GOOD EVIDENCE MATTERS

GEMs of the Week

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FPIN
Family Physicians Inquiries Network

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Has Resistant Hypertension Met Its Match?

Lorundrostat in Participants with Uncontrolled Hypertension and Treatment-Resistant Hypertension: The Launch-HTN Randomized Clinical Trial

Saxena M, Laffin L, Borghi C, et al. Lorundrostat in Participants with Uncontrolled Hypertension and Treatment-Resistant Hypertension: The Launch-HTN Randomized Clinical Trial. *JAMA*. 2025;334(5):409-418. doi:10.1001/jama.2025.9413

KEY TAKEAWAY: When added to standard therapy, lorundrostat significantly lowers systolic blood pressure (SBP) in adults with uncontrolled or resistant hypertension (HTN).

STUDY DESIGN: Multicenter, double-blind, randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: HTN remains a major cardiovascular risk factor, and despite treatment with multiple antihypertensive medications, many adults fail to achieve adequate blood pressure (BP) control. Aldosterone dysregulation is a contributor to uncontrolled BP, yet medications that target aldosterone are often underused. This trial evaluates lorundrostat, a novel aldosterone synthase inhibitor, as an add-on therapy for uncontrolled or resistant HTN.

PATIENTS: Adults with uncontrolled HTN

INTERVENTION: Lorundrostat

CONTROL: Placebo

PRIMARY OUTCOME: SBP reduction in six weeks

Secondary Outcome: Systolic <130 mmHg at six weeks; maintained reduction at 12 weeks

METHODS (BRIEF DESCRIPTION):

- Adults recruited from 159 outpatient sites across 13 countries with uncontrolled hypertension on 2–5 antihypertensive medications.
- Mean age 62 years old; 47% female; 29% African American, 68% Caucasian; 63% BMI ≥30
- Patients with advanced kidney disease, hyperkalemia, or recent use of mineralocorticoid receptor antagonists were excluded.
- Participants were randomized 1:2:1.
  - Lorundrostat 50 mg daily for six weeks followed by 100 mg for six weeks
  - Lorundrostat 50 mg daily for 12 weeks
  - Placebo for 12 weeks
- The primary outcome assessed SBP at six weeks.
- The secondary outcomes assessed SBP <130 mmHg at six weeks and maintained reduction at 12 weeks.
- BP was measured using automated in-office measurements at six weeks and at 12 weeks and were taken after rest with five seated readings with one-minute intervals. The mean of last four readings was used.

INTERVENTION (# IN THE GROUP): 808

COMPARISON (# IN THE GROUP): 270

FOLLOW-UP PERIOD:

- Primary endpoint: Six weeks
- Secondary endpoint: 12-week total double-blind treatment

RESULTS:

Primary Outcome –

- Lorundrostat reduced SBP by compared to placebo (between-group difference –9.1 mmHg; 95% CI, –13 mmHg to –4.9 mmHg).

Secondary Outcome –

- More patients achieved SBP <130 mmHg with lorundrostat at six weeks compared to placebo (44% vs 24%, respectively; odds ratio [OR] 3.4; 95% CI, 1.5–7.8).
- SBP reductions were maintained with lorundrostat after 12 weeks compared to placebo (least squares mean difference –10 mmHg; 98% CI, –14 to –6.1).

LIMITATIONS:

- Evaluates efficacy and safety for 12 weeks, limiting conclusions about long-term outcomes and durability.
- Automated office BPs were used rather than ambulatory BP, which may not fully reflect 24-hour BP control.
- Lacked an active comparator such as spironolactone, limiting direct comparison with established treatment options.
- Industry funding and sponsor involvement in study design, analysis, and manuscript development may increase the risk of bias.

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Low Dose Oral Semaglutide: A Needle Free Approach in Obesity Management

Oral Semaglutide at a Dose of 25 mg in Adults with Overweight or Obesity

Wharton S, Lingvay I, Bogdanski P, et al. Oral Semaglutide at a Dose of 25 mg in Adults with Overweight or Obesity. *N Engl J Med*. 2025;393(11):1077-1087. doi:10.1056/NEJMoa2500969

KEY TAKEAWAY: Oral semaglutide significantly reduces body weight compared to placebo in participants with a body mass index (BMI) ≥30 or ≥27 with an obesity related comorbidity.

