Episode Transcript

Alan Flanagan: Hello and welcome to Sigma Nutrition Radio. This is episode number 473. And as you can possibly tell by my voice I am Dr. Alan Flanagan, in relief of much needed rest for Mr. Danny Lennon. And today I think you're really going to enjoy this episode. We'll be discussing diet and depression research but specifically really digging into some methodological aspects of doing research in this area.

And there'll be a nice overlap between nutrition and psychology methodology and research. Today's guests on social media has been described as "a more cheerful version of me". That's not particularly a high bar. And given that she is a clinical psychologist specializing in cognitive behavioral therapy that is reassuring as well. I'm joined by Nicole Lippman-Barile. Nicole, thank you for coming on to Sigma Nutrition Radio. How are you?

Nicole Lippman-Barile: Hi. Thank you so much for having me. I am great. How are you?

Alan Flanagan: I'm good, yes. It's evening time here, so it's the end of my week. This is a good way to wrap it out. I think for our listeners, I'm sure some of them now are familiar with your work on social media but if you might give

them a little bit of who you are, what you do and a little bit of your background.

Nicole Lippman-Barile: Yeah, sure. So I am a clinical psychologist. I am technically trained in cognitive behavioral therapy. and I do specialize in the treatment of OCD and other compulsive disorders along with anxiety disorders and depressive disorders. So that's really what I do in my practice in terms of treatment. And, on the side, for fun and the slight obsession, I am really interested in the psychology behind beliefs and misinformation and how that plays out on social media and how that has infiltrated our current culture. So I spend a decent amount of time reading about it and then trying to make content about it to try to help people think about this more broadly instead of just person to person.

And I'm also still obsessed a little bit with the diet-mental health relationship and really care about being very accurate regarding talking about that relationship. If there is one that exists and try to do that with a lot of transparency on social media.

Alan Flanagan: Yeah, and I think, for people that are familiar with your work on social media, they'll know that a big focus of yours, which I actually think is quite unique in terms of talking about health information, misinformation and science specifically, is a real focus on language and how claims are often framed. Less so about the substance of the claim and more so about the rhetorical devices that are being deployed to either raise doubts or "dog whistle" to some conspiratorial thinking. And I think that's a really useful way for people to actually think about claims that they're hearing beyond just the technicalities of "is this the case or not?" and the language really matters. And I think certainly when we come to discuss one of the big hyped up trials of diet and depression, I think that's going to become important in terms of the language deployed potentially.

Nicole Lippman-Barile: Yeah, definitely. I hope it's helpful for people. I hope, I don't want it just to be entertaining necessarily. I do hope that it is actually helpful and helps to also orient people towards really what they can actually trust online.

Alan Flanagan: Yeah. And scientific accuracy. And I think, with nutrition there is a degree of truth to criticisms that abound of nutrition science and not

even just your generic "bro" on social media saying all nutritional epidemiology is worthless or one of these kind of blanket statements that I just don't pay attention to anymore. Within the published literature, there are a lot of quite strongly argued claims against nutrition as a science; it's reliability, it's validity, and there are grains of truth to some of the critiques. And then some go too far.

One, of course is the nature of the intervention itself. Diet can be difficult to really conceptualize. It can depend whether we're talking about just a whole food dietary pattern whether we're talking about manipulating specific macronutrients or whether we're talking about specific micronutrients.

And actually each of those layers are important with the picture of diet and mental health generally. And obviously related to depression. And it is a difficult science to conduct good intervention trials because it's messier than simply allocating people to a pill and comparing that to a zero exposure.

And I think that's going to be focus of what we discussed today. So just for listeners, one thing that's important as a recap, it's something Danny and myself have discussed on the podcast before when we're getting a bit technical about methodology, is that just because a study is a randomized trial and comes out with a finding does not necessarily mean that we can then make causal claims in relation to whatever the intervention was.

There are assumptions that go into the internal validity of an RCT; i.e., how well external factors were controlled, and those assumptions need to be satisfied if we're going to make a valid causal inference. And there's a number of these but I'll just highlight a few. One is that we, make an assumption of exchangeability. So when we randomize participants to an intervention and control group, we want them to be relatively as similar as possible on important characteristics. And then an assumption of randomization is that if there are characteristics we don't know about yet, then they are equally distributed between those groups.

So the principle here is that when you deliver the intervention, the only difference materially between the intervention and control group is that intervention that can be difficult to do. And as we'll discuss with some of the diet and depression research, you basically have two wildly different groups doing wildly different things.

And another assumption that's really important is that after randomization, you don't have additional variables that are introduced that could influence the outcome. Again, when we discuss diet and depression research with Nicole today, a big part of this is going to be that there are additional layers to an intervention in terms of how much time they're getting with a practitioner who's delivering the intervention and what they're being compared to. That's all going to really matter.

I think before we get into the specifics of any research, Nicole, I know put out some content related to some of the diet and depression research. What are the big picture points that you'd like people to have in their mind as we move forward discussing this area?

Nicole Lippman-Barile: That's a good question. I have come, I think, to a conclusion around where I think diet might matter for something like depression. So based on things that I've read in my in specific studies and also in these meta-analysis, it seems to me that if you have mild depression without any sort of extensive mental health history or any sort of extensive medical history, then changing your diet, perhaps, especially if your baseline diet is one where it's not really including what we consider a healthy dietary pattern.

If you're, especially if you're starting from there and you have mild depression, and again, you don't have that other larger context of extensive chronic mental health issues or other sort of medical conditions that can exacerbate that. Then perhaps changing your diet to be more nutritious, to be what we consider a healthy dietary pattern that may produce some positive results in your depression symptomology, maybe.

