
DANNY LENNON: Okay, here we are. Welcome to Episode 377 of Sigma Nutrition Radio. My name is Danny Lennon. I'm here with Alan Flanagan. I think, well, we had our big bit of excitement with our sodium episode, which people seemed to enjoy, and there's actually a lot of good discussion and comments off the back of that. So thanks for anyone who sent that. But actually, today's episode, I think is going to be useful to tie some of that together, not only the sodium episode, but in episodes where we've dealt with dietary cholesterol or LDL cholesterol or other aspects of nutritional science, specifically in these diet disease relationships, and to try and kind of zoom out and, at a higher level, understand nutritional science a bit. Now, of course, we've done a similar episode like this in relation to meta-analyses. and in today's conversation, we're going to look at nutritional epidemiology specifically. these conversations, I think, are quite important because they're not often had, but I think they lay the groundwork for being able to really get to grips with some of those concepts, we discussed, for example, in the sodium episode of understanding these diet-disease relationships, looking at assessment methods, or how we are able to integrate these

into a bigger picture of risk. So I think this will hopefully prove useful to people.

ALAN FLANAGAN: Yeah, so I think, I mean, just going from first principles with epidemiology, we're talking about the study of the distribution of disease and the determinants of disease in a human population, and the prevalence and incidence and how that prevalence and incidences of a given disease is influenced by factors that we think might have a relationship with that particular disease process. And with nutrition, we're faced with a particular logistical challenge, in that, the diseases that we would call chronic, chronic diseases, cardiovascular disease, type 2 diabetes, neurodegenerative disease, and cancers are diseases that largely have long latency periods, i.e. they take a long time to develop; and the processes that influence the incidence of that disease later in life can be at play earlier in the lifespan. So we know, for example, that with atherosclerosis, that can actually start to develop from the second decade of life, from the late teens onwards. So nutritional habits and practices earlier in the lifespan can be influencing and determining the incidence of disease later on. And that becomes very challenging from a methodological perspective to try and study and to try and understand; and it means that from a practical perspective, randomized control trials really aren't an option to study the relationship between an exposure and an outcome over a 40-year period or a 30-year period. And even if you were to undertake that, the assumptions that go into an RCT would be eroded very soon after randomization. You would essentially end up with an observational study after a certain period of time.

So we're faced with a logistical challenge in nutrition science with trying to understand the relationship between diet across the lifespan or at a certain stage in life, and the incidence of disease later in life. And our understanding, biologically, of every nutrient interaction in the body is likely never going to be complete. So,

ultimately, epidemiology is a very important part of how we start to implement policy around diet or make recommendations generally to the population. And as such an important part of the evidence base, it's a very maligned field; epidemiology and medical sciences generally is a maligned field for reasons, some of which are just and some of which are quite unjust; and I think the purpose of today's conversation, nutritional epidemiology in particular, is subject to some criticisms, that it's important that we keep criticisms to where they're due and valid, but there's a lot of overreach with criticisms towards nutritional epidemiology or a misunderstanding of its purpose and its place in the evidence base that I think can be reconciled by thinking through it a bit more. And the reality is, it's not going anywhere, the relationships between these exposures and disease outcomes isn't going to change. Cardiovascular disease on average still occurs between 65 and 70 is when most first events happen.

So we're not going to randomize people at the age of 20, and wait until they're 70 for an event and then say, aha, this was what happened in the intervention group, and this is what happened in the control group. So people in a way kind of need to get over themselves a little bit with some of this, with some of the kind of more, I guess, sophist arguments that we would see, leveled against epidemiology, and we need to bring it back to research being a tool, and any findings from a study being a data point that we then insert into an overall body of evidence and try and look at it. When we consider multiple lines of evidence, many of the findings in nutritional epidemiology are not inconsistent necessarily with RCTs, and are not entirely consistent with even tighter controlled studies either. And that's how we reconcile the evidence base is by factoring in these converging lines of evidence. But epidemiology provides us with an important part of that overall evaluative process.