STUDY DESIGN: Multicenter, double-blind, randomized controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to high risk of bias of study sponsor)

BRIEF BACKGROUND INFORMATION: Injectable semaglutide 2.4 mg is effective for weight management in those with overweight or obesity but limited by the need for subcutaneous administration. Oral semaglutide 25 mg offers a noninvasive alternative for injectable and higher dose pharmacologic options.

PATIENTS: Adults with BMI ≥30, or ≥27 with comorbidities

INTERVENTION: Oral semaglutide 25 mg

CONTROL: Placebo

PRIMARY OUTCOME: Percentage change in body weight and a reduction of ≥5% body weight at 64 weeks

Secondary Outcome: Reduction in body weight of ≥10%, ≥15%, and ≥20%, and physical function

METHODS (BRIEF DESCRIPTION):

- Eligible participants were adults ≥18 years old without diabetes who had a BMI of ≥30, or a BMI of ≥27 with at least one obesity related comorbidity (hypertension, dyslipidemia, obstructive sleep apnea or cardiovascular disease), who reported one unsuccessful weight loss efforts via diet.
- Participants were randomized 2:1 to receive oral semaglutide 25 mg daily or placebo, alongside lifestyle interventions.
- Lifestyle interventions included counseling on diet (500 kcal daily deficit) and physical activity (150 minutes weekly) provided by a dietician at each trial visit.
- Oral semaglutide dosing was initiated at 3 mg daily, followed by fixed dose escalation to 25 mg over 12 weeks. The maintenance phase lasted 52 additional weeks, followed by a seven-week follow-up.
- The primary outcome measured the percent change in body weight and a reduction of ≥5% body weight.
- The secondary outcomes assessed the following:
  - Reduction in body weight of ≥10%, ≥15%, and ≥20%.
  - Physical function was measured via the Impact of Weight on Quality of Life-Lite Clinical Trials Version. Scores range from 0–100, with higher scores indicating better function.
- All end points were assessed from baseline to 64 weeks.
- Efficacy was analyzed in the full analysis population using both treatment policy (intention to treat) and trial product (hypothetical) estimands. Missing data were handled with multiple imputations, and results were tested hierarchically with type I error control.

INTERVENTION (# IN THE GROUP): 205

COMPARISON (# IN THE GROUP): 102

FOLLOW-UP PERIOD: 64 weeks

RESULTS:

Primary Outcome –

- Oral semaglutide significantly reduced body weight compared to control after 64 weeks (–14% vs –2.2%, respectively; estimated difference –11 percentage points; 95% CI, –14 to –9.0).
- Participants treated with oral semaglutide were significantly more likely to have body-weight reductions of ≥5% compared to control at 64 weeks (79% vs 31%, respectively; odds ratio [OR]; 95% CI, 4.2–13).

Secondary Outcome –

- Participants treated with oral semaglutide were significantly more likely to have body-weight reductions of ≥10% compared to control at 64 weeks (63% vs 14%, respectively; OR 9.1; 95% CI, 4.7–17).
- Participants treated with oral semaglutide were significantly more likely to have body-weight reductions of ≥15% compared to control at 64

weeks (50% vs 5.6%, respectively; OR 16; 95% CI, 6.2–40).

- Participants treated with oral semaglutide were significantly more likely to have body-weight reductions of ≥20% compared to control at 64 weeks (30% vs 3.3%, respectively; OR 12; 95% CI, 3.7–40).
- Oral semaglutide improved IWQOL-Lite-CT function scores (physical function, self-esteem, sexual life, public distress, and work perception) at 64 weeks compared to control (16 vs 8.4 points, respectively; OR 7.7; 95% CI, 3.3–12).

