GOOD EVIDENCE MATTERS

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FPIN
Family Physicians Inquiries Network

Volume 6 Issue 28

Ironing Out Anemia: Can One IV Dose Outperform Daily Pills?

Single-dose Intravenous Iron vs Oral Iron for Treatment of Maternal Iron Deficiency Anemia: A Randomized Clinical Trial

Derman RJ, Bellad MB, Somannavar MS, et al. Single-dose Intravenous Iron vs Oral Iron for Treatment of Maternal Iron Deficiency Anemia: A Randomized Clinical Trial. *Am J Obstet Gynecol*. 2025;233(2):120.e1-120.e18. doi:10.1016/j.ajog.2025.01.037

KEY TAKEAWAY: Single-dose intravenous ferric carboxymaltose reduces low-birth-weight (LBW) risk compared with oral iron, and both IV formulations improve treatment response and reduce rescue therapy use. These results support single-dose IV iron as an efficient option for maternal iron deficiency anemia.

STUDY DESIGN: Multicenter, three-arm, semi-blind randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Maternal iron deficiency anemia is common and associated with complications such as low birth weight and preterm birth, and oral iron remains the recommended first-line therapy. Prior studies comparing IV and oral iron show mixed or low-quality evidence, particularly regarding single-dose IV formulations in early pregnancy. Determining whether IV iron improves maternal and neonatal outcomes is clinically important. This study evaluated whether single-dose IV iron is superior to oral iron in reducing low birth weight and improving anemia.

PATIENTS: Pregnant patients 18–40 years old with singleton pregnancies

INTERVENTION: Single-dose IV ferric carboxymaltose and single-dose IV ferric derisomaltose

CONTROL: Oral ferrous sulfate

PRIMARY OUTCOME: LBW and maternal nonanemic state (NAS)

Secondary Outcomes: Hemoglobin (Hgb) change, iron indices including serum transferrin saturation (TSAT) and ferritin, nonresponse to therapy, need for rescue therapy, use of predelivery transfusion, nonstudy iron use, pregnancy loss, preterm birth, small for gestational age (SGA), neonatal morbidity, safety concerns

METHODS (BRIEF DESCRIPTION):

- Pregnant individuals 18–40 years old with singleton pregnancies at 14–17 weeks and moderate iron deficiency anemia were enrolled. Major exclusions included fetal anomalies, hemoglobinopathies, cardiovascular disease, and contraindications to iron therapy.
- Participants were randomized to single-dose IV ferric carboxymaltose (20 mg/kg, max 1,000 mg), single-dose IV ferric derisomaltose (20 mg/kg, max 1,000 mg), or oral ferrous sulfate 60 mg twice daily; clinicians and participants knew oral vs IV assignment but were blinded to the specific IV formulation.
- IV doses were administered once, and oral iron continued through delivery. All participants received folic acid and routine anthelminthic treatment.
- Hgb and iron indices were measured at 20 weeks through delivery, and serum phosphate was monitored in IV recipients.
- The primary outcomes assessed the following:
  - LBW defined as <2,500 g within 72 hours
  - Maternal NAS defined as Hgb >11.0 g/dL at 30-34 weeks or at delivery
- Secondary outcomes included change in Hgb, iron indices including serum TSAT and ferritin, treatment nonresponse, need for rescue therapy or transfusion, pregnancy loss, preterm birth, SGA infants, neonatal morbidity, and safety outcomes assessed through delivery and six-week postpartum.

INTERVENTION (# IN THE GROUP):

- Ferric carboxymaltose: 1,462
- Ferric derisomaltose: 1,456

COMPARISON (# IN THE GROUP): 1,450

FOLLOW-UP PERIOD: From randomization at 14–17 weeks gestation through delivery to six weeks postpartum

RESULTS:

Primary Outcome –

- IV ferric carboxymaltose reduced risk of LBW compared to oral iron (25% vs 29%, respectively; relative risk [RR] 0.87; 98% CI, 0.75–0.99).

