
DANNY LENNON: And now it's time to bring on research communication officer here at Sigma nutrition. Alan Flanagan. Alan, what is up man?

ALAN FLANAGAN: What is going on?

DANNY LENNON: Let us know about how things are? What's the latest report?

ALAN FLANAGAN: Things are good. And we're taken over I've been kind of chipping away on a couple of papers putting the lockdown to good use. One is just a kind of general rule of Corona review. And the other is an interesting paper on thermic effect of feeding. So yeah, I'll send you send you that when it when it lands.

DANNY LENNON: Some secrets are being held back here at the moment. So they'll be announced at some point in the future. In relation to our last episode around vegan diet I'm sure you've got similar feedback hopefully to me that quite a lot of people have been messaging me about that and found it both useful, but also had some really good, interesting questions and feedback. So I'm wondering what it's been like for people engaging with you off the back of that?

ALAN FLANAGAN: Yeah, I think that's thankfully a reflection of the Sigma audiences, the engagements is is going to be positive and people are going to have positive contributions to make as opposed to histrionics over

casting doubt. So for the adequacy of vegans for one year olds, and but no, I've had some really positive dialogue. And even you know, with regard to today's subject, some kind of dialogue as to Oh, well, you know, why don't you race Dean Ornish and S.L. Steen's [PH] research. I thought it shows that you can reverse heart disease through diet and you're kind of getting into independent effects and causality, but overall, it's been positive. I've had some, you know, interesting conversations about the interventions that we discussed. I think perhaps two of the points of conversation that have been most common have been in relation to the infancy aspects that we talked about and whether it is adequate or even ethical to, you know, just put children or infants should I say, on a entirely vegan diet and different considerations that need to be taken into account. And then the other one on protein quality, which has been interesting, which I had some discussion about in the Barbell Medicine group about the idea of from an athletic perspective, if you're consuming enough total protein, if it's wholly plant based, like is it still sufficient? And I think, you know, the reality is the Tracer studies are something that are relatively new in the context of looking at protein digestibility. So I think perhaps, we need to leave the door open on that still, because it looks like the previous protein quality scoring systems were probably a little inadequate or certainly overestimate digestibility of certain plant proteins. So yeah, so there's been some good dialogue.

DANNY LENNON: Yeah, I've got a report the same and people highlighting some interesting papers and having interesting comments that have been actually quite useful to see. It's always nice, the quality of the interactions, we get to have the typical listener of this podcast, people who are coming from a vegan background and people who are not it's been equally. So I think very positive. Thankfully.

ALAN FLANAGAN: Well coming coming at the tail end of the string of ethics podcasts, it was just like, okay. Now we have to maybe come to the consideration that may arguably be the least importance in terms of environment and ethics. And from my perspective the health considerations of going vegan would probably be thirds in the context of environments and/or ethics and whatever hierarchy in individual's value, constructs and puts those in. But most of the dialogue that I was having with people was with people who are themselves vegan. And I think that's always helpful as well.

DANNY LENNON: Yeah. So here's the hopefully more thoughtful feedback and interactions off the back of this discussion. And as you mentioned on some of those questions you got probably brought up a topic that we're going to discuss today, particularly as it relates to causality in nutrition research. And in fact, this is something that reared its head on previous conversations we've had for the podcasts, most notably around understanding heart disease, where we talked about causality in that sense. However, there's oftentimes maybe misconceptions about determining causality and then particularly as we apply that to nutrition science specifically. So maybe, could you just set the stage for us then of what is this issue/problem that we may be need to address that you think is important for people to understand around nutrition science and determining causality.

Today's topic In Focus

ALAN FLANAGAN: I think I started thinking quite deeply about this last year, because I felt that a lot of the conversations that we were having around various topics, whether it was, like you said, a lot of it's a rose with some of our recent Sigma statements and podcasts, and LDL and issue of causality, and also the red meat article where, you know, one or two responses were like, well, you know, you focused a lot on epidemiology and not on RCTs. And I was like, well, if you can find me a 20 year RCT, a 30 year RCT, I'm all ears, but in the absence of that, we are left with what we are in nutrition. So I started realizing that a lot of the conversations that I was having, were not necessarily to do with evidence. We were discussing evidence, but the inability to resolve the perspectives was to do with a failure of epistemology in terms of considering evidence, what it means the value of different trial designs, and what causality even means. And what I've realized is and I think this is a handy point of departure is all we're talking about with evidence and proof is with evidence, we're talking about a sufficiency of information to support a conclusion. So you know, taking the even the scientific sting out of it, this applies to a lot of different fields, but it's the actual body of information that support the conclusion that you're coming to. And then in terms of proof, the term proof is a sufficiency of information to support that given conclusion. So evidence is the actual body of information. And then proof is a sufficiency of information to support a given conclusion. And the point is, I think that people

have a very narrow view of the concept of proof, and that it's absolute or that it's 100% and it never is. And the best analogy that I think I can come up with here is actually a legal analogy. So what's important as a point of departure is to separate the hierarchy of evidence. So when people talk about evidence and proof, if you've done a biomedical degree or a bio sciences degree, the hierarchy of evidence that pyramid is drilled into your brain. And you probably most people probably don't even remember what comes after the third rung because it's considered so irrelevant. So the third rung being observational epidemiology. There's obviously different types of study design within that but the third rung is generally prospective cohort studies because they're considered the epidemiological design that minimizes a number of biases that others don't. Second is obviously RCTs, which in the biomedical model are considered the gold standard and by RCT, specifically meaning double blinding, placebo controlling, randomized interventions. And then a top of the pyramid is meta analyses, preferably of these RCTs that are double blinded, placebo controlled and otherwise and on the assessment criteria to raise the risk of bias and the quality of a study for meta analyses is generally predicated on drug trial criteria. So if a trial doesn't have double blinding, or it didn't have a placebo control, it's downgraded in the assessment of the quality of the evidence. And again, these are problematic issues for nutrition science. So that hierarchy people assume is static. And people also assume that the hierarchy itself is proof, i.e. an RCT is more proof than a prospective cohort study and a meta analysis is more proof than anything. And epistemology like from an epistemic standpoint, that's just not correct. So the analogy that I think is best to use is maybe something people can grasp with is let's consider law for a second, right? So people would say, well, science and law are completely different. Okay. Yes on paper, but from an epistemic standpoint, not necessarily. Both start with a question to be tried. You have to bring evidence to support your position in answering or testing that question. And different standards will be in place for you to meet in order to be deemed to have “proven” whatever your case is. So if we take a murder trial, for example, if someone's on trial for murder, then the standard of proof that has to be met is being beyond all reasonable doubt. Now, it's obviously not going to be peer review. But it will be a jury of peers. And the evidence that will be required to satisfy such a high onus standard of proof is much higher. And that evidence would be

