GOOD EVIDENCE MATTERS

# GEMs of the Week

## SPOTLIGHT

### Antipsychotic Medications Increase Blood Glucose: A Sweet Deal?

### Does a Short Lifestyle Intervention Improve Health Behaviors in Healthy Young Men?

### Antidepressants:

Lifting Spirits, Lifting the Scale? What 6 Years of Data Reveal

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# Antipsychotic Medications Increase Blood Glucose: A Sweet Deal?

**Antipsychotic Drugs and Dysregulated Glucose Homeostasis: A Systematic Review and Meta-Analysis**

Smith ECC, Agarwal SM, Panganiban KJ, et al. Antipsychotic Drugs and Dysregulated Glucose Homeostasis: A Systematic Review and Meta-Analysis. *JAMA Psychiatry*. 2025;82(10):977-991. doi:10.1001/jamapsychiatry.2025.2240



**KEY TAKEAWAY:** Antipsychotic drugs (APs) increase the risk of elevated fasting glucose, fasting insulin, and hemoglobin A1C (HbA1C) in adolescents and adults with severe mental illness and healthy volunteers.

**STUDY DESIGN:** Systematic review and meta-analysis of 127 randomized controlled trials (RCTs) (N=57,893)

**LEVEL OF EVIDENCE:** STEP 1

**BRIEF BACKGROUND INFORMATION:** APs are regularly prescribed for mental health conditions. APs are known to cause weight gain and changes to blood glucose. Researchers investigated if the changes in blood glucose are independent of the weight gain that patients experience.

**PATIENTS:** Adolescents and adults with severe mental illness and healthy volunteers

**INTERVENTION:** APs

**CONTROL:** Placebo or no intervention

**PRIMARY OUTCOME:** Changes in fasting glucose, fasting insulin, and HbA1C

Secondary Outcome: Changes in insulin resistance, changes and risk of hyperglycemia

**METHODS (BRIEF DESCRIPTION):**

- The researchers used multiple clinical databases to collect data from RCTs about antipsychotic drugs and blood glucose.
- Articles were searched from the earliest database available date until February 2025.
- Of 163 studies that met selection criteria, 127 had data that could be meta-analyzed. 12% focused on those who were 10–17 years-olds, 86% focused on individuals who were 18–64 years old, and 2% focused on adults who were ≥65 years old.
- The study population included patients with severe mental illness, the majority of which had schizophrenia spectrum disorder or bipolar disorder, and healthy volunteers were either exposed to Aps or placebo.
- Studies included patients with or without previous AP exposure. A total of 15 different AP drugs were included in the review including aripiprazole, lurasidone, quetiapine, and ziprasidone.
- Studies were excluded if they had patients with type 1 diabetes and any disease with symptoms of weight gain or weight loss.
- Intervention and control groups were compared by using mean difference, measured in mg/dL or % change in HbA1C.
- Changes in insulin were measured using homeostasis model assessment-estimated insulin resistance (HOMA-IR).
- Risk of hyperglycemia was measured using odds ratio (OR).
- Meta-regression analysis was used to analyze the data.
- Researchers assessed heterogeneity and risk of bias.

**INTERVENTION (# IN THE GROUP):**

- Fasting glucose: 21,440
- A1C: 8,221
- Fasting insulin: 8,384

**COMPARISON (# IN THE GROUP):**

- Fasting glucose: 11,141
- A1C: 4,510
- Fasting insulin: 4,197

**FOLLOW-UP PERIOD:** Mean 11 weeks (median 6 weeks)

**RESULTS:**

Primary Outcome –

- AP treatment increased fasting glucose compared to placebo (96 studies, n=32,581; mean difference [MD] 0.72 mg/dL; 95% CI, 0.54–1.1).
- AP treatment increased fasting insulin compared to placebo (37 studies, n=12,581; MD 0.72 mg/dL; 95% CI, 1.3–2.6).
- AP treatment increased HbA1C compared to placebo (30 studies, n=12,731; MD 0.04%; 95% CI, 0.02–0.05).

Secondary Outcome –

- AP treatment increased drug resultant hyperglycemia compared to placebo (36 studies, n=7,722; odds ratio [OR] 1.3; 95% CI, 1.04–1.6).

- AP treatment did not significantly change insulin resistance compared to placebo.

**LIMITATIONS:**

- There was a loss of individual differences in antipsychotic drugs associated with combining results.
- There was an unequal number of studies for each antipsychotic drug.
- The outcomes were combined, regardless of duration of treatment and previous exposure to antipsychotic drugs.
- Most studies focused on individuals who had either schizophrenia spectrum disorder or bipolar disorder, with fewer studies for healthy individuals and those with major depressive disorder.
- Heterogeneity data is not reported on result outcomes.
- The overall results, while statistically significant, may not yield clinical significance.

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# Does a Short Lifestyle Intervention Improve Health Behaviors in Healthy Young Men?