Alan Flanagan: Okay. So the severity of the condition itself at baseline is an important moderating factor for the effect in that. A question that I would have is do we know even from wider psychology research, whether the measurement tool, because I note from the research there are various different tools used to assess an individual's depressive status is, do we know from wider literature whether the tool itself there are differences in potential kind of magnitude of effect depending on what's used to measure depression or anxiety?

Nicole Lippman-Barile: Yeah, absolutely. So there are plenty of reliable and valid measures to assess both depression and anxiety, and they can be good. However, if we're comparing that to a clinician who's evaluating someone, that's going to look very different. The clinician is going to be sensitive and is always, and is also going to look for additional information outside of just what the questionnaire is going to be asking the individual.

So a questionnaire can be really good at identifying the core symptoms of... let's say if we're talking about depression, it can identify the core symptoms. It can even try to quantify that in terms of severity for a person, and that could be very valid. However, if you're comparing that again to a clinician, there's going to be a difference in terms of sensitivity.

There's going to be other things that the clinician is going to ask that there's going to be outside of those core symptoms, and that's going to create a bigger, more in depth profile about the person in front of you, right? So it'll give you additional and more specific information.

Alan Flanagan: So if a clinician is delivering an assessment this is introducing a degree of subjectivity in the assessment or in the ultimate grading of that individual's depressive status?

Nicole Lippman-Barile: When I am meeting with someone for the first time, a first session is typically a psychological intake. So that's the evaluation, right? So if I'm using, let's say it's becoming pretty obvious that this person has major depressive disorder as an example, and I'm using as an additional sort of tool to validate that.

So sometimes clinicians will do that as a way to validate what they're thinking as a potential diagnosis. It also helps for rule outs. It also helps to provide measurements going forward in terms of looking at progress. So it's a helpful tool from that, like clinical kind of perspective from people.

But I think, as a clinician, just because I do this and also I've used measures is that thinking broader than just the measure, right? You're thinking that this is important, like these questions matter and this information is good, but there's usually other things that you want to understand outside of the questionnaire that's going to give you more of a valid diagnostic, especially because that's what we need to do during the first session anyway. So it's a

good tool. But there is, I think the clinician also, because, we have the training and we have the expertise is that you're looking at a whole picture, not just specific core symptoms as well.

Alan Flanagan: And so that, I think brings up a potentially interesting factor to consider with the available evidence from intervention trials, which is to what degree are these trials like in your assessment, say that the interventions that you've looked at, having that level of practitioner influence or input on the tool being used, the measurement method being used in a given study.

Nicole Lippman-Barile: So I haven't come across many studies that are using a mental health professional who's providing the assessment and doing the assessment and evaluation. I can't even recall, to be honest if I've even read that. There may have been. I think there is a meta analysis from 2017 that talks about maybe one study that ended up using a practitioner. But that's the only one that I can really recall that's done it.

Alan Flanagan: And this is my sense of it as well, is that most of the assessments, obviously in these nutrition interventions are delivered by nutrition researchers. And then of course, the dietary interventions delivered by a dietitian or a nutrition professional. Though there are some studies where the delivery of the dietary intervention has not been from a qualified nutrition professional they actually are differences in outcomes observed. But that's one of those methodological points that I think we'll get to.

I think a good point of departure is the Opie and colleague systematic review from 2014. And this was not a quantitative synthesis, so this was just a systematic review of evidence with no meta analysis. But we will on to discuss the most recent meta analysis of these intervention trials next. But for me, the systematic review itself threw up some interesting, points and tabs that we can open.

One was that in terms of the magnitude of effect, the reported effect size range from 0.19 to 2.02. For people listening, although there are various crude definitions for what is a small, medium and large effect size, and it may differ from field to field. As a general rule of thumb, an effect size of say 0.1 to 0.2 is... 0.1 would be considered negligible, 0.2 to 0.4 would be considered in the range of small to modest, and 0.5 to 0.7 would be considered

medium/moderate effect size. And anything over 0.8 would be considered a large effect size. So if we're going from 0.19, which would be a fairly small effect size to 2.02, that's an enormous swing and really indicates that there is quite substantial variability in the magnitude of effect that is likely being influenced by some of the factors that we've discussed already and perhaps even more.

But one of the findings from this systematic review was that of the studies reviewed and there was about 17 reporting depression, 85% of those studies had a positive outcome when the intervention was delivered by a professional. And then less than half, only 44% of studies had no difference between intervention and control group when those studies were delivered by, for example, just a postdoc researcher or a layperson.

And obviously this isn't even talking about clinically, a clinical psychologist or psychiatrist delivering the intervention. This seems to me to be quite an important point that who is delivering the intervention really matters. What do you think is possibly going on here in terms of these differences?

Nicole Lippman-Barile: I'm thinking back to when I was a postdoc, and I'm not going to say how many years ago that was, but obviously you're still in the process of learning and at that point you don't you don't have as much clinical expertise and experience at that point.

At least I can only speak in terms of being a psychologist at that point. I maybe were seeing patients for three years versus now, it's 10 plus. So there's a wide, I would say there's a very big difference in terms of just having experience and understanding what to look for, knowing what the subtle signs of depression are, understanding what's a warning sign.

You might not pick that stuff up, if you don't have the clinical experience there. And that can only really come with clinical experience in treating people. So I think there's a level of sensitivity that's not yet there, not yet developed. So I wonder if part of maybe something like that.

Alan Flanagan: One of the things I know we've discussed this just privately is I guess two factors that could potentially be just of relevance in the totality of this diet and depression or anxiety intervention research is... One, it seems to me from wider I was looking at this for a deep dive recently, and it was a

systematic review of and meta-analysis of CBT, cognitive behavioral therapy, trials.

