

## *Detailed Study Notes*



# *Do Vegan Diets Cause Depression?*



## ***Table of Contents***

- [Introduction to this Episode](#)
- [Connection to Previous Episodes](#)
- [Suggested Mechanisms](#)
- [Cholesterol & The Brain](#)
- [EPA & DHA Omega-3 Fatty Acids](#)
- [Choline](#)
- [Carnitine](#)
- [Michalak et al., 2012](#)
- [Beezhold et al., - Seventh Day Adventist Study](#)
- [Askari et al., 2022 Meta-analysis](#)
- [Lee et al., 2021 Cross-sectional Study](#)
- [Difficulties with Diet-Depression Evidence](#)
- [Final Messages](#)

## ***Introduction to this Episode***

In this episode, the Sigma team explores the question: “Do vegan diets increase risk of depression?”

This is a question that emerges from a few different places. First, it’s common to hear such a claim from proponents of largely animal-based diets. Some reference is often made about how vegan diets can, at best, worsen symptoms or, at worst, even cause depression. Or conversely, they may state that moving away from a plant-based diet will improve mental health outcomes, including depression.

And while all of those specific claims aren’t within the scope of this episode, such claims do get people wondering if a plant-exclusive diet is actually a cause of various mental health ailments.

But is there a basis for such claims?

In this episode we explore the evidence from two ends:

1. the research related to the proposed mechanisms by which a vegan diet could cause problems
2. current outcome data looking at the impact of such diets.

## ***Connection to Previous Episodes***

### [#342: Are Vegan Diets Superior for Health?](#)

- In this episode, Alan and Danny discussed a range of topics related to claims about the health impact of plant-exclusive diets.
- This included an examination of various intervention trials comparing diets, and the potential benefit of a plant-exclusive diet.
- This was followed by asking could the benefits of a vegan diet be gleaned whilst including animal foods? And is veganism suitable across the lifestage?

### [#438: Diet, Brain Health & Cognitive Function](#)

- In this episode the Sigma team looked at cognitive decline and the evidence relating to a variety of nutrients, foods and dietary patterns, including: vitamin D, omega-3 fatty acids, B vitamins, caffeine, flavonoids, coffee and green leafy vegetables.

## ***Suggested Mechanisms***

Most of the claims that are made about a vegan diet increasing the risk of depression (or even more strong claims of it causing depression), center on some mechanisms that range from legitimate questions to pure speculation.

So, with the mechanistic rationale, some of this may be valid, but some are a misunderstanding or misrepresentation.

Some of the commonly hypothesized mechanisms include:

1. Low cholesterol being problematic for the brain
2. Lack of direct source of EPA & DHA omega-3 fatty acids
3. Low choline status
4. Low carnitine
5. Plant “toxins” causing damage

## ***Cholesterol & The Brain***

It is known that cholesterol is an important molecule for cellular function generally, including in the brain. However, it's important to note that it can be directly synthesized by each cell in the body. And this synthesis is sufficient for physiological function.

But, as we discussed at length back in [episode 424 \(Is Low Cholesterol Bad For You?\)](#), the confusion arises because some people will take the fact that cholesterol is required for physiological function, to then extrapolate that to mean: “if you have very low levels of serum cholesterol, or low levels of LDL-C, then that’s problematic for the brain (or hormones, etc.)”. But this is just not the case. Elevated serum cholesterol is not required (and in fact is problematic, as it relates to ASCVD). Similarly, dietary cholesterol is not required. And certainly not in high amounts. This does not undermine that cholesterol still plays important roles in the body.

When it comes to the brain specifically, there is indeed some connection between cholesterol and certain brain-related disorders. For example, there's evidence showing disordered cholesterol metabolism is related to the amyloidogenic pathway in the brain, i.e., the pathway that results in the production of amyloid beta, the protein that builds up in plaque in

Alzheimer's and dementia. But note here that high levels of free cholesterol in the brain are actually more likely to *cause* problems.

And remember, a serum total cholesterol or LDL-cholesterol measure is telling you about cholesterol in circulation within these lipoproteins. It isn't saying anything about cellular synthesis, efflux, or presence of cholesterol in membranes. So having a low serum cholesterol level doesn't mean harm to cells, including in the brain.

So the level that is required by the brain is relatively small and is easy to synthesize endogenously. So we don't need high levels of either dietary cholesterol or serum cholesterol.