- IV ferric derisomaltose did not significantly reduce the risk of LBW compared to oral iron (29% vs 29%, respectively; RR 0.98; 98% CI, 0.86–1.1).
- There was no difference in maternal NAS for ferric derisomaltose and ferric carboxymaltose compared to oral iron:
    - IV ferric derisomaltose (RR 1.1; 99.95% CI, 0.98–1.2)
    - IV ferric carboxymaltose (RR 1.1; 99.95% CI, 0.97–1.2)

Secondary Outcome –

- Hgb values were higher in both IV groups compared to oral iron at visits five, six, and seven (20–34 weeks gestation), and no difference at visits eight and nine (delivery and 6 weeks postpartum).
    - IV ferric derisomaltose
        - Visit 5 (MD 0.47; 95% CI, 0.39–0.54)
        - Visit 6 (MD 0.47; 95% CI, 0.39–0.56)
        - Visit 7 (MD 0.32; 95% CI, 0.23–0.40)
    - IV ferric carboxymaltose
        - Visit 5 (MD 0.40; 95% CI, 0.32–0.47)
        - Visit 6 (MD 0.41; 95% CI, 0.33–0.49)
        - Visit 7 (MD 0.28; 95% CI, 0.19–0.37)
- Iron indices including TSAT and ferritin were higher at visit five and six (20–30 weeks gestation) compared to oral iron. Iron indices were similar at visit 9 (6 weeks postpartum). Iron indices were not assessed at delivery.
    - TSAT with IV ferric derisomaltose
        - Visit 5 (geometric mean ratio [GMR] 1.3; 95% CI, 1.3–1.4)
        - Visit 6 (GMR 1.2; 95% CI 1.1–1.2)
    - TSAT with IV ferric carboxymaltose
        - Visit 5 (GMR 1.3; 95% CI, 1.3–1.4)
        - Visit 6 (GMR 1.2; 95% CI, 1.1–1.2)
    - Ferritin with IV ferric derisomaltose
        - Visit 5 (GMR 3.3; 95% CI, 3.1–3.5)
        - Visit 6 (GMR 1.6; 95% CI, 1.5–1.7)
    - Ferritin IV ferric carboxymaltose
        - Visit 5 (GMR 3.6; 95% CI, 3.4–3.9)
        - Visit 6 (GMR 1.7; 95% CI, 1.6–1.9)
- Treatment nonresponse was lower in IV groups compared to oral iron.
    - IV ferric derisomaltose (RR 0.53; 95% CI, 0.47–0.60)
    - IV ferric carboxymaltose (RR 0.52; 95% CI, 0.52–0.66)
- Rescue therapy was less frequent in IV ferric derisomaltose group compared to oral iron (RR 0.25; 95% CI, 0.11–0.54), while IV ferric carboxymaltose was not significant.
- Predelivery transfusion was less frequent in IV groups compared to oral iron.
    - IV ferric derisomaltose (RR 0.22; 95% CI, 0.08–0.57)
    - IV ferric carboxymaltose (RR 0.26; 95% CI, 0.11–0.64)
- Use of nonstudy iron was lower in the IV groups compared to oral iron.
    - IV ferric derisomaltose (RR 0.29; 95% CI, 0.23–0.36).
    - IV ferric carboxymaltose (RR 0.32; 95% CI, 0.26–0.40)
- Pregnancy loss was lower in the IV ferric carboxymaltose compared to the oral iron (RR 0.63; 95% CI, 0.40–0.98), but not statistically significant for IV ferric derisomaltose.
- Preterm birth, SGA infants, neonatal death, and maternal complications (such as hemorrhage and hypertensive disorders) were not statistically significant across groups.

LIMITATIONS:

- Partial blinding may have introduced bias.
- Conducting the trial in rural and semi-urban India limits generalizability.
- Secondary outcomes were not powered for statistical significance.
- Oral iron adherence was self-reported.
- Rescue therapy decision varied across sites.
- Despite randomization, the study did not stratify by anemia severity beyond inclusion criteria.

