



FEBRUARY 2023

DEEPPDIVE SUMMARIES

- ◇ [Is Zinc Beneficial for the Brain?](#)
- ◇ [Depressing Microbes: What is the Role of Gut Bacteria in Depression?](#)
- ◇ [Dairy Fat and Cholesterol Levels: Why the Difference?](#)
- ◇ [Do Edible Oils Influence Inflammation in Ulcerative Colitis?](#)

Is Zinc Beneficial for the Brain?

Agh F, Hasani M, Khazdouz M, Amiri F, Heshmati J, Aryaeian N. The Effect of Zinc Supplementation on Circulating Levels of Brain-Derived Neurotrophic Factor (BDNF): A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Int J Prev Med.* 2022 Sep 20;13:117.

Background

- The human body contains ~2-3g of zinc, and zinc exerts diverse biological functions with over 300 enzymes being zinc-dependent.
- There is evidence that zinc levels may be lower in individuals with depression, and that supplementation may improve depressive symptoms.
- One proposed explanation is that zinc supplementation may enhance levels of brain-derived neurotrophic factor [BDNF], which is crucial for cognition.

The Study

- A systematic review and meta-analysis of randomised controlled trials investigating the effects of zinc supplementation compared to a placebo on BDNF levels. Secondary outcome was changes in serum zinc levels.

Findings, Strengths & Limitations

- Four RCTs were included in the study, for a total number of participants of 185; $n = 92$ and $n = 93$ from intervention and control groups, respectively. Three trials used zinc gluconate at 30mg/d, while one trial used zinc sulphate at 25mg/d.
- Zinc supplementation increased BDNF levels compared to controls with an effect size of 0.31, a small effect size. This effect was primarily evident at 30mg/d zinc.
- Zinc supplementation increased serum zinc levels compared to controls with an effect size of 0.88, a large effect size.
- Strengths included pre-registration of the review, clearly defined inclusion criteria, and similarity of designs in the included RCTs. Limitations includes only a handful of studies in the analysis, very small sample sizes, and very different patient populations.

Context

- In some of the included studies in the present meta-analysis, serum zinc was bumped above the reference range, although this would likely be transient as the mechanisms regulating zinc homeostasis adapted.
- Both human and animal studies show high concentrations of zinc in amyloid plaque, suggesting zinc may promote beta-amyloid plaque development, which may be due to overactivity of zinc transporters leading to higher concentrations of brain zinc.
- The effect size for exercise on BDNF in healthy individuals is 0.53. This may be a better option, if increased BDNF is a desired outcome, given potential risks of zinc supplementation.

Application

- The evidence to suggest zinc as an intervention for brain health is insufficient at this point.
- There is, generally, little evidence to suggest a need for supplementation in otherwise healthy individuals, except for individuals who have an inadequate intake of dietary zinc. In that context, proceed with caution: there appears to be little reason to supplement beyond 25-30mg/d zinc.

Depressing Microbes: What is the Role of Gut Bacteria in Depression?

Radjabzadeh D, Bosch JA, Uitterlinden AG, et al. Gut microbiome-wide association study of depressive symptoms. *Nat Commun.* 2022;13(1):7128.

Background

- The “gut-brain axis” includes the central nervous system, the autonomic nervous system, and the enteric nervous system; bi-directional communication allows for the brain to influence functions in the gut, and the gut to influence brain function.
- At the core of the gut-brain bi-directional axis of communication is the microbiota, i.e., the compositions of bacteria in the human gut.
- Could the microbiota be associated with depression?

The Study

- The study undertook two analyses; one analysis of Dutch participants from two cohorts, followed by a genetic analysis of associations between microbiota and major depressive disorder [MDD].
- The first analysis investigated bacterial diversity and associations with depression in the following cohorts.
- The second analysis used genetic data to conduct a Mendelian Randomisation [MR] analysis of the potential causal links between genetic variants representing the microbiota identified from the cohort analyses and MDD.

Findings, Strengths & Limitations

- In the cohort studies, less diverse gut microbiota was associated with higher depressive symptom scores. 9 genera of bacteria were negatively associated with depressive symptoms, i.e., lower abundance of these bacterial genera was associated with higher depressive symptom scores.
- In the genetic analysis, a genetic variant for only 1 bacterial genus, *Eggerthella*, was significantly associated with MDD.
- Strengths include the large [$n = 2,593$] sample size, adjustment of relevant covariates, and inclusion only of participants not using anti-depressive medications. Limitations include the use of different scales to assess depressive symptoms, the low overall depressive scores in each cohort, and weak genetic variants for the MR analysis.

Context

- Is a certain microbial composition merely a fellow traveller of other depression-related factors, or a causal contributor to those factors?
- This is what we do not know, and anyone pretending that we have any definitive answers around the microbiota and mood is out over their skis on the evidence.
- However, there is one broad conclusion that may be helpful: that greater bacterial diversity appears to be consistently associated with positive health outcomes, including depressive symptoms.

Application

- The composition of the microbiota is responsive to diet, in particular complex, non-digestible carbohydrates – fibres and non-starch polysaccharides – that result in bacterial fermentation and a diverse bacterial community.

Dairy Fat and Cholesterol Levels: Why the Difference?