## **EPA & DHA Omega-3 Fatty Acids**

Previously: [#342: Are Vegan Diets Superior for Health?](#)

When it comes to depression specifically, most of the data that we have points slightly more towards EPA (than DHA), certainly in terms of evidence from intervention trials.

Meta-analysis from [Sublette et al. 2011](#)

- Benefit of supplement with EPA > 60%
- 15 RCTs
- 916 participants total – so not large for a MA
- Supplements with EPA  $\geq$  60% showed benefit on standardized mean depression scores:
  - **EPA  $\geq$  60%** = 0.558, 95% CI = (0.277, 0.838), z = 4.195, p = 0.001
  - **EPA < 60%** = -0.026, 95% CI = (0.200, 0.148), z = -0.316, p = 0.756
- improvement determined by the dose of EPA in excess of DHA, within the range 200 to 2,200 mg EPA.

There is some mechanistic hypotheses as to why EPA may have an impact:

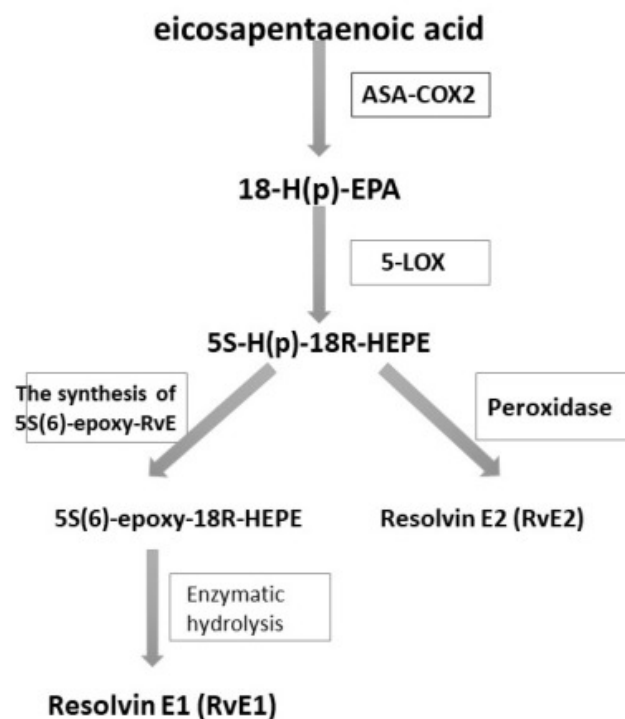
1. Resolvins
2. Modulation of central nervous system
3. Prevention of gray matter atrophy

EPA is the precursor to **resolvins**.

- Resolvins are compounds that act as mediators to terminate any inflammatory process.
- So this might be important in terms of the associations between neuroinflammation and depressive symptoms.

Some other mechanistic research has suggested that EPA might reduce depression by modulating central nervous system activity and reducing high frequency brain waves associated with anger and emotion. And there's some work suggestive of the prevention of gray matter atrophy.

## The synthesis of AT-dependent resolvins (Aspirin-dependent)



From: [Tułowiecka et al., Int J Mol Sci. 2020 Oct; 21\(20\): 7628.](#)

# Choline

## Connection & Food Sources

- Because choline is found predominantly in the highest amounts in animal-derived foods, vegetarians and vegans may have a greater risk for inadequacy.
  - Eggs are a leading source.
- The US Dietary Guidelines, and others, do identify several potential nutrients of concern in a vegan diet, including choline.
  - Note: All the food patterns recommended by the 2015-2020 Dietary Guidelines for Americans are currently insufficient to meet the AI for choline in most age-sex groups.
- However there are non-animal sources:
  - Soy milk contains choline.
  - Beans, peas, and lentils are also important dietary sources of choline
- For deep dive on choline and how it relates to DHA and its relevance in pregnancy, see [episode 443](#) with Kevin Klatt.

## In the Brain

- Choline is particularly important for brain health, as it synthesizes acetylcholine, which plays a role in some really important processes that are vital at different stages of life.
- Acetylcholine in the brain helps to [alter 'neuroexcitability'](#) and directly influences communication between neurons. So this influences synaptic transmission and plasticity, which is important during periods of development or learning and as we age.
- Emerging evidence suggests that maternal choline intake during pregnancy, and possibly lactation, has lasting beneficial neurocognitive effects on the offspring ([Wallace et al., 2018](#)).