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Melt the Fat, Fix the Liver: How GLP-1s Might Be the MASH Game-Changer

Comparative Effectiveness of GLP-1 Receptor Agonists and Dual Agonists in the Treatment of Patients with Metabolic Dysfunction Associated Steatohepatitis: A Systematic Review and Meta-Analysis

Li M, Hu J, Han Chin Y, Chew HSJ, Wang W. Comparative Effectiveness of GLP-1 Receptor Agonists and Dual Agonists in the Treatment of Patients with Metabolic Dysfunction Associated Steatohepatitis: A Systematic Review and Meta-analysis. *Front Endocrinol (Lausanne)*. 2025;16:1681965. Published 2025 Oct 8. doi:10.3389/fendo.2025.1681965

KEY TAKEAWAY: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and dual agonists significantly improve metabolic dysfunction-associated steatohepatitis (MASH) and hepatic fibrosis compared to placebo in middle-aged patients. While they improve comorbid cardiovascular dyslipidemia, achieving >10% weight loss crucially determines the overall effectiveness of these treatments.

STUDY DESIGN: Systematic review and meta-analysis of six qualitative randomized controlled trials (RCTs) (N=1,726)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to large variation in patient population, treatment duration, and fewer eligible studies limiting generalizability)

BRIEF BACKGROUND INFORMATION: GLP-1 RAs and dual agonists are approved for treatment of type 2 diabetes (T2D) and obesity. They significantly reduce body weight and show histological improvements in patients with MASH. However, there is limited histological evidence of their effectiveness in improving hepatic fibrosis as well as their impact on cardiovascular parameters. This study investigated how the degree of weight loss (specifically the ≥10% threshold) achieved with GLP-1s impacts hepatic fibrosis, LDL-C, and cardiovascular risk in patients with MASH.

PATIENTS: Participants 43–65 years old with biopsy-confirmed MASH and comorbid cardiovascular risk factors and T2DM

INTERVENTION: GLP-1 RAs and dual agonists

CONTROL: Placebo

PRIMARY OUTCOME: Histological resolution in MASH without worsening hepatic fibrosis

Secondary Outcome: Body weight, changes in cardiometabolic parameters

METHODS (BRIEF DESCRIPTION):

- Studies were selected after an extensive systematic search using five electronic databases and 1,681 registers. 1,549 records were screened and 76 reports were sought for retrieval. Of those reports, 37 were found eligible for personal screening and subsequently, six studies were chosen for inclusion.
- The mean age of participants was 54±11 years old with mean body mass index (BMI) of 36±6.3 kg/m^2. Patients were comprised of 43% males and 57% females. Among MASH patients that were biopsied, 36% were classified as F2 and 56% as F3 for hepatic fibrosis. 50% of patients had comorbid T2D.
- Studies that did not utilize liver biopsy to determine severity of fibrosis were excluded as this is the gold standard for diagnosing MASH.
- Patients received four various forms of GLP-1RAs and dual agonists as well as different durations of treatment. Patients grouped based on type of GLP-1, dose, and duration of therapy.
- Patients in control group received placebo in the same frequency, route and duration according to their respective subgroup analyses as intervention group.
- Primary Outcome: Resolution of MASH without worsening hepatic fibrosis, an improvement with ≥1-stage improvement without worsening MASH, and concurrent resolution of MASH with ≥1-stage improvement in hepatic fibrosis.
- Secondary Outcomes: Changes in lipid profiles (LDL-C, total cholesterol [TC], and Triglycerides [TG]), hepatic enzyme levels (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), and body weight.
- Subgroup analysis further examined the primary and secondary outcomes in relation to the amount of weight loss, specifically <10% (GLP-1 RAs) and ≥10% (DAs).
- Statistical analyses were completed using the Stata version 18 and Review Manager (RevMan) version 5.4.1.

- Two independent researchers assessed bias across six domains using the Cochrane Risk of Bias Tool 2.0 (RoB-2), covering selection, performance, detection, attrition, reporting, and other potential bias sources. All included studies were rated as high quality with low risk of bias.

