GEMs
GOOD EVIDENCE MATTERS

# GEMs of the Week

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## What's in this week's issue?

**Week of September 2 - 6, 2024**

**SPOTLIGHT:**
**Food for Thought: Probiotics as a Supplement Treatment for Depression**

- Can Creatine Give You a Leg Up on Repeated Treadmill Sprints?
- Redefining the Status Quo: Opt-Out Tobacco Cessation
- Infertility Treatment and Autism Risk

# Food for Thought: Probiotics as a Supplement Treatment for Depression

**Acceptability, Tolerability, and Estimates of Putative Treatment Effects of Probiotics as Adjunctive Treatment in Patients with Depression: A Randomized Clinical Trial**

Nikolova VL, Cleare AJ, Young AH, Stone JM. Acceptability, Tolerability, and Estimates of Putative Treatment Effects of Probiotics as Adjunctive Treatment in Patients With Depression: A Randomized Clinical Trial. *JAMA Psychiatry.* 2023;80(8):842-847. doi:10.1001/jamapsychiatry.2023.1817

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**KEY TAKEAWAY:** Adjunctive probiotic therapy is tolerable and improves depression severity in patients at four weeks, but not at eight weeks in individuals diagnosed with major depressive disorder (MDD) who are already taking anti-depressant medication.

**STUDY DESIGN:** Double-blind, randomized, placebo-controlled trial

**LEVEL OF EVIDENCE:** STEP 2

**BRIEF BACKGROUND INFORMATION:** When treating MDD, anti-depressants such as selective serotonin reuptake inhibitors (SSRIs) are often the first treatment of choice. However, for patients who have incomplete relief of their depressive symptoms on this standard therapy, the microbiota-gut-brain axis has become a target of recent research efforts to find possible adjunctive treatments. Probiotics are being studied as an adjoining therapy for MDD alongside the standard SSRIs, and the assessment of their tolerability by patients is essential for clinical applications.

**PATIENTS:** Adults with MDD taking anti-depressant medication

**INTERVENTION:** Probiotic capsules

**CONTROL:** Placebo

**PRIMARY OUTCOME:** Depression severity changes

Secondary Outcome: Treatment adherence, tolerability

**METHODS (BRIEF DESCRIPTION):**

- Adults 18–55 years old with MDD taking an anti-depressant medication for at least six weeks were included in the study.
- Patients were blinded and randomized 1:1 to one of the following treatments:
  - Four probiotic capsules taken daily for eight weeks.
  - Four placebo capsules taken daily for eight weeks.
- Patients had a follow-up at baseline, week four, and week eight to obtain depression scores and assess tolerability.
- Depression severity was measured using the Hamilton Depression Rating Scale (HAMD-17). Scores range from 0–50, with higher scores indicating more severe depression.
- Tolerability to the probiotics was measured by gathering information on side effects and adverse reactions.
- Adherence was measured by capsule counting, which revealed which participants took their assigned treatments as instructed and which did not.

**INTERVENTION (# IN THE GROUP):** 24

**COMPARISON (# IN THE GROUP):** 25

**FOLLOW-UP PERIOD:** Eight weeks

**RESULTS:**

Primary Outcome –

- Depression severity improved to a greater extent at four weeks in the probiotic group compared to the placebo group (mean score 11 vs 14, respectively; *P*=.04).
- Depression severity was not statistically significant at eight weeks in the probiotic group compared to the placebo group (mean score 8.8 vs 11, respectively; *P*=.19).

Secondary Outcome –

- The probiotic and matching placebo were well-tolerated, as the participants adhered to their assigned interventions with 97% of doses adhered to.
- No serious adverse reactions occurred. 16 participants reported having adverse effects, which encompassed brief nausea and indigestion.
- Gastrointestinal symptom scores decreased in both groups and were not significant between groups.

**LIMITATIONS:**

- A conclusion cannot be made on whether the improvements in depression severity were a result of the interaction between anti-depressant

medication and the probiotic. Further studies are needed to provide more data.

- Patient adherence was measured by capsule counting, which may not reflect true adherence.

