



Episode Transcript

Danny Lennon: Hello and welcome to Sigma Nutrition Radio. This is episode 463 of the podcast. You are very welcome. This is an episode brought to you by the Sigma Nutrition team. So we are here. Hello to Niamh and Alan. How are you?

Niamh Aspell: Yeah, doing good. Life is good. No complaints on my side.

Alan Flanagan: God that sounds tyrannical.

Niamh Aspell: That's the typical answer you give when you're not going to sit and complain, isn't it? Not a good start to the show.

Danny Lennon: Let's start with some complaints... Alan, how are you? How is life?

Alan Flanagan: Well, because I'm quarter vegan I'm now wondering: am I my genetically higher risk of depression? It's worrying. It's keeping me up at night.

Danny Lennon: We will try to find an answer to that question for you today. So indeed, today we are exploring this question of do vegan diets increase

risk of depression? And this question emerges from a few different places. So first of all, let's start with the fact that you will likely hear such a claim many times online from proponents of largely animal based diets, with some reference often being made to how vegan diets cause depression or very least worsened symptoms.

Conversely, you also have this idea of moving away from a vegan or a plant-based diet has tended to improve mental health is commonly a story you may hear this is perhaps most widely heard of by the masses, at least from people like Jordan Peterson or Mikhaela Peterson, both of whom talked about such a journey on Joe Rogan's podcast about their experiences of alleviating depression, essentially with a carnivore diet.

And while that claim specifically isn't what we're addressing today, it does get people wonder. If a plant based or a plant exclusive diet could actually cause various mental health ailments. And this is something that gets reinforced by many of the "carnivore doctors". What a ridiculous term that is by the way. But nevertheless, "carnivore doctors" essentially talk about vegans and mental health quite a lot. We have others, for example, Georgia Ede, I think is a psychiatrist who often talks about all based diets for mental health. We have others who talk about vegan diets being bad for brain health and a variety of other claims centered around mental health or even specifically depression.

So then we have to ask "is there a basis to this?". As a way to explore that, maybe there's two different ways we can look at. First, there are some proposed mechanisms by which a vegan diet could cause problems, and we can talk about those. And then there's some associational data that we can again, look at that maybe show benefits for meat eaters and we can address whether there's something to that.

So let's start with the mechanistic rationale. Some of this may be valid, some of it might just be a misunderstanding or misrepresentation, so we'll maybe take each one separately. The first one that I'm going to come to is one that we've actually discussed before in the podcast, Alan. But it's worth giving a quick overview of again, and it's this importance of cholesterol in the brain and the idea that a vegan diet has both lower dietary cholesterol in it, as well as vegans tend to have lower serum cholesterol as well. And therefore, this causes a problem because cholesterol's so important to the brain, therefore

there is going to be impacts on mental health or things like depression. Can you maybe just first give a recap over this idea about the importance of cholesterol to the brain and then what that actually means for consuming something like a vegan diet?

Alan Flanagan: Yeah. I think this is fairly consistent with the framing of the role of cholesterol that they will use to angle some of their narratives about cardiovascular disease as well. And we can synopsise this thinking as: "we need cholesterol. We should consume cholesterol in the diet. And if we have high levels of cholesterol in the blood specifically if that's carried in LDL cholesterol, then that's actually a good thing if you are 'metabolically healthy' because that cholesterol is required for these important functions."

And they'll typically rattle off a few... sex steroid hormone synthesis will be one. And then they'll, in this specific context make claims about the requirements of cholesterol in the brain and central nervous system. And it's a path well trodden now is a point we've tried to make in response to this, which is a lie that is half a truth is ever the blackest.

The argument of the body needing cholesterol is just accepted. No one's ever argued against that. It doesn't tell us how much cholesterol we do need for these important physiological whether they're in peripheral tissues or the central nervous system in the brain. And in this specific context, really doesn't, or I was going to say, doesn't acknowledge it might just flat out, ignore or be unaware of the role of excess cholesterol in the brain and the pathogenesis of dementia, Alzheimer's disease disordered cholesterol metabolism which may relate to lack of adequate omega-3 long chain omega-3 fatty acid intake is implicated.

It's still a lot of mechanistic based understanding, but implicated in the overall pathophysiology and development of neuro fibrile tangles and beta amyloid plaque. The idea that low cholesterol in the body correlates with some of these outcomes is always a little difficult to sustain based on our capacity for upregulating and dodging a synthesis to match requirements.

The fact that cells can autonomously synthesize their own cholesterol and our levels of cholesterol that we know are sufficient for physiological function at thresholds, which do not also correlate with the progression of atherosclerosis and give or take, as we've talked about before, that may be

somewhere around a kind of upper limit of maybe 80 milligrams per deciliter or about 1.8 milli per liter.

And within that range we've got sufficient capacity. For production of cholesterol, for all of these important requirements, which it's not, again, denied that cholesterol does, it does all those good things. But within those ranges, then we have the capacity to meet that physiological requirement without the capacity of having two prolonged and elevated a cholesterol residence time in the circulation that ultimately has LDL knocking on the door of our arteries and getting I think that this ties into a range of the claims that are typically made. I find it ironic that Jordan Peterson is talking about meat and mental health, because it clearly hasn't solved his problems. that this really does extend to a common theme I think we'll end up touching on, because the focus, certainly as the emphasis relates to red meat consumption, or at least an omnivorous dietary pattern, will typically come back to arguments in favor of, say, the amino acid profile of meat.

So it's rich in tryptophan and tyrosine and these amino acids that we need for neurotransmitter synthesis. We've got choline and animal based products, egg and meat. That's an important amino acid for the. We've got vitamin b12. And then of course there's other animal derived foods, not necessarily from red meat, but the long chain marine omega-3 fatty acids as well.

And they'll all come at it with a similar kind of angle, which is essentially these foods contain these nutrients in higher amounts, and that's why they're good for. Alleviating depression or offsetting depression. But as it relates to cholesterol, I think that there's a really important part of the story that they conveniently omit.

And that's the reality that if we are talking about, and this isn't necessarily related to depression, but certainly long term neurodegenerative disease, then the inverse of their argument, the exact opposite is the case and high levels of cholesterol and high levels of saturated fat in the diet consistently and strongly associated with adverse neurocognitive outcomes over the longer term.

And that may relate to disordered cholesterol metabolism in the brain and the accumulation of excess cholesterol in. Those tangles and plaques that we associate with Alzheimer's path of physiology.

Danny Lennon: Yeah, I think you're right. There are going to be a number of parallels across some of the nutrients we'll look at. And indeed there are more of those micronutrients to come to. But as you mentioned, saturated fat. That might give us a moment to look at dietary fat in general as one of the macronutrients that is, again, proposed as a reason why vegan diets are going to be suboptimal for brain health generally. But then specific in this framing around depression, that for many of the vegan dietary patterns, particularly let's say a whole food vegan diet that you would have a very low intake of dietary fat. And then there's, again, speculation around the importance of dietary fat to the brain because of the presence of fat in the brain, or the presence of certain types of fatty acids in cell membranes, and how this all plays this role in brain health generally.

So therefore, a very low fat diet is going to be problematic. Do we have any data or are you aware of anything that would lend itself towards this argument, Niamh, in relation to the intakes of say, dietary fat? And if we actually do indeed see differences on that basis? For an outcome like depression or an other type of mental health outcome?

Niamh Aspell: Yeah, I think historically fat has been pretty much demonized because there's obviously some types of fat, cholesterol I suppose to a certain degree, but it's knowing the exact limits which are appropriate in terms for brain health and general health overall. But there's, there was a kind of a belief that was taught to raise our there is a very well good understanding that it raises our risks of heart disease and cardiovascular problems, which then secondary outcomes in terms of brain health are of course are demonstrated as well.

But a lot of meta-analysis of kind of cholesterol related trials have shown that people on cholesterol lowering diets were significantly, these kind of created a lot of controversy, these studies, but these are initially published in the early nineties. But the cholesterol lowering diets were significantly more likely to die from non-disease relation related deaths of suicide accidents or violence.