required to be quite robust and sufficient to meet that standard of proof. But if you're suing someone for breach of contract, well, no one's died. It's a civil case. So the standard of proof is now on balance of probabilities. It's a much less rigorous test than beyond reasonable doubt. But it's still a standard of proof that's appropriate to the question that's being tested and tried. So the level of evidence that you have to produce would not be the same as you would have to produce in a murder trial. You don't need fingerprints on the gun. You might need a signature on a contract. But you don't need the same equivocal level of evidence. However, you're still talking about proof. What you are proving is simply a different standard to the murder trial example. And these considerations apply to science and apply to certainly nutrition. So the reality is that if we're talking about a standard of proof and having a sufficiency well, with science, we tend to want certainty. So in an individual study, there's obviously the use of statistics to make the actual results, your evidence as objective as possible. Those we don't need to get into any more detail, we can just leave it as that's the goal. But in terms of deciding that particular exposure causes an outcome, well, the levels of proof will also differ. If we're deciding for example that we might want to recommend public health wise to cover the whole population of reduction in sugar. That's a just as an example, in free sugars, the level of evidence that you would need, the standard of proof to be matches, would not be the same as if you were trying to demonstrate that LDL cholesterol causes atherosclerosis. It doesn't make them any difference in terms of proof. It just means that what actual proof, the standard to be matches differs. And therefore the level of evidence i.e. the body of information required to support that conclusion required is different. And these considerations apply equally to science. And just to wrap this up the whole I think, concept for people to try and grasp listening to is that proof is a process. So it's a threshold that exists on a kind of continuum where different levels satisfy different criteria. So not every trial demonstrates causality. And a body of evidence might infer causality. And then the final consideration with terms of inference or demonstrable causality is one has to ask, do we need to demonstrate causality in order for this recommendation or intervention to be effective. And oftentimes, the answer is going to be no. And so it's important that we kind of try and grasp these issues a bit more so we can have more productive conversations. On the flip side, unfortunately, people use these concepts to be

completely obstructionist in engaging with a body of evidence as well. So that can be problematic.

DANNY LENNON: There's lots of stuff in there and I think because most of it is so important, I'm going to just try and do my own amateurish recap of those points you made, just that it may be helpful to people. So essentially what you've outlined is that we have this distinction to be aware of between evidence and proof, with evidence being the body of information whereas proof we're talking about having a sufficiency of information to prove a certain question or theory. And beyond that the standard of proof that needs to be met will differ depending on what that theory/ question is going to be. And within science, generally, we're never really proving to a point of 100%. But we're looking at these probabilities. And so what you're saying is the threshold that is required for us to state this, we have sufficient proof to act on something is going to be different depending on that question. Critically with this difference between evidence and proof then you also said that, sometimes people don't make that distinction. In other words, they think of the trial design or the study design as indicating the strength of the proof of that study, as opposed to that Just being an indicator of where it lies in the hierarchy of evidence, but that doesn't necessarily correlate to sufficient amount of proof.

ALAN FLANAGAN: Yes.

DANNY LENNON: When you talk about those different standards of proof, would this be an example where we could think of the standard of proof that is required for rolling out the use of a drug is going to be at a different level than we're going to have for public health advice on nutrition because of the potential implications of that. So the implications of any decision number one can have an impact but second, what I think is that with nutrition, we don't have the ability to sit and wait to see we need demonstrable proof from RCTs we're still going to eat every single day. And so there's going to be these different standards based on that.

ALAN FLANAGAN: Yeah, I think it was Robert Heaney, now deceased, the great nutrition, Prof. who talked about the difference between the biomedical standard of if you're releasing a drug into the supply either for OTC, use over the counter use or for prescription that carries with it a potential for harm and side effects. And you're

talking about a risk benefit ratio in terms of a decision of a physician to give someone that drug and they will obviously know what the potential side effects are otherwise. But I say risk benefit quite deliberately because it's the risk analysis that comes first factoring in the benefit that's known from the drug, from the trials that got it to circulation and to use. For nutrition it's somewhat different. It's the opposite. It's a benefit risk ratio. So at the first instance, we need foods as an empirical fact. We need nutrients as an empirical fact for survival. And so we don't have to prove that nutrients vitamins or minerals, or energy is required to sustain life. It's just an empirical fact. The world is round. We need nutrients. So the question then becomes, you know, a scale of if someone's insufficient or deficient or has too much, but generally speaking, with a couple of known exceptions, you know, toxicity thresholds going to be difficult to meet for a lot of nutrients unless someone's doing something a bit outlandish. So the question becomes, what is the cost of inaction if we're considering benefit first, and factoring in risk. Because it is, I think the other flip side of this the adverse of this coin is people often assume that oh, it's food, walk, where's the harm, I can recommend anything I like and this is a justification that I see a lot of kind of bad nutrition advice on social media being justified with. Well where's the harm? People just eat more fruits and vegetables or they'll just eat more revise to combat COVID-19. So you know, that can be used in a negative sense, but we're talking about ultimately benefit first. So if it's benefit risk assessments, then the threshold for consideration is lower than it would be for putting a drug into circulation and prescription. And the question that flows logically from that is what's the cost of inaction. You know, if we have evidence, let's say it's exclusively epidemiological, for example, but the direction of effect is consistent and the magnitude of effect is significant in a number of different cohorts in different countries. So even accounting for limitations of observational research, what would be the cost of not making recommendations based on that finding? And I think that's an important secondary question we have to ask ourselves out when we're considering nutrition evidence, what's the cost of acting, what's the cost of inaction.

DANNY LENNON: Essentially, the idea that risk doesn't, can't be calculated in the vacuum of what is the risk of this intervention it only makes sense when it's weighed up against what is the risk of that intervention

versus the risk of not implementing that same intervention. And the difference between those as opposed to this thing and the fact.

ALAN FLANAGAN: Yeah, there is a really good example now. It's not a nutrition example but I like it because it really highlights everything we've discussed so far. And it relates to sudden infant death syndrome. So there was an interesting in New Zealand's in the late 1980s they had quite high prevalence of SIDS, Sudden Infant Death Syndrome, cut deaths, basically colloquially known. And they did a case control study, where they compared a number of infants who had tragically died by Sudden Infant Death Syndrome to group of about 500 controlled infants, babies who were all alive. And essentially what came out of this case control study, you know, think about the hierarchy of evidence case control studies like fifth, maybe fourth. So it's pretty down. No one would consider a case control study is anything worth. But what came from this case control study was that's putting babies to sleep in a prone position, dramatically increased risk just comparing the death, you know, circumstance and certificates of children who had died from SIDS versus these controls. Now you're not doing an RCT to put babies in the prone position. You don't really have other research outputs. They enacted a public health intervention recommending that children not be put to sleep the probe position and drastically reduced rates of SIDS of incidence of Sudden Infant Death Syndrome. Now coming back to this idea of proof. So the question here was, was that proven? And it's like, well, in what way are we talking about proof? Did it demonstrate that sleeping in a prone position caused Sudden Infant Death Syndrome? Absolutely not. It's the case control study. Was it sufficient proof to act on having regard to the level of evidence there and the options for obtaining other evidence? Absolutely. It was sufficient proof for action in that circumstance, and the magnitude of effect, the huge benefit of the public health intervention, then corroborating and confirming the case control study results. So I think that's a nice example of, even though it's not nutrition related, how we think about these ideas of what's sufficient in terms of proof is going to differ relative to the question that we're asking and the available information that we have. And it turned out that in that context, that was sufficient proof for action. And the question then would be what would have been the cost of inaction? If someone had said, that's a case control study, I'm going to need an RCT. Where's my meta analysis? Like, it's ludicrous thinking. Now using

an example like that people would be like, Oh, well, that's ridiculous. No one would ever ask for a meta analysis or RCT. We're having, obviously these conversations all the time when it comes to diet and mortality from cardiometabolic disease. So we might read nice article that we the statement that we did, for example, you know you can't show that this, you know, proves that the even unprocessed meat... And I'm like, I can't demonstrate causality. No, but there's a consistent enough body of evidence that I can infer that there is a causal increase in risk, because when that exposure is not there, that risk isn't there either. So, you know, it's about expanding our thinking I think about these issues.