INTERVENTION (# IN THE GROUP): 1,208
COMPARISON (# IN THE GROUP): 518

FOLLOW-UP PERIOD: Variable (ranged from 48–72 weeks)

RESULTS:

Primary Outcome –

- GLP-1RAs and dual agonists improved MASH resolution without worsening hepatic fibrosis compared to placebo (6 studies, N=1,726; odds ratio [OR] 4.5; 95% CI, 3.7–5.5; I^2=52%).
- GLP-1RAs and dual agonists improved hepatic fibrosis by ≥1-stage without worsening MASH compared to placebo (6 studies, N=1,726; OR 1.8; 95% CI, 1.5–2.2; I^2=23%).
- GLP-1RAs and dual agonists achieved both MASH resolution and a ≥1-stage improvement in hepatic fibrosis compared to placebo (6 studies, N=1,726; OR 7.4; 95% CI, 3.0–18; I^2=82%).
- In the subgroup analysis of MASH resolution without worsening of hepatic fibrosis, the <10% weight loss group (GLP-1RAs) showed statistical improvement (5 studies, n=926; OR 3.9; 95% CI, 2.7–5.8; I^2=23%), whereas the ≥10% (DAs) weight loss group demonstrated a more robust response (5 studies, n=926; OR 23; 95% CI, 17–30; I^2=0.0%) suggesting homogeneity across the studies.
- For a ≥1-stage improvement in hepatic fibrosis without worsening MASH, GLP-1RAs and DAs showed no statistical improvement in patients with <10% weight loss, however in patients with ≥10% weight loss, there was a significant improvement appreciated (5 studies, n=926; OR 9.6; 95% CI, 4.0–15; I^2=0.0%).

Secondary Outcome –

- GLP-1RAs and dual agonists reduced body weight compared to placebo (6 studies, N=1,726; weighted mean difference [WMD] –8.9 kg; 95% CI, –11 to –6.9 kg; I^2=72%).
- GLP-1RAs and dual agonists improved TC compared to placebo (6 studies, N=1,726; WMD –4.2 mmol/L; 95% CI, –13 to –4.8; I^2=85%).
- GLP-1RAs and dual agonists improved TG compared to placebo (6 studies, N=1,726; WMD –18 mmol/L; 95% CI, –22 to –13; I^2=27%).
- GLP-1RAs and dual agonists improved in hepatic enzymes compared to placebo, specifically ALT and AST.
  - ALT (6 studies, N=1,726; WMD –32 U/L; 95% CI, –38 to –25, I^2=50%)
  - AST (6 studies, N=1,726; WMD –26 U/L; 95% CI, –33 to –20; I^2=64%)
- GLP-1RAs and dual agonists did not show a significant improvement in LDL-C.
- In the subgroup analysis assessing LDL-C, the ≥10% weight loss group (DAs) showed a significant reduction (5 studies, n=926; OR –3.5, 95% CI, –10 to –3.2; I^2=63%).
  - Weight loss of <10% (GLP-1RAs) was not associated with a significant improvement in LDL-C.

LIMITATIONS:

- Combined that GLP-1RAs are an extremely new medication and patients required a biopsy for diagnosis of MASH there were fewer eligible studies which limited generalizability.
- Large variations in patient populations included in each study placed high risk for confounding variables, despite methods to limit this impact.
- Large variation reviewed between types of GLP-1RAs along with duration of treatment

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Change in Weight Status from Childhood to Young Adulthood and Risk of Adult Coronary Heart Disease

Ohlsson C, Bramsved R, Bygdell M, Martikainen J, Rosengren A, Kindblom JM. Change in Weight Status from Childhood to Young Adulthood and Risk of Adult Coronary Heart Disease. *JAMA Pediatr*. 2026;180(2):179-186. doi:10.1001/jamapediatrics.2025.4950

KEY TAKEAWAY: Weight loss from an overweight body mass index (BMI) in childhood to a normal BMI in young adulthood may reduce the risk of adult coronary heart disease (CHD) to be equivalent to individuals with a normal BMI in both childhood and adulthood, while weight gain from a normal childhood BMI to an overweight BMI in adulthood is associated with the highest risk of adult CHD.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: CHD is the leading cause of death in men and women across the world. With the obesity epidemic in developed nations such as the US, the medical advancements that have reduced CHD mortality in the last 50 years could be eclipsed. Current literature recognizes that increased BMI in childhood, even BMI above the 50th percentile and that is still considered "normal", increases the risk for cardiovascular events and heart failure (HF) in adulthood, but it is not known if achieving normal weight by young adulthood reduces this risk.

