 30–55 years old from the Nurses' Health Study and men 40–75 years old from the Health Professionals Follow-up Study who had a diagnosis of T2DM at baseline or that developed during the follow-up period.
- Participants completed surveys on dietary habits, lifestyle factors, and medical history.
- Participant's consumption of specific beverages was defined as consumption of SSBs, ASBs, coffee, tea, plain water, low-fat milk, and full-fat milk.
  - Consumption was divided into various frequencies.
- All-cause mortality, CVD incidence, and CVD mortality were compared across the consumption frequencies using hazard ratios.
- Results were adjusted for age, duration of diabetes, sex, ethnicity, physical activity, smoking status, alcohol consumption, menopausal status, hormone use, family history of T2DM or myocardial infarction, total intake of calories, modified Alternative Healthy Eating Index score, comorbidity disease status of hypertension, hypercholesterolemia and associated medications, aspirin use, and diabetes drug use.

INTERVENTION (# IN THE GROUP): 15,486

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Mean 19 years

RESULTS:

Primary Outcome –

- SSBs were associated with increased all-cause mortality when comparing <1 serving/month vs >1 serving/day (hazard ratio [HR] 1.2; 95% CI, 1.0–1.4).
- The following beverages were associated with decreased all-cause mortality:
  - Coffee <1 serving/month vs >4 servings/day (HR 0.74; 95% CI, 0.63–0.86)
  - Tea <1 serving/month vs >2 servings/day (HR 0.79; 95% CI, 0.71–0.89)
  - Plain water <1 serving/day vs >5 servings/day (HR 0.77; 95% CI, 0.70–0.85)
  - Low-fat milk <1 serving/month vs >2 servings/day (HR 0.88; 95% CI, 0.80–0.96)
- SSBs were associated with increased CVD incidence when comparing <1 serving/month vs >1 serving/day (HR 1.3; 95% CI, 1.0–1.5).
- Coffee was associated with decreased CVD incidence when comparing <1 serving/month vs >4 servings/day (HR 0.82; 95% CI, 0.69–0.98).
- ASBs, tea, plain water, and low-fat milk were not associated with a change in CVD incidence.
- SSBs were associated with increased CVD mortality when comparing <1 serving/month vs >1 serving/day (HR 1.3; 95% CI, 1.0–1.6).
- The following beverages were associated with decreased CVD mortality:
  - Plain water <1 serving/day vs >5 servings/day (HR 0.77; 95% CI, 0.65–0.91)
  - Low-fat milk <1 serving/month vs >2 servings/day (HR 0.84; 95% CI, 0.72–0.99)

- ASBs, tea, and coffee were not associated with CVD mortality.

LIMITATIONS:

- Additional confounders may be contributing to outcomes, as beverage consumption may be correlated with other dietary and lifestyle risk factors.
- Self-reported dietary logs and diagnosis may have introduced recall bias.
- Preventative care for associated chronic diseases like hypertension and dyslipidemia has changed considerably since the start of the study in the 1980s.
- Participants are predominantly White and limited to healthcare professionals in the United States.

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Is Activity Restriction Really Necessary for Women in Arrested Preterm Labor?

Activity Restriction for Women with Arrested Preterm Labor: A Randomized Controlled Trial

Saccone G, Della Corte L, Cuomo L, et al. Activity restriction for women with arrested preterm labor: a randomized controlled trial [published correction appears in Am J Obstet Gynecol MFM. 2023 Dec;5(12):101199]. *Am J Obstet Gynecol MFM*. 2023;5(8):100954. doi:10.1016/j.ajogmf.2023.100954

KEY TAKEAWAY: Activity restriction may not be effective in reducing the risk of preterm birth in singleton pregnancies with arrested preterm labor.

STUDY DESIGN: Randomized, unblinded, single-center controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to lack of blinding)

BRIEF BACKGROUND INFORMATION: Activity restriction in women with arrested preterm labor to prevent preterm birth is controversial. In women with an incompetent cervix and threatened premature labor, the American College of Obstetricians and Gynecologists recommends avoiding aerobic exercise. However, no official recommendations for activity restriction exist for women in arrested preterm labor. Studies show that up to 95% of obstetricians recommend bedrest or other forms of activity restriction for these patients. The study aims to investigate whether activity restriction would reduce the rate of preterm birth in women with arrested preterm labor.

PATIENTS: Women with arrested preterm labor

INTERVENTION: Activity restriction

CONTROL: No activity restriction recommendation

PRIMARY OUTCOME: Preterm birth <37 weeks gestation

Secondary Outcome: Gestational age at delivery, adverse neonatal outcomes

METHODS (BRIEF DESCRIPTION):

- The study was conducted at a single center in Italy.
- Women 18–50 years old with a singleton pregnancy and arrested preterm labor at 24 0/7 weeks to 33 6/7 weeks of gestation were included.
- Arrested preterm labor was defined as not delivering after 48 hours of hospitalization for threatened preterm labor, with cervical length ≤25 mm, no other labor symptoms, and cervical dilatation <3 cm.
- Patients with multiple gestations, symptoms of possible uterine contractions, rupture of membranes, cerclage or pessary in situ, and vaginal bleeding at the time of randomization were excluded from the study.
- Participants in the intervention and control groups were generally similar with a mean age of 29 years old and 32 years old respectively, and a mean BMI of 25.
  - Both groups were predominantly White.
- Participants were randomized at hospital discharge by a web-based block system to receive one of the following recommendations:
  - Activity restriction: Pelvic rest, no sexual activity, reduced work and/or nonwork activity
  - No activity restriction
- The primary outcome was preterm birth <37 weeks gestation.
- Secondary outcomes included mean gestational age at delivery, latency (length of time in weeks from randomization to delivery), and adverse neonatal outcomes (defined as neonatal intensive care unit [NICU] admission, death, or any one of necrotizing enterocolitis, respiratory distress syndrome, intraventricular hemorrhage, bronchopulmonary dysplasia, retinopathy of prematurity, sepsis, neonatal death).

INTERVENTION (# IN THE GROUP): 60

COMPARISON (# IN THE GROUP): 60

FOLLOW-UP PERIOD: 28 days post-delivery

RESULTS:

Primary Outcome –

- Activity restriction resulted in a similar risk of preterm birth as compared with no activity restriction (25% vs 38%, respectively; relative risk [RR] 0.65; 95% CI, 0.38–1.1).

Secondary Outcome –

- Mean gestational age at delivery was similar between groups (38 weeks in activity restricted group vs 37 weeks in the control, mean difference [MD] 0.80; 95% CI, –0.30 to 1.90).

- Latency was slightly longer in the intervention group (8.2 weeks in activity restricted group vs 6.7 weeks in the control, MD 1.5; 95% CI, 0.24–2.8).
- There were no significant differences between groups for any neonatal outcomes.

LIMITATIONS:

- The observed rate of preterm birth was lower than expected and suggests that the study may have been underpowered to detect a significant difference.
- The trial was not powered for other secondary outcomes and these outcomes should be considered hypothesis generating.
- Compliance with activity restrictions was not assessed.
- The study design was single-center and unblinded.

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