DANNY LENNON: That just in that point you mentioned right at the end, I think that's really critical to hammer back on that you've just said, even in cases where we don't have this demonstrable causation or that we can't demonstrate causality, there we still have this ability to infer that there is this causal connection between something and a certain effect. Can you maybe just explain that, again, for people that difference between how can it not be demonstrating causality but still we can have this causal connection that we're fairly confident in.

ALAN FLANAGAN: Demonstrating causality is really difficult. So I got to get a bit technical with the concept of causation as we have inherited it from the biomedical model, but it's helpful. Generally, when we're talking about demonstration causation, it's going to be from a randomized control trial, where there's blinding, there is a placebo control and there is an intervention. And the results of that, then demonstrate that the intervention compared to the placebo did X, have X effect. Now here's what needs to be satisfied in order to demonstrate causation. And this is completely lost in the conversation about nutrition, unfortunately. So one of the principles of randomization is that it balances known variables that could impact the results between two groups. And that's something that the researchers can actively do. So if BMI might affect the results. If your vitamin D status might affect the results, if your gender might have effecti results, just sticking with those three. Then you can design a randomization that will balance those characteristics equally between the intervention group and the control group. Now, you can also do the same and observational research achieve relatively the same effect by adjusting by having a multivariate adjustment model where you adjust for those variables. But we can come back

to that. The second and this is what observational evidence cannot achieve, is this is an assumption that what randomization achieves is if there are unknown variables, if there's stuff we don't even know about, yet in science that we haven't discovered that could influence the results. Then there's an assumption that randomization balances those equally between groups. But the assumption I keep repeating the word assumption here because the trial designs are all built on certain presuppositions or assumptions, and that we can never know to be true. So just as an example, let's say you're doing a trial on diet and cognitive decline, and we know that the APOE-ε4 allele is strongly associated with increased dimension Alzheimer's risk, and it's about 25% prevalence in the population, right. So let's assume we're doing a trial of 100 people. 25 people have the APOE-ε4 allele but let's say we don't test for it. So we're unaware for this. We're assuming that randomization will balance the numbers that have that particular genetic variant equally. But that's an assumption. We could end up with 20 in the intervention group and five in the control group equally that's a possibility. So these assumptions are not necessarily. Now that's an extreme example, because we do know about that and if that was the intervention, you would test for it and everything. But here's the thing. Let's assume now that we have these the first level we've equally balanced known covariates. The second level, we're acting on the assumption that unknown factors are equally balanced now between our intervention and control group. To demonstrate causation, we then need to have no additional covariates, no additional variables introduced post randomization, right and this is something that I don't think is appreciated, because if you did, you might influence the results. So no variable is being introduced post randomization is much more achievable if we're doing a drug trial, for example, because we're going to take a drug that is not an ordinary course circulating in your body. I don't have some statin floating around my body right now. I don't have the little. I don't have I have none. But I have some vitamin C, for example. With nutrients people in interventions have at least baseline in sufficiency levels of the nutrient that's often an exposure. With a drug trial, the intervention group is getting something that is foreign to the body and is completely measurable and distinguishable from other factors. And you can compare that because it's a foreign agent essentially, to a zero exposure. And you can make sure that there are no other factors introduced posted randomization, you know, you're not

starting the intervention. You don't also give them Ezetimibe. We don't also let the control group, you know, change their saturated fat intake, drop it by 10% and see what happens to their cholesterol, for example. So you make sure that those things don't happen. And if you meet all of those criterias and assumptions, then you can say, well look this intervention reduced cholesterol by 40%. That's demonstrated a cause effect relationship. The issue is those assumptions are even in some ways untenable for nutrition. If I'm doing a free living intervention on this, I'm keeping people in a ward, let's say, let's take the premed example. If I'm randomizing people to an exposure of olive oil or nuts, and that's what they're going to be eating every day. And it's going to be five years of follow up. The idea that no variables are introduced post randomization is ludicrous because people don't eat the same foods every day. They might change other aspects of their diet. They might eat more fiber, less fiber. So yes, you've got this intervention, which is definable. But you can't assume that it's necessarily independent from anything else that happens with someone's diet afterwards. So a lot of these criteria that we have to demonstrate causality, the concept of demonstrable causality comes from drug trials. And a lot of those assumptions can't be mess for or highly difficult, very methodologically challenging to me for nutrition interventions, because it's difficult to assume independence of effects. It's difficult to have a clearly defined exposure that's independent of other factors, or that even comes on top of a certain amount of nutrients intake you already have. And it's impossible to have a placebo unless it's a supplement trial. If it's a food trial, there is no zero exposure in human nutrition. So even a control group, if calcium supplementation is the intervention and bone health is the outcome, the control group will probably at least have enough calcium to that we know is at a level where their bone health is probably protected anyway. So there are some methodological challenges for demonstrable causality that are difficult to overcome. And I think the one that's really out of the conversation that people don't think about nutrition is the concept of no covariates post randomization being introduced.

DANNY LENNON: Yeah, and I think there's probably a lot of people listening that have some degree of education or training in some sort of scientific field, many in some sort of medical related field as well. And I think one of the first things we typically learn when we think about causality

is there's these certain criteria that evidence must meet for it to be causal, and there must be some sort of time precedence between cause and effect. There's a correlation but then importantly, like you mentioned, the effect can't be caused by some other variable that's interacting with it. And so the more you go in that direction of thinking about causality with that perspective of how do I increase my confidence in making sure that this link is in fact causal. And the more you try and drill down in the area, by nature, you're having to increase internal validity, typically, you're going to have to control more within that study, you're going to try and have a closed system where only one of these variables is changing. And the more and more you go in that direction, you're inherently moving away from more of a real world scenario. But particularly with nutrition that becomes problematic not even because of its real world application just because of how nutrition interacts on a systems level. And so it moves away from this kind of systems thinking that we typically try and foster when it comes to nutrition science that maybe isn't sometimes appreciated much in other sciences would you say?

ALAN FLANAGAN: Yeah. Absolutely. Because I mean high internal validity which is assuming that all of these presuppositions and assumptions have been met in an RCT. That's, you know, great if again, if the exposure is a drug, and also you don't need to worry necessarily about external validity or the generalizability of that result to the population because a drug is going to be prescribed. Now if it's an intervention or like a surgical procedure, yes, these factors matter. But for nutrition, you're right, the gap, the spectrum between high internal validity, and real world application and nutrition is by orders of magnitudes different it's quite substantial. So if you're doing a very tightly controlled study, like some of Kevin Hall's research, for example, metabolic ward, people living in the lab, you have them on a sleep wake cycle. You're controlling environmental and behavioral factors variables, you're taking blood at specific times, you're controlling everything down to the macronutrient level and micronutrient level even you're preparing that food in a metabolic kitchen very precisely, you know that research by definition, A is really expensive. So most groups don't have the luxury of doing that as their habitual output. Two, it's, by nature going to be a short duration trial. I think the longest he's done an ward is a month and you're generally confined in terms of the

people that you can recruit to live in a lab for a month is going to be lads between about 20 and 25. You could pay off with some bare money. So and that comes with its own issues in terms of you know, that the actual makeup of people we do research in, and that might give us a much more robust examination of manipulating a specific exposure and variable and give us more confidence of demonstrable causality to a degree, but the idea that that's then generalizable to the whole population or applicable in the whole population is an assumption we also then can't make. So we're walking this and I think it's important to clarify for people because when we talk about RCTs, were by nature conditioned to think of this high internal validity, double blind placebo control. There are other RCTs. There are pragmatic RCTs, for example, which are on the other end of the spectrum. Pragmatic RCTs are designed for external validity. They dispense with factors like blinding, because the investigators are giving a particular exposure in a real world setting. It might be something that's undertaken in a clinical context. it might be something that's undertaken in the community. So a pragmatic trial is done in the context or circumstances in which that intervention will actually be applied. So you don't get to say at the end of a pragmatic RCT that the intervention calls the outcome, but you do get to say this intervention worked and led to this outcome. And so the difference is internal validity RCTs, high internal validity RCTs are testing efficacy. Does this work on pragmatic RCTs? Are testing effectiveness? How does this work? And does this work in the real world?