DANNY LENNON: So as a kind of brief recap, if we're thinking about epidemiology, here, we're looking at this measure of the risk of a particular disease or death in a population exposed to something, compared to that risk in a, let's say, unexposed population. So if we account for all other variables, exposure to something, how does that relate to risk? Now with nutritional epidemiology specifically, therefore, we're looking at these diet disease relationships in humans, and as we'll probably come on to later, the exposure in the context of nutrition is going to be very important and in many ways unique. And we're really trying to look at, well, what is this relationship between that exposure of the dose, the duration, and then this risk or end outcome at the end. And then you noted that there's some real kind of logistical challenges with looking at diet-disease relationships that make nutrition science have this kind of quite unique aspect to it. And so, we need to have a good understanding of those challenges to be able to assess what methods of researching this field are useful, and that's where looking at epidemiology comes in. And just towards the end, you started to mention that there's often drawbacks, some maybe a bit more nuanced, some sometimes can be a bit blunt and very overly simplistic, for example, simple narratives like observational data is not good for determining causality. So we need an RCT to know that something's causal, and therefore epidemiology should be thrown out when it comes to nutrition. I think we've discussed some of that before, and definitely on the previous podcasts, you discussed this biomedical centric reductionism that can sometimes happen as well, that kind of pushes epidemiologists to decide.

ALAN FLANAGAN: So one of the one of the most common things you'll hear is someone declare association isn't causation. Right? And that's offered as if it's a critique, it's not, it's just a statement of fact that no one in epidemiology pretends that association is causation, association is

association, association is correlation. That doesn't mean that it's not valid. And many of our decisions have to be based off association, and demonstrable causality is not very common in biological sciences for multiple reasons, it's really difficult to kind of prove. Even if you think about all of the determinants for cardiovascular disease, for example, with 80 years of research under the belt, only really LDL cholesterol has actually been deemed causal in a way that we would use that word, deterministic of the progression of the primary feature of that disease, which is atherosclerosis.

So, I think there's a fundamental misunderstanding with the needs, for demonstrable causality to underpin every decision that we have; and that therefore, if epidemiology doesn't demonstrate causality, then it's not valid for assessing associations or assessing cause-effect relationships, and that's incorrect. We use causal inference, sure, and that does require a much more thorough process of thinking through, and causal inference in epidemiology is the subject of an entire literature from Bradford Hill and his kind of initial criteria, although he didn't call it a criteria, it's been called that since. So this idea that association isn't causation, well, no one ever said it was. So that's not a critique. It's just a statement of fact. And actually, association is important, and if that association continues to occur, and we observe it in different populations from the same exposure, and we can start to even look at whether there's a similar effect with regard to dose or duration of exposure and all of these other variables, then you can start to piece together a picture, that if you marry it up with some degree of biological – if we've got biological plausibility with it – then you can make a causal inference that a given exposure increases or decreases the risk of a particular outcome.

Now, whether that is the causal factor is an irrelevant question, because we're never dealing with single univariate causal

relationships for most biological exposures and outcomes. So it doesn't matter if it's not the specific causal, for example, nutrient or that there is other stuff going on, which inevitably there is. The question is, what would change in that exposure due to the incidence of disease. Right? If we change that exposure, do we reduce incidence of disease? And depending on whether the answer is yes – or reduce or increase, for example. So that's the question, and there's a much more kind of widespread analytical process that has to be undertaken to get to that kind of conclusion. But once there, the idea that you then dismiss whatever the conclusion is, because "association isn't causation", it's not a very thorough way of thinking through these relationships.

DANNY LENNON: And I think on some previous episodes, we've discussed this ability for epidemiology to be able to infer causality, I think, particularly in reference to prospective cohort studies, which we'll maybe mention in a bit more detail in a moment. But in that sense, prospective cohort studies can infer causality presuming they're done appropriately; and we've also kind of referenced how, like you just said, public health decisions oftentimes need to be made in lieu of having RCT determined causality, and I think in some of the heart disease episodes, we discussed trans fats and heart disease as a particularly good example.