And researchers theorized the time that lowering cholesterol had an impact on central serotonin. And this in turn then increased kind of impulsivity or aggression and depression, which raised the suicide rates. But there's also a lot of studies looking at more low diet versus low carbohydrate dietary

patterns, and whether there is more likely to be depressive symptomology over time.

There was one particular French cohort study that followed people up for a 10 year period. Those, it was a large population based study of about 12,000 people, and they found that men who were on a low fat diet were more likely to be depressed after one year than men who weren't on a low fat diet.

And then after 10 years, their risk of depression remained even higher. So this continual low fat diet, dietary restriction they were more likely to be depressed. Whereas women who are on a low fat diet were more likely to be depressed by 37% after a year, which was quite higher than the male proportion, but still showed a trend for both of them.

These were also energy match. So it wasn't that they were reducing entirely their, they weren't restricting their energy intake, they was just restricting fat as a component of their diet. There's a number of these studies, there's another long term. It was a 11 year follow up of 12,000 people, and they found specific fat components.

So those who consumed olive oil, polyunsaturated fatty acids, monounsaturated fat, fatty acids were more likely to become depressed. So it was related directly to certain types of fats, but more people who ate, obviously trans fats or trans fatty acids, they're more likely to become depressed as well.

So those conflicting kind of findings on both sides, those good fats and also bad fats. So if you consumed less of the good, you're more likely to be depressed. And if you consume more of the bad, you're also more likely to be depressed as well, which to a certain degree, that's making quite, they're quite spiritist correlations.

There are quite obvious. Other lifestyle behaviors that influence those dietary patterns that might lead to different kind of mental health outcomes. There is other RCT data. There was one, it's an older study now, but it was followed people up for five year period. They have to eat low fat diet, which came to 20% of their calories from fat, and then another group then has to take 30% of their calories from fat, which is the normal range.

this particular study, it was just healthy females. So the women had normal kind of BMI and they were on a lower fat diet the ones who were on the lower fat. So even just lowering it to the 20% experience, higher levels of stress and sleep problems. So disorders not particularly depression, but other related disorders.

So both groups of women were, had equivalently low depression levels at the beginning, and it showed that there was a slight increase in some behavioral aspects of that as well. But I think what it comes down to is certain components with different fat components that there's a lot of work you've already mentioned around cholesterol, and I think there's some very plausible mechanistic evidence for that as well.

There's when you talk about the relationship between brain cholesterol and central serotonin and depletion, there's strong associations with the onset of depression for those who have low central serotonin levels. Central serotonin is the main target for SSRIs or the kind of first line antidepressants as well?

So there's some suggestive people have suggested that there's lower cholesterol may then risk the increase the risk of depression, but other perspectives suggest that the causation runs obviously in the opposite direction, that depression may lead to a reduction in appetite.

So those with, low energy intake or low fat intake might, might be not eating as much because of their depressive symptoms. So there's a lot as well, we can go into the different breakdowns of different types of fats or the omega 3s. Clearly in a vegetarian or a strict vegan diet that eliminates fish, they're not getting their major kind of dietary source of EPA and DHA.

And these are important regulators of brain cell structure and function, whereas omnivore diets that are low in these components have been linked to impaired mood states, or increased risks of depression as well. So there's a kind of general consensus that deficiency in the omega fatty acids can impact cognitive processes.

So a lot of the evidence is linked to learning memory, done a lot of work in older adults, but in humans', deficiency has also been associated with other mental disorders. So like attention deficit, dementia, bipolar, as it's a key

component of the neuro membrane and as the human body's pretty inefficient at synthesizing DHA, we're pretty reliant on it.

As true our diet and vegans typically don't. But they don't. Most vegans, there's a lot of flexibility in terms of what's consumed in a vegetarian and vegan diets, and some do take out fish, but those very strict vegetarians or very strict vegans are reliant on getting DHA or their omega 3s from other sources.

Danny Lennon: Yeah, so that raises a couple of important questions and one. Of course that it is not a question of inherently if someone has a certain type of diet that is going to answer this question of whether that's going to cause depression per se. But as you've outlined that if someone adopts different types of dietary patterns, and in this case we're talking about veganism or vegan diet, I should say, that could lead to certain choices that impacts their overall fat intake as an example.

But that is, of course, not just one inherent function of a vegan diet. You can reduce fat intake without that. Or determine what types of nutrients they're getting otherwise. And so it's important to that we drill down and find out what actually could explain some of these associations if they do actually play out.

And you've touched on one there, Niamh in relation to omega three fatty acids. And in particular when we look at EPA and DHA, the omega 3 fatty acids that we get for our marine sources. And that can't be gotten from plants. And of course this is a topic that Alan, you and I went into in quite some detail in episode 342, that people can go back and listen to where we looked at vegan diets for health generally.

And one of the things that you noted there is that this question, particularly around DHA and it's difficulty to get or almost impossible to get as a direct source unless you supplement on a vegan diet, that this is still very much an open question and that. We shouldn't be too quick to jump to the assumption that just because you can get ALA from plants, another type of an omega three that this is going to be sufficient.

Now at this point, there's a couple of questions here I'll put to you first in relation to EPA and DHA, we're talking about their importance for brain

health. Do we see that carry over into, let's say, the depression as an outcome specifically, and then more so what do we or what way would you recap for people about the importance of an omega-3 fatty acids and is there then some plausibility to the claim that because there's a lack of EPA and DHA directly in a vegan diet, that could be a cause for concern for, let's say, mental health outcomes?

Alan Flanagan: Yeah, so most of, when we talk about the long chain marine omega-3 fatty acids in the brain, we end up primarily focused on DHA because as Niamh said, it's the primary fatty acid in brain and central nervous system membranes. Over half of the brain's dry weight is fat. Half of that 30% is polyunsaturated fats and EPA, or sorry, DHA comprise comprises over 90% of total omega-3 fatty acids in the brain.

So that includes both EPA and DHA. And it also includes and when we're considering like EPA's role in the brain it includes a consideration of the distinction between how they both might act in the brain. So for DHA it's primarily going to be its role in central nervous system membranes.

And with EPA, the thinking is that it might be slightly different. So because EPA isn't high in those membranes, it raises a question over what's EPA up to in the brain and the modest demands that it presents. And the thinking is that it might relate to its effects in the circulation and in brain plasma.

And so a number of studies have indicated that EPA, not DHA, is associated with lower risk of depression. If we're focusing in on depression, specifically DHA, again, other associations in terms of neurocognitive outcomes cognitive function potentially lower Alzheimer's and dementia risk. But with EPA specifically, there's been a couple of levels of evidence that focus more on depression specifically. So while it's low in brain tissue itself higher plasma levels of EPA have been associated observationally with reduced depression, and associated dementia risk. Higher cerebral plasma EPA has been associated with the prevention of gray matter atrophy in the brain.

And these have been looking at functional MRI scan, observational research. And then we have intervention trials which offer up a kind of an interesting finding in relation to the role of EPA in relation to depressive symptoms. There was a meta analysis in 2017 by Sublet and colleagues and what they

were looking at wasn't just the effects of omega-3 supplementation, but they were trying to tease out kind of dosage ranges.

And what they found was that the benefit of EPA as a supplemental intervention on depression was observed with a minimum effective dose averaging about a gram of EPA a day, but specifically where the supplement comprised over 60% EPA. So these were supplements where EPA comprised the majority of the fatty acids and where DHA was usually either 200 milligrams or less in the supplement.

This again, may relate to some of these Roles that EPA might have in acting in, in its presence in cerebral plasma rather than, again, in contrast to DHA, which is rapidly incorporated into central nervous system membranes and acts accordingly. And another mechanism that potentially is quite important then with EPA with these doses is the fact that EPA is a precursor as well as DHA of anti-inflammatory mediators known as resolvins.

And EPA is the precursor to resolvins. And these are compounds which do exactly what their name implies. They're involved as mediators to terminate any inflammatory process. And that might be particularly important in terms of the associations between neuroinflammation and depressive symptoms.