And basically their main conclusion was that the strongest predictor of beneficial outcomes in participants was the intensity of the intervention. By "intensity" in this context, for listeners, we mean the number of contacts a participant or patient has with a practitioner, like how many times are they face-to-face. So that was one.

And then the other is this concept that I'd never heard of before called "behavioral activation". And I wonder, just sitting with that finding from that systematic review of, this positive outcome when it's delivered by, and in this case it's a nutrition professional, not even a mental health professional, but between these two factors, the intensity of an intervention in terms of practitioner contact and the potential for behavioral activation whether you could speak around those points and what we know from some of the wider psychology literature even on these issues.

Nicole Lippman-Barile: Yeah, absolutely. And to that point of frequency of contact, the other really strong predictor of positive outcomes is the therapeutic relationship. It's literally the rapport that you have with your practitioner. This is despite the treatment that you're doing that's really seen across the board so that's also suggestive of something as well.

But to the point of behavioral activation. So maybe I'll speak like broad and specific about this. Behavioral activation is technically, it's a behavioral treatment for very much used for the treatment of depression. And it's typically used under the framework of cognitive behavioral therapy or just doing sort of straight behavioral therapy and the whole thinking behind that treatment.

Like the reason that treatment was created was because of the behavioral theory of depression. And basically the hypothesis was that depression was caused by these low rates of response contingent positive reinforcement. So basically meaning that a depressed person's environment is basically devoid of opportunities for a person to experience positive reinforcement.

And usually things that allow us to do that are things that also allow us to feel a sense of mastery and a sense of pleasure. So the thinking was that, okay,

creating a treatment around this theory means that we start getting the person to increase their engagement in adaptive behaviors that will allow them to access positive reinforcement, to access feelings of mastery and pleasure, and at the same time also decrease their engagement in withdrawal behaviors or anything that would exacerbate their depression.

So behavioral activation is literally like to, its basic core in terms of what that looks like in practice is first, we're getting a person oriented towards: your behaviors affect your thoughts, they affect how you feel, they affect your future. Like they, it is all this triad, right? So it's getting a person oriented towards that, and then it's getting a person to start connecting what, how do you feel after X?

How do you feel when you do this? How do you feel before you do this? What's your thought process like? It's getting a person to be really aware of these connections. And so that the next step is helping someone increase engagement in these adaptive behaviors. And that's going to look different from person to person, depending on what's going on in a person's life.

Someone with severe depression, they might not be able to get out of bed, right? So literally a behavioral activation would look like, okay, at 10:00 AM I want you to stand up out of bed and go downstairs into your kitchen. Like it would literally look like that. And for someone who has more mild depression, that's going to look different. Maybe that's about less social isolation and getting a person to actually schedule in their week: "I'm going to call my friend on Friday at three o'clock", or "I'm going to go to lunch on Saturday with my friend at 12 o'clock". So behavioral activation is a very active strictly behavioral approach to treating depression, and it can work really well.

Alan Flanagan: Okay. And is the magnitude of that effect, am I right in recalling greater in people with mild depression? Rather than more severe forms?

Nicole Lippman-Barile: Yeah, greater in, I would say mild to moderate depression.

Alan Flanagan: Yeah. So for people who are, in a trial randomized to the intervention group and told they're going to make these changes and, not all

of these trials are necessarily disguising the intent of the intervention very well. So there could be this expectation of "oh, great I'm going to be eating my omega three s now, or all these greens." Is there the potential that making dietary changes that are perceived to be positive for that individual's health could trigger this behavioral activation or give rise to it?

Nicole Lippman-Barile: I think so. I think, to be honest, the way that I think about it is that's inherently what's going on. Yes, you're telling a depressed person to start cooking for themselves at home. Even if you just take the action, forget about the content of the food, you're asking someone to engage in a adaptive behavior on a regular basis, right?

So cooking for themselves regularly and trying to stick to that. And not only is that what's happening, the dietician or whoever is also administering the instructions and treatment is also problem solving with them, such that they adhere to this protocol as best as possible. So you really are actually, my argument is really that I think you're actually doing behavioral activation. That's the form of treatment that you're doing regardless of the diet, that you're actually getting a person to eat.

Alan Flanagan: Yeah. And that, I think, opens up some interesting elements in this literature. One of which I think this is really the last aspect of the systematic review, we'll discuss before we move on to the meta-analysis.

But what they found in this systematic review was 100% of studies that resulted in no significant difference between intervention and control groups for depressive outcomes were told in the intervention group to reduce red meat or select lean meats or to follow low cholesterol diets, or were told to lose weight.

And I remember, because obviously we had spoken about the behavioral activation thing before, and then I read that and I thought "could there be an inverse effect?" If people are told to do a behavior that they're like, I don't really want to do this. I don't want to eat chicken instead of my steak. Could there be, an opposite effect essentially terms of like mood generally that we end up seeing no difference in the intervention versus control group.

Nicole Lippman-Barile: Maybe. If you get a carnivore bro in there, then yeah, you're definitely going to have that. Yeah.

Alan Flanagan: Yeah, if it's perceived as a negative or some form of behavior that they actually don't want to do. "I don't want, I'm not trying to lose weight or I struggle to lose weight or,.." . I find that interesting.

Let's, I think because, we'll circle back to that particular point with some of the outcomes from this meta analysis. So this was, this is the most recent synthesis of the evidence from randomized control trials in diet and depression or anxiety.

It was by Firth and colleagues and it was published in 2019. So they included 16 RCTs quite for dietary interventions. The total sample size in the meta-analysis was 45,800 people; non clinically depressed participants in 15 of those trials. And so going to Nicole's point about, the severity of depression being a very important potential moderating factor in relation to outcomes. The one trial in which individuals had a diagnosis of depression was the SMILES trial. But we're going to discuss that in its own right separately. We'll park that a little bit for now.