ALAN FLANAGAN: And this doesn't even confine itself as a criticism to nutrition science, like, if we had to wait for public health policy to be grounded in RCTs, we wouldn't have public health policy. And I think we've used this example before, but an example that I think is useful here is the incidence of sudden infant death syndrome in New Zealand, SIDS – well, it was globally kind of had a high prevalence. This is in the 1980s in a case control study, which is an observational study, but considered to be lower down the hierarchy of evidence than say, a prospective cohort study, was undertaken to try and get some data on potential risk factors. And one of

the risk factors that was by orders of magnitude associated with incidents was sleeping in the prone position. So I've used this example before and it's a dark and somewhat sophist example, but you're not going to do an RCT, randomizing babies to sleep in the prone position. Right? So on the back of that finding, and because the magnitude of the association was so strong, public health policy was introduced to recommend not avoiding sleeping in the prone position, and the incidence of SIDS declined exponentially.

So not only did you have the basic data to inform the policy, you retrospectively then had the benefit of the policy to confirm and corroborate the initial findings and say, actually, this policy has been successful. And that's an example of a study in terms of its methodological kind of setup and design and consequently, limitations that people would consider very low evidence, but it was sufficient evidence to inform a policy that had a beneficial outcome. So we get a bit, and this is something we've talked about before, is this overly rigid perspective of the hierarchy of evidence. Well, whether evidence is sufficient for a given question, depends on multiple factors and depends on the nature of the question, prior knowledge, what we know at the time, other lines of evidence. So it's not determined just by the design of the study, it fits into an overall picture and it's a question of whether it's sufficient for whatever question we're trying to answer.

DANNY LENNON: So you just mentioned case control studies, we've mentioned prospective cohort studies – so if we maybe just lay out some of the typical trial designs that come under the umbrella of nutritional epidemiology, because we often reference them, but they can sometimes maybe be confusing or sometimes not exactly clear, unless people have looked into it, so even if we take general classes of cohort studies, case control studies, cross sectional studies, probably covers most of what people will come

across at a very overview level without us having to get too deep into the weeds, how should we conceptualize what each of those classes of studies are?

ALAN FLANAGAN: So with case control studies, you're talking about taking information or data from patients with a disease or with a specific outcome, and then comparing it to healthy controls. So for example, you take a group of participants that actually have a diagnosis of type 2 diabetes, for example, and you compare them then to subjects without that disease. And so, it's just really a comparison, you haven't looked at the determinants of what – you can make some inferences based on the data that you collect, but it's not prospective in time. You're simply taking kind of these two populations as they exist at that point, and comparing disease versus healthy. With cross sectional studies, you're doing something similar in terms of a comparison at a specific point in time, so you're taking a group, and you can split them based on some characteristic that you're interested in looking at, and then look at whatever exposure and how that may differ from group to group.

But again, you're taking in that kind of design, you're taking people as they are at that point in time, and then we have prospective cohort studies, and the key in that title is prospective. And this is generally considered the best design that we have available for nutritional epidemiology. It allows us to deal with some of the bias issues that arise in some of these other studies, so, for example, recall bias or otherwise. And you're studying crucially, for what we talked about earlier, the time course of disease, having long latency periods with the outcomes we're interested in; prospective studies, you're taking people who are healthy a baseline, and screening them for that health status; so they don't have type 2 diabetes, they don't have cardiovascular disease, and you're following them over time, prospectively; you're taking them at, let's just say, for example, the age of 40, and they're healthy at that time that

they enter the study, and you're following them over 10, 15, 20 years, and you're looking at the incidence of whatever disease outcome you're interested in, in that cohort, relative to measures that you took when they were healthy earlier in the time course. So it minimizes the opportunity for some retrospective biases to come in later on. So you've assessed them before any disease, and you're able to then with a slightly better context than other designs in epidemiology, you are able to then look at, you've assessed, for example, diet, before disease has occurred, and you're able to see how that might have a relationship then with the actual outcome itself.