And then some other research, mechanistically has suggested that EPA might reduce depression by modulating central nervous system activity and reduce high frequency brain waves associated with anger and emotion. And then again, we have that finding that was suggestive of the prevention of gray matter atrophy.

So when it comes to depression specifically, most of the data that we have points slightly more towards EPA, certainly in terms of evidence from intervention trials. Now, that Sublet and colleagues analysis included 15 RCTs, but they were not big trials. So the total sample size of in the meta analysis was about 916 participants.

But it still found a moderate effect size. The standardized mean difference was 0.5, which would be bang on that moderate effect size range. But it was very specifically pointing the needle towards EPA as the supplemental intervention in the context of around an average dose of a gram a day with DHA levels of less than around 200 milligrams in that supplement.

So they may, that's not to say that DHA may have no role in depression at all but in terms of our evidence for interventions, that certainly is where the evidence points to. But when we factor in the other roles that DHA plays in the brain and the importance of DHA in some of these processes that do associate with depression like neuroinflammation and cognitive function more broadly, then I think it would provide certainly a biologically plausible basis to suggest why there could be some of these associations with entirely plant exclusive diets or vegetarian diets that do exclude direct sources of these long chain fatty acids.

Danny Lennon: Indeed. So we definitely have some mechanistic rationale to work with there, and we'll come back when we look at some of the outcomes in relation to dietary patterns a bit later on.

But to continue with looking at some of these potential mechanisms for now, let's talk about choline, which is one that has been brought up a couple of times at this point because choline is a nutrient found predominantly in animal derived foods. And so it is relatively well accepted that vegetarians and vegans can be at a greater risk of an inadequate intake.

Eggs is typically shown as one of these leading sources. It is contained of course, within certain plant foods; beans, peas, and lentils, but certainly not to the same degree as it would be in animal based foods. And so typically this is well accepted. And in most guidelines you hear reference to choline being one of those nutrients of concern if someone is going to follow a vegan dietary pattern to pay attention to where they could be getting some choline.

But interestingly, of course, I think most people across the population struggle to get enough choline regardless of their diet. And whilst much of the focus has been in relation to pregnancy and lactation, one of the interesting things that come out of that literature has been around the potential for choline intake during pregnancy and maybe even during lactation, to have a lasting impact on some neurocognitive effects in offspring.

And again, along these lines, then we see this potential mechanism for if someone adopts a vegan diet, and they're not going to be getting the same degree of choline because of the typical food choices they're making. Is this going to be an issue? So maybe first, before we actually look at the impact of,

say, moving to a vegan dietary pattern and what it does to choline status first let's talk about the actual association between choline intake or choline status and an outcome like depression.

What we generally know about the importance or the role of choline for maybe brain health generally, but then even if we have some specific data in around depression or related outcomes.

Niamh Aspell: Choline is particularly important for brain health. So the reason for that is it synthesizes acetylcholine and acetylcholine when in the brain alters a couple of different processes, really important processes that are vital at different stages of life, but not to equal measures.

So acetylcholine in the brain, it helps to alter what they would call "neuro excitability" and which directly influences communication between neurons, which is what keeps her brain strong. So this influences synaptic transmission and plasticity, which becomes quite important as we're, true periods of development or learning or as we get older.

And it helps also coordinate kind of different groups of neurons in the brain. So it's believed to do so as a result. Then this can change what you'd say is maybe the state of the networks of neurons in the brain. So this can essentially then modify your response to different situations or how you might deal with different different inputs, different external or internal inputs.

So this is what would be described as a classical kind of neuro modulating role. And it's believed that choline plays an important role in this. So there has been a lot of kind of observational studies or cross-sectional studies. There was one published in 2009 and this is called The Hordaland Health Study, and they looked at the association between circulating so plasma choline, concentrations and different outcomes, so anxiety and depression. So they had different, they used different markers for anxiety and depression. And we'll get into these probably a bit more with some of the other studies. But for this one, they used a hospital anxiety and depression scale, which is a crude, but a clinically valid measure of anxiety and depression.

And they assessed this in a sample of almost 6,000 adults who they also had information on their plasma and choline concentrations as well. So it's a

simple correlation study to see if there is any differences in, in the levels of choline. And they had shown, or they demonstrated through this dataset 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. There's been a number of studies that's been one of the larger population based ones, but there's been a number of different studies have shown the opposite of this as well.

So some have shown that there is a direct link between depressive symptoms. One thing that I think is difficult with all of these studies is to determine the level of choline that they deem to be adequate or deemed to be important for neuro benefits. And that's why I think there's a lot of different conflicting results. But it is always seen in lower volumes in vegetarian populations just due to the difficulty that there is in obtaining it from very limited vegetable sources.

Danny Lennon: Yeah. One of the interesting things that you see, and I think one of the papers that I may have shared was one by Julie Hess only from a couple of months ago, where they took the three recommended healthy dietary patterns from the US dietary guidelines, and those of course, come in different calorie amounts.

One of those three dietary patterns talked about in that document is the healthy vegetarian dietary pattern. And Julie Hess in her work modeled out what would happen if you replaced some of those suggested foods in that pattern with vegan alternatives to the dairy and eggs, for example. And indeed, you do see that the choline intake that would arise from eating a healthy pattern, but in line with the vegan model that she put or that she outlined was below.

DRI for choline. So for example, for the 2000 calorie diet option, it gave a choline intake of 325 milligrams per day, which is below the 425 milligrams per day DRI for females between 19 and 50 years old, which would be a group that would, they would tend to equate in those guidelines to the 2000 calorie per day diet.

However, of course, what you look at when you see any of these dietary patterns or any of the healthy vegetarian dietary patterns offered is that the DRI is above the intake for any of those patterns that they outline. So it's a struggle to get choline, no matter the dietary pattern that they're looking at.

And I think in a follow up paper, she actually showed if you apply certain types of strategies for following a vegan diet, you could meet that requirement. But nevertheless, it does seem to be a challenge to meet some of those requirements overall, and hence why it's talked about as a nutrient of concern.

But I think, again it raises up those big questions of first of all, does going on a vegan diet mean someone's choline status declines? If so, to what degree? And then most importantly, at what point do we actually see an impact on a hard outcome and let's say like the development of depression, for example.

So in relation to those big questions and this overall literature in relation to choline, what is your take on this Alan? Particularly in relation to outcomes like depression or what open questions do you still have about it?

Alan Flanagan: I think the open questions relate to the specificity of choline in the context of overall healthy dietary patterns. Yes, we have that mechanistic understanding of its importance in the synthesis of acetylcholine. And we know that acetylcholine as a neurotransmitter is particularly important for learning memory and cognitive processes. There's some suggestion of a potential role for betaine as well in, in terms of maybe providing like in a vegan dietary pattern, let's say, for example, where someone could potentially consume a lot of betaine.

But potentially there could be some kind of interaction with at least I wouldn't say substituting for choline intake as a direct source, but providing some kind of substrate alternative. Overall, I think that the difficulty is when we look at the overall body of evidence for nutrition and depression, I think there's a couple of things that arise.

One is how depression is quantified in the first instance. This is a major issue that permeates through this entire literature, whether we're talking about observational research or intervention trials, if we talk about just healthy dietary patterns overall. Most of the research is in non-clinical depression.

Most of the research suggests relatively small modest effect sizes. In terms of RCTs, Brendan Stubbs' meta-analytic group produced a paper a couple of years ago, 15 trials, non-clinical depression. That's really important. The only trial that we have to date, I think that's had major depressive disorders. The SMILES trial, and there's a lot of questions over some methodological issues with the study. Notwithstanding it's quite large effect size. And so what I come back to with some of these single nutrient status questions that we may have and choline is one of these is in the context of, and I hate using this term well planned vegan diet, because we could have a well planned any type of diet.

I don't think necessarily that's a way to qualify diets. But assuming that it is easier to slip into some insufficiencies of intake in a context of a diet that excludes all animal produce. And for choline, in particular, with eggs being the primary source population wise, a vegan diet is going to exclude eggs in entirety.