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# Can Creatine Give You a Leg Up on Repeated Treadmill Sprints

**Effects of Oral Creatine Supplementation on Power Output During Repeated Treadmill Sprinting**

Bogdanis GC, Nevill ME, Aphamis G, et al. Effects of Oral Creatine Supplementation on Power Output During Repeated Treadmill Sprinting. *Nutrients*. 2022;14(6):1140. Published 2022 Mar 8. doi:10.3390/nu14061140

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**KEY TAKEAWAY:** Supplemental creatine may increase power and speed in the second half of short sprinting in healthy, active males.

**STUDY DESIGN:** Double-blind, randomized control trial

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

**BRIEF BACKGROUND INFORMATION:** Creatine is well-known for its ability to aid in strength training, weightlifting, and running. However, specific information on creatine supplementation on sprinting performance is lacking. This study examined the effect of creatine supplementation on the power output and speed of repeated sprinting. The findings could be beneficial for primary care providers to optimize their care of individuals engaged in competitive sports and athletic activities.

**PATIENTS:** Recreationally active males

**INTERVENTION:** Creatine supplementation

**CONTROL:** Placebo (glucose) supplementation

**PRIMARY OUTCOME:** Power output and running speed

Secondary Outcome: Body mass, plasma ammonia level

**METHODS (BRIEF DESCRIPTION):**

- Healthy males 19–30 years old, active in recreational sports, and familiar with sprinting were included in the study.
- Weight loss program members; tobacco, dietary supplements, and medication users; vegetarian or vegan adherents; or those with endocrine, metabolic disorders, or medical problems were excluded.
- Before the baseline repeated sprints test, participants underwent practice sessions of sprinting and running to become familiar with the protocol.
- All participants took five days of placebo (glucose) supplementation while following and keeping a record of their usual diet and training patterns.
- Participants were then randomly assigned to the creatine or placebo group and took five days of supplementation while they continued their pre-recorded dietary and exercise regimens.
- Pre-post testing comprised six, 10-second sprints on a non-motorized treadmill with a 30-second rest between sprints.

**INTERVENTION (# IN THE GROUP):** 8

**COMPARISON (# IN THE GROUP):** 8

**FOLLOW-UP PERIOD:** Five days

**RESULTS:**

Primary Outcome –

- Creatine supplementation improved the mean power output in the last five seconds of the six sprints compared to pre-testing (average 4.5%; *P*=.005).
- Creatine supplementation increased mean running speed in the last five seconds of the 4$^{th}$, 5$^{th}$, and 6$^{th}$ sprint (4.2%, 6.0%, and 7.0%, respectively; *P*=.005 to *P*=.001).

Secondary Outcome –

- Creatine supplementation increased body mass compared to pre-testing (1.0 ± 0.8 kg; *P*=.007).
- Creatine supplementation decreased plasma ammonia compared to pre-testing (20%; *P*=.04).

**LIMITATIONS:**

- The number of subjects in the study was small.
- The study only examined how creatine supplementation affected one exercise.
- Creatine supplementation was assessed over five days only and thus, long-term effects are unknown.

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*The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Army Medical Department, the Army at large, or the Department of Defense.*

# Redefining the Status Quo: Opt-Out Tobacco Cessation

**The Effects of Opt-Out vs Opt-In Tobacco Treatment on Engagement, Cessation, and Costs: A Randomized Clinical Trial**

Richter KP, Catley D, Gajewski BJ, et al. The Effects of Opt-out vs Opt-in Tobacco Treatment on Engagement, Cessation, and Costs: A Randomized Clinical Trial. *JAMA Intern Med.* 2023;183(4):331-339. doi:10.1001/jamainternmed.2022.7170

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**KEY TAKEAWAY:** Opt-out treatment for tobacco cessation achieved similar abstinence at one month compared to opt-in treatment with a better-reported sense of therapeutic alliance.

**STUDY DESIGN:** Single-site, randomized, prospective, adaptive Bayesian design trial

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

**BRIEF BACKGROUND INFORMATION:** Most national guidelines require people using tobacco to opt-in to care. Studies regarding human immunodeficiency virus (HIV), vaccine safety, and colorectal cancer screening demonstrate opt-out leads to 2–4 times higher levels of engagement. People are more likely to opt for the status quo and this study investigates opt-out for tobacco cessation.