DANNY LENNON: And I think, when we try and think of things in this too neat fashion have this linear causality of here's this one cause and we're looking to see what one effect that's going to have that obviously doesn't apply to nutrients and foods because these nutrients are going to not only have an effect on certain causes, there can be bi directional effect. They can have many impacts on many different tissues. They can have lead to many different outcomes. There's some sort of synergy with other nutrients. There is this interaction of them all together that are leading to the emergent property of a certain outcome that doesn't occur with isolation. So there is all this messy systems interaction going on that doesn't fit neatly into “this one cause has this one effect”, which would ideally be lovely.

ALAN FLANAGAN: There is really nice example of that. It was a trial that looked at Dawson Hughes was the lead author, sort of a couple of years ago,

but basically, it was a trial that was looking at calcium and vitamin D supplementation, and bone BMD was was the outcome. What was interesting was they did a if I remember it was a post hoc analysis of who preserved better BMD relative to their dietary protein intake. And we know that dietary protein has positive impacts on calcium uptake in the guts. So you get more calcium uptake from a higher dietary protein intake. And protein itself has some positive properties on or effects on bone mineral density. And what was interesting was the group even though they were both having the same all the intervention group had the same calcium D supplements intervention, the sub-group with higher protein intake had greater preservation of BMD. Now, the biomedical purists and someone would say that's confounded. Well that's imperceptibly reductionist thinking in my opinion. It's not confounded at all. That's the nature of nutrients. I mean, if you wanted to show an independent effect of the calcium supplement, yes, this is something that you could say is confounded you would control for in a future study. But I actually think it's a really good example of that point you just made of how nutrients don't necessarily act in a vacuum, and we should be thinking about and it was Robert Heaney, who made this point as well, we should be thinking about optimizing confounders insofar as confounders are synergistic actions of nutrients that may have this interactive effect, for example, a positive impact on protein on calcium uptake and both of these options BMD as opposed to saying, oh, well, you know, it's an indication of how nutrients are interactive. And I think it's really important with when people are looking at RCTs and nutrition think about whether the trial is no by design. What I mean by that is often ethics committees won't allow baseline participants at baseline or their intervention, any part of the participants to have insufficient levels of a given nutrient. That makes it really hard to detect an effect because nutrients have a bell curve of activity. So as another example, and again, this was another calcium example, the Women's Health Initiative RCT looked us and this was from a biomedical perspective, this was gold standard. This was double blind, placebo controlled RCT of calcium vit D supplement BMD and outcome after I think it was two years there was basically no, there was a slight difference in the intervention group. There was no real significant difference between the intervention and placebo group. But if you look at the baseline characteristics of the control group, they averaged around 800 milligrams of calcium a day.

That's easily sufficient and otherwise healthy, middle aged women for preservation of bone health. And because nutrients more is not necessarily better so supplementing 1200 milligrams of calcium on top of already around 800 milligrams of intake, you're not going to see an effect and they didn't see an effect. Now, of course, what happens then, from the biomedical peers perspective is, oh, this is nonsense, you know, the supplements don't work or whatever. And it's like, well, what would be the difference between that intervention group and the control group if you had the control group with 200 or the intervention group, for example, would arrange 200 milligrams of calcium intake insufficient, and then you gave them a supplement.

DANNY LENNON: Yeah. And I think in some of the previous statements, there's been particular attention paid to making sure what is being compared to what and like what is the difference in those ranges. And if you have, particularly if you're changing intake of a nutrient, if you're not going to detect the difference, that may just be because that range is artificially restricted to something that's not meaningful.

ALAN FLANAGAN: I think that's a fundamental point for for nutrition, both epidemiology in particular, and also RCTs is the magnitude of the exposure contrast, like how particularly because with some micronutrients maybe we could be comparing milligrams of intake and it's difficult to see an effect. So I've got a really good example actually, that pertains to vitamin E. So the epidemiology on vitamin E, and neurodegenerative diseases Alzheimers is really strong. But if you were to read a paper on it, you might see it framed as inconsistent results. If you dig into the inconsistency, what you realize is all of the cohort studies that found large reductions in dementia risk, like, you know, a minimum often of like 30% reduction. Had people consuming a minimum of kind of 15, 16, 17, sometimes 18, 19, 20 milligrams a day of vitamin E and those groups were compared because we compare high versus low because there's no zero exposure to groups consuming 8 milligrams a day. So 20 versus 8 is a decent contrast in the exposure and you could detect an effect. Whereas in some of the studies that have found no impact the Washington Heights in Woods projects, communities projects was a cohort in the states in Washington in D.C. and surrounding areas, biracial cohorts that was looking at a number of factors, the cognitive decline vitamin E. Now, I found no association with vitamin E. But if you look at the comparison, it was

tertials. So three levels of vitamin D intake, the highest group, the highest, had a mean of around 4.7 milligrams of vitamin E intake, the highest compared to the lowest which was less than, you know, it was one basically. So it wasn't that there was no effect of vitamin E or no association. It's simply that there was one, a deficiency of intake relative to what we know, essentially from wider research, but there was just no contrast in that exposure. And similarly, in some other studies, there's been no effect when people are consuming under six. But if you were to then increase that, if you were to compare that group consuming 4 to the group consuming, say 18 you're going to get A big effect because of that comparison. And this has relevance for RCTs because most RCTs of vitamin E supplements have failed. Leaving aside the fact that they've all used synthetic razmik mixtures of alpha tocopheryl alone, which is one of 8 Vitamin E isoforms. If you actually and it was, again, the Women's Health Initiative, also had vitamin E intervention on cognitive decline, and they found no effect of 430 milligrams of vitamin E supplements a day. But they did a pre-specified subgroup analysis relative to baseline vitamin E intake. And what they found was there actually was in effect, a positive effect in the group whose baseline vitamin E was less than 6 milligrams a day. Now that stacks up with the epidemiology. So that suggests that this range of less than 6, that 6, 4 is closer to insufficiency than 10, for example, because our our RDA is 15. And that suggests that if someone does have that low level, and you increase their vitamin E, preferably through diet, actually, you do get a benefit. So these results, these kinds of broad conclusions that oh well, A, epidemiology is inconsistent or B, the nutrient doesn't do what we think it does from epidemiology because these RCTs found no effect. That's fundamentally flawed thinking for nutrition. Because often the disconnect could be at the RCT level. For those reasons I've outlined people didn't have an insufficiency of the nutrient of exposure, or they, you know, they essentially tested the wrong hypothesis, which was that the supplemental form would have an effect whereas really a lot of the associations are from dietary intake.