LIMITATIONS:

- Study population was predominantly Caucasian females, which may limit the generalizability of the findings.
- The relatively small number of participants in certain subgroups reduced the ability to assess differential treatment effects.
- Approximately 20% of participants did not complete the trial, necessitating imputation for efficacy analyses.
- Absence of an active comparator (such as oral semaglutide 50 mg or subcutaneous semaglutide 2.4 mg) prevented direct comparisons of efficacy and safety across different doses or administration routes.
- The sponsor, Novo Nordisk, was responsible for signing the trial, preparing the protocol and performing the statistical analysis.

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Beyond Blood Sugar Control: SGLT2 Inhibitors vs GLP-1 Receptor Agonists Impact on Dementia Prevention

Comparative Effectiveness of SGLT2 Inhibitors and GLP-1 Receptor Agonists in Preventing Alzheimer's Disease, Vascular Dementia, and Other Dementia Types Among Patients with Type 2 Diabetes

Sun M, Wang X, Lu Z, et al. Comparative Effectiveness of SGLT2 Inhibitors and GLP-1 Receptor Agonists in Preventing Alzheimer's Disease, Vascular Dementia, and Other Dementia Types among Patients with Type 2 Diabetes. *Diabetes Metab*. 2025;51(2):101623. doi:10.1016/j.diabet.2025.101623

KEY TAKEAWAY: Sodium glucose cotransporter-2 inhibitors (SGLT-2is) reduce the overall risk of dementia compared to glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in adults with type 2 diabetes (T2DM).

STUDY DESIGN: Retrospective observational study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: T2DM is prevalent worldwide and is associated with dementia. Both SGLT-2is and GLP-1 RAs have been shown to be neuroprotective, but direct comparative data are limited. This study aimed to compare the efficacy of SGLT-2is to GLP-1 RAs in preventing dementia.

PATIENTS: Adults with T2DM without dementia

INTERVENTION: SGLT-2i

CONTROL: GLP-1 RA

PRIMARY OUTCOME: Incidence of dementia

Secondary Outcome: Incidence of dementia subtypes, all-cause mortality

METHODS (BRIEF DESCRIPTION):

- Patients were identified using a large, global electronic health record (TriNetX) from 2004–2024.
- The patients included were adults with T2DM without dementia, either taking an SGLT-2i or GLP-1 RA, documented by at least 12 months of medication therapy history.
- Exclusion criteria included patients with prior use of both drug classes, concurrent use of drug classes, use of DPP-4 inhibitors, and documented diagnosis of dementia.
- Follow-up began after a 12-month washout period and lasted until observation of the outcome, loss to follow-up, or end of study.
- The primary outcome was overall dementia incidence.
- The secondary outcomes included incidence of dementia subtypes e.g. Alzheimer's disease, vascular dementia, and all-cause mortality.
- The two patient cohorts were matched 1:1 using propensity score matching with a caliper width of 0.2 standard deviations to control for confounders.
- The outcomes were measured by time-to-event analyses using Kaplan-Meier survival curves and Cox proportional hazards models.
- Two-sided statistical analyses were performed and considered significant with $P<.05$.

INTERVENTION (# IN THE GROUP): 221,883

COMPARISON (# IN THE GROUP): 221,883

FOLLOW-UP PERIOD: Eight years

RESULTS:

Primary Outcome –

- SGLT-2i therapy was associated with a lower incidence of overall dementia compared to GLP-1 RA therapy (adjusted hazard ratio [aHR] 0.92; 95% CI, 0.89–0.95).

Secondary Outcome –

- SGLT-2i therapy was associated with a lower incidence of vascular dementia compared to GLP-1 RA therapy (aHR 0.89; 95% CI, 0.84–0.95).
- SGLT-2i was associated with a lower incidence of Alzheimer's disease compared to GLP-1 RA therapy (aHR 0.90; 95% CI, 0.86–0.94).
- There was no significant difference in the incidence of other types of dementia between SGLT-2i and GLP-1 RA therapy.
- SGLT- 2i therapy was associated with lower all-cause mortality compared to GLP-1 RA therapy (aHR 0.95; 95% CI, 0.92–0.98).