PATIENTS: Men and women in Swedish cohort

INTERVENTION: Overweight or obesity in childhood, young adulthood or both

CONTROL: Normal BMI in childhood and young adulthood

PRIMARY OUTCOME: Risk of CHD events in adulthood

METHODS (BRIEF DESCRIPTION):

- This was a retrospective analysis of linked data between the BMI Epidemiology Study (BEST) Gothenburg cohort (people residing in Gothenburg, Sweden born 1945–1968), which collects childhood BMI data; a National Patient Register in Sweden, with adulthood BMI data; and the Swedish Cause of Death Registry, which collects data on adult CHD incidence and onset.
- Inclusion criteria were BEST cohort men and women who were followed from 22 years old until they were registered with a CHD diagnosis, death, migration, or until December 31, 2021.
- Exclusion criteria included individuals who did not have childhood and/or young adulthood BMI variables, and those who reached an endpoint before 22 years old (28% excluded).
- The cohort included 103,232 patients among whom 45% were women, 55% were men, and 86% were born in Sweden.
- The mean childhood BMI for the cohort was 16 kg/m^2 (SD 1.5) and mean young adulthood BMI was 21 kg/m^2 (SD 2.5).
- Childhood BMI values were taken at seven years old for girls and eight years old for boys and calculated using the International Obesity Task Force Cutoffs; a high BMI was defined as >85th percentile and low BMI was defined as <15th percentile.
- Young adult BMI values were defined for women at 18 years old and men at 20 years old as BMI >25 or >30 respectively.
- Three comparator groups included:
  - Overweight/obese BMI in both childhood and adulthood
  - Overweight/obese BMI in childhood and normal BMI in adulthood
  - Normal BMI in childhood and overweight/obese in adulthood
- The control group was comprised of those who had normal BMI in childhood and young adulthood.
- Outcomes were measured by the number of patients who experienced CHD events after 22 years old.
- Results were adjusted for sex, socioeconomic status, birth year and country of birth, and early and late CHD was defined as before and after either 44 years old or 58 years old.

INTERVENTION (# IN THE GROUP):

- Normal childhood BMI and overweight young adulthood BMI: 4,374
- Overweight childhood BMI and normal young adulthood BMI: 4,073

- Overweight childhood BMI and overweight young adulthood BMI: 2,375

COMPARISON (# IN THE GROUP): 92,161

FOLLOW-UP PERIOD: Mean of 38 years

RESULTS:

Primary Outcome –

- The cohort with overweight childhood BMI and normal weight in young adulthood had no difference in risk of CHD vs the comparison group (hazard ratio [HR] 0.98; 95% CI, 0.84–1.2).
- Overweight BMI in both childhood and young adulthood was associated with an increased risk of CHD vs the comparison group (HR 1.5; 95% CI, 1.3–1.8).
- Normal childhood BMI and subsequent overweight BMI in young adulthood had the highest risk of CHD vs the comparison group (HR 1.8; 95% CI, 1.7–2.0).

Secondary Outcome –

- Those with overweight BMI in both childhood and young adulthood were at the highest risk for early CHD <44 years old (HR 3.2; 95% CI, 2.1–4.9).
- Those with normal childhood BMI and overweight in young adulthood were at the highest risk for early CHD <58 years old (HR 2.0; 95% CI, 1.8–2.3).

LIMITATIONS:

- Because of limited variables in the dataset, authors could not adjust for lifestyle risk factors or comorbidities that could have confounded the results, including smoking.
- The population predominantly identified as White and severe obesity rates were low, which limits the study's generalizability.

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Well-Being Outcomes Among LQBTQ Older Adults

Older Adults in the United States: A Systematic Review

Preston R. Quality of Life among LGBTQ Older Adults in the United States: A Systematic Review. *J Am Psychiatr Nurses Assoc*. 2024;30(2):221-239. doi:10.1177/10783903221127697

KEY TAKEAWAY: The results demonstrate a gap in literature of a marginalized population that is rapidly growing. These results highlight that older LGBTQ adults may have a lower quality of life due to the discrimination they face, especially for those identifying as "double minorities."