Nevertheless, the overall dietary pattern research that we have would be suggestive that simply the change in diet overall towards a more healthful pattern is better than any sort of like control or better than a kind of nutritionally inadequate or poor quality diet. And that extends even to within a vegan or vegetarian context versus, these quantifications of healthy plant-based versus unhealthy plant-based diets.

So at this point, I'm inclined to think that in a really complex outcome definition that has contributions from all sorts of myriad other factors, social, genetic, environmental, psychological, and otherwise that are often poorly controlled for, if even considered in any sort of adjustments.

Certainly in observational studies that I'm still not ready to jump on the fact that a single nutrient is likely to explain any sort of association between any dietary pattern, vegan diets included, and depression, and that extends to choline. I personally think this area is an absolute mess as far as the literature goes.

So I think some more direct evidence for choline specifically would be required before there's any conclusion that I would be comfortable coming to other than a actual healthy, plant based dietary pattern. Is, appears to be likely to be okay as far as depression goes.

Danny Lennon: You've raised a number of points that I think we'll open a tab on. Cause I definitely wanna revisit when we come to some rounding up conclusions here. One of those was, first of all, when we are talking about a question alike, say depression risk. And the only qualifier we're talking about is a diet, a vegan diet, or not a vegan diet. That is largely meaningless because it doesn't really tell us much of anything about the actual makeup of the diet apart from a few key things, right?

We know certain foods won't be there, but like you say, we don't know if that's a healthy dietary pattern, unhealthy or so on. The second point you outline is when it comes to something as complex as depression and we look at people online talking about a cure or a fix from that, from a dietary perspective, not only is that quite myopic, but probably is very omnipotent in some way of, and it feeds into this rhetoric of... if you see diet as something that is the cure all for everything, and particularly if you have one type of diet that is good or one type of diet that you say is bad, and then you have to paint every outcome in that fashion, you will see that, oh, the solution here is always going to be a certain diet or a certain nutrient.

Where for some things that may not be the case. There are definitely big questions to explore. We'll come back to those towards the end, I suspect. But to before we get into some specific trials, just make people aware there are other mechanisms that we don't have to necessarily go through.

People suggesting like carnitine, which is going to be lower in vegan diets, for example. Or you'll have others of course talk about the impact of plant toxins, oxalates, lectins you'll have others talk about gluten, all these types of things that would suggest potential issues with a vegan diet. But as we've hopefully made clear at this point, there is some mechanistic basis to this question, so it's more worth looking at actual outcomes and actual diets.

So let's start working through some of the studies that we thought might be particularly useful in exploring this issue. And let's start first with one Niamh that you outlined as one that potentially showing increased risk. This was Michalak and colleagues 2012 paper that showed associations between a vegetarian diet and some mental disorders.

Niamh Aspell: Yeah, this one is this one gets a lot of attention when you look at any of the systematic reviews or any of the literature reviews that are done

in this area. And it's deemed to be one of the, one of the better designed or better reviewed. Studies. So the study's entitled Vegetarian Diet and Mental Disorders.

And this was findings that they took from a representative community survey that they conducted in Germany. So the researchers analyzed data that was drawn from a study called the German Health Interview and Examination Survey, and they specifically chose participants who took part in one of the modules related to mental health.

So they included participants based on their dietary pattern as either being completely vegetarian or being predominantly vegetarian. So they weren't specifically looking at people who were following exact fegan diets. They also the total cohort was about 4,000 people. If we're looking at the number of people that were vegetarians, so complete vegetarians, they had a small number of, oh, just over 50 people and then predominantly vegetarian.

There was 190. So it's a relatively small sample size in comparison to the wider sample. But until the 242 people that they deemed to be, to vary degrees of vegetarian, and then they had 3,800 who were non-vegetarian participants, they also included a sample of that 3,800. So they were of, so a sample of that 3,870 participants who are non-vegetarian, they took a sample of those who were matched socio demographically to the group who were vegetarian so that they could do a comparator analysis as well to rule out if there was a sociodemographic influence in terms of what their dietary pattern was or their likelihood of depression, which was a quite nice addition, I think, to the analysis, which could only be done in these kind of larger sample studies.

So for vegetarian status, this was determined doing a nutrition survey. So they were simply just asked a question to determine like a self-reported dietary pattern of being a vegetarian. They asked them, do you currently follow a vegetarian diet? Which they define as having no meat, which they also note in this paper as well, that in Germany, so in this sample, they would not consider chicken or poultry or white meat to be meat.

So for these participants, they are answering it based on that question. So that's open to interpretation of what they consider to be a diet that c involves eating meat or did they follow a diet, a vegetarian diet in the past. So that,

quantified that group. So participants could either answer: 'yes', 'no', 'yes completely', which was one of the vegetarian groups, or 'yes predominantly', which is also one of the vegetarian groups. So it's potentially I suppose leaking into that flexitarian group of vegetarians as well. So their, to a varying degree were strict in terms of their dietary intake. And they also got them to report the age at which they started their vegetarian diet, which I think is quite interesting for some of the results that we'll discuss as well, that have also been seen in a lot of other studies that have looked at similar outcomes and dietary patterns. So they did another analysis of their nutrient intake. So they wanted to see consumption patterns of different food products they ate over the last 12 months so that they could corroborate if they said they were vegetarian, that it was likely that they were based on the foods that they consumed.

And then for their mental health, they looked at a psychiatric diagnosis and they assessed that using a standardized questionnaire or diagnostic tool. They did a really strong assessment actually. So they had typically a 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 was quite intensive.

So it was done by a clinically trained professional. And then for their analysis, they were interested in a couple of different kind of temporal outcomes. So they wanted to look at their one month, their 12 month, and their lifetime prevalence rates of the onset of having a depressive disorder and anxiety disorder.

And then they looked at other disorders as well. So things like hypochondria and body dysmorphic disorders. But it would maybe just focus on the depressive outcome. Sorry. So when they analyzed the data that they had, that they found, the vegetarians displayed higher prevalence rates for depressive disorders, anxiety disorders, and those hypochondria and body dysmorphia. Specifically looking at complete vegetarians, they had a higher rate at one (month) or 12 (months) or a lifetime prevalence of depressive disorders. There was a substantially lower rate in the meat consumers. So there was a marked difference. If we look at one month, it was seven point 0.4% prevalence of depressive disorders compared to 6.3. So not a kind of marked difference, but if you look at the lifetime prevalence of depressive disorders, you can see a much bigger difference.

So it was 35% prevalence rate for complete vegetarian. So they were much more likely to have a depressive disorder than meat eat, which was down at a 19%. And that was looking at the full sample. If you look at the socioeconomically matched sample, that was 20%. So still around the same as what you would expect for a typical meat consumer.

So what they had proposed was irrespective of the socioeconomic status of the group of either vegetarian or meat eaters. The rates of depressive disorders were lower in people who ate meat. They went one, one step further in this where they wanted to look at is it a kind of chicken or egg situation?

So they wanted to analyze the age at which the person started the vegetarian diet, and then also the onset of the mental disorder. And they showed that the adoption of the vegetarian diet, whether it's complete or partial, tended to follow the onset of the mental disorder. So if somebody was diagnosed with a depression or an anxiety, they were more likely to adopt a vegetarian diet after that.

And typically within a couple of years of their diagnosis. So 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 they inferred that. The proposed, to a certain degree that the mental disorder or the depression or anxiety, because they group both may lead to adoption of a meatless diet.

So the person might, be taking on other healthy behaviors or self-protective behaviors and to try and manage and their disease. That was what the kind of concluding statement was. They also included, just on a final point, they also included that a small number of people in their sample had an eating disorder.

So they had reported either, either or through the clinical assessment, they had noted that they had an anorexia or bulimia and they found a strong association with the eating disorder and the likelihood of also adopting a vegetarian diet, which I think is quite important.

Danny Lennon: Yeah, and we may touch on that later on because there are some similar associations. Alan, with the Michalak paper, what stood out to you from that?