DANNY LENNON: And actually, I think that's a critical point now that you mentioned that oftentimes there is this belief that is often given as a criticism of nutritional epidemiology, that if there is a disagreement between the epidemiology and RCT, then that must be proof that the

epidemiology is wrong. And it's never viewed in the opposite direction. And I mean, there's lots of critics that have placed that saying, look at all these things that we would believe from nutritional epidemiology, but we have an RCT that show that didn't hold. And in some cases that has been accurate, but in other cases, it may not as we've just outlined, and I don't know how much we want to get into this particular topic, but as you were talking, it kind of reminded me of this bigger issue of knowing that there's this importance we place on understanding what is the dose, and duration of exposures, in particular trials and details about even who the population is of a study is and how that can influence results. How the fetishization of meta analyses can be quite dangerous for that same reason because there's very little rigor based on those individual trials, and it's very unlikely you're going to get complete coherence across all the trials included with those different factors.

ALAN FLANAGAN: Yeah. I think we're really hampered by the application of biomedical frameworks through which to assess evidence. And even this ridiculous paper about the familial hypercholesterolemia diet recommendations, you know, in evidence rezone and one of the statements in the introduction was we need to apply a medical standard of evidence. It's like, well, no, you don't, you can't, because people that get diagnosed with fH are put on highly intensive statin regimes plus often additional is that Ezetimibe or a PCSK9 inhibitor now to reduce their cholesterol levels. So, you know, to get a signal in the noise of a dietary intervention, let alone the ethical implications of saying, hey, we're going to put these people on like a diet of 18% saturated or whatever it is just you're not going to have that level of evidence. And so that's an example of where saying we need medical levels of evidence is actually obstructionist. It's a deliberate obstruction of what we do know and what we're acting on right now. A meta analysis has become a real problem I think four findings in nutrition because of the ability to just have a completely obscure a body of evidence from one study. And often the inclusion criteria are based of, you know, Cochrane Collaboration requirements, which are for drug trials, or like the gray criteria that we kind of discussed at length in the red meat statement. So if people want a bit more of a discussion of the problems with the grade system applied to nutrition, reread that. The reality is that what isn't the two most important factors that could be, that really

needs to be matched for nutrition specifically or not in any of these considerations. So if you're doing an RCT, or if you're doing a meta analysis of prospective cohort studies, well, we know cohort studies compare high versus low. But just come back to this vitamin E example. In the Rotterdam study high is 18.5 milligrams compared to less than 10, which was a Dutch cohort obviously. In that Washington study high is 4 milligrams compared to basically 1. So they're nowhere near equivocal, but they would be assumed to be equivocal because they compared “high versus low” and they would be mashed in together in the same forest plots, and completely lead to an obscure conclusion in relation to that exposure and outcome. We've seen the same with multiple saturated fat meta analyses were one recent one that said oh, you know, and it did the rounds amongst the “bros” was saturated fat, high saturated fat intake reduces risk of stroke. And you go and look at the three or four studies that contributed the most statistical kind of weights or inputs, should we say to the meta analysis. They were all studies in Japanese populations, where the average saturated fat intake was 21 grams a day 18 to 21 grams a day, not even percent grams. So this idea that high and this paper gets sited, gets posted on social media as an example of how our guidelines are wrong. It's like this paper supports our guidelines. This paper confirms that a dietary saturated fat intake of less than 10% reduces risk of stroke. That's not how its interpreted because people haven't, you know, bothered to look at the included studies. And the researchers haven't been appraised of these issues sufficiently to think okay, well, I'm going to make sure that I match the exposure contrast as closely as I can, either as a percentage or in grams a day and take in the high versus low comparison so I get more of a kind of true representation. So meta analyses in particular, although it may sit atop this pyramid, and be assumed to be a conclusive summary of the evidence, it's not. And the problem is Sander Greenland's the the famous epidemiologist at UCLA talks about this a lot. You can use meta analyses for a couple of tools, but what everyone uses them for is to obtain a single summary point estimates, a number that gives you an overall effect size. Again, that can be helpful if you're comparing at the same statin or the same ACE inhibitor blood pressure medication, where the trials, same duration, same intervention, same population group because obviously the drug is for people with high blood pressure, but the assumption that even the same diet exposure is invariant across populations is an incorrect

assumption. So that's another factor that really hampers this idea that meta analysis to get a single point estimate, or we're going to get a summary point estimates of the effect of low fat milk on diabetes risk. It's like, what the idea is the low fat milk consumption from your Swedish cohort is occurring in the same context as the low fat milk consumption in your Australian cohorts. They're not so that, and that's why relative risk is important because risk of the same exposure is not homogenous across populations. And we also really dug into that concept in the statement on red meat.

DANNY LENNON: The point you just made kind of circles us very nicely back to that original point of that distinction between the hierarchy of evidence and the standards of proof in that it's very easy now for people just to try and look out for a meta analysis in a particular topic, or when one does get waived about that seem to be more useful or more important than any other study that's out there where in reality, as you just outline, a poorly done meta analysis can be more problematic. And in fact, you could got a lot better use from looking at a handful of really well done prospective cohort trials without ever looking at them in and out or RCTs. And it's interesting, like you mentioned the importance of those population types that are in particular studies, because another one that I've seen is in relation to sodium intakes and fatal hypertensive disease, you can often see people say, well, look, it's actually not really a big deal. And they will look at trials where you might see someone, let's say their baseline blood pressure, on average is like 123 over 80. And going on the low sodium diet drops it like to 120. It's like, well, that's not meaning, that's not very many That's not going to make any real difference. But that's not really the question we should be asking. It's like, well, what would that change in sodium do for someone whose blood pressure is 140, 150 and so you have this artificial restriction of range. David Epstein has a great example in his book, if you go and look at take a cohort of NBA players, and you try and answer the research question, is height important to be a good basketballer, you would probably say, well, not really like because there's no major difference, because they're all like 6'5” to 6'8”. And then he says, you could take the same and then you could take that group and say, is height important for who are the best three point shooters, and you'd find them the opposite that yeah, actually, to be a better three point shooter, you're going to have to be smaller. So then all parents are going to try and find the small kids to get into

basketball because you'll surely be the best. And it's this restriction of range that's not been in terms of the population type that's not being taken care of. And so there are things they are easier for people to identify when we go deep on really well done studies then trying to take a meta analysis and try to piece between it. And often the result of those is like, nothing matters.

ALAN FLANAGAN: Nothing and it's interesting that some of the really obstructionist kind of voices in nutrition when it comes to these discourses, will... I think was it Layne Norton had a good meme. So maybe it was Spencer had a good meme about like, you know, kind of people that like carnivores that like dismiss all epidemiology, but then one epidemiological study confirms something for them and they're like waving at everywhere. That happens, like the people who often completely dismiss nutritional epidemiology will then wave a meta analysis of prospective cohort studies around like it is definitive, comprehensive proof of the nothingness that you just described, because most of these meta analyses, because they're including all of these studies that are completely different in terms of the contrast of exposure, the duration of exposure and the population essentially find nothing. They find no association for anything. And so I think meta analysis particularly is this assumption like if RCTs are a gold standard meta analysis is a platinum standard. I don't think that's tenable for nutrition research, and as you said, I would place more stock on a really well conducted prospective cohort study on a particular research question than a meta analysis of cohort studies on that same research question.