Basically, in the systematic review there was quite a wild spread of effect sizes. The meta-analysis probably gives us a slightly more representative quantitative synthesis of the evidence in this area and the overall effect size from these dietary pattern interventions - so these were not manipulating a single nutrients or macronutrients - was an effect size of 0.28. So this is in that small to modest effect size range. And this was compared to the control.

But a really interesting finding within this was that whether the dietary intervention group was compared to an active control or an inactive control, the effect size differed rather substantially. So an active control is where the control group, for example, maybe aren't changing their diet, but are still getting some form of or some other active aspect of the intervention. Maybe for example, the control group are exercising but making no dietary change and the intervention group are making dietary change and exercising. So it's an active control. And an inactive control is where the placebo or control group are literally just being told "carry on with your habitual diet routine, whatever". And the effect size versus an active control was 0.17. So this is a negligible effect size really, whereas the effect size versus an inactive control was 0.30. So it's still in that small to moderate range, but it's really getting up towards more of the upper end of the small to modest effect sizes, more towards moderate effect sizes. So clearly, the level of intervention, so to

speak in a control group or whatever that control group is doing, is influencing the outcome.

And I think this goes to your theory that in fact, diet itself is possibly having exaggerated effect sizes in certain contexts. And actually in terms of if we were trying to isolate the independent effects of diet, it really may not be that much of a significant factor relative to other of these behaviors and otherwise we're talking about.

Nicole Lippman-Barile: No, absolutely. And that I think highlights that really well, because there's such a clear difference that exists in there.

Alan Flanagan: So one of the, I think, interesting aspects of this analysis as well, and I wonder whether you could speak to this because I have no idea what could possibly be going on, but there were completely oppositional directions of effect relative to sex in the trial.

So the studies in which there was a positive effect size, i.e., the dietary intervention was shown to have or was associated with, I think is better language to use for these trials, with an improvement in depressive symptoms in trials that had majority or 100% female participants. In trials with majority or 100% male participants there was an inverse effect: i.e., Their depressive symptoms worsened. What's going on?

Nicole Lippman-Barile: I would wonder, I would want to know was the adherence rates as equal in terms of their down dietary adherence?

Alan Flanagan: I think to be fair, because the...and nutrition is one of the very few fields where women are in fact overrepresented relative to burden of disease in the population. The norm for biomedical research on the whole is that women are underrepresented relative to the burden of disease. In the general population that isn't typically the case with nutrition. And so one thing that I think that a pinch of salt I would take with this is that the vast majority of the weight in this meta analysis was driven.

So the female participants, for example, in those trials, there was eight trials in total with the majority female participants. Nearly 18,000 participants in the intervention and 26,000 in the controls. Whereas in the male, or either majority or all male, we're talking about 300 in total in the included trials. So I

would be conscious of the potential for the much smaller sample size to be influencing it.

But I guess the question is, do we know even independent of diet research, specifically from wider psychology or psychiatry research, whether there is some form of noted sex difference in responsiveness, even if it relates to some of these factors like behavioral activation or otherwise, where, for example, female participants are more receptive to the change or more willing to engage or adhere. Do we have evidence of that from wider literature?

Nicole Lippman-Barile: Not that I think of. The only the one sex difference with regards to depression is that females tend to have higher rates of depression than males. But then sometimes that comes down to a question, are males just not seeking help or they're not seeking evaluations, but so that's that is the one sex difference. That's been pretty constant as it relates to differences related to depression. But in terms of engagement in treatment or willingness to engage or let's say form of treatment with regards to sex differences? I don't know. I don't know if you have that. Really.

Alan Flanagan: Men have stoicism now... so you know what? They don't need therapy. (laughs) They need Marcus Aurelius quotes!

Nicole Lippman-Barile: Or Jordan Peterson.

Alan Flanagan: And a carnivore diet.

Nicole Lippman-Barile: That's what it is, maybe.

Alan Flanagan: Carnivore and stoic philosophy. Yeah.

Nicole Lippman-Barile: Supplement yourself into stoicism.

Alan Flanagan: Yeah so I think for this meta-analysis I think the most interesting finding is this difference between active and inactive controls.

And this really says to me that if we're trying to isolate the independent effects of diet, then it doesn't look like diet as having any sort of particularly spectacular effect size. And that the question that I have then, and I know

we've spoken about this privately, is can we actually attribute this effect size to diet?

And this is why for listeners, I introduce those assumptions of randomization beforehand, if we're going to make a causal inference that the reason that there is this effect size is because of the dietary treatment, but we know that there are factors like number of practitioner contacts, like the therapeutic alliance, like the expertise or experience of the professional delivering the intervention, like the fact that just simply making a change that they perceive to be positive is itself going to potentially be improving mood. And if after all of that, when it's compared to an active control, that's also doing something given an effect size of 0.17... I think there's a legitimate question to ask as to whether diet is in fact explaining any of this relatively negligible effect size, independent of say the dietary changes the behavior that they're doing and receiving some sort of positive effect. Do you think that's a fair assessment or are we going too far?

Nicole Lippman-Barile: So fair. So fair. You're reading my thoughts. And also to add into that, because again, this is where there's a lot of complexity here. The other thing that we know from just behavior change research is that if you tell someone to track a change, that within itself tends to start improvement.

So if I just said to you "I want you to start tracking how many times you meditate this month", and without giving you any instruction about increasing your meditation practice, likely what's going to happen is that you're going to increase your meditation practice simply because you're aware of it and you're tracking it. So there's another aspect I think that's potential influence.

Alan Flanagan: I think I'd go the other way (laughs) ! I end up with anxiety. I end up with anxiety because I miss a day and I can see it in the calendar that it's recording and I'm like "I can't change that. I can't have that day back." It's why I had to stop tracking my sleep. Those things I end up going... ,they don't help me. (laughs)

Nicole Lippman-Barile: Yeah, no, that's fair. That's another thing we tend to see more, more often than not.