Bard JM, Drouet L, Lairon D, Cazaubiel M, Marmonier C, Ninio E, Bal Dit Sollier C, Martin JC, Boyer C, Bobin-Dubigeon C; INNOVALAIT Study group. Effect of milk fat on LDL cholesterol and other cardiovascular risk markers in healthy humans: the INNOVALAIT project. Eur J Clin Nutr. 2020 Feb;74(2):285-296.

Background

- The epidemiology of dairy foods confirms a now well-established concept for nutrition research; that the food matrix is a highly relevant determinant of health effects beyond what nutritional content alone may explain.
- These differences suggest that the effects of the same amount of total dairy fat differ relative to other characteristics of that dairy fat.
- To date, most studies have compared cheese to butter, with or without additional protein and/or calcium, and whether milk fits into this picture of different effects is less well established.

The Study

- The study was a randomised, double-blind intervention trial investigating the effects of vegetable fats compared to dairy fats in participants with mildly elevated blood cholesterol levels [LDL >130mg/dL]. There were three dairy fat diets; one based on spring milk [SM], one based on winter milk [WM], and one based on winter milk with added calcium [WM-Ca]. 20% of fat was derived from dairy foods or the vegetable fat control.

Findings, Strengths & Limitations

- 154 participants completed the study. After 8-weeks, LDL-C decreased by 14mg/dL on the VF diet, 4mg/dL on the SM diet, 6mg/dL on the WM diet, and 13mg/dL on the WM-Ca diet.
- Total cholesterol decreased by 23mg/dL on both the VF and WM-Ca diets.
- Strengths include the clearly stated aims and outcomes, strong design, repeated assessments of diet, and control of fat sources and intake. Limitations include sloppy reporting of data and results, changes in background diet between groups, and lack of baseline blood measures [first measures taken 4-weeks into the trial].

Context

- The milk fat group with additional calcium showed the same magnitude of reductions in TC, LDL-C, and ApoB, as the VF diet group. Prior evidence suggests that calcium inhibits specifically the absorption of saturated fatty acids, leading to their excretion bound in calcium “soaps”.
- The present study suggests that the effects of milk fat may be mediated by enrichment with calcium of foods high in milk fat. This builds on a body of prior evidence suggesting that both the food matrix itself, and the calcium content of the diet, are important mediating factors of the effect of dairy fats.

Application

- Given that calcium is generally high in foods like cheese, and most of the research for benefits of specific dairy foods continually isolates cheese both in epidemiology and in interventions, for those that do consume dairy this is the most evidence-based, food-based advice to emerge from the study of this food group.

Do Edible Oils Influence Inflammation in Ulcerative Colitis?

Morvaridi M, Jafarirad S, Seyedian SS, Alavinejad P, Cheraghian B. The effects of extra virgin olive oil and canola oil on inflammatory markers and gastrointestinal symptoms in patients with ulcerative colitis. *Eur J Clin Nutr.* 2020 Jun;74(6):891-899.

Background

- Inflammatory Bowel Disease [IBD] is an umbrella term for gastrointestinal conditions characterised by chronic inflammation, including Crohn's Disease [CD] and Ulcerative Colitis [UC].
- There is evidence of a complex interplay between environmental factors, dysbiosis i.e., disturbed balance in the gut microbiota, diet, and genetics, in risk for developing IBD.
- Most of the attention in this area is given to dietary fibres, however, dietary fat intake is also a crucial characteristic of diet that may influence the microbiome.

The Study

- The study was designed as a randomised, crossover, single-blind, controlled trial in participants with a diagnosis of UC. The interventions in this study were 50ml of extra virgin olive oil [EVOO] or canola oil [CO] per day consumed for 20 days. The crossover design meant that participants were randomised to the order of oil intake, with a 14-day washout period between diet phases.

Findings, Strengths & Limitations

- 32 participants completed the study.
- In the EVOO phase, erythrocyte sedimentation rate [ESR; an systemic inflammatory marker] decreased by 1.18mm/h, while hs-CRP [a systemic inflammatory marker] decreased by 1.31mg/L. In the CO phase, ESR increased by 1.87mm/h, while hs-CRP increased by 0.36mg/L.
- In the EVOO phase, the overall gastrointestinal symptom score decreased by 13-points, while in the CO phase there was a decrease of 4.2 points.
- Strengths include the clearly stated aim and outcome measures, crossover design, and validated outcomes for UC disease severity and symptoms. Limitations include the small sample size, poorly executed statistical analysis, and limited dietary assessment.

Context

- The analysis only compared the before and after scores for each diet, rather than compare the differences *between* the effects of each diet. However, the baseline symptom score in the EVOO phase was higher, and these baseline differences were not accounted for in the statistical analysis, which may have overexaggerated the effects of the EVOO.
- Based on both the overall wider literature and the levels of specific inflammatory markers in the present study being all within normal ranges, caution is required against interpreting the finding of very minor increases in these markers on the CO diet as evidence of a detrimental inflammatory effect in these participants with UC.

Application

- There is a lack of evidence currently to make specific recommendations and doses for EVOO intake, or any specific oil, in individuals with IBD. At least the evidence supports the general health benefits of unsaturated fat rich oils, including both EVOO and CO.