DANNY LENNON: One thing that I do want to get to before we wrap up this particular topic, and it relates to evidence based practice, which I'm sure is going to be an important thing for hopefully most of people listening here who are practitioners in various forms, and one of those core ideas of evidence based practices that we make decisions based on the highest quality evidence that's available. And in fact, we've been working wasn't some sort of secret project, reveal this? Yeah. But within that, you wrote something that really jumped out at me that I thought was particularly important related to this idea when people what comes to mind when they think of what the highest quality evidence available means and sometimes what that actually means it can be very different. Can you maybe discuss that concept of how we should conceptualize as practitioner what it means to make decisions based on that highest quality evidence?

ALAN FLANAGAN: Yeah, like this idea that highest quality evidence has to correspond to a particular trial design is what we're kind of reared on whether we do in nutrition undergrad or medical undergrad. Even coming back to that Sudden Infant Death Syndrome example that was the highest quality evidence available at that time. There was no other evidence. Therefore the decision is based on that case control study as the highest quality available evidence. So what highest quality means, really is what coming back to this idea of what is evidence a body of information to support a conclusion. Well what's the body of information before you and if that body of information is absent RCTs there is no intervention for example, you are a colorectal dietician and you have people saying, well, you know, there isn't an RCT that shows that I should cut out processed meat. I love bacon was like the highest quality available evidence that you have may not include RCTs boss, you have numerous cohort studies across the world in different populations, different ethnic backgrounds, all pointing in the same direction of effect, all with a large magnitude of effect, all fairly similar in the dose exposure, and that association gets stronger over time. Well, that's the best available evidence that you have. And that's robust evidence. That's not weak evidence simply because there is an absence of a certain trial design. And so best practice would be following that recommendation of well, yeah, there is a risk to process meat consumption for colorectal cancer. It's a causal increase in risk. It's not demonstrable causality, but there's a causal increase in risk. And I think that's really important because for nutrition, people in clinical practice are going to be faced with the reality of making decisions because you have to intervene. People need to eat, and they're going to eat, you have to make a decision and intervene and you can't like you said at the start, you can't just wait for this unicorn RCT that tells us everything we want to know to come along. Nor can you necessarily rely on meta analyses and that's where a lot of great care is taken. So this isn't to say that you're always going to be relying on cohort studies. It's simply to highlight the best quality of best available evidence means is going to be relative to the question that you're being asked, the benefit risk ratio that we talked about earlier and it's not going to mean I have to have X trial design available to me showing this before I act. And another interesting example and I was actually speaking to the colorectal example I was I was having a conversation with a friend of mine hair who is a colorectal dietitian about do you ever hear of the specific carbohydrate diet?

DANNY LENNON: I have heard. It is –

ALAN FLANAGAN: Yeah. So it's a kind of adult it's designed to mimic an exclusive enteral feeding basically. And that's if you're dealing with ulcerative colitis, you know, exclusive enteral feeding is kind of, you know, possible for more long term for particularly with children, but like as people get into their adult life, and they're going about their daily life. It's a bit inconvenient. Anyway, there's a couple of published case reports from a hospital in Seattle, where they view and it's not a nice intervention and involves like, really restrictive amounts of foods that are boiled and pureed. So you are mimicking enteral feeding, essentially. You're peering everything into into, you know, smoothie type thing. And there is some published case reports of people going into remission who have had UC flare ups in an area, you see where unlike Crohn's where there's a bit more evidence of things to do for people, but you see, there's really the overall evidence is quite sparse and quite poor. So what would you do if you were faced with that scenario? Is this something that you might do? And I'm not having the answers here, but I'm just saying that's an example of where you have an intervention that could work for someone where there's only really case reports published, by the way, the same group at a hospital in Seattle, I think it was two or three and you're kind of looking thought going, is this actually the best available evidence? Would it be enough to act? Then maybe not. Maybe someone might look at it and say, I'm actually we're not doing this. That's fine. But it's an example of how and it's an extreme example of how in sometimes in nutrition, people are simply going to be faced with an area or a question that they don't have a lot of answers for, based on research in front of them that's of a certain quality.

DANNY LENNON: Before we move on to our next section. Is there anything related to causality that we haven't addressed that you think is important that you want to bring up? Or are you happy with what we covered there.

ALAN FLANAGAN: I think yeah. I think one thing I would just kind of invite people to maybe cultivate is a bit more thinking about this concept and not just default back to these kind of rather simplistic, you know, heuristics of causation. And whether you need demonstrable causality to show that, you know, intervention X or dietary

recommendation Y is going to benefit either an individual or a population.

DANNY LENNON: Perfect. So with that, let's jump into our listener question of the week, I guess. We got quite a few good ones. We weren't meant to cover all of them, as is nature. So we're going to pick one here in particular. In fact, before I get to our actual question, I did get one that I enjoyed from Rebecca who we both know, and it relates to our discussions around association versus causation. And she asks if people strongly associate Alan with veganism, does that cause him to be vegan?

ALAN FLANAGAN: That's excellent. I think we are resting on inferred causality in that context, as opposed to demonstrable causality. So I leave causal inference to people who could maybe piece together some different strands of evidence.

DANNY LENNON: That's actually good. That's a piece of homework, people from the podcasts based on everything we've learned today. It's now your job to go and investigate this question as to Alan's veganism.

ALAN FLANAGAN: Yeah.

DANNY LENNON: So with that our actual question for this week comes in from Agnieszka [PH]. And she asks, Why are women not picked as study participants as often as men are?

ALAN FLANAGAN: Yeah, I think this is really important because it obviously feeds into a lot of recent criticism of medicines, like you're doing drug trials in men only. For example, we don't know that this works in a lot of women's health issues that have become quite topical in recent years, whether it's polycystic ovarian syndrome, endometriosis, uterine fibroids, you know, these kind of female specific conditions, where there's such poor research, such little evidence to support any interventions because, you know that there's aren't the trials done. There, there are some really, you know, kind of sweeping conclusions that are often jumped to in this context “oh well it's just sexism” or that there's a little the, you know, the truth is somewhere in the middle as always. And from a biomedical perspective, I think we have to remember thalidomide example, and that's, you know, not, that was quite a kind of shock, an example of the potential well, pitfalls of doing bad research, but also, there is a general hesitancy, certainly, it seems with drug interventions to do those interventions

in women during reproductive age for for appropriate reasons I would argue. I think that there are other social factors factors that do lead to a gender bias. So for example, women of young children might not have the ability to take 10 days to go into a metabolic ward, for example, or go into a long term intervention or there there may be other barriers to participation, where, you know, if you're a research team in the university, you can recruit, you know, 20, 21 year old lads and poke and prod them and whatever. So, I think there are both legitimate reasons why there is depending on the intervention, sometimes a hesitancy and that does relate to, particularly if you're doing drug trials, you know, there's always put what is considered a potential risk. But nonetheless, that really has left a gap in terms of, you know, sex differences and even you know, drug metabolism and all this kind of stuff that quite constant, could be consequential and I think Hazel's writing a book about a lot of these issues specifically. So that's going to be interesting when it comes out. But, you know, from a nutrition perspective, like, you know, I think it's a combination of some of these social factors as well. Recruiting is really difficult for all studies. And if you need people to give up their time, if you need people to follow a specific protocol in their real life, you know, that can often be a lot easier for someone who's 26 and living alone, you know, and then it can be for someone who's got a family life and has school runs and you're still asking them to eat certain foods for breakfast, you know, it can be difficult. So I think there's a combination of some hesitancy for legitimate reasons and also some clear you know, bias, gender biases, and barriers to participation as a result of gender bias, and that are present as well. So, you know, often it can just be, particularly if you're doing a kind of pilot study, it can just be like a lot easier to access to recruits like I said, a group of 10- 22 year olds, males to pile into your study.