Alan Flanagan: And this is really interesting because, in their discussion, and we're still on this meta-analysis now, they made the point that while improvements, positive effects for depressive symptoms were observed in studies where the control was inactive and where the control was active.

So there must be a benefit of dietary interventions beyond just general intervention effects. And I think this is the point that we're really raising a few question marks over whether we can actually substantively make that claim with any confidence which I think really leads us to the trial that everyone thought solved everything...

So in the previous meta analysis of 16 trials included 15 were in nonclinical depression. And as Nicole has outlined, this is a really important factor to consider in terms of some of the outcomes and indeed the magnitude of effect. But the one trial that was actually in individuals with moderate to severe depression was the SMILES trial, conducted in Australia.

The initial trial findings were published in 2017 and the SMILES trial was a 12 week randomized control trial parallel group. So the intervention group and the control group ran at the same time for the 12 weeks and what they were looking at was an adjuvent dietary intervention. So the participants being moderate to severe depression were either engaged in therapy and/or on pharmacotherapy for their symptoms.

And then the intervention itself was a modified Mediterranean diet. What you would expect in terms of general best practice for a good old Mediterranean diet, increasing dietary fiber, fruits and vegetables, lowering saturated fat, increasing monounsaturated fat intake, adequate omega three s and all this good stuff.

But as far as the intervention goes, the participants in this group received seven individual dietary support sessions that were an hour long delivered by an accredited practicing dietician. There was weekly sessions. For the first month, and then biweekly sessions thereafter for the remainder of the intervention.

The first sessions were about getting them up and running with the diet and confident that they could execute the diet and adhere to it. And then the subsequent sessions used motivational interviewing techniques and also

encourage the participants to set personalized goals. Now, the comparison control group was something that they called social support.

And this was essentially what they termed befriending protocol. Now, in the paper they said befriending is commonly used as a control group in psychotherapy interventions. What befriending consists of is that neutral topics are discussed with our participants: sport, music, the news. And the aim is to retain that neutrality in the conversation.

So if the individual didn't want to talk about that, they'd play a board game or something like that, or a game of cards. So the aim was just to keep participant engaged, but the actual I guess the emotional charge, relatively neutral. So this was the control. There was no instructions in relation to diet. And there was a continuation of whatever treatment that they were getting otherwise.

And over the course of 12 weeks, the between group difference was an effect size of 1.16. That's enormous for a nutrition intervention generally it's enormous. For a psychotherapy related intervention it's enormous. And there were similar effect sizes for other metrics. So I think there's a couple of layers at which we'll start to work through this Nicole, because there was the actual tool that they used for the primary outcome: the Montgomery Asberg Depression Rating Scale. And then they also used other rating scales.

I think before we so we've discussed the kind of the effect size of the primary outcome. I think there is also, in terms of the within-group differences, the effect size for the control condition was 0.63. So although we obviously this trial blew up and did the rounds everywhere and actually continues to get enormous press because of the effect size the intervention compared to the control group, what's overlooked is that the control group themselves still had an effect size that is greater than the average effect size in cognitive behavioral therapy interventions, in antidepressant interventions, and basically larger in the effect size generally than like drug trial placebo comparisons.

So I think at the outset, I think let's start more at the design level before getting into the results of the kind of characteristics we've been discussing. One was language and this concept of expectation bias or expectation effect. You've mentioned the language used in recruitment and in delivery of the

intervention in this. I wonder if you could yeah, just expand on that and how it may have played into this enormous effect size.

Nicole Lippman-Barile: Yeah, so within the paper there's the section called "sample recruitment". So the last line that they have there, it says "ethics committee requirements meant that we needed to be explicit regarding our planned intervention with the advertisement stating, we are trialing the effect of an educational and counseling program focusing on diet that may help improve the symptoms of depression". So already you understand the point of the study, you understand what we're trying to achieve in the study. You have a lot, that's a lot of information that a potential subject is faced with before even being introduced to anything related to the methodology or being randomized. So that's I would argue too much information for someone to know before engaging in any form of treatment.

Alan Flanagan: And then in terms of some of these factors that we've touched on there was two things that struck me in the methods. One was this use of motivational interviewing specifically. And then the second was that they were asked to set personalized goals. I know we just joked about tracking but in this context how might these have... because it's not now just a dietary intervention compared to someone pretending to be the control participant's friend.

Nicole Lippman-Barile: Yeah, that's true. So if the addition of personalized goals, so that to me as a clinician, translates into behavioral goals, right? So this is about orienting a person towards positive and adaptive actions to try to work towards that goal, right? And when you have support and you have a personalized goal, that's a very powerful combination in trying to actually achieve that kind of goal, right? So I think that it beyond just like that, is very different than just asking someone to adhere to these instructions in this sort of diet, right?

So it also introduces another cognitive element perhaps, like this is me hypothesizing, but again, if we're asking someone for a specific goal, that to me is sometimes connected to values. So that goal is going to differ from person to person, depending on what it is that they value, based on their diet, based on their lifestyle, based on what they want for their life. And that's a different cognitive orientation to make towards somebody versus again, just saying, here's the instructions and just follow these instructions.

Alan Flanagan: And so we've got this, we've got these additional layers now to the intervention beyond diet. One thing that I thought was interesting I know that in their statistical model there were there was consideration of for example, like the treatment order, the interaction between treatment group and like the assessment occasion as they called it.

So that the actual contact that the individual in the intervention group is having with a dietician and control group is having with their pretend friend. But it doesn't seem to me that there has been any real attempt with their modeling to account for the treatments that were on.