DANNY LENNON: Yeah, and I suppose the reason why so much focus, or at least, a lot of the time, we have placed focus on prospective cohort studies, or why they can be so useful is for a number of those reasons you just referenced, and how they can offset some of those potential biases or problems that can crop up in other types of studies. But in terms of do we want to mention anything about dietary assessment, and how that might relate here?

ALAN FLANAGAN: Rather than getting into the nitty gritty for different food frequency questionnaire versus 24-hour recall, etc., I think just at the kind of level of principle or the conceptual ideas underpinning it, I think it's important for people to think about diet as an exposure. If we're talking about other exposures that could have a relationship with mortality like smoking, it's quite defined, 10 cigarettes maybe a day or 20, or whatever it is, but it's quantifiable in that way; or a car accident, for example, generally is going to be a one-off. Someone is in an accident and unfortunately people have died as a result of that accident, so it's an exposure, they could be instant, they could be the one exposure, they could be smaller and quite definable. Diet's different to all of this. Diet is something that people will consume multiple meals a day, and the exposure isn't just the putting of food in the

mouth. We could be digesting a meal depending on its energy content and macronutrient composition for up to five, six, seven hours after having consumed that meal. So if you consume three meals a day, you're in this constant state of exposure, so to speak, in terms of the impact of that diet on physiological processes that are associated with disease, whether that's blood pressure or blood cholesterol levels or blood glucose levels, or even other kind of more nitty gritty mechanistic stuff.

So that's a very large cumulus of lifetime exposure, that's daily, that is not just the act of eating itself, but the processing of that food afterwards. And it's important then that we have some ability to be able to grasp that and people tend to eat differently from day to day. So some of the methods like say, for example, 24-hour recalls, they have some benefits, but if you just did one or even two, you would miss that day to day variability that someone has, you wouldn't capture their true intake, or this comes back to something we discussed on the sodium episode. So generally, the best tool that we have for nutritional epidemiology for a prospective cohort study that wants to assess diet at baseline, and even do repeated analyses over the course of the cohort – depends on the cohort and how it's executed – but the best tool that we have so far is a food frequency questionnaire. It's semiquantitative. So there are prompts in the question like two slices of bread, for example, a glass of milk, but it will give a certain kind of millimolar amount or a milliliter amount, for example; or cup measures if it's an America, a cup of pasta, a cup of rice, this kind of thing.

So that tool, generally, depending on what we're talking about as an exposure, but for many macronutrients, if the tool has been, what they call, validated, which is when it's compared to another kind of, what's considered maybe more objective measure, like, getting people to weigh food intake and measure food

intake for seven days and then comparing how well the food frequency questionnaire answers compared to that, generally we get decent correlations with the objective measure, such that when people say nutritional epidemiology is inaccurate, well, that as a blanket statement doesn't hold, because the answer to that is, it depends. So is it inaccurate for, for example, total fat? Not really. Not particularly. Is it inaccurate for beta carotene or folate? Yes. It wouldn't have a great accuracy or kind of correlation with it.

So when we talk about accuracy, the answer is, it really depends. It depends on the nutrient that you're talking about, and that's a really important thing to consider. So try to avoid the broad brush assumptions when thinking about epidemiology. And while certainty there are inaccuracies, even in the nutrients, we can measure with better validity, with better correlation such as total fat, saturated fat, carbohydrate intake, and some of the other macronutrients, and some micronutrients as well, but the reality is, it depends, the accuracy depends, and the inaccuracy and degree of error is still comparable to other aspects of biological science. So the predictive, the value of how blood cholesterol levels, for example, over time, or blood pressure, or even blood glucose levels, the major macronutrients and nutrients of interest that we have in nutritional epidemiology often have the same strength of correlation as some of these other measures, and these measures are uncontroversial. No one suggests that prospective cohort studies looking at the relationship between blood cholesterol level and heart disease are hocus pocus in accuracy. But we do get the same criticism leveled at nutritional epidemiology.