DANNY LENNON: I do think sometimes people have the presumption and sometimes I'm sure it's true, but maybe not always that investigators are purposely doing it just because it's easier for physiological/ hormonal reasons. And for certain trials, you can see how that would come into play if it's a short term trial, and it's going to be influenced by having a menstrual cycle.

ALAN FLANAGAN: Yeah.

DANNY LENNON: That could be a consideration, right? But there's also probably down to, like you say, not only the type of study, but who is doing the recruitment in terms of who's that group. So as an example, I've not looked into this actually must ask Hazel [PH] if this actually plays out, but just from the seeing different studies and trying to think of like, who are lead authors on that, and who are the participants and so on and I would suspect something like in dietetics and IBS, something that specifically that you actually would have a greater representation of women than men in a lot of those trials. You definitely see it in any research related to health at every size interventions.

ALAN FLANAGAN: They're, almost exclusively female, aren't they intermediate.

DANNY LENNON: Right and then it probably depends on if you have a really strong lab headed up by a woman in dietetics, that maybe it's just more likely that women are going to want to enroll then going into a sports nutrition studies where the whole faculty is guys. So there's some of these issues mixed in with in physiological reasons. On top of those other things you say.

ALAN FLANAGAN: And also the practicality because like, just example that the study we ran last year, we ran it in four sessions, aiming for four or five people per session. The first session was all guys. The second session, we had one girl. Third session, we had one girl and the fourth session, we had old girls, all four were women. So for a study like that, we actually went all of a sudden done ended up with a nice like male to female, pretty much 50/50 balance. But that was completely random. Going into the fourth cohort, we were looking at only having two women. So it was just that we got and I guess what I'm saying is, bear in mind that there are a lot of it. You don't just get someone that says yes, I want to do your study and you throw them into it. Like there's a really protracted screening process that goes on with research where, you know, you're looking at people's medical histories, their ability to attend. Perhaps they've recently been on a medication for example, that you know, is going to be contraindicated or potentially confounding, if you're looking at a specific, you know, physiological parameter. And maybe the oral contraceptive pill is one of those factors as well. And so there's just, there's a lot of randomness, just because life is life to having, you know, your eight or four weeks even, or sometimes three weeks out from your actual study start date, and you've got eight

candidates, you know, and you're only going to end up with four and maybe all of them were technically able to pass screening, but no one's going on holidays or, you know, one's kids on midterm. We have this happen. So it was as simple as one of them the study dates coincided with midterm and school. So she was unable to do it. So, you know, I think there's a lot of those considerations as well. I wouldn't just presume that's it's a verse intended by researchers. There is is always going to be, I think the gender bias is comes from a lot of these additional lifestyle factors. And that's obviously a barrier and something that, you know, research communities should look to try and get, you know, to remove some barriers. But like you said, it's going to depend on the field, it's going to depend on who heads up the research group potentially. It's also just going to randomly depend on who has passed your screening, and who is available to do your study. So I think we need to think about those things as well.

DANNY LENNON: And I think it's important that it's not mutually exclusive that there is some gender bias as well as the idea that there's this randomness at times as well or that anytime you see a disparity between any two groups, not always is that an intended or a result of some sort of discrimination, and in some cases, it is. So those two things aren't completely mutually exclusive. Both can be occurring within science, which is probably the case that it's both of those things are occurring, some randomness, some that is some bias, either overtly or unintentional. And then there's also practical reasons for physiology or exclusion criteria, etc.

ALAN FLANAGAN: I wonder as well whether it's as pronounced a difference as biomedical sciences. I really do because, you know, you think of like, you know, the nurses health study, enormous cohort in the states is entirely female. The women's health initiative RCT was obviously entirely field. We have trials and large cohort studies in nutrition that are exclusively females. So I am not saying obviously nutrition is perfect. I'm just saying I wonder whether when people talk about, oh, this massive under representation of women in research, often I hear that in the context of medical research, and I wonder whether it's as pronounced in nutrition, I'm not saying it doesn't exist. It obviously does.

DANNY LENNON: Yeah, that would be interesting to look at. So maybe someone can go and do that analysis for us. I think even within nutrition

research, I would hazard a guess that it would differ among subcomponents. I think you're going to see a big difference between sports nutrition versus some of the dietetic field as examples I gave and probably depends on the condition as well, that you see different representation of that. So I would suspect that's the case but that's, I think our best answer for now. With that, do you think we should get to our quack asylum for this week? How does that sound?

ALAN FLANAGAN: Yeah, I think we should ride off.

*The quack asylum.*

DANNY LENNON: Okay.

ALAN FLANAGAN: I think there is a fairly obvious winner, slash winners, for the first time. There are people sharing the podium. Eight of them.

DANNY LENNON: So yeah this was actually already mentioned earlier in this discussion but maybe to revisit that for people who maybe have no idea of this paper that came across it was also overview that you can mention about our joint winners.

ALAN FLANAGAN: Yes. The quack asylum this week we're entering multiple people. I think if you've paid attention to any of the conversations that, you know, have circled around kind of high fat diet saturated fat, low carb and the carb insulin debase, you know, you'll recognize and particularly, you know, certainly from some of my social media stories, I have overtly named multiple of these people, whether it's the Aseem Malhotra, Zoe Harcombe. You know, who else was on David Diamond is the lead author. And basically, this paper came out it was published last week, and it was talking about dietary recommendations for familial hypercholesterolemia which for those of you unfamiliar is a genetic condition where you're born with an under function, massive loss of function of what's known as the LDL receptor, which uptakes cholesterol into your cells, thus you don't have a lot circulation. And so because they can't get cholesterol, they have hugely high really high levels of LDL cholesterol. And if fH is left untreated, people will often suffer you know, cardiac, heart disease mortality as early as 35, 40, 45. So it tends to be it's still under diagnosed but when people are diagnosed, they're on pharmacotherapy for life. They're on statin, high intensity statin interventions often immediately from maybe

you know, the age of 10, 11,12. And plus some of the other pharma options that are now available as co-therapy to statin. And the dietary advice has generally centered around best practice dietary advice for heart disease management. This paper was almost a who's who... Oh, that was the other guy... Uffe Ravnskov was stuck for a name.

DANNY LENNON: We also have a Malcolm Kendrick.

ALAN FLANAGAN: Oh yes. So this is going to give you cut. So I have taken two Googling authors, obviously a lot for, sometimes just out of interest, see where they are with their researches. But if a paper is a spin like this, or if it's a very like Pro, either low carb or plant based paper, I'll Google the authors and often you find that they have affiliations that reflect their dietary belief system. For these authors, five of them I think, are members of what's known as THINCS, which is the International Society of Cholesterol Skeptics. And there for those of you interested there's a good article. It's from 2008 on science based medicine about this quack organization with this is an organization that is literally the quack asylum. Three of the authors of this paper have their own rational wiki page which I highly recommend you check out. So the Aseem Malhotra, Zoe Harcombe and Malcolm Kendrick and if you're to check out one check out Malcolm Kendrick's rational wiki page, he's a GP somewhere in the UK. I sincerely hope that he doesn't practice or see patients in the real world. But like, the rational wiki page is amazing because it's like claims he's made, which is there is only one expert and that is Malcolm Kendrick is a claim about like, well, saturated fats can't be bad for you because they're so delicious. Like, well, that's science. And this paper has sadly though, like Jeff Volek, who a lot of people would know from and would consider, you know, a really legitimate scientist in the low carb space and has done a lot a lot of research on low carb ketogenic diets specifically in sports performance. And I have to say it was quite I know he's got that bias. But it was quite disappointing, I think to see someone that's considered a legitimate academic to put their name to something like that. In any event, the paper is just a fallacy from start to finish. It makes the point that there are no RCTs for diet and fH. Therefore, there is no evidence and therefore everything is wrong, and you should go on a low carb diet and not worry about saturated fat. Well, of course, there's no RCTs about diet in fH because people are treated with drugs immediately upon diagnosis,