When I look for example at this, at baseline in, 69% of participants were on psycho pharmacotherapy. 45% were getting psychological therapy. This was relatively similar numbers wise between intervention and control group in terms of its distribution. And so again, if we're going back to those assumptions of randomization, we might say this factor was equally distributed between groups, but it seems to me that you're then introducing this additional factor.

So if they're getting psychological therapy and now you're adding motivational interviewing techniques and personalized goals into the mix it looks to me, based on everything we're discussing, like an additional variable is being introduced post-randomization here that's beyond just a little bit of a Mediterranean diet.

Nicole Lippman-Barile: Yeah, I agree. I would also add onto that, that here's where I think another important element exists, which is that participants were provided with food hampers and they were given recipes and meal plans. Now you think of a clinically depressed person. You have now just eliminated significant obstacles and roadblocks for them to start actually engaging in this practice. And that, that's very different than something else. So I think that's another treatment element actually that's being provided, right? Because again, inherent within depression is the ability for people to engage in these things.

 If you're providing ways that make it easier for a person to do this of course that's going to increase their engagement in, again, a very positive behavior. And again, it's a goal-oriented behavior and that is hugely positive for a depressed person.

Alan Flanagan: Yeah, I think this is all very I guess damning a little bit to the idea that there are isolated effects of diet because based on the design and execution of the study isolated effects of diet have not been separated from some of these other component parts. There was an editorial published in response by a group in the Netherlands, in a psychology department at Leiden University in the Netherlands. And what was interesting was they noted that on the recruitment, so you were discussing, material that they had to be explicit about the intervention to participants. But it looks like even in the recruitment the study's website, there were messages and they have quotes here: "bananas look like a smile, but can also help you smile because they contain tryptophan, which is a mood stabilizer" or "banana, Brazil nuts, broccoli: they all have something in common apart from starting with the letter B. They all contain nutrients which can stabilize mood" or for example, "the fear that we are eating our way to depression is prompting governments to take action".

And that was accompanied by testimonials, including "the solution to my depression is good quality food". And th this seems to be unsubtle, let's just put it that way I think if we're being kind. And so the potential for an enormous level of expectation to be created by someone with moderate to severe depression, wanting to participate in research, showing up and being told that the solution to depression is good food and bananas will smile because tryptophan or something huge.

Nicole Lippman-Barile: Yeah that's a huge influence. So based on that, and I think even just their other advertisement that's already I think two major red flags and being really cautious about interpreting any of this.

Alan Flanagan: And again, typical of these very imbalanced intervention trials and at the start, I alluded to, there are criticisms of nutrition research. Some of them go a bit too far and lack a bit of context or domain specific knowledge. Some of them are on point and one of them that's on point is you have these really imbalanced arms in an intervention where you end up having quite an excessive dropout rate. Now, statistically, I know that they used intention to treat and but again, you're talking about the potential I think is too great in this trial that there was such a difference in the type of treatment that essentially this befriending control seems to me to be fairly inactive. I wonder whether you think that would be an accurate description

of having a neutral conversation about sport or playing a board game? Would you describe this as an inactive control?

Nicole Lippman-Barile: That's hard because from a clinical perspective, getting a depressed person to connect with a person on a topic for an extended period of time, multiple times sounds like an intervention. They were calling it social support intervention. That is what it is. But that is in itself can be very powerful for a depressed person because, and it's depends on their symptom profile; let's say that person is isolating and then, and now they're put into a group where they get weekly contact or every two weeks they have the same contact. How, probably, hugely beneficial that is for that person.

Alan Flanagan: Okay. So it's not, and again I think it's important to remind our listeners that even the effect size in the control group seems to have been quite large in and of itself. So a benefit in the control group over 12 weeks to what that benefit was attributable to, of course is a different matter. Because again, we're talking about participants who are the majority or certainly the majority are on psycho pharmacootherapy, and half are on or engaged with psychotherapy.

And again, one has to question then whether some of these other factors like therapeutic alliance et cetera. They do mention in their methods that befriending is aiming to control for those relative to the intervention group. So it's aiming to try and control for therapeutic alliance, the expectancy compared to the intervention. And perhaps with the effect size we obviously see it benefit. Nevertheless, it seems that just at the basic level of principle of executing well conducted randomized control trials to isolate the independent downstream effects of an exposure on an outcome. I just can't say that they've achieved that here because the ideal design that would've achieved, that would've had the control group getting about as much of a replication of what the intervention group were getting. So even if they weren't getting dietary counseling in the weekly sessions, that they were getting the motivational interviewing and personalized goals and these other additional factors that were introduced in the intervention group. I think you have to hold as many variables constant in your control group other than diet. And I just don't see that being achieved in this trial.

Nicole Lippman-Barile: I agree. And I don't think it's been achieved yet. I know that there was another more recent study, I think it was called the "AMMEND" study. It was like a three week really short intervention, I think using college males and very similarly large effect sizes. Not as large as this. But again, I see the same problem, the same issue as some of these factors just not being accounted for. And so the assumption then is "oh, it must be diet". But must it be?

Alan Flanagan: Yeah. I think people, and I see this really with the diet and mental health research overall, they want it to be true. And so if the conclusion is there for them to take, they'll take it. Because everyone wants, diet to be as potent as drugs because it means no one has to go on drugs then and so everyone wants a treatment to be natural because then they don't have to go onto an unnatural treatment. And all of these fallacious thinking, that I guess you become quite familiar with if you work in health sciences generally speaking, or nutrition or psychotherapy.

With this overall evidence, then I think we could possibly characterize it as the SMILES trial really is an anomaly in terms of its magnitude of effect as an intervention. It did not achieve isolated, independent effects of diet such that we can say that it was the diet that led to this enormous effect size compared to the control.