**PATIENTS:** Adults who smoke tobacco

**INTERVENTION:** Opt-out program

**CONTROL:** Opt-in program

**PRIMARY OUTCOME:** Abstinence at four weeks

Secondary Outcome: Abstinence at six months, therapeutic alliance

**METHODS (BRIEF DESCRIPTION):**

- Participants were patients ≥18 years old from the University of Kansas Medical Center inpatient system recruited from the electronic health record who currently smoked.
- Inclusion criteria were patients who smoked 25 out of the last 30 days, spoke English or Spanish, had access to a phone, and were medically eligible to use nicotine replacement therapy.
- Patients who were pregnant and/or breastfeeding had substantial comorbidity (life-threatening illness or altered mental status), were receiving cessation pharmacotherapy, were already treated for tobacco during the hospital stay, currently enrolled in a cessation program, or were hospitalized for more than three days or nearing discharge were excluded.
- The mean age of participants was 51 years with 53% males, the mean age of smoking initiation of 17 years, an average of 13 cigarettes smoked per day, 58% of participants used medication or counseling in the past to quit and 50% of participants currently lived with another smoker.
- Patients were randomized using adaptive design to opt-out or opt-in tobacco cessation.
- During inpatient admission, opt-out language was used to convey cessation as the status quo, providing medication and counseling to help smokers quit.
    - Upon discharge, opt-out patients received a post-discharge medication prescription, a two-week starter kit of nicotine patches, treatment planning, and four outpatient counseling calls.
- The comparison group was offered inpatient medications in an opt-in manner.
    - Those unwilling to quit received a brief counseling session while those willing to quit were offered components of care listed above in an opt-in manner.
- The primary outcome was verified by seven-day point prevalence abstinence at week four which was confirmed by salivary nicotine results of no more than 56.75 ug/L.
    - For patients who reported abstinence from the use of nicotine replacement therapy, a carbon monoxide measurement or salivary anabasine was used.
- The secondary outcome included verified abstinence at six months using the same method as above and included therapeutic alliance which was measured using a four-point scale (higher scores indicating better perceived therapeutic alliance).

**INTERVENTION (# IN THE GROUP):** 420

**COMPARISON (# IN THE GROUP):** 229

**FOLLOW-UP PERIOD:** Six months

**RESULTS:**

Primary Outcome –

- Patients in the opt-out group had similar rates of abstinence at week four compared to patients in the opt-in group (posterior mean difference 0.057; 95% credible interval, 0.0–0.11).

Secondary Outcome –

- Patients in the opt-out group had no difference in abstinence at six months compared to patients in the opt-in group.
- Patients in the opt-out group had greater therapeutic alliance compared to patients in the opt-in group.
    - Opt-out group (posterior mean 3.4 points; 95% credible interval, 3.3–3.4)
    - Opt-in group (posterior mean 3.2 points; 95% credible interval, 3.1–3.3)

**LIMITATIONS:**

- Patients were paid for participation, creating potential bias.
- Due to the chronic relapsing nature of tobacco use disorder, it may be beneficial to have a longer study duration.
- There were many components to the opt-out program making it difficult to discern the effect of each individually.
- Providing counseling may be time-consuming, language-dependent, and may not be realistic for practice.

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# Infertility Treatment and Autism Risk

**Infertility and Risk of Autism Spectrum Disorder in Children**

Velez MP, Dayan N, Shellenberger J, et al. Infertility and Risk of Autism Spectrum Disorder in Children. *JAMA Netw Open.* 2023;6(11):e2343954. Published 2023 Nov 1. doi:10.1001/jamanetworkopen.2023.43954

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**KEY TAKEAWAY:** Infertility, whether treatment-assisted or not, is associated with a higher incidence of autism spectrum disorder (ASD) at ≥18 months, mediated by certain adverse pregnancy outcomes.