## The Hordaland Health Study

- [Bjelland et al., Am J Clin Nutr. 2009 Oct;90\(4\):1056-60.](#)
- Researchers looked at the association between circulating/plasma choline concentrations and different outcomes, including anxiety and depression.
- They used a hospital anxiety and depression scale, which is a crude, but a clinically valid measure of anxiety and depression.
- They assessed almost 6,000 adults (a simple correlation study to see if there is any differences in the levels of choline).

- Results demonstrated that the lowest choline quintile was significantly associated with higher levels of anxiety, which is directly impacted by some of those pathologies or some of those actions in the brain, but they found no significant association in corresponding analysis in relation to depression.

**Key questions:** Do vegan diets lower choline status? What impact does this have?

### Analysis by Julie Hess

- [Hess et al., The Journal of Nutrition, Volume 152, Issue 9, September 2022, Pages 2097–2108](#)
- Hess took the 3 recommended healthy diet patterns recommended in the Dietary Guidelines, which come in different calorie amounts. With one of those 3 being the Healthy Vegetarian Dietary Pattern (HVDP)
- And modeled the impact of replacing the suggested foods with vegan alternatives to meat, dairy and eggs. But keeping a healthy diet pattern.
- The dairy food group was replaced with a dairy alternative group composed of soy milk and soy yogurt.
- For the vegan model, eggs were replaced with equal proportions of vegetarian protein foods.
- And for the 2,000 kcal/d diet for example, it gave a choline intake of 325 mg/d. Which is below the 425 mg/d DRI for females 19–50 y old, which would be a group where this 2,000 kcal diet is an average intake suggestion.
- However... the vegan model with no eggs had no meaningful change in choline amounts from the original HVDP.
- Choline was provided in amounts <90% of the DRIs in all models, including the original Healthy Vegetarian Dietary Pattern (HVDP)
- Interestingly, a dairy-free nutrient profile had roughly double the choline content of the original dairy food group nutrient profile. Due to the presence of choline in soy milk/yogurt.
- A month later there was a follow-up paper talking about application of such modeled diets: [Hess & Comeau, 2022](#)



**TABLE 5**Impact of replacing dairy and eggs in the 2000-kcal/d HVDP with vegan alternatives for females 19–30 y old<sup>1</sup>

	DRI: females 19–30 y old	HVDP	Model 2: vegan pattern	Change from HVDP, %	Change from DRI, %
Macronutrients					
Calories, kcal	2000	1998	2065	3.37	103.26
Protein, g	46	80	72	-10.20	128.02
Carbohydrate, g	130	250	255	2.10	196.19
Fiber, g	28	29.9	31.4	5.05	112.31
Total fat, g	20%–35%	54.3	61.3	12.76	Within range
Micronutrients					
Niacin, mg	14	16.5	18.4	11.52	131.46
Vitamin B-6, mg	1.3	1.83	1.77	-3.59	135.88
Vitamin B-12, µg	2.4	3.85	6.55	70.09	272.92
<b>Choline, mg</b>	<b>425</b>	<b>300</b>	<b>325</b>	<b>8.40</b>	<b>76.40</b>
Vitamin K, µg	90	139	158	14.18	175.72
Folate, DFE, µg	400	612	648	5.88	162.00

Adapted from: [Hess et al., The Journal of Nutrition, Volume 152, Issue 9, September 2022, Pages 2097–2108](#)

## Carnitine

Those that claim a vegan diet increases the risk of depression also point to low carnitine as a potential mechanism to support their claim (e.g. [claims here](#)).

- We can synthesize it endogenously from lysine and methionine
- The claim that this is a problem for a vegan dieter is perhaps based on findings where vegetarians reliably have lower plasma carnitine stores than omnivores.
  - However... one of the interesting things is that they actually tend to have comparable muscle carnitine stores ([Novakova et al., 2016](#))
- And it seems that homeostasis can be maintained ([Blancquaert et al., 2018](#))
  - Perhaps due to slow turnover rate
- Laura Blancquaert 2018 study – Ghent University, Belgium
  - Carnitine and carnosine homeostasis was *unaffected* by a 3- or 6-month vegetarian diet
- Also is present in some plant foods (e.g. potatoes, nuts)