Which brings us back to that Firth and colleagues meta-analysis and possibly, again, that's more a true reflection of the overall effect of diet on depression, which is a fairly small modest effect. in summary and then even within that small effect, how much can we actually attribute to change in diet versus some of these other factors? Would you think that's a fair summary?

Nicole Lippman-Barile: I do think that's fair. I do. And I think that the, there's things of within the SMILES trial, I think that could have been perhaps written more accurately because there's clearly a benefit. But however, I think that the fact that it's just being attributed to diet is just missing so much other information.

To me, even their hypothesis, if you look at the hypothesis that stated in the paper: "It's hypothesize that structured dietary support focusing on improving diet quality, using this diet model would be superior to a social support control". Inherently, within that, they're acknowledging structured

dietary support. But then if you look more at the conclusion, it says in summary, this is the first RCT to explicitly seek to answer the question, if I improve my diet, will my mental health improve? But that's not what happened. That's not what you tested.

Alan Flanagan: Yes. That's, yes. Absolutely. Again, yes, your attention to language coming through I think that's really important because I, I see this basically as the standard kind of interpretation now for this literature overall I see people really eager to reach a conclusion that diet is the causal variable in improving depression and or anxiety. The SMILES trial is typically the first in line as a reference to support that claim. And I agree that the hypothesis has way more of an intervention that sounds more like a psychotherapy intervention to me anyway. And then the conclusion is then this broad claim in relation to kind of diet and mental health which is very different from the actual nature of the intervention that was delivered for this study. Yeah, exactly.

Nicole Lippman-Barile: And I think that, that could have been be better like summarized because it would've been legitimate to say: a structured dietary support intervention conducted by a registered dietician helped to improve depressive symptoms. You could say that. Sure. Not that dietary changes improved depression. It, there's just so much more that's occurring for people and it's hard and similar to nutrition science, psychotherapy research is hard because there's also a lot of variables that are just difficult to account for. How do you account for the therapeutic alliance?

Alan Flanagan: And I think this is, although we are obviously, coming in with some strong critique here it's not, like any sort of overall negative on researchers who are trying to do good research because, as you've said, like both our fields are very difficult to conduct randomized trials. And part of the problem is the paradigm of research necessarily that we're trying to operate in very much assumes that we can take a "drug trial-esque" approach to RCTs where we've got just an intervention and that is not in your control group and you can have this straight comparison between your exposure and a zero exposure.

And there's so many moving parts to this that I think it's just very difficult to try and account for all of this and execute in an actual trial. But I do think in

terms of nutrition, certainly as a field trying to improve its credibility. I think these are the hard design questions that we need to start thinking about.

And part of the problem with nutrition, to defend it a little bit, is it's grossly underfunded relative to the burden of disease in the population. I think it's just recently increased, but historically it's been 5% of NIH funding, for example, in America. So the resources and critics of nutrition science turn around, they say this is just terrible. This is 67 people, large effect size, come back to me when you've done a proper RCT and it's give them the money to do a proper RCT. I just have an appreciation that conceptually we can, discuss this stuff, but unless the resources are there, to allow for a scale of intervention to be developed that truly provides the ability to isolate independent effects of diet, then we're likely to, still end up with these small trials producing, fairly inflated effect sizes and not conducted with a level of methodological rigor that actually allows us to make any sort of causal conclusion in relation to diet.

Nicole Lippman-Barile: Definitely. And, as a clinician I would love diet to be efficacious for people who are depressed. For people who are anxious, that would be wonderful. That would be a, another tool to use for people. And that's exactly what we need. However, I just think we really need to be cautious, otherwise we're going to create this narrative. And we don't need more. Incorrect wellness narratives around food anymore, right?

Otherwise, we're going to this narrative around: "okay, you're depressed. The first thing you should do is change your diet". And that is really the completely wrong interpretation and assessment here. So I think us critiquing this is more about like, how can we make more accurate interpretations around this so that this actually helps a clinical population who is in desperate need, actually desperate need of alleviating their suffering.

Alan Flanagan: Yeah. I don't think that we can divorce research from the social context in which it's occurring. And of course right now we have this big problem, I guess with "wellness culture" and people with any number of serious health conditions whether of the mind or physiology, metabolic, for example are being led down the garden path by thinking that is going to be a cure causative, intervention for whatever condition they have.

And I think there's some really dangerous expectations with that if it's at the expense of proper treatment with a psychotherapist, for example. Or, if it's at the expense of chemo, there's horror stories out there in that, in oncology about people saying "no, I'm going to, juice, raspberries and whatever". I do think we need to factor in moderating the message of what it is that diet may and may not do when it comes to depression and anxiety.

Nicole Lippman-Barile: Yeah, definitely. And I also think that, because nutritional psychology, nutritional psychiatry is becoming something it's starting to become a field. I hope, I don't get crucified for saying this, but I, there's sometimes where I feel like we are on the verge of being pseudoscientific because the claims that are being made are, again, my opinion are being overly exaggerated. And there in lies the danger of this not being respected as a really true scientific discipline.

Because if we're not actually following the current literature and the data that we already have and not looking at this critically, then we are going to go down nutritional psychology and nutritional psychiatry can easily go down that path. And I really would hate to see that happen. .

Alan Flanagan: Yeah. Yeah. And I think you're right. That's the danger when any area and the researchers in it, and I'm not making any claims, for example, that any of the researchers involved in the SMILE trial, for example, fall into this bracket. But we see this in different disciplines when and I could name a few in nutrition not in this particular area of diet and depression or mental health, where they become essentially activist scholars.

For whatever outcome they suddenly have decided they believe to be true. And I think it's a really dangerous place for any area of scientific inquiry to get to, and particularly for the researchers in that area to get to. And I have to concur that I notice in the rhetoric around nutritional psychology and psychiatry, that the enthusiasm really is out over its skis in relation to the evidence.