STUDY DESIGN: Systematic review including 58 studies comprised of 44 surveys, 14 mixed qualitative and/or qualitative studies

LEVEL OF EVIDENCE: STEP 3 (downgraded due to systematic review of surveys, lack of statistical analysis, specificity of survey tools used, and poor assessment of the quality of studies)

BRIEF BACKGROUND INFORMATION: As the population in the United States continues to age, so does the number of older adults who identify with an LGBTQ identity. In addition to challenges the aging population faces, the LGTBQ population faces additional, unique challenges to their demographic. This systematic review identifies existing literature on how multiple unique psychosocial and socioeconomical changes affect the well-being of older lesbian, gay, bisexual, transgender, and queer (LGBTQ) adults.

PATIENTS: American or Canadian adults with an average minimal age of 50 who identify as part of the LGBTQ population

INTERVENTION: Quantitative and qualitative measures of quality of life

CONTROL: Cisgender and heterosexual, older adults

PRIMARY OUTCOME: Quality of life in older LGBTQ adults

METHODS (BRIEF DESCRIPTION):

- Preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines were used to perform a systematic review to include:
  - Studies that assessed outcomes for peer-reviewed, published studies in English between January 1, 2000 and December 31, 2020 that looked at quality of life within LQBTQ populations in older adults with a modal starting 50 years old in the United States or Canada.
  - Additional inclusion criteria specified that studies must have measured quantitative or qualitatively assessed at least one dimension of quality of life.
  - Cumulative index to nursing and allied health literature (CINAHL), PsychInfo, PubMed, and Scopus were the databases used for the literature search.
- Search terms were related to LGBTQ population status, older adult populations status, and quality of life outcomes.
  - A total of 77 LGBTQ-related search terms were used.
  - 12 search terms related to older adults were used.
  - Five search terms related to quality of life were used.
- Individual articles from the meta-analysis compared standardized quality-of-life measures in multiple groups including heterosexual middle and older adults, women, and heterosexual men, transgender younger and middle-aged adults, heterosexual adults with human immunodeficiency virus (HIV), middle-aged heterosexual women, cisgender individuals, and heterosexual adults.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Not available

RESULTS:

Primary Outcome –

- A lifetime history of discrimination was related to a worse general quality of life and loneliness (n=8).
- Anticipated discrimination, specifically form the medical community, was detrimental to the well-being of LGBTQ older adults (n=5).
- History of victimization with violence was related to negative quality of life outcomes (n=3).
- Internalized stigma played a factor in leading to poor quality of life (n=8).
- Identity affirmation showed a positive impact on late life quality of life (n=3).

- A small social support network was more likely to detrimentally affect quality of life in LGBTQ older adults compared to cis-gender older adults (n=13).
- There are mixed results on whether LGBTQ older adults have worse quality of life than cis-gender older adults, with some suggesting worse outcomes; factors including physical health problems, disability and low socioeconomic status affect both communities (n=18).
- Black and Hispanic LGBTQ older adults had worse quality of life outcomes and experienced more anti-LGBTQ discrimination compared with non-Hispanic White LGBTQ older adults (n=2).

LIMITATIONS:

- This study may have further benefitted from being a meta-analysis to further assess the data; there was no biostatistical review of evidence to compile and summarize results, assess for significance of results, or assess for heterogeneity of studies.
- "Quality of Life" is a broad term that may be interpreted differently; only five search terms related to quality of life were used in the methods.
- Despite study inclusion criteria specifying adults >50 years old, seven studies were included in the review that had age thresholds between 39–49 years old.
- This review looked at studies done only in the United States or Canada; different countries have different views of the LGBTQ populations.
- No formal appraisal of validity/evidence of articles included in the review; the methods would have benefitted from having an approach to appraise articles used to determine if they contained good evidence.

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Does High-Dose Influenza Vaccine Really Keep Older Adults Out of the Hospital?