LIMITATIONS:

- Could not establish causality due to study design or fully account for unknown confounders.
- Limited exposure data (i.e. lack of specific medication therapy, medication adherence, dosing, and total duration).
- The TriNetX database may not capture all demographics equally.

- Relying only on ICD-10 codes to measure outcomes may lead to incorrect diagnoses, skewing the results.

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To Fast or Not to Fast: What are the Benefits?

Cardiometabolic and Molecular Adaptations to Six-Month Intermittent Fasting in Middle-aged Men and Women with Overweight: Secondary Outcomes of a Randomized Controlled Trial

Barve RA, Veronese N, Bertozzi B, et al. Cardiometabolic and Molecular Adaptations to 6-month Intermittent Fasting in Middle-aged Men and Women with Overweight: Secondary Outcomes of a Randomized Controlled Trial. *Nat Commun*. 2025;16(1):11370. Published 2025 Dec 13. doi:10.1038/s41467-025-66366-8

KEY TAKEAWAY: In adults who are overweight, 2–3 vegetable-only fasting days per week for six months lead to significant weight loss, decreased body fat, and improved cholesterol and triglycerides, even when eating a Western diet on non-fasting days.

STUDY DESIGN: Randomized controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size)

BRIEF BACKGROUND INFORMATION: Cardiovascular disease continues to be a leading cause of illness and death worldwide. Obesity and dyslipidemia are modifiable risk factors, but maintaining daily calorie restriction can be difficult. Intermittent fasting (IF) can be a potentially practical approach, but its effect on overweight adults remains unclear. This study examined the effects of six months of IF on body composition, lipid profile, and cardiometabolic risk factors in overweight adults.

PATIENTS: Adults who are overweight

INTERVENTION: Intermittent fasting

CONTROL: Diet as usual

PRIMARY OUTCOME: Weight and body composition, lipid profile, and cardiometabolic risk factors

METHODS (BRIEF DESCRIPTION):

- Participants recruited from the St. Louis metropolitan area in the United States had a mean age of 49 years, were 41% women, and had a mean body mass index (BMI) of 30 kg/m^2.
- Individuals with a stable weight (<2 kg change over ≥3 months), followed a Western diet, and were nonsmokers were included in the study.
- Individuals with diabetes, cardiovascular or chronic kidney disease, neurologic or musculoskeletal issues, smoking, pregnancy, alcoholism, or exercising >2 times a week were excluded from the study.
- IF involved a vegetable-only diet and a usual Western diet on non-fasting days.
- Participants were randomly assigned to the IF group or the diet as usual group.
- The IF participants fasted as follows: Two days per week for BMI between 24–28 kg/m^2 and three days for BMI between 28–35. Fasting frequency dropped to two days per week when BMI was <28.
- The diet on fasting days included only non-starchy vegetables and up to two tablespoons of olive oil, vinegar, or lemon dressing, amounting to <500 kcal/day.
- The IF participants had monthly dietitian meetings with weight tracking and dietary guidance. Adherence and body weights were monitored weekly, and a four-day food diary was kept.
- The non-IF participants received no dietary intervention or counseling.
- Both groups maintained their usual physical activity.
- All participants received a comprehensive baseline medical evaluation that included:
  - Height and waist circumference were measured to the nearest 0.1 cm.
  - Body weight was measured twice using a calibrated scale after an overnight fast, with participants wearing hospital gowns and no shoes. IF participants tracked weekly at-home weight using digital scales.
  - Body composition was evaluated using dual-energy X-ray absorptiometry.
  - Plasma lipid and lipoprotein-cholesterol concentrations were assessed from venous blood samples collected by technicians blinded to the intervention assignments.
  - Plasma glucose was measured via the glucose oxidase method.
  - Insulin was evaluated by radioimmunoassay, and the insulin resistance index (HOMA-IR) was calculated using the homeostasis model.
  - Blood pressure was assessed in the morning after a 12-hour fast with participants in a seated

position using an oscillometric blood pressure monitor and standardized protocols.
    - High-sensitivity C-reactive protein (hsCRP) was measured using a particle-enhanced immunoturbidimetric assay.
    - Carotid intima-media thickness was measured using a high-resolution β-mode ultrasonography with an 11-MHz transducer.