## Michalak et al., 2012

- [Michalak, Zhang and Jacobi, Int J Behav Nutr Phys Act. 2012 Jun 7;9:67](#)
- Participants drawn from the German Health Interview and Examination Survey and its Mental Health Supplement (GHS-MHS).
- Completely vegetarian (N=54) and predominantly vegetarian (N=190) participants were compared with non-vegetarian participants (N=3872) and with a non-vegetarian socio-demographically matched subsample (N=242).
- Example survey questions:
  - ‘Do you currently follow a vegetarian diet or did you follow a vegetarian diet in the past?’
    - Participants could answer either ‘no, never’, ‘yes, completely’, or ‘yes, predominantly’.
    - Additionally, vegetarian participants were asked to indicate the age at which they adopted a vegetarian diet.
  - ‘How often do you consume the following food products (from a list of 35 items)? Please consider the past 12 months.’
- For their mental health assessment, they looked at a psychiatric diagnosis and they assessed that using a standardized questionnaire or diagnostic tool.
  - Did a really strong assessment
  - One hour interview with either a psychologist or a medical doctor.
  - A lot of the nutrition studies typically just have the clinical researcher conduct a short screen, whereas this study was quite intensive.
- Looked at their one month, their 12 month, and their lifetime prevalence rates of the onset of having a depressive disorder and anxiety disorder.
- “Vegetarians displayed elevated prevalence rates for depressive disorders, anxiety disorders and somatoform disorders.”
  - a) Depressive disorders: Major depressive disorder, Persistent depressive disorder
  - b) Anxiety disorders: Panic disorder, agoraphobia, specific phobias, social phobia; OCD, generalized anxiety disorder;
  - c) Somatization disorder is a disorder characterized by recurring, multiple, and current, clinically significant complaints about somatic symptoms.
- The analysis of the age at adoption of a vegetarian diet and onset of a mental disorder showed that the adoption of the vegetarian diet tends **to follow** the onset of mental disorders.
  - So they wanted to analyze the age at which the person started the vegetarian

- diet, and then also the onset of the mental disorder.
- They demonstrated that the mean age or the average age of somebody to become a vegetarian was around 30, but their mean age of onset of depression was likely at around 25.
  - So the diet wasn't causing the depression. In fact, it could be inferred that in many cases someone with depression may adopt a new diet (like a vegan/vegetarian diet) in an attempt to improve their symptoms.
  - Due to the matching procedure, the findings cannot be explained by socio-demographic characteristics of vegetarians
    - e.g. higher rates of females, predominant residency in urban areas, high proportion of singles
  - Issues with this paper:
    - Lack of accounting for covariates: No adjustment or consideration of covariates leaving us with these essentially crude odds ratios.
    - Selection bias: With such a small sample size (54 completely vegetarians, 190 predominantly vegetarians), particularly against such a large comparator group, there's a real chance of selection bias being introduced into the findings.