Alan Flanagan: Yeah, I think the most important thing, Niamh touched on this and I think it's really important to highlight that this paper really does get a huge amount of weight attached to it. So in the i. Dobersek and colleagues systematic review, they called it "the most rigorous study reviewed".

And I think that's clutching at straws a little bit. The biggest issue I think with this is that there's basically no adjustment or consideration of covariates. The way that they've done that or attempted to do it, which is not even explicit, is this idea of we'll have our overall comparison between omnivores and then our kind of complete vegetarians and predominantly vegetarians.

But then we'll match them across a number of factors. We'll have the subgroup where we've matched them, and that was across sex, age, education, status, size of the community they lived in, and marital status. Now if we're thinking about depression, there are myriad other factors that could potentially be involved.

And this is really just a matched comparison. It's not necessarily controlling for or adjusting for those potential levels of these across the relationship between the exposure and the outcome. So the effect sizes in these are presented as odds ratio and confidence intervals, which is normal for a cross-sectional study.

But in effect and they are quite large, to look at some of the effect sizes is to, look at in some cases like doubling of risk associated with the, some of the vegetarian diets. And I think the biggest problem is these are in effect crude odds ratios.

That is a major limitation of the paper. I think in a sense, a Niamh discussed how small the contribution of vegetarians were to the overall. So I think factoring in the, and it's really important then the result that Niamh talked about, the kind of reverse causality that there was a greater likelihood of adopting a vegetarian diet following a diagnosis.

So these factors are really important to then think about: A) would we see these prospectively in prospective studies over time, which can maybe better account for the temporal relationships? B) I think the really small contribution; 54 completely vegetarians, 190 predominantly vegetarians.

Anytime we've got a sample size that small, particularly against such a large comparator group.

There's a real chance of selection bias being introduced into the findings, and then the complete lack of any sort of adequate statistical adjustment leaving us with these essentially crude odds ratios. I think for me, puts a lot of kind of amber lights over the study, particularly in the context, as Eve said, of other systematic reviews really saying, "this is the best evidence we've got".

And I think if that is the best evidence that anyone is going to argue for an increased risk in vegetarian diets, then I would say from a methodological standpoint, notwithstanding some the good parts to this analysis, they would be on thin ice a little bit. And, without maybe having to make this point in terms of every study that we'll go through, like the systematic reviews and meta analyses in particular, this is a major issue across this whole area.

Most of the meta analyses are based almost exclusively on cross-sectional studies. The adjustment models in those cross-sectional studies in some cases are non-existent. Like they have done no statistical adjustments for potential covariates. And in some cases are just a very crude model of say, age, sex, BMI.

Some of the prospective studies have done better on this but for an exposure outcome, for an exposure as complex as diet and an outcome is messy as depression, particularly when these studies are largely not considering the clinical definitions of depression, like major depressive disorder, persistent depressive disorder. So most of the outcomes we're looking at here are either non-clinical or normative and transient minor depression. And that in and of itself is really important for considering how we weigh up the evidence in relation to these.

Danny Lennon: Niamh, do you share some of those same concerns regarding the statistical analysis here?

Niamh Aspell: Yeah, There's a number of things, like one of the most important things if we're going to look at a lifestyle or dietary pattern and different health outcomes, particularly mental health, is other health

conscious behaviors. So if we, typically vegetarians or vegans are, generally less likely to smoke.

They're usually of a kind of a normal BMI. All of these kind of important factors. So if they're very self-driven in terms of how they consume their foods and how their dietary choices are determined, there's lots of other health conscious behavior behind that as well.

They're more likely to be physically active and for most of the papers that I've looked at, they haven't included this as Alan has said in a lot of their statistical analysis. And this is one of the best papers. If we look, there's another meta-analysis that we'll probably talk about later.

And a lot of the weight in terms of showing in effect in that is coming from this study as well. And it is a very crude study when it comes to determining vegetarian diets or vegan diets. Most of the studies are really lacking in how they assessed vegetarian diets or vegan diets. And then it comes down... I know, Alan, you've touched on that kind of term of it being appropriately planned diet, but I think to a certain degree we need to have a better understanding of the diet quality. So just because you're vegan doesn't necessarily mean that you're eating well, you could be the opposite of what I just described.

You could spend, your day smoking and just living on like lentil chips or something like that. So it doesn't necessarily mean that just, because you followed that diet. So I think as another step, we need to better understand diet quality, irrespective of what box you're putting yourself in.

And also a lot of the studies looked at Self-identified vegetarians, which this study has as well. And there was a recent publication that reviewed dietary intakes of self-identified vegetarians, and it showed that up to 80% reported taking meat as well. So I think there's, it's quite, and to be fair as well, the study is probably one of the earliest ones as well.

So I think in terms of it being a little bit more in depth is based on that. It's it was 10 years old and I think there's probably has been some better ones since that we might talk about. But yeah, I think it is lacking in some way, but it was the earliest piece of evidence I think that really tried to identify the link.

But again, like Alan said, it is all just linkages. There's there's very few. Control trials, which are just extremely difficult to implement. But yeah.

Danny Lennon: Yeah. One of the things you mentioned there, Alan, was questioning whether we would see similar results if this was prospective rather than retrospective. And this kind of speaks to the point that you alluded to, that people can make a change for certain dietary pattern on the basis of a diagnosis or to address a current health issue. And sometimes, unless that is accounted for, that can get caught up in the mess and therefore explain maybe why someone is finding some positive associations because someone has followed a certain diet to try and address that already existing condition. Can maybe just speak to that a bit more just so it's clear for people listening.

Alan Flanagan: If we're taking a cross-sectional study, we're taking a group of people at a, essentially a present moment in time, and we're stratifying them, we're dividing them along the lines of. The particular exposure we're looking at.

So in this case for example, we are looking at people's diet and we're putting them into these groups that we're defining as vegetarian and in some iteration or non-vegetarian, or defining it as meat consumption versus meat abstinence. And so we're then looking at essentially at that moment in time a section of the community where we're looking for the prevalence or the odds of the exposure or non expos group exhibiting whatever our outcome is. In this case, we're looking at kind of depression. And so cross-sectional studies are really useful in certain contexts. If we're looking to gather characteristics potentially that distinguish a population that we could then identify certain risk factors and move forward into a prospective study either of an observational or even an intervention they're useful for identifying risk factors in that regard.

They're useful for identifying characteristics that may distinguish, for example, a population at risk versus a population at lower risk. But they come with the inherent limitations of essentially being a snapshot in. And what they don't necessarily always tell us is the factors that have led someone to that point.

So if you're looking at a group for example, that have type two diabetes and you've got them matched against people who are otherwise healthy and do not have type two diabetes, but the people you're looking at have already developed this condition. So you don't know what water is under the bridge as far as getting to that point.

You can try and put together a bit of a picture in terms of questionnaires and otherwise, but you're still just essentially getting a snapshot at that moment in time. And if we're looking then over time, prospective studies obviously allow us to minimize some of the bias that can creep into other observational designs.

Particularly if we're taking people who are otherwise healthy at baseline, that will mitigate reverse causality. It will mitigate recall bias or retrospective bias. And to a degree it, it mitigates selection bias because you're not, in this case, they're coming and they're picking specifically people who are following vegetarian diets.

And again, as Niamh said, there's all these other lifestyle and behavioral correlates of diets, any diet, vegetarian, vegan, omnivorous or otherwise. And so that introduces these potential biases into the, into these kinds of studies. And the major limitation of this total body of evidence from an observational perspective is that they are cross-sectional studies.

And when we, I find it instructive to an extent that if we do find prospective studies they typically haven't necessarily looked at vegetarian diet patterns per se. But there's three prospective studies that were included in a 2017 meta analysis as an example, just to round this point off, which was by Zang and colleagues.

And they were in different populations, one was in Australia, one was in Spain, one was in Taiwan. What they were comparing was high versus low in quintiles levels of meat consumption. So a kind of classic epidemiological, high versus low comparison. And overall meat consumption in this analysis was actually associated with a kind of a modest 13% higher risk of depression in the perspective studies. And the range in terms of the confidence intervals was like 3% to 24%. So it's not a particularly precise finding, and it was only based on three studies, but. For me, this was indicative of, okay, we're seeing

one thing in the, in some of the cross-sectional studies to really emphasize that point.