INTERVENTION (# IN THE GROUP): 21

COMPARISON (# IN THE GROUP): 20

FOLLOW-UP PERIOD: Six months

RESULTS:

Primary Outcome –

- After six months, IF reduced body weight and adiposity compared to control:
    - Weight (–5.9 kg vs 1.1 kg; *P*<.0001)
    - BMI (–2.0 vs 0.3 kg/m^2; *P*<.0001)
    - Waist circumference (–8.4 cm vs 1.1 cm; *P*<.0001)
    - Body fat (–3.1% vs 0.8%; *P*<.0001)
    - Trunk fat mass (–2.8 kg vs 0.6 kg; *P*<.0001)
    - Total lean mass (–1.0 kg vs 0.2 kg; *P*<.0001)
- After six months, IF improved lipid profile compared to control:
    - Total cholesterol (–5.0 mg/dl vs 11 mg/dl; *P*=.03)
    - LDL-cholesterol (–3.1 mg/dl vs 6 mg/dl; *P*=.05)
    - Non-HDL cholesterol (–8 mg/dl vs 8 mg/dl; *P*=.001)
    - HDL-cholesterol (3 mg/dl vs 1 mg/dl; *P*=.15)
    - Cholesterol to HDLc ratio (–0.5 vs 0.1; *P*=.01)
    - Triglycerides (–25 mg/dl vs 13 mg/dl; *P*=.01)
    - Triglycerides to HDLc ratio (–0.9 vs 0.2; *P*=.20)
- The pre-post change after six months of IF was not significant for cardiometabolic risk factors such as fasting glucose, fasting insulin, HOMA-IR, systolic and diastolic blood pressure, hsCRP levels, and thickness of carotid arteries (all *P*>.05).

LIMITATIONS:

- The sample size was small.
- The study was short in duration. Cardiovascular effects resulting from improvement in weight, body mass, and lipid values may become more evident with a longer study.
- The findings from a relatively healthy adult population may not be generalizable to other demographic groups such as patients with comorbid obesity and diabetes, the elderly, or diverse ethnic groups.
- The protocol was not completely fasting, consisting mainly of switching to eating vegetables only, which limited the potential benefit of total decrease in food consumption during those hours.

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The views expressed herein are those of the author and do not necessarily reflect the official policy of the Department of the Army, Defense Health Agency, Department of Defense, or the U.S. Government.

Wherefore ART thou, Arterial Lines? Is Arterial Catheterization Always Necessary in ICU Admissions for Shock?

Deferring Arterial Catheterization in Critically Ill Patients with Shock

Muller G, Contou D, Ehrmann S, et al. Deferring Arterial Catheterization in Critically Ill Patients with Shock. *N Engl J Med*. 2025;393(19):1875-1888. doi:10.1056/NEJMoa2502136

KEY TAKEAWAY: Non-invasive blood pressure monitoring (NIBP) is not worse than early arterial catheterization (AC) for all-cause mortality at 28 days in critically ill patients with shock.

STUDY DESIGN: Multicenter, open-label, randomized, non-inferiority trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: AC is often recommended for continuous blood pressure monitoring in intensive care unit (ICU) patients with shock, based on the expert opinion that theorizes it allows for superior hemodynamic management. However, this practice is not supported by evidence from randomized trials and carries risks such as infection and hematoma. This trial aimed to determine if a non-invasive monitoring strategy is noninferior to early AC for managing patients in shock.