**Efficacy of a Short-Term Lifestyle Change Intervention in Healthy Young Men: The FASt Randomized Controlled Trial**

Donato F, Ceretti E, Viola GCV, et al. Efficacy of a Short-Term Lifestyle Change Intervention in Healthy Young Men: The FASt Randomized Controlled Trial. *Int J Environ Res Public Health*. 2023;20(10):5812. Published 2023 May 13. doi:10.3390/ijerph20105812



**KEY TAKEAWAY:** A short, individualized lifestyle intervention improves healthy eating behaviors in healthy young men.

**STUDY DESIGN:** Single center randomized controlled trial (RCT)

**LEVEL OF EVIDENCE:** STEP 2

**BRIEF BACKGROUND INFORMATION:** Young adults often have poor dietary habits that can adversely affect long-term cardio metabolic health. Short, tailored lifestyle programs may improve diet quality and activity, this study tested whether a four-month lifestyle program including, motivational counseling and exercise advice could improve diet adherence and nutrient intake in healthy young men.

**PATIENTS:** Healthy men 20 years old

**INTERVENTION:** Four-month lifestyle program

**CONTROL:** Written information

**PRIMARY OUTCOME:** Mediterranean diet adherence (PREDIMED score)

Secondary Outcome: Food/nutrient intake, physical activity, and changes in macro-/micronutrient consumption

**METHODS (BRIEF DESCRIPTION):**

- Healthy young men, who were non-smokers, had normal weight and normal labs, and no chronic diseases or metabolic disorders were recruited from local universities.
- Participants were randomly divided in a 1:1 ratio into the intervention and control group.
- The intervention group received personalized Mediterranean diet plans prepared by nutritionists, physical activity guidance, motivational counseling, provision of some organic food samples with follow-up visits at four and eight months.
- The control group received only a leaflet with basic information about the Mediterranean diet (no follow-up or counseling).
- The primary outcome measured Mediterranean diet adherence using the PREDIMED (Prevention with the Mediterranean Diet) questionnaire. Scores range from 0–14, with higher scores indicating better adherence to the Mediterranean diet.
- The secondary outcome measured the following:
  - Food and nutrient intake were measured in gm/day using the European Prospective Investigation into Cancer and Nutrition Food Frequency Questionnaire (EPIC-FFQ). Improvement was indicated by increased intake of Mediterranean-type foods and reduced intake of less healthy foods.
  - Physical activity was measured using the International Physical Activity Questionnaire (IPAQ) and reported as metabolic equivalent of task minutes per week (MET-minutes/week), where higher values indicate greater physical activity.
  - Macro- and micronutrient intake was calculated from the EPIC-FFQ and reported as daily intake values, with improvement defined as movement toward recommended dietary intake ranges.
  - Outcomes were measured at baseline (t0), four months (t4), and eight months (t8).
- The researchers used an analysis of covariance (ANCOVA) to compare changes between the intervention and control groups, adjusting for baseline values to account for any initial differences.
- A per-protocol analysis was performed, which included only participants who completed all study visits and questionnaires at zero, four, and eight months.

**INTERVENTION (# IN THE GROUP):** 66

**COMPARISON (# IN THE GROUP):** 63

**FOLLOW-UP PERIOD:** Four months and eight months

**RESULTS:**

Primary Outcome –

- The lifestyle intervention improved Mediterranean diet adherence compared to the control group at four and eight months:

- Four months (9.9 vs 7.0; *p*<.001).
- Eight months (9.1 vs 7.7; *p*<.001).

Secondary Outcome –

- The lifestyle intervention increased vegetable intake compared with control at four and eight months.
  - Four months (208 vs 166 g/day; *p*<.0001)
  - Eight months (191 vs 164 g/day; *p*=.0021)
- The lifestyle intervention increased fruit intake compared with control at four and eight months.
  - Four months (317 vs 246 g/day; *p*=.0003)
  - Eight months (296 vs 217 g/day; *p*=.0003)
- The lifestyle intervention increased legume intake compared with control at four and eight months.
  - Four months (36 vs 25 g/day; *p*<.0001)
  - Eight months (30 vs 24 g/day; *p*=.0011)
- The lifestyle intervention reduced red meat intake compared with control at four and eight months.
  - Four months (58 vs 83 g/day; *p*<.0001)
  - Eight months (64 vs 78 g/day; *p*=.0428)
- The lifestyle intervention reduced saturated fat intake compared with control at four and eight months.
  - Four months (31 vs 37 g/day; *p*<.0001)
  - Eight months (29 vs 36 g/day; *p*<.0001).
- Both groups reported a small increase in physical activity, but the difference between them was insignificant.

**LIMITATIONS:**

- The study was not blinded because it was a lifestyle program, so participants knew which group they were in. This could have influenced how they reported their diet and activity.
- The researchers analyzed only participants who completed all parts of the study, which may cause bias since those who dropped out might have had different results.
- The study lasted only four months, so it's unclear whether the healthy habits would continue long-term.
- The study included only young men, so the results may not apply to women or older adults.
- Diet and activity were measured using self-reported questionnaires, which can be inaccurate because people may forget details or report what they think sounds better.
- Dropouts were higher in the control group (17% at 4 months, 30% at 8 months) compared with the intervention group (7% and 21%, respectively).