## ***Beezhold et al., - Seventh Day Adventist Study***

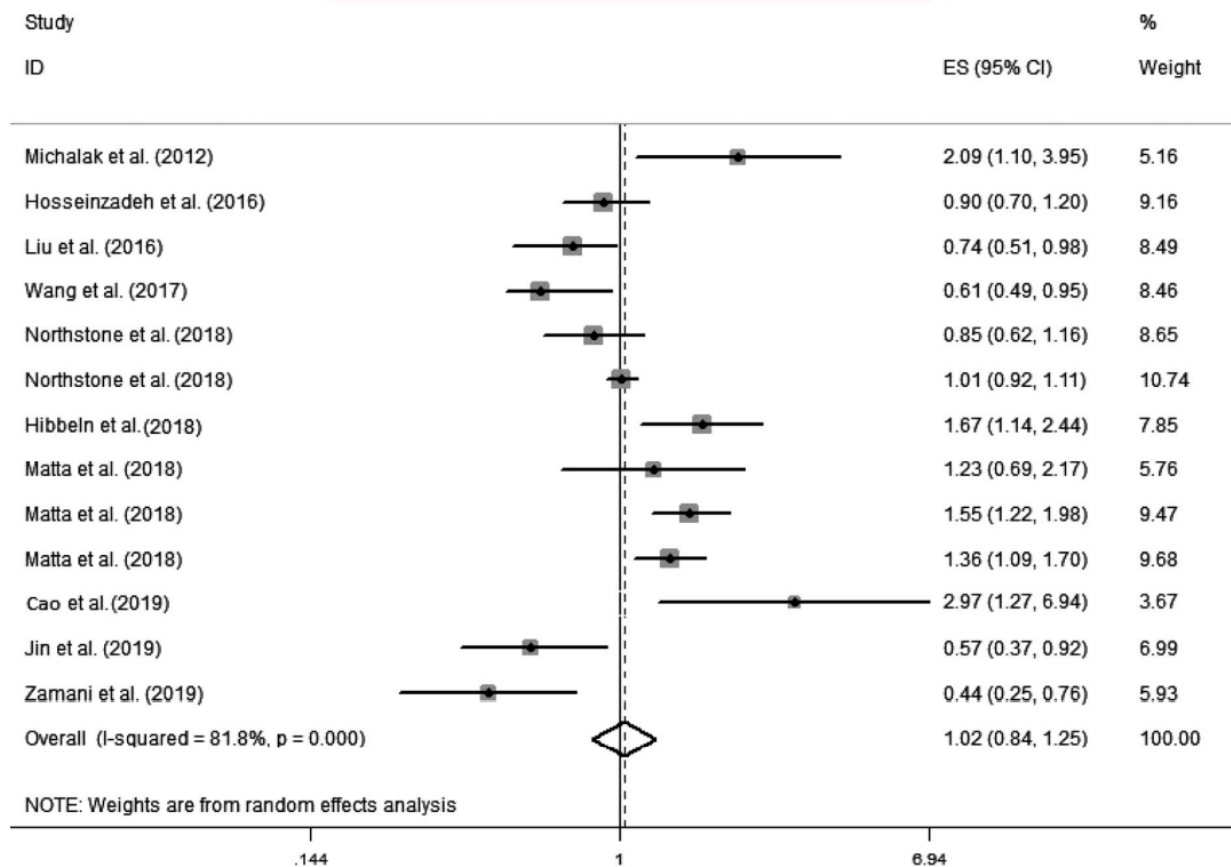
- [Beezhold et al., Nutrition Journal volume 9, Article number: 26 \(2010\)](#)
- Mood state and polyunsaturated fatty acid intake
- Participants follow either a vegetarian (n = 60) or omnivorous diet (n = 78)
- Cross-sectional study of 138 healthy Seventh Day Adventist men and women residing in the Southwest United States
- Participants completed a FFQ, Depression Anxiety Stress Scale (DASS), and Profile of Mood States (POMS) questionnaires.
- Vegetarians reported significantly lower mean intakes of EPA, DHA, and the omega-6 fatty acid, arachidonic acid.
- Vegetarians reported higher mean intakes of shorter-chain  $\alpha$ -linolenic acid and linoleic acid.
- Vegetarians reported significantly *less* negative emotion than omnivores

## Askari et al., 2022 Meta-analysis

### [Askari et al., 2022](#)

- No association between the consumption of a vegetarian diet and depression
- The actual effect size was 1.02 (CI = 0.84, 1.25)
- 13 publications (four cohort studies and nine cross-sectional studies)

Forest plot of the association between a vegetarian diet and the risk of depression:



From: [Askari et al., Crit Rev Food Sci Nutr. 2022;62\(1\):261-271.](#)

### Others to Note

- [Jain et al., 2022](#) systematic review
  - Narrative review of 19 studies found conflicting information
  - Some studies suggested that those who adhered to vegan and vegetarian dietary patterns had higher depression rates, while others indicated they were associated with decreased depressive symptoms.
  - Findings are in line with broad data regarding the protective role of diet in mental health and brain function.

## Lee et al., 2021 Cross-sectional Study

[Lee MF, Eather R, Best T, BMJ Nutrition, Prevention & Health 2021:e000332](#)

- Cross-sectional study of 219 adults aged 18–44
- Explored the associations between an estimate of overall plant-based diet quality and depression in:
  - vegans (n=165)
  - vegetarians (n=54)
- Online survey
- Used a 20-item tool that's used in most clinical practice for determining depression: Centre for epidemiological studies depression (CESD)
  - Short term measure of mental health
  - If a score is 16 or greater, it would indicate that you've got some depressive symptoms.
- Overall plant-based **diet quality** was associated with depressive symptoms in vegans and vegetarians, accounting for 6% of the variation in depressive symptoms.
- For those without depression, higher diet quality was protective against depressive symptoms
- For those with depression no association with diet quality was found

## Difficulties with Diet-Depression Evidence

### Self-report Data

- Self-reported dietary status may lead to misclassification because there is a clear and important distinction between merely reporting that one avoids meat and actual meat-abstention.
- Also a designation of 'vegetarian' or 'omnivore' doesn't provide us with a measure of diet quality.