PATIENTS: Adults admitted to the ICU for shock

INTERVENTION: NIBP

CONTROL: AC

PRIMARY OUTCOME: 28-day all-cause mortality

Secondary Outcome: Severity of organ failure, days free from ventilator support, renal replacement and vasopressor therapy, catheter-related infections, patient-reported pain

METHODS (BRIEF DESCRIPTION):

- The trial enrolled adults admitted to one of nine ICUs in France within 24 hours of ICU admission for shock.
- Patients were included if they had signs of hypotension (systolic blood pressure [SBP] <90 mmHg or mean arterial blood pressure <65 mmHg) for ≥15 minutes or required low dose vasopressor therapy and had at least one sign of tissue hypoperfusion.
- Patients were excluded if blood pressure readings could not be obtained, they were on high dose vasopressor therapy, body mass index (BMI) >40, pregnant, had severe traumatic brain injury (TBI), or were receiving extracorporeal membrane oxygenation (ECMO).
- The average participant age was 66 years old, with most participants being male and having a BMI of 27.
- Patients were randomized 1:1 to either the NIBP group (with an automated brachial cuff) or the early AC group (AC placed within 4 hours of randomization).
- The NIBP group was not permitted to have AC placement before 28 days unless certain prespecified safety criteria were met (e.g need for high-dose pressors, inability to display pulse oximetry, need for ECMO).
- The primary outcome was all-cause mortality at day 28, analyzed for noninferiority with a margin of five percentage points.
- The following were measured as the secondary outcomes:
  - Severity of organ failure was measured using the Median Sequential Organ Failure Assessment (SOFA). Scores range from 0–24, with higher scores indicating more severe organ failure.
  - Number of days free from life support interventions (e.g. ventilator support, renal replacement therapy, vasopressor therapy).
  - Catheter-related infections
  - Patient-reported pain using an 11-point numeric scale. Scores range from 0–10, with a score of 10 indicating maximum pain/discomfort.
  - Adverse events

INTERVENTION (# IN THE GROUP): 504

COMPARISON (# IN THE GROUP): 502

FOLLOW-UP PERIOD: 28 days

RESULTS:

Primary Outcome –

- There was no significant difference in all-cause mortality at 28 days for NIBP compared to AC (34% vs 37%, respectively; adjusted risk difference –3.2 percentage points; 95% CI, –8.9 to 2.5).

Secondary Outcome –

- The incidence of arterial catheter-related bloodstream infections was lower in the NIBP group compared to the early AC group (1 vs 3 per 1,000 ICU days, respectively; incidence ratio 0.18; 95% CI, 0.06–0.54).
- There was no significant difference in severity of organ failure at seven days or patient-reported pain from the monitoring device for NIBP compared to AC.
- At 28 days, the median duration of ICU stays and days free from organ support (ventilator, vasopressors, renal replacement therapy) were similar for NIBP compared to AC.

LIMITATIONS:

- The trial was not blinded, which may have introduced bias in the assessment of secondary outcomes.
- Pain assessment was limited as only 22% of the NIBP group and 15% of the early AC group were able to self-report.
- The patient population excluded those with a BMI >40 and had few trauma or post-surgical patients, which may limit generalizability.
- The study did not assess the impact of either strategy on hospital staff satisfaction or workload.

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Cracking the Connection: Egg Consumption and Alzheimer's Risk in Older Adults

Association of Egg Intake with Alzheimer's Dementia Risk in Older Adults: The Rush Memory and Aging Project

Pan Y, Wallace TC, Karosas T, Bennett DA, Agarwal P, Chung M. Association of Egg Intake with Alzheimer's Dementia Risk in Older Adults: The Rush Memory and Aging Project. *J Nutr*. 2024;154(7):2236-2243. doi:10.1016/j.tjnut.2024.05.012

KEY TAKEAWAY: One or ≥2 eggs consumption per week is associated with a significantly lower risk of developing Alzheimer's dementia (AD) in older adults, and this protective effect appears to be partly mediated by dietary choline, a key nutrient in eggs that supports brain health.

STUDY DESIGN: Prospective longitudinal cohort study

LEVEL OF EVIDENCE: STEP 4 (downgraded due to lack of generalizability)

BRIEF BACKGROUND INFORMATION: Eggs are rich in nutrients important for brain health especially choline and omega-3 fatty acids which support memory, cell membranes, and reduce inflammation. While previous studies suggested that these nutrients may protect against cognitive decline, no US based studies had directly examined whether regular egg consumption is linked to a lower risk of AD or its brain pathology in older adults living in the community. This study aimed to fill that gap using data from the Rush Memory and Aging Project.