High-Dose Influenza Vaccine to Reduce Hospitalizations
Pardo-Seco J, Rodríguez-Tenreiro-Sánchez C, Giné-Vázquez I, et al. High-Dose Influenza Vaccine to Reduce Hospitalizations. *N Engl J Med*. 2025;393(23):2303-2312. doi:10.1056/NEJMoa2509834

KEY TAKEAWAY: Adults who receive the high-dose influenza vaccine may have fewer hospitalizations for influenza and pneumonia compared to those who receive the standard dose vaccine.

STUDY DESIGN: Registry-based, open-label, randomized, active-controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to lack of blinding and low event rate)

BRIEF BACKGROUND INFORMATION: Influenza is a major cause of morbidity and mortality in older adults, but standard-dose inactivated influenza vaccine has lower effectiveness in preventing influenza in this population. High-dose influenza vaccine, containing four times the antigen of the standard formulation, is more effective against laboratory-confirmed influenza in adults ≥65 years old. However, it is unclear if high-dose influenza vaccine decreases hospitalizations compared to standard-dose vaccine in this target population.

PATIENTS: Adults 65–79 years old

INTERVENTION: High-dose inactivated influenza vaccine

CONTROL: Standard-dose influenza vaccine

PRIMARY OUTCOME: Composite of hospitalization due to influenza or pneumonia

Secondary Outcome: Hospitalization for cardiorespiratory disease, hospitalization for any cause, death from any cause

METHODS (BRIEF DESCRIPTION):

- The trial was a registry-based, open-label, randomized controlled trial that utilized health system data to assess hospitalization rates among adults vaccinated with either standard-dose or high-dose influenza vaccine.
- Participants were community dwelling adults 65–79 years old, excluding nursing home residents, in Galicia, Spain.
- Participants were 72 years old on average, 54% were men, 16% had hypertension, and 13% had chronic cardiovascular disease.
- Over two consecutive influenza seasons from 2023–2025, participants were randomly assigned in a 1:1 ratio to receive either high-dose or standard-dose inactivated influenza vaccine.
- The primary endpoint was a composite of hospitalization for influenza or pneumonia, identified through a patient data-linked Galician Health Services registry, which included hospitalization rates, mortality and International Classification of Diagnosis ICD-10 discharge diagnosis codes.
- The secondary endpoints were hospitalizations for influenza, pneumonia, cardiopulmonary disease, or any cause, and vaccine serious adverse events, defined as hospitalization or death.

INTERVENTION (# IN THE GROUP): 67,093

COMPARISON (# IN THE GROUP): 66,789

FOLLOW-UP PERIOD: May 31 following influenza vaccination

RESULTS:

Primary Outcome –

- Due to a low event rate, the trial failed to meet its expected power, and thus only descriptive events are reported.
- Fewer participants in the high-dose group than the standard dose group were hospitalized due to influenza or pneumonia (0.26% vs 0.34%, respectively; relative vaccine effectiveness 24%; 95% CI, 6.6–38).

Secondary Outcome –

- Fewer participants were hospitalized for influenza in the high-dose group than in the standard-dose group (relative vaccine effectiveness 32%; 95% CI, 5.0–51).
- Fewer participants were hospitalized for cardiopulmonary disease in the high-dose group than in the standard dose group (relative vaccine effectiveness 8.4%; 95% CI, 0.1–16).
- There was no difference in rates of hospitalizations for pneumonia, any cause, or death between the two groups.
- Similar numbers of participants experienced serious adverse events in the high-dose group (2,953

patients) and the standard-dose group (2,983 patients).

LIMITATIONS:

- The study lacked blinding.
- The study lacked power to detect a difference should one exist as it did not reach the expected number of events, and therefore no statistical testing was performed.
- The study was done in a single region Galicia, Spain, and the results may not be generalized to the outside population.
- The study excluded high-risk adults like nursing home residents and adults >79 years old.
- The study did not compare deaths due influenza, nor did it compare relevant outcomes from hospitalizations for influenza.
- Patients who died within 14 days of vaccination were excluded.

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