This is not even consistent within the body of available cross-sectional studies. Nevertheless, some of the higher quality cross-sectional studies do suggest that kind of higher risk of depression or other of these outcomes in vegetarians versus non-vegetarians. And yet the prospective data, the limited prospective data, while not specifically testing that diet have suggested possibly the opposite.

And then also there was another systematic review and meta analysis by Askari and colleagues. This included the Michalak paper that we were talking about, but in this meta-analysis, it was actually only, it contributed. 5% of the statistical weight overall. There were 10 studies included, of which four of them were cohort studies.

And again the outcome in this analysis of a vegetarian diet specifically in depression was null. The actual effect size was 1.02. And the confidence intervals we're doing the splits right across 1.0 ranging from 0.84 up to 1.25. Like literally no direction of effect that we could even glean from that.

So I think when we start to think about looking at and considering more of the prospective data, the kind of strength of the association for vegetarian diets, in my opinion, looking at this evidence starts to fall away. And even that where we include cohorts in cross-sectional studies in the context of a meta analysis, then we also see that kind of more suggestive effect of a vegetarian diet from earlier cross-sectional research fall away a little bit.

Danny Lennon: So yeah, that's really important. You mentioned the Zang and colleagues, I believe, meta analysis where the meat consumption suggested potentially a higher risk.

You then mentioned the Ascari and colleagues meta-analysis showing no association between the consumption of the vegetarian diet and depression. And then within that, there's also this important point that you allude to that is worth digging into because. Thus far, we've really spoken about how there are suggestions that a vegan diet could increase the risk or could be problematic.

But there's also another side to contend here where there could be a claim made that in fact, a vegan diet is the best thing for prevention of depression or maybe even a curing depression to some degree. That is another claim people will likely hear online. And so with that, it's probably worth looking to see some of the data that gets put forth there.

One of the studies that does show a vegan or vegetarian diet potentially decreasing risk is the Beezold and colleagues paper, of course coming from the Seventh Day Adventist cohort, which is quite common when we look at this type of dietary pattern. So maybe if we dig into this, because this is likely to be a study, someone might hold up and say, look, here's a decreased risk from this dietary pattern. And you are correct, there is no increased risk. But we're going to go a step further and say, in fact, it's actually the best thing for prevention or risk decrease. Nevo get maybe you to start us off on the bees hold paper. What are some of the key points that are worth outlining and then we'll really get into some conclusions from there.

Niamh Aspell: Yeah. So I think with this study, and there's a couple of studies that have looked subcultures or subgroups who adopt a vegan or a vegetarian diet more as a long term lifestyle pattern. And it's done as a, in a kind of more of a community setting to a certain degree.

So it's a lot of the other studies that we've previously looked at, it's the, I suppose the direct motivation for becoming vegan wasn't described or hasn't been described, which I think is quite important. So who what's driving the desire to become vegan? And that could answer some of the questions that we have around, does it become before or after a mental disorder, mental health issue with this particular study and there's others on buddhist monks as well, where they try, indicate that a vegetarian diet is the value and that is that there's a subculture of practice and that might be associated with improved levels of mental health. It's easier to assess it in certain populations such as the that of the Beezold study because the Adventists typically don't eat any meat or fish or poultry. So it's a, it's more of a kind of a lifestyle, which typically vegetarian and vegan diets were. So in this particular study, they wanted to explore different mood states, but they were also very much so interested in dietary fats, specifically polyunsaturated fatty acid intake as a result of an end adherence.

So that to be able to measure adherence to vegetarian or an omnivore diet. Again, this was a cross-sectional study, so it's just showing the relationship between the diet of 138 healthy individuals who are a part of the seven day events. So it was men and women. And this is based obviously in the US and they were recruited from this study as they are quite a homogenous group in terms of how they live, so their lifestyle characteristics.

And they got them to complete food frequency questionnaires and they did some pretty I'd say they're crude questionnaires around depression, anxiety, and also their mood. So there's one called the POMS, which is profile of mood states, which is very commonly used in these types of studies.

And then there's a depression, anxiety, stress scale as well. And they also conducted the food frequency questionnaire, but they modified it so that they could also include some foods that are very commonly consumed to a vegetarian. So it's not necessarily validated, but they modified a validated food frequency questionnaire and they did that as well to support in the estimating their Omega-3 intake as well.

They did note for this, it was good that they did this, but they tested half of the participants for anemia. As if you're vegetarian, you're more likely to be anemic, although they didn't report the results of that. So that was unless I missed them in the paper, but I couldn't find what the results of that.

But you would potentially assume that they might have been anemic. That's another thing that a lot of these studies don't confine for is other deficiencies related to vegetarian status. Most of them haven't assessed whether people take a supplement or whether people have a certain measured, iron level that's adequate, or B vitamin or vitamin D.

But anyway they reported on data for 138 participants and 60 of those were determined to be vegetarian, and they reported, the vegetarians reported significantly less negative emotion than people who ate meat. So the vegetarians were at a better mood state than. The same group who consumed meat as well.

And that was measured on both of the scales that I mentioned for depression and also mood. But the scores were quite big. So there was a, there was quite a big difference in their mean till scores for depression. So for the D score,

which is a depression score, they scored an 8.3. If you're a vegetarian, so much lower on the scale compared to more than double that if you're a meat eat.

So you're much more likely to be experienced depressive symptoms. A lot of these scales as well are, like Alan says, a snapshot of time. They get you to reference how you've been feeling over the previous week. So they haven't collected any data on, have you experienced any particular event in the last week that would lead to you being more depressive than typical?

But irrespective of that the vegetarians also reported a significantly lower intake of omega three, specifically EPA and DHA as well as a omega six fatty acids as well.

Alan Flanagan: I was going to say, what I found bizarre about that study is that they, what they found that the participants with low EPA and DHA had better mood and that was like red flag. Because of what we know from even intervention trials, it's just I found that quite implausible. The finding of higher ALA intake better moods wouldn't be necessarily something that you would take much issue with, but I thought that was a bit, and given that, given the tiny size of the study, 60 vegetarians, 78 omnivores in, as you point out, a population that are really unique and for whom a vegetarian dietary pattern is a part of a lifestyle that encompasses a range of health promoting behaviors, abstinence of smoking and alcohol, they've got really interesting meal timing patterns in the Seventh Day Adventist community as well.

Yeah, just think there's, again, the cross-sectional nature of the study. There's so many factors as it would relate to depression that I think, are just unaccounted for.

Niamh Aspell: Yeah. In regard to the reported EPA and DHA intake levels, they said that this was "an unrecognizable benefit of the vegetarian diet". It's indicated like this is just an absolute phenomena that we still don't understand. But yeah it's clear, it's clearly giving us the result that we're particularly interested in. But there's been lots of studies in other groups. I think there was another one published last year in Buddhists who may be more likely to have grown up vegan, which I think is an interesting proposal if we're looking at outcomes like mental health.

And I think it's important since reason or motivation for adopting these types of diets might reflect mental health status? I think it's good to look at them, that if they were adopted, adopted for different reasons as opposed to trying to improve health or maybe trying to, live better in terms of, environmental impacts or different ethical beliefs.

So there, there was another cohort, again, just a cohort study in Buddhist, in Taiwan and they looked at very similar kind of study. Looked at a large sample of vegetarians against non-vegetarians, and they reported that Taiwanese vegetarians had a lower risk of developing depressive disorders as well compared to vegetarians.

And that they indicate that the diet might be an important component of prevention of depression, which is just one step a million times too far, but, Yes. Similarly, I think these groups are more interesting and a lot of people who are your populations who typically adopt a vegetarian diet aren't usually covered in a lot of nutritional science.

I think if like exploring this in Indian populations or area where areas where research isn't typically conducted where larger proportions of these groups and you do better sub-analysis and kind of better confounding and of all of those different factors that are very likely to influence kind of modern western living and, adoption of vegan diets.