And I think we need to temper that expectation. I think we need to really stop using causal language in describing these outcomes of these interventions. In reality, I think that these are not really more powered than a prospective cohort. The idea that they were randomized, making them of greater

methodological quality really doesn't hold relative to the assumptions of randomization that we outlined at the start.

And I think when we really synthesize the evidence and we end up with this small to modest effect size that could be explained by some other factors, then people really should be pulling back on the enthusiasm for saying that improve your diet will improve your mental health. And I worry about the potential implications that might have for someone that really needs help, in a psychotherapeutic sense.

Nicole Lippman-Barile: Yeah, I agree. And the, the nu nutritional psychology and nutritional psychiatry is too close to the "food is medicine" narrative. They're overlapping there. And again, they're making those causal influences and they're, it's very suggestive that this is this new amazing tool to breakthrough. Yeah. And that's, yeah, it's also being marketed as being accessible, and I don't think that's true either. It's not very accessible actually for people to just figure out how to cook for themselves and a Mediterranean style diet that's not super accessible for people to do.

Alan Flanagan: It's not accessible to be telling people that they need extra virgin olive oil and salmon and a certain amount of dark green leafy vegetables. And this obviously is not unique to the diet and depression research. This really applies across the board with nutrition, where we have a massive external validity and generalizability issue where you have areas of research where the majority of the data is in participants that are for example, middle-aged white, Caucasian, middle class women.

And then we're taking a finding from a study like that and assuming it would apply in any number of other populations. So I think we need to be careful with extrapolation. Who are we, who is the population or populations in these studies? And how is that potentially feeding into our considerations of where this applies?

Nicole Lippman-Barile: Exactly. And I understand it's new, it's exciting, it's trendy, it's interesting. Of course, it's interesting. But again, if you look at, if you look at other interventions in psychotherapy for treating depression or treating anxiety, there's almost no comparison. There's really almost no comparison. If we're, again, if we're looking at behavioral activation as a treatment for depression, if you're looking at cognitive interventions for

treatments of depression, that would be a more interesting study to me to look at a dietary intervention versus like a cognitive therapy treatment for depression and compare those against each other.

Alan Flanagan: This is, as much as we're discussing the inherent challenges of methodology and of isolating effects of, say, for example, diet or otherwise, if they can design effective interventions for psychedelics, they can do it for diet. And I remember listening to a presentation by one of the main researchers Rick Doblin, he's been one of seminal researchers and these trials the large trials in the States. And he was talking about, you can't blind people because as soon as they're "lit", they're fairly aware they're in an intervention group.

So for the MDMA trials for example, what they did was they made sure that both intervention and control were getting the same intensity and style of psychotherapeutic intervention. But then they gave the control group a low enough dose that they wouldn't necessarily be aware of an effect, but that there will be some effect.

And then they were giving the intervention group the dose, they intended to be a noticeable effect. So it was always plus psychotherapy. So it was always both of them on the same psychotherapy and the same intensity of that psychotherapy intervention, which is one on a really low dose and the other on an actual intended dose.

And that allowed for them to essentially be able to say the psychotherapeutic aspect of this was the same. Whereas what I see with all of these kind of diet and depression trials is that like the controls are all over the place either they're inactive and they're just left to their own devices or they're just not getting the same level of treatment, independent of diet that the intervention group are getting.

And so I always come back to that. I'm like, if they can do it for in that area. And really think about the methodology that they're employing to have an intervention and control group with a comparison that's the drug on top of the therapy in that case. Whereas what we want to know is the diet on top of the therapy.

And I think what's happening maybe with this research is everyone's slightly too enthusiastic for diet, like diet's going to do it. And it's I think if they viewed this more as a psychotherapy intervention, that's what your intent is, plus some diet changes, then perhaps it might actually lead to some better methodology. The only real true difference between these two groups was they did X, Y, Z with diet. But until then I don't know that we can come to any conclusions in relation to diet in isolation. Yeah.

Nicole Lippman-Barile: Yeah. No I agree with that. You'll have to do that study. Someone will have to do it.

Alan Flanagan: Yeah, someone will have to do it. I'm happy enough with my low mood.

Nicole Lippman-Barile: You just want to stay less cheerful.

Alan Flanagan: Yeah. Exactly. I'm the less cheerful one.

Nicole Lippman-Barile: That's fair. Someone has of the two of us.

Alan Flanagan: Exactly. Someone has to see humanity for what it is. On that cheery note, thank you for that. I think that was, I think that we hopefully haven't just upended diet and depression research, but I hope that listeners have a lot to think about not just in terms of what this evidence may or may not show, but also in terms of the themes we were discussing in terms of language and how we frame interpreting scientific literature in a way that's really representative and congruent with the evidence that is there, not the evidence that people would like to be there. Nicole, where can people find you on the internet of things?

Nicole Lippman-Barile: Find me on social media at Feed Your Mental, that's all one word. I also have a website, www.feedyourmental.com. I practice in the state of New York, so if you need help and I'm an expert in what you need help in, there's also a potential there too.

Alan Flanagan: Do you do online clinics and stuff for people?

Nicole Lippman-Barile: Yes, absolutely. Telehealth is absolutely available. I'm just limited in terms of like, where I'm licensed to practice.

Alan Flanagan: Excellent. Thank you very much for joining us. Everyone do follow Nicole at Feed Your Mental on Instagram, maybe Twitter. I'm not on Twitter, as you probably know. But her way of really breaking down language, rhetoric, and how we think about science is worth the follow. I hope that was helpful. We'll be back in a couple of weeks and fear not Mr. Danny Lennon will be back at the helm. And until then, take care.