### Defining Depression Outcomes & Quantifying Impact

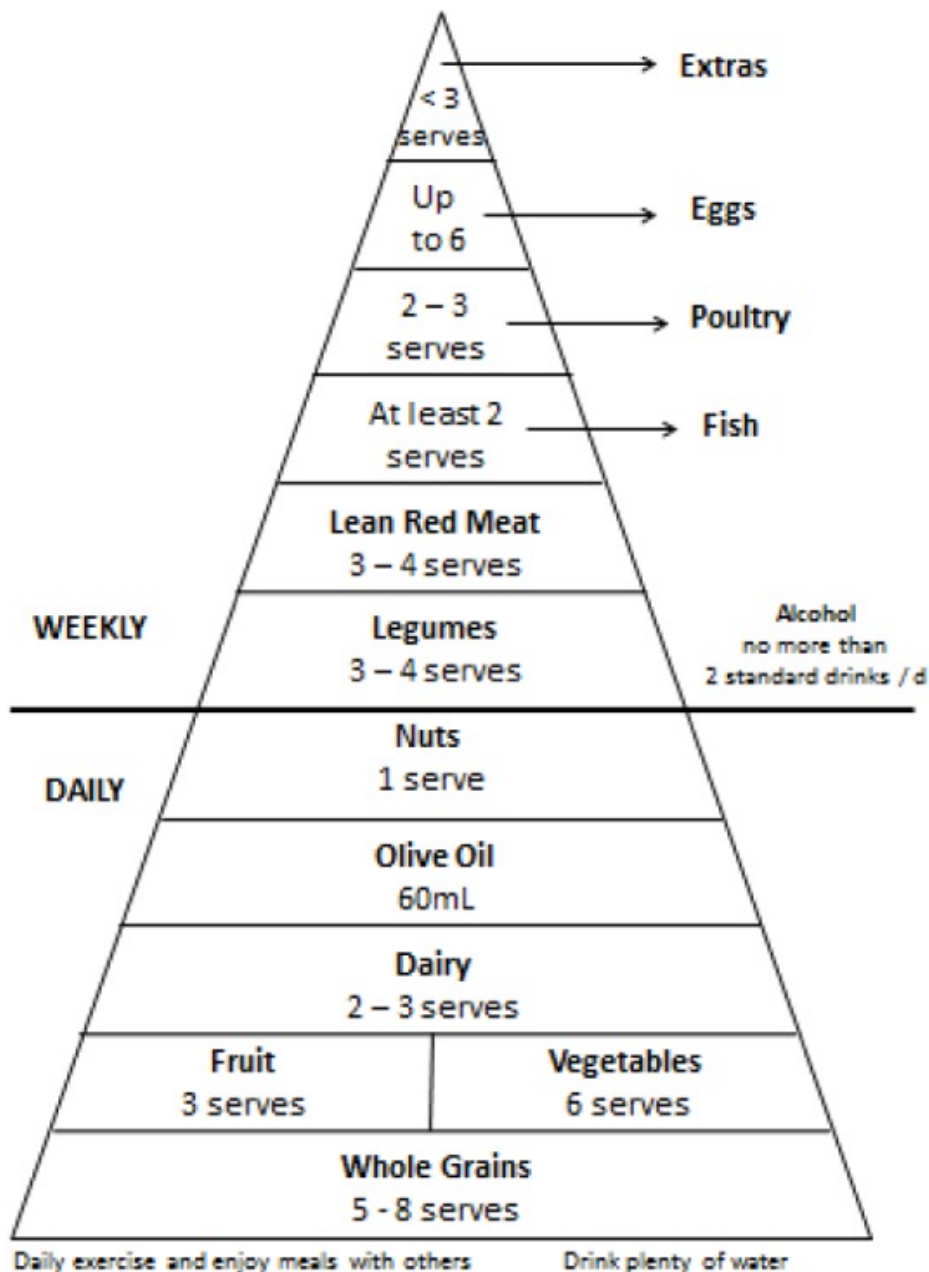
- One of the major issues in the diet-depression literature (whether we're talking about observational research or intervention trials) is that when looking at dietary patterns, nearly all of the research is in **non-clinical depression** specifically.
- And most of the research suggests relatively small modest effect sizes.
- In terms of RCTs, Brendan Stubbs' meta-analytic group produced a paper ([Firth et al., 2019](#)) of 16 trials, with 15 of those being in non-clinical depression.
  - Found that dietary interventions significantly reduced depressive symptoms.
  - However, importantly, this is virtually all in non-clinical depression.
- The only intervention trial that we have to date that's looked at **major depressive disorders** and diet is [The SMILES trial](#), out of Australia ([Jacka et al., 2017](#)).