What we see now would help maybe just at least clarify some of the issues or at least to explore them a little bit better, even if they are only cross-sectional.

Alan Flanagan: They used to do a lot of research in these kind of communities, religious communities, in like the seventies and eighties because it was deemed to be a really good way of controlling for Western lifestyle factors. They did a few, there was a study in Italy I remember where they were comparing nuns in two different monasteries or "nunaries", I dunno... This is me not paying attention to Sunday school... (Danny: "Convents") Convents, there we go! And they were looking at like blood lipids, blood cholesterol levels. And the whole idea was like, yeah, things like stress and all of that would be essentially controlled for, because they're like super zen. But, and you still saw some differences. So then they're looking at diet and stuff. I think that there's a lot of I think there are community

religious communities generally do provide a really interesting, almost defacto control group to look at some more direct questions of diet.

But I think you're right even so far as that, this actually provides a very good piece of the evidential puzzle in this area, which is largely a mess because. You are able to at least make some inferences about the role of diet. If we're saying in some of these other cohorts that there is this increased risk association with the diet and characteristics of the diet, we can actually look at these and say maybe it's not necessarily the diet.

And that of course then brings us back to the inadequacy of the models that are considered in terms of covariates and adjustments that in, in the western population studies, regardless of where in kind of Europe or North America or Australia, they've been conduct.

Danny Lennon: If this specific dietary pattern was as bad as some people online would claim, you should see it across all these cohorts, even when you have something as specific as the Seventh Day Adventist where you have controlled for all these other Western lifestyle factors.

Alan Flanagan: Yeah. Or Buddhist monks who are living a life of solemn prayer. The idea that if the diet was causally associated with an increased risk, I think you should see it nevertheless, in a community who are, otherwise "down with the Tao".

Danny Lennon: And if you're then willing to forego that and base it purely on mechanisms of which some may have some validity, you need to then also accept the other mechanistic rationale for which a certain diet, like a vegan diet could decrease risk, right? The intake of polyphenols or intake of vegetables and fiber, the typically lower levels of LDL cholesterol, you'd have to also accept them with equal fervor as you do for choline and cholesterol and that yeah, there is a, there doesn't seem to be a matching up of that.

I think one of the interesting things we've touched on a couple of times now is that when we're thinking of this question, generally we need to zero in on why we might see this conflicting set of data that there's some positive, some negative, some null findings from a few of the meta-analyses that we've outlined.

And one of the things that speaks to potentially what this depends on is A) the diet quality, and B) the preexistence of the condition essentially, which we've both touched on. And one paper that alluded to this was a paper by Lee and colleagues 2021, that touches on the potential role here for looking at diet quality and preexistence of a condition rather than inherently just do vegan diets increase, decrease risk.

Niamh Aspell: Yeah, this is quite a new study and I think this is it definitely moving things in the right direction to a certain degree with some of the study design. Because they are particularly focused on diet quality. They look specifically at plant-based individuals. So I think this is just a new term to group vegans or vegetarians together.

But they're specifically looking okay, you're vegan, but what type what kind of vegan are you in terms of the quality of your diet? And then depressive symptoms. This again, is, it's a cross-sectional study in an Australian population, but still it's probably a little bit better designed than some of the previous ones that we've spoke about.

So they wanted to explore the association between vegans and vegetarians and depressive symptoms and the researchers hypothesize that a high quality plant-based diet would be associated with lower risk of depression depressive symptoms. Okay, so that's they're not going obviously in the other direction, but diet quality.

So it, it typically indicates the agreement between your dietary pattern and then links that back to some evidence based recommendation about food and nutrition or food and nutrient intake in terms of its promotion or reduction of chronic diseases. So diet quality can be measured in lots of different ways.

You might take an individual's intake and compare that with a. Predetermined standards. So like a national nutrition recommendation or a samples intake distribution as well if you've got a large enough sample and then you just look at different components within that to determine the overall quality of the diet.

So some components might be determined as adequate or things that you require. So the higher the intake in those, the fruits and vegetables say you'll

get a higher score for your diet quality. And then there's moderate components which are inversely scored. So the higher the intake, the lower the score.

And these would typically be things like ultra processed foods or foods that contain lots of sugars. So just to distinguish between the diet quality and just determining if someone's is vegan or not. This was a relatively small cross-sectional study. What was pretty small, there was only 219 adults who took part and they were young to midwives at 18 to 44.

And they explored different associations between the vegans. Comprised 165 people in this, and then also the vegetarians. There's 54 vegetarians in the group as well. The, one of the big problems with this, which is just really unfortunate for the investigators, is that they conducted the survey online.

It was an anonymous survey, but it was sent to the participants between July, 2020 and September, 2020, which was just an absolute nightmare of a time for everybody in the world. So most of these people were living through covid and probably isolating and stuck in a room. And globally, I think everybody's general kind of wellbeing or mental health took a wobble at that point in the year.

So it was quite an unfortunate time to do some of this research. But anyway, that that's when it was done. So they used a typical tool that's used in most clinical practice for determining depression. It's called the Center for Epidemiological Studies Depression. One thing with this is though that it only determines depressive symptoms in the seven days previous.

So it's a very kinds of short term measure of mental health, and you would look for scores if a score is 16 or greater on this particular scale, would indicate that you've got some depressive symptoms. And then they use a dietary screening too as well. So this is a 20 item questionnaire that just asks the participants to provide an estimate of the intake.

The frequency of specific foods. Okay. So again, the limited collection of information or in diet to determine diet quality. I think they probably could have done a more in depth analysis of dietary intake to then extrapolate that based on diet quality. But anyway, it was an attempt to do that.

So they showed that a higher diet quality score meant that, participants were eating more fruits and vegetables and stuff that they would determine to be more commonly consumed on a vegan or vegetarian diet. And overall, the plant-based diet, when they did the analysis was associated with depressive symptoms in vegans and vegetarians, and it accounted for about 6% of the variation in depressive symptoms compared to other factors that were determined.

So BMI was they had more kind of con controls in this, but not too many. They had BMI, which was deemed to be a significant contributor to the model, which is which makes which makes sense. And then they suggested that those who followed a plant post diet were more likely to be above that 60 and cut off for their depression.

For those without depression, higher diet quality was protective against depressive depressive symptoms. So those who didn't have a depression on the scale had a higher diet quality. According to the cross-sectional analysis, but it's potentially suggestive that a higher quality plant place diet.

I'm not sure they could have had it. It might have been nice to look at a cohort as well who had a high quality omnivore diet and to look at different attributes of that and to look at their depressive scores in line as well. But those, there is some indication that there is a relationship between a high quality and plant-based diet and a pattern towards reduced risk of depressive symptoms, which is contrary to a lot of the other cross-sectional papers that have been published.

Danny Lennon: Yeah, so, suggestive of that, and we can't know beyond these patterns that looked in this study, but you could imagine that would be similar for other dietary patterns, that if there is going to be an impact of diet, then higher diet quality generally is probably going to be more protective than something that is a very poor overall diet quality.

But importantly, you note that in situations where people did have a diagnosis of depression, the, even the high diet quality in this case didn't really seem to have an impact at least found in this particular study. Anything that stood out in that particular paper to you, Alan, before we move on?

Alan Flanagan: I thought it was a really useful addition. I think based on everything we've talked about before that it's important to quantify the kind of healthfulness of a plant-based dietary pattern. And, we've seen that even be relevant for other outcomes like cardiovascular disease. So yeah, again, although this, although the kind of the level of statistical adjustment was also light and it would've been really helpful to have a comparison with an omnivorous group also characterized along healthy and unhealthy.

And we typically also don't see that with omnivorous dietary categories. Which I think is a problem in some of these comparative research studies that are looking to. Basically look at differences between dietary patterns, defined along some degree of animal food inclusion or exclusion. But I thought it was just adding some weight to the argument that what we might really be coming back to here is a kind of an effect of total dietary pattern.