PATIENTS: Older adults free of dementia

INTERVENTION: Eating 1–3 eggs per month, one egg per week, and >2 eggs per week

CONTROL: No egg consumption or eating <1 egg per month

PRIMARY OUTCOME: Development of AD

Secondary Outcome: AD pathology confirmed via postmortem brain autopsy

METHODS (BRIEF DESCRIPTION):

- The study used data from the Rush Memory and Aging Project.
- The intervention was dietary consumption of eggs, specifically categorized as:
  - 1–3 eggs per month
  - One egg per week
  - ≥2 eggs per week
- The comparator was no egg consumption or eating <1 egg per month.
- For both the intervention and the comparator, dietary consumption of eggs was measured by using
- a modified Harvard Food Frequency Questionnaire (FFQ) which participants self-reported how often they consumed eggs over the past 12 months.
- Participants completed an annual AD diagnosis assessment to evaluate overall cognitive functioning.
- The assessment produced a clinical diagnosis of no AD or AD and an impairment score, which reflects the degree of cognitive impairment adjusted for educational attainment.
  - A lower impairment score indicates better cognitive functioning and less decline.
  - A higher impairment score reflects greater cognitive functioning and worsening decline.
- A subgroup of participants donated their brains for postmortem analysis to assess Alzheimer's pathology.
- The study analyzed the association between egg consumption and AD risk using Cox proportional hazards models, adjusting for age, sex, years of education, body mass index (BMI), smoking status, physical activity, participation in cognitive activities, vascular risk, apolipoprotein E status, dark green leafy vegetables, strawberries, seafood, and total energy intake.
- Mediation analysis was conducted to explore whether choline intake partly explained the observed protective effect.

INTERVENTION (# IN THE GROUP): 1,024

COMPARISON (# IN THE GROUP): 1,024

FOLLOW-UP PERIOD: 6.7 years

RESULTS:

Primary Outcome –

- Eating one or ≥2 eggs per week decreased the risk of developing AD compared to no egg consumption or <1 egg per month.
  - One egg per week (hazard ratio [HR] 0.53; 95% CI, 0.34–0.83)
  - ≥2 eggs per week (HR 0.53; 95% CI, 0.35–0.81)

- Eating 1–3 eggs per month did not increase the risk of developing AD compared to no egg consumption or <1 egg per month (HR 0.94; 95% CI, 0.62–1.4).

Secondary Outcome –

- In the subgroup of 578 participants with brain autopsies, eating one or >2 eggs per week decreased the risk of developing AD compared to no egg consumption or <1 egg per month.
  - One egg per week (HR 0.51; 95% CI, 0.35–0.76)
  - ≥2 eggs per week (HR 0.62; 95% CI, 0.44–0.90)
- Eating 1–3 eggs per month did not increase the risk of developing AD compared to no egg consumption or <1 egg per month.
- About 39% of the protective effect of egg consumption on AD risk was explained by dietary choline intake.

LIMITATIONS:

- A cohort study can show associations but cannot prove causation between egg intake and risk of AD.
- Egg intake was measured only once at baseline using a single question in FFQ.
- Mixed dishes containing eggs were not counted, which could underestimate total egg consumption.
- Participants were mostly female (75%), predominantly from northeastern Illinois retirement communities potentially limiting applicability to other populations.
- The secondary outcome was based on 578 participants, smaller than the main cohort, which could reduce statistical power for some analyses.

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Effects of Dulaglutide on Alcohol Consumption During Smoking Cessation

Effects of Dulaglutide on Alcohol Consumption During Smoking Cessation

Probst L, Monnerat S, Vogt DR, et al. Effects of Dulaglutide on Alcohol Consumption During Smoking Cessation. *JCI Insight*. 2023;8(22):e170419. Published 2023 Nov 22. doi:10.1172/jci.insight.170419

KEY TAKEAWAY: Three months of dulaglutide reduces weekly alcohol intake compared to placebo among those who drink alcohol and are attempting to quit smoking.