because if they're not, they'll die at 40. And because the magnitude of effective diet is so small, if they're on all of these high intensity drugs, there's almost kind of little point in doing a dietary intervention to try and tease out an additional little benefit on top of all of these drugs to try and get a signal in the magnitude of the effect they're having on controlling their cholesterol from drugs. So it's a complete red herring that there's no RCTs in fH, it's to anyone with a normal brain that doesn't want to kill people. You know, it's not that, you know, particularly shocking. There are one or two, I think, that are getting designed now. And, and then it goes on to make points about the usual that you would expect from this. Well, LDL isn't an accurate predictor of heart disease, but it makes a point about lipoprotein A or LPa, and as an example, and people can go back and read our cardiovascular statements. But the what's really interesting for these low carb nutjobs to focus on LPa versus LDL, is that LPa is basically an LDL. It's an LDL molecule. It's basically the same in composition as LDL. So for example, LDL carries about, say 45 milligrams of cholesterol, whereas an LPa carries about 35. I think give or take 35 to 40. So near equivocal, and some nice Mendelian randomization studies that we have, show that where you reduce LDL by 38 milligrams, or you reduce LPa by 100 milligrams so the actual size of reduction because they are different sizes is different. But the mass per mass they have of those two weights, they have the exact same cholesterol content. So you reduce heart disease by the exact same amount. Of course you do because you've reduced the cholesterol content is what matters. So they've almost defeated themselves with that specific argument. But I think fundamentally, although we wekind of joke around with the quack asylum like this is a really dangerous paper in many respects because you know, familial hypercholesterolemia, you know, diet is going, you have and here's the thing. Remember that I said that fH is defined by loss of function of the LDL receptor. People seem to kind of forget this when it comes to saturated fat. The way that saturated fat increases your blood cholesterol levels is via the LDL receptor downregulated. That's the exact same mechanism by which the drugs that are designed to treat cholesterol act through. So the mechanism is the same. So the idea that there is some distinguishing factor there, it might increase your blood cholesterol levels as much. I'm sure a low saturated fat diet might not reduce your blood cholesterol levels as much. But the idea that people with fH should go on a low carb diet given the interventions that we have

showing there was a group in Norway that did a really tightly controlled study last year and otherwise healthy young man should have 44% increase in LDL cholesterol from proper low carb high fat diet. And so this isn't just like a kind of throwaway banal paper. It's potentially really harmful, particularly because there are GPs all over the UK who by this shift from these particular advocates of this diet. So it's not benign. The consequences of publishing something like this are not benign.

DANNY LENNON: It was pretty amazing when that paper came out. Number one, it was great to see that list of authors all that are on. It was like we said, like all starting not good way. But it's also particularly useful for this topic that we've had today because it exactly highlights all of the potential problems that we've heard or discussed, and, yeah, it's, as I mentioned to you, a couple of months ago, I think it was off the back of some of our heart disease podcasts, I had some interaction with the lead author David Diamond, on Twitter, who goes by the Twitter handle LDL skeptic 2, presumably LDL skeptic 1 was taken. And given that all we've talked about causality in nutritional science today, one of his tweets to me was a copy and paste of a dictionary definition of cause being the verb to make something happen, and fitting that as evidence that LDL, in fact, is not causal in cardiovascular disease. So that's kind of what we're dealing with but I will link to their paper in the show notes on the list for people to go and check it out and.

ALAN FLANAGAN: Yeah and I think we will also link to the Deighton and Cartwright paper, which is more of a thesis called understanding and misunderstanding RCTs. It's about 20 pages. But it's worth with a cup of coffee one day and really chewing over and I recommend their work. Nancy Cartwright in particular has, even though she's coming from an economics field, has published excellent kind of very epistemic analyses of the problems with methodological prejudice, and the pitfalls of complete obsession and veneration of RCTs. And so that's a good starting point for people to kind of go on from.

DANNY LENNON: Awesome. So with that, let's round out here with some random recommendations for this week.

*Something Random*

ALAN FLANAGAN: So it's actually it's another Netflix series, but there was a book. So I'm not sure if people are fans of historical fiction, but when it's done well, its excellence kind of transported you to an alternate plausible world. And there's a book by an author called Len Deighton, called SS-GB as in SS is in Hitler's SS and GB in Great Britain. And the plot of SS-GB was you know, Germany won the Battle of Britain, invaded Britain and Britain is now essentially a kind of German occupancy. And it's centered on a detective who they've kept the British institutions as of stage running somewhat separately. And it's only one series because it's from the book. It's five episodes, but it's really good. A, the series is fantastic. But B, it's just a really kind of cool plot if to chew over it. But yeah, it's really good series.

DANNY LENNON: And again, for people I will link to that in the show notes for you to go and check out if you wish. I think for mine, the one that's on the top of my mind is I really listened to an audio book called Stumbling on Happiness by Daniel Gilbert. It sounds like a self help book. But I can assure you it is not. It just has a terrible title. But it is essentially about psychology research. So Daniel Gilbert is a well-known psychology researcher and has done a lot of fascinating stuff that looks into essentially cognitive biases that we hold and how we can trick ourselves, how we can be very poor at trying to imagine the future. And so that's inherently the thing that humans have over other creatures that we can think into the future and imagine. And he talks about how we have this ability where when we think of the future down the line, it always is way more similar to our current president than in reality will actually be. And so we dramatically underestimate differences where we don't accurately appraise how we're going to feel at that certain point. And we do the same thing retrospectively. We have a really bad ability of remembering how we actually felt in a moment. So we experienced something, have a certain emotional response to it. And if a year down the line, we were to look back at that time and ask how did you feel that point, we actually have a really bad ability to appraise them correctly. And so he talks about really our only way to get past a lot of these biases that we are knowing the present is correct.

ALAN FLANAGAN: Right and that's it.

DANNY LENNON: And that's pretty much it. So but it's really-really good. And the reason why I recommend the audio book is he narrates himself and

just has a really, really good delivery of a like, really enthusiastic, pretty well done. And yeah, I thought it was very, very good.

ALAN FLANAGAN: I think that's a feature for audiobooks when the actual author.

DANNY LENNON: Yeah, I can only do it if it's actually a good audio delivery.

ALAN FLANAGAN: Yeah.

DANNY LENNON: So that's it. For people listening, given the nature of this conversation today and some of the topics that we got into that there may be some questions that pop up on this. So feel free to send them in either email, social media, or you can do that via the website. I think it's just sigmanutrition.com/question. And at a future point, we may be able to address those if there's a sufficient number that weren't going into detail on if anything here wasn't particularly clear, or you'd like to hear more about. And that's pretty much it. Check out the show notes for all the details and links. And Alan do you want to say goodbye to our good listener?

ALAN FLANAGAN: Good buy good listeners. Yeah if you do have questions, do submit them because it could be something that we, you know, expand on in some medium.

DANNY LENNON: Take care until the next episode. And that's it.