And we don't know Niamh said earlier, with a lot of those other studies that have just quantified, vegetarian diet without really any sort of dietary assessment in a lot of the studies then you know that this actually gives us a little bit more of a good insight into the dietary pattern, a more quantified dietary pattern that a lot of previous cross-sectional studies simply didn't do. And often really crudely defined. What constituted being vegetarian and certainly didn't necessarily consider other factors like diet quality or otherwise in that Ascarri paper.

Niamh Aspell: The meta-analysis that was published this year, I think one of the... they had highlighted in terms of determining vegan or vegetarian, a large number of the studies that they included had used a principle component analysis to identify the vegetarian dietary pattern which is just very different than, it's a more data driven approach. So it works by reducing variables at a food frequency data set, if you've got a lot of data collected and it's, it reduces the accuracy of what you're trying to determine.

But if you've got a very large data set, there is support for it. So it's essentially just like a correlation metrics of food intake variables to help identify different kind of common patterns of food consumption. And then you're determining, okay, they follow the same kind of thing that the vegetarian would.

So it's not necessarily comparable then to the other studies within that paper where I think a large proportion were just self-identifying to be vegetarian and then others then were determined based on my food frequency. But I'm at a more kind of basic kind of level basic interpretation.

So it, it's the same in all nutrition studies, isn't it? If we could just standardize how we're determining things and just all get on the same page, it would be a lot easier then to check all these results together and try and see what a kind of global Indication is, whereas, yeah, even some of the good, like that meta-analysis is quite good to a certain degree.

But the, what's come true, I think in all of the systematic reviews or meta-analysis is that the quality of the study, so the quality assessment of all studies has come out as really poor. So it's just this very, "junk in, junk out".

Alan Flanagan: Yeah, I think principle components and factor analyses can be really useful for actually identifying a dietary pattern and putting some definitions on what characterizes that pattern.

But that doesn't appear to have been done in that analysis as far as like a consideration of what was the ultimate pattern that came out that analysis. And it also, yeah it doesn't say, it doesn't imply that pattern was necessarily the same from one population to the next. Yeah, again, this is hugely, you can see, I think in their, in the far plot, in that paper, you can get a fairly good idea of the kind of spread of individual studies and the effect sizes in both directions as far as a suggestion of an increased risk of depression or a decreased risk of depression.

And there's no real pattern to it. And they did use like they did look at it as far as the pooled outcome as an effect size which would certainly the assumption would be it would, allow some degree of combin ability between studies that have used, different actual outcome measures.

Even still, for the couple of studies that show, a higher effect size in the direction of increased risk or the studies that show a lower effect size, like it just all washes out. Doesn't it affect to nothing?

Niamh Aspell: They included an L-squared statistic to try and determine the amount of heterogeneity between the studies and the one that they used. If it

was, over 50% in that statistic, then it would be indicating a high level of heterogeneity, and then that pools analysis. I think the overall's 82 or something like that. Yeah. So it's these are all just wildly different, but let's put them in and get a general conclusion.

But they did I think one of the important things in that paper is that they evidenced that, yes. They were really able to determine that heterogeneity and, they did find no association, but I don't think they were strongly saying, there's literally, there's no link here. It was more like there's no link in all of this. If we throw all of these pots and pans together, we're not going to find anything that we're looking for.

Danny Lennon: Yeah. So maybe let's finish on some take home messages if we can leave any for people. I think as we've discussed a number of times so far, this is a particularly messy literature base to use your term, Alan.

And particularly when we look at not only the studies that have been done to date, but with the outcome we're trying to address. There's a lot of complexity here. We've noted that there's a huge degree of conflicting results here. There's very little to take from either some of the specific studies or even from some of the systematic reviews and meta analyses in terms of clear conclusions, and there's certainly need for more work.

And what that should point to, at least for people, is that when they're hearing very strong statements in either direction about the use of a vegan diet, For increasing or decreasing depression risk, they maybe should take some pause. And certainly when people are using cause of language in that is probably a large red flag.

So with all that conflicting evidence and kind of confusion in trying to get to the bottom of that pragmatically, what are some take home messages you think are useful for people to take away when they're considering this particular topic or this question? If they either end up discussing it with someone else, hear about it online, what are some of the either interesting elements of the evidence base, do you think?

What are interesting components this question, or what would you leave them as your thoughts on this question? Do vegan diets increase depression risk? And maybe I'll start with you, Alan.

Alan Flanagan: So I think. When it comes to any of these issues, we obviously consider it through our lens, which is diet-nutrition. But I think the top line for any of this more 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 that we just won't get into cause it's not our kind of domain specific expertise in this context. Again, 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, if we think about meta analyses of even randomized control trials, 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 Marin, 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 or poor kind of standard western diet. Beyond that, is there any veracity that we can give to the claims that specific new nutrients of concern, if we are going to call them that 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. And ultimately, I think that those bases can still be covered in the context of a vegan diet. It's possible to supplement with an algal based EPA and d. It's possible to consume lots of bean green vegetables, polyphenols, all that good stuff on a vegan diet.

I don't think that the absence of meat can be considered to be causally related to these increases in depression here. But if someone makes a significant amount of changes in their food intake in a short timeframe and are not really doing much to consider what they're replacing those foods with, if you suddenly stop eating eggs and dairy and you just start eating.

The quote, the vegan junk diet, and you're just eating Cheerios with some almond milk now that's possibly not going to be optimal or ideal. So I think that dietary pattern quality in the context of plant exclusive diets is likely going to be, at this point, what we could say would be the best thing to do for people that do follow those dietary patterns.

Niamh Aspell: Yeah, I agree with it all. I think the most important point is that there's what we started the podcast on and mentioning kind of people who are quite influential and can push these diets and reach large audiences and kind of the Jordan Peterson's and not specifically talking about anyone, but I think there's a responsibility for certain people who are maybe not qualified to give that advice or also to give such stark advice that it, one specific diet is going to cure me of so many different things.

There's no, there's currently no research to support that. A meat only diet is going to be favorable. Long term if, if people are experiencing general benefits by changing their diet and becoming more restrictive on certain things, that might be an immediate response to removing " bad foods" as such (inverted commas) , but from the diet in the short term.

But then long term then there can be impacts there as well and it's also potentially due to a placebo effect and it just change will make people feel a little bit better. I think other things that were noted by a lot of these people who support these diets are generally, weight loss, other benefits that will help mood, but long term, do you want to just be eating meat every day? I don't think for the general population that's going to do anything to improve mood. I think it's quite dangerous, particularly with the cohort that we're talking about today, where there's maybe mental health issues or mental health challenges that people are quite impressionable or desperate as well to look for alternatives.

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, the disorder themselves. And I think that this is just really quite worrying that these are the broad, the broader kind of messages coming from people who maybe shouldn't be delivering the messages at all.

The final thing that in the last week, which I think is really interesting, is that Spain has introduced a new guideline for meat consumption. So it's a new dietary guideline by their food safety and nutrition group, where they are now recommending that people eat between zero and three portions of meat every week.

And this is based on, getting people to be more in line with the Mediterranean diet. This has also got, impacts in terms of environmental impacts as well on their food system. But I think this is an interesting, first, I think member state to do this, and I think that we'll probably start to see other member states to do this to the.

To do the same, but it's quite, I think it's big for Spain as they're also one of the, or the largest meat consumers in all of Europe as well. So it'll be interesting to see how that ts if it does t in any way. But I think we're going to probably start to see people encouraging a reduction in meat, but not, maybe not a total admittance altogether.

Danny Lennon: Yeah. So in relation to our question, conflicting evidence and be wary of absolute claims, particularly if they come from I dunno, doctors that walk around supermarkets with their shirt off shouting at vegetables, they might not be a worthy source of information. Yeah. So if you are indeed eating more vegetables in your diet, do not be concerned on that account.

So I think that does us for this particular question, a big thank you to Alan and to Niamh for all their input throughout this episode. For those of you listening on Sigma Nutrition Premium, you can get detailed study notes to this episode as well, so you can click through and hopefully that supplements your learning.

We will be back with more episodes very soon. So thank you everyone for listening in. Hopefully this has been useful and you've enjoyed and talked to you soon.