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

LEVEL OF EVIDENCE: STEP 3 (downgraded due to being a secondary analysis of RCT)

BRIEF BACKGROUND INFORMATION: GLP-1 receptor agonists influence appetite and reward pathways with animal studies suggesting this can also reduce alcohol intake. A single prior trial found no reduction in heavy drinking days among patients treated for alcohol use disorder (AUD) with a GLP-1 agonist. Further data is needed to determine if this pathophysiologic hypothesis equates to real world outcomes.

PATIENTS: Adults with tobacco use disorder

INTERVENTION: Dulaglutide weekly SQ injection and smoking cessation therapy

CONTROL: Placebo weekly injection and smoking cessation therapy

PRIMARY OUTCOME: Difference in alcohol consumption (standard drinks/week) at 12 weeks

Secondary Outcome: Relationship between alcohol change and smoking status, smoking abstinence, heavy drinker subgroups, other drug use

METHODS (BRIEF DESCRIPTION):

- This trial was a prespecified secondary analysis of a single center, double-blind, parallel group trial conducted at University Hospital Basil Switzerland evaluating effect dulaglutide on smoking cessation.
- This trial was a prespecified secondary analysis of a single center, double-blind, parallel group trial conducted at University Hospital Basil Switzerland evaluating effect dulaglutide on smoking cessation.
- Patients were smokers 18–75 years old with >10 cigarettes smoked per day or a Fagerstrom score (scaled 0–10 with higher scores indicating more dependence on smoking) ≥5 recruited from the University Hospital Basel of Switzerland who were willing to quit and receive varenicline.
- Patients were excluded with pregnancy, prior GLP-1 use, severe renal impairment, and unstable psychiatric illness.
- Patients were mean age of 42 years old, 61% identified as female, average cigarettes per day was 20, average pack year history was 20 and average alcohol consumption was three standard alcohol drinks per week.
- The intervention group received Dulaglutide 0.75 mg subcutaneous week one, then 1.5 mg subcutaneous weekly during weeks 2–12 in addition to smoking cessation program with varenicline (dosed per national standard dosing guidelines) and behavioral counseling.
- The comparison group received a placebo saline 0.5 mL injection weekly as well as the smoking cessation program with varenicline and counseling.
- The primary outcome of alcohol intake at drinks/week was measured via a structured self-report at week 12, using standard of drinking 3 dL of beer, 1 dL of wine, and 0.3 dL of spirits approximating 10 g of ethanol.
- Secondary outcomes were assessed at 12 weeks and included total alcohol usage, heavy drinking defined as >7 drinks per week for females and >14 drinks per week for males.
- Correlation with smoking cessation defined by end-expiratory exhaled carbon monoxide of ≤10 ppm, and other use of drugs per self-report, and overall drug usage.

INTERVENTION (# IN THE GROUP): 76

COMPARISON (# IN THE GROUP): 75

FOLLOW-UP PERIOD: 12 weeks

RESULTS:

Primary Outcome –

- Patients treated with dulaglutide had lower alcohol consumption during attempts for smoking cessation compared to patients who received placebo (adjusted relative effect 0.71; 95% CI, 0.52–0.97).

Secondary Outcome –

- Patients treated with dulaglutide had no correlation with alcohol use and smoking cessation during attempts at smoking cessation compared to patients who received placebo at week 12.
- Patients treated with dulaglutide and considered initially to have heavy alcohol usage and undergoing attempt at smoking cessation did not have significant differences in alcohol usage compared to patients who received placebo.
- Patients treated with dulaglutide during attempts for smoking cessation had no difference in other drug usage compared to patients who received placebo.

LIMITATIONS:

- The secondary analysis for heavy alcohol usage was not powered to determine significant difference.
- The report of alcohol was self-reported and without biomarker confirmation.
- The study was limited to 12-week of follow-up data and more data is needed to determine long-term efficacy.

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