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# Antidepressants: Lifting Spirits, Lifting the Scale? What 6 Years of Data Reveal

**Trajectories of Antidepressant Use and 6-Year Change in Body Weight: A Prospective Population-Based Cohort Study**

Lassale C, Lugon G, Hernáez Á, et al. Trajectories of Antidepressant Use and 6-year Change in Body Weight: A Prospective Population-based Cohort Study. *Front Psychiatry*. 2024;15:1464898. Published 2024 Dec 24. doi:10.3389/fpsyt.2024.1464898



**KEY TAKEAWAY:** Repeated or any use of antidepressants leads to significantly greater weight gain and increases risk of obesity compared to non-use in a Spanish population.

**STUDY DESIGN:** Prospective cohort study

**LEVEL OF EVIDENCE:** STEP 3

**BRIEF BACKGROUND INFORMATION:** Antidepressant use is widespread and has been linked to weight gain, a common and often concerning side effect for patients and clinicians. The relationship between depression, antidepressant use, and obesity is complex and potentially bidirectional, creating uncertainty around causation. Short-term trials suggest certain antidepressants, especially selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs), may contribute to weight changes. This study aimed to examine how different long-term patterns of antidepressant use are associated with changes in body weight and the risk of developing obesity.

**PATIENTS:** Spanish adults

**INTERVENTION:** Antidepressant use

**CONTROL:** No antidepressant use

**PRIMARY OUTCOME:** Percent change in body weight
Secondary Outcome: Incidence of obesity in those who were not obese at baseline

**METHODS (BRIEF DESCRIPTION):**

- Inclusion criteria included adults (average age 56 years old, 54% women) free of terminal disease, not institutionalized, and had lived in the area for ≥6 months from the REGICOR population-based cohort in northeastern Spain, with data collected at two time points approximately six years apart.
- Patients were excluded from the study if they were outside of the study region, defined as having serious disease, death during the study period, were lost to follow up, or were unavailable/decided not to participate.
- Participants self-reported the use of antidepressants including SSRIs, norepinephrine and dopamine reuptake inhibitors (NDRIs), and TCAs categorized into four trajectories:
  - Never used
  - Started using (new use at follow-up)
  - Stopped using (initial use discontinued)
  - Continued use (repeated use at both time points)
- Outcomes were measured at both baseline and follow-up visits. Nurses recorded participants' body weight and height, which were used to calculate body mass index (BMI).
- The primary outcome was percent change in body weight, which was calculated as the difference in weight between follow-up and baseline divided by baseline weight, expressed as a percentage.
- The secondary outcome was incidence of obesity, which was defined as having a body mass index (BMI) ≥30 kg/m² at follow-up in participants who were not obese at baseline.
- Statistical analysis adjusted for results according to four models:
  - Model 0: Age and sex as covariables
  - Model 1: Age, sex, educational level, civil status, smoking, mediterranean diet score, physical activity, diabetes, and hypertension as covariables
  - Model 2: Further included depression status
  - Model 3: Further included baseline BMI

**INTERVENTION (# IN THE GROUP):** 3,127

**COMPARISON (# IN THE GROUP):** 2,614

**FOLLOW-UP PERIOD:** Six years

**RESULTS:**

Primary Outcome –

- Antidepressant use was associated with greater weight gain compared to no antidepressant use.
- Initial users experienced significantly greater weight gain than non-users (β 1.8%; 95% CI, 0.62–3.0).
- New users gained significantly more weight than non-users (β 2.2%; 95% CI, 1.1–3.3).

- Repeated users gained significantly more weight than non-users (β 2.0%; 95% CI, 0.78–3.2).

Secondary Outcome –

- Repeated antidepressant users were more likely to develop obesity than non-users (odds ratio [OR] 2.0; 95% CI, 1.03–3.9).
- Initial users and new users did not demonstrate a statistically significant increase in incident obesity compared with non-users.

**LIMITATIONS:**

- Self-reported antidepressant use may lead to misclassification; participants could have underreported or inaccurately reported use, especially between visits.
- No continuous tracking of medication uses as antidepressant use was only assessed at two time points, so intermittent or short-term use between visits was not captured.
- Lack of blinding as outcome assessors were not blinded to exposure status, introducing possible measurement bias.
- Exposure grouped broadly as all antidepressants were combined into one group, with limited analysis by specific drug classes (e.g., SSRIs, TCAs), even though weight gain can vary by type.
- Residual confounding as although many factors were adjusted for (e.g., depression, diet, activity), unmeasured or unknown confounders could still influence the results.
- Generalizability as the study population (middle-aged, White, Spanish adults with universal healthcare) does not reflect all communities.

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