### SMILES Trial ([Jacka et al., 2017](#))

- 'SMILES' was a 12-week, parallel-group, single blind, randomized controlled trial
- Dietary intervention in the treatment of moderate to severe depression
  - The intervention consisted of seven individual nutritional consulting sessions delivered by a clinical dietitian.
- Diet was a modified Mediterranean dietary pattern ("ModiMedDiet")
  - Aimed at "supporting the consumption of the following 12 key food groups" (recommended servings in brackets):
    - whole grains (5–8 servings per day)
    - vegetables (6 per day)
    - fruit (3 per day)
    - legumes (3–4 per week)
    - low-fat and unsweetened dairy foods (2–3 per day)
    - raw and unsalted nuts (1 per day)
    - fish (at least 2 per week)
    - lean red meats (3–4 per week)

- chicken (2–3 per week)
- eggs (up to 6 per week)
- olive oil (3 tablespoons per day)
- While also aiming to reduce intake of sweets, refined cereals, fried food, fast-food, processed meats and sugary drinks (no more than 3 per week).
- It showed quite a large effect size but there are some big questions over some methodological issues with the study.
  - E.g. [Molendijk et al. \(2018\)](#) propose that expectation bias and difficulties with blinding might account for the large effect size.
    - Note: [Authors reply here](#).





***The ModiMedDiet Food Pyramid***

Image created by Rachele Opie (r.opie@latrobe.edu.au), © 2012  
 The ModiMedDiet Food Pyramid was created by Dr. Opie for the SMILES trial.



## Final Messages

### **Alan:**

“... I think the top line for any of these mental health related aspects as outcomes is to really highlight that the most effective intervention **is not diet**. The most effective evidence-based intervention for people struggling with depression is to get therapy. And there are various different modalities of therapy but getting therapy in and of itself is the most effective intervention with the largest effect size. And obviously then there's pharmacotherapy. These are interventions that are going to be of orders of magnitude greater in their effect than worrying about whether someone is eating eggs or not.”

“That said, the body of evidence that we do have overall, does suggest that overall dietary improvements towards basic nutritional best practices that we know of in terms of increasing fruit and vegetable consumption, lowering dietary saturated fat intake potentially emphasizing some nutrients of interest like omega-3 fatty acids if they are low in the diet. A high intake of polyphenols and flavonoids and an overall healthy dietary pattern in that context does appear to be better than a control.”

“Beyond that, is there any veracity that we can give to the claims that specific ‘nutrients of concern’ in a vegan or vegetarian diet are likely causally increasing risk of depression in a vegan or vegetarian context? I don't think we can say that with any degree of certainty at all.”

### **Niamh:**

“We know from a lot of clinical studies that a lot of people who are diagnosed with a depression don't want to initially take pharmacological treatments or maybe don't want to engage in therapy and want to manage the disorder themselves. And I think that this is just really quite worrying that the broader kind of messages (about specific diets, e.g. carnivore diets) are coming from people who maybe shouldn't be delivering the messages at all.”

**Danny:**

“So in relation to our question (do vegan diets impact depression risk?), there is conflicting evidence and very little to suggest that they are causing issues per se.

So be wary of absolutist claims, particularly if they come from doctors that walk around supermarkets with their shirt off shouting at vegetables. They might not be a worthy source of information.

So if you are indeed eating more vegetables in your diet, do not be concerned on that account.”