**STUDY DESIGN:** Retrospective, population-based cohort study

**LEVEL OF EVIDENCE:** STEP 3

**BRIEF BACKGROUND INFORMATION:** One in six couples are diagnosed with infertility. Epigenetic changes have been found in children of women with infertility and those conceived by intracytoplasmic sperm injection. Those with subfertility or receiving infertility treatments are at increased risk of pregnancy complications and adverse outcomes. This study examined the association between infertility, with or without assisted conception, and the incidence of ASD.

**PATIENTS:** Singleton and multiple hospital live births at ≥24 weeks gestation

**INTERVENTION:** Subfertility and infertility with treatment

**CONTROL:** Unassisted conception

**PRIMARY OUTCOME:** Diagnosis of ASD at ≥18 months

Secondary Outcome: Adverse pregnancy factors

**METHODS (BRIEF DESCRIPTION):**

- Existing linked administrative health data from the Better Outcomes Registry and Network (BORN) Ontario database from Ontario, CA was analyzed.
- Live births occurring between April 2006 and March 2018 among mothers 18–55 years old were included in the study.
- Surrogate pregnancies, pregnancies ending in induced abortion, child death <18 months old, and pregnancies with incomplete records were excluded.
- The intervention included fertility treatments consisting of ovulation induction (OI), intrauterine insemination (IUI), in-vitro fertilization (IVF), or intracytoplasmic sperm injection (ICSI).
    - Mode of conception and pregnancy characteristics were gathered from databases.
- The primary outcome measured the incidence of ASD diagnosis in the mode of conception.
    - Children were followed starting at 18 months old for a mean of 8.1 years, with interest in ASD diagnosis from two or more outpatient sources (pediatrician, psychiatrist, etc.) and/or one or more hospitalization records.
- The secondary outcome measured adverse pregnancy factors.
    - Adjusted hazard ratios were calculated for each method of conception and risk of ASD in preeclampsia, cesarean birth, planned cesarean birth, unplanned cesarean birth, multiple pregnancy, preterm birth <37 weeks, and severe neonatal morbidity.
- Adjustment for covariates including maternal age, parity, income quintile, rurality, immigration status, smoking, illicit substance use, alcohol use, pre-pregnancy diabetes or chronic hypertension, obesity, pre-pregnancy and postpartum history of mental illness, and infant sex.

**INTERVENTION (# IN THE GROUP):** 185,128

**COMPARISON (# IN THE GROUP):** 1,185,024

**FOLLOW-UP PERIOD:** Median 8.1 ± 3.1 years, starting at 18 months old

**RESULTS:**

Primary Outcome –

- Subfertility and infertility with treatment are associated with a higher risk of ASD compared to unassisted conception:
    - Subfertility (adjusted hazard ratio [aHR] 1.2; 95% CI, 1.2–1.3)
    - OI or IUI (aHR 1.2; 95% CI, 1.1–1.3)
    - IVF or ICSI (aHR 1.2; 95% CI, 1.0–1.3)

Secondary Outcome –

- OI or IUI resulted in increased risk of the following:
    - Cesarean birth (aHR 1.2; 95% CI, 1.1–1.3)
    - Multifetal pregnancy (aHR 1.2; 95% CI, 1.1–1.3)
    - Preterm birth (aHR 1.2; 95% CI, 1.1–1.3)
    - Severe neonatal morbidity (aHR 1.2; 95% CI, 1.1–1.3)

- IVF or ICSI resulted in an increased risk of the following:
  - Cesarean birth (aHR 1.1; 95% CI, 1.1–1.2)
  - Multifetal pregnancy (aHR 1.1; 95% CI, 1.1–1.2)
  - Preterm birth (aHR 1.2; 95% CI, 1.1–1.2)
  - Severe neonatal morbidity (aHR 1.2; 95% CI, 1.1–1.2)

**LIMITATIONS:**

- Parents in the infertility treatment group were older and resided in higher-income areas.
- Absence of information about the cause of infertility (PCOS, endometriosis, tubal factor, male factor).
- Absence of familial information (family composition (heterosexual couples, same-sex couples, or single parents by choice).
- Absence of specific information about fertility treatment (donor oocyte or sperm, type of IVF procedure used, or use of preimplantation genetic testing).

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