So I think that’s the one thing I think from the perspective of dietary assessment that's important to get across. It's not just a blanket, it is inaccurate. The answer to whether it is inaccurate or not depends on the nutrients of interest, depends on how the individual study

has conducted its assessment, and it's something to consider and look at in more detail. And it's not a blanket dismissal of potholes and accuracy across the board.

DANNY LENNON: And if people do want more detailed discussion around dietary assessment methods, in Episode 263 of the podcast I had Dr. Brenda Davy, where we just specifically discussed dietary assessment methods. And within that, some of those points that you just referenced, were made a number of times of, it's not like nutritional epidemiologists are unaware of the shortcomings of the assessment methods, and are completely clueless that there may be inaccuracies, or that these are perfect measures of intake; it's that there's these various different assessment methods that each have pros to them and cons to them. And then depending on what type of study you're doing, and what you're trying to evaluate, you would make a decision on what best fits. And then when you combine all that evidence together, as we kind of discussed so many times, you start to see that clearer picture emerging, as opposed to saying, well, this method can exactly quantify what someone is consuming of this particular nutrient, therefore, what's the point, it's a waste of doing this study, which is sometimes some of the narrative we hear. So I think, yeah, we can dismiss that as kind of overly sensationalist and...

ALAN FLANAGAN: Overly sensationalist, yeah. And I think the best way for people to think about, so, for example, a food frequency questionnaire, is always ask, when it comes to dietary assessment, what is the exposure that the measurement instruments, whether it's a questionnaire or recall, is trying to capture. And diet is generally as most people think, would kind of intuitively, maybe, at least kind of be able to conceptualize this, diets average over time. Right? That’s what dictates the healthfulness of a diet. It's not that I had a cheeseburger, deep fried cheeseburger for lunch, that's not dictating heart disease. That

one meal is not dictating whether I have heart disease in X amount of years. So generally, people might vary their diet day to day, but what characterizes human eating is day to day variation superimposed on an underlying consistent pattern. So food frequency questionnaires are designed to capture average intake over time. Right? And that's why, conceptually, there's a slight advantage to using them over other methods. But they're not trying to, and as you say, like, it's such a good point, because this assumption that people in epidemiology or nutritional epidemiology kind of aren't alive to these issues, these 50 years dedicated to trying to improve how we measure diet in a population that you're studying. And it's an ongoing improvement and technology might provide some quite exciting advances in that, which I think she talked about on that episode, if I remember correctly. But trying to capture average intake over time, if you do it in enough people, it doesn't have to be 100% accurate to give us a picture of some of the determinants from a dietary perspective of disease. We want to capture average intake over time, because it's more representative of overall general habitual diet in a population.

DANNY LENNON: Based on a number of things that you've alluded to so far, there seems to be two key things that I think we should spend a good bit of time looking at. And this is really those issues that make determining those diet disease relationships quite difficult to navigate. And as two kind of broad issues, first relates to something you just mentioned a moment ago about exposure of interest in nutritional science, and there's a number of unique aspects to that which we should get into some detail on, I think; and the second that we'll maybe come to afterwards, with nutrients, and with food, and with diet, the impacts they make or the differences they can have are relatively small, but accumulate over a long period of time as it emerges within chronic diet disease; and so, there's kind of that temporal aspect, which we'll get into. So those two kind of big

topics of exposure of interest and those temporal relationships. So first, if we think about that exposure of interest, one aspect of that was this idea that we don't have this nutrient-free state, and this is something I particularly remember you discussing before in relation to comparisons to biomedical RCTs and drug interventions in the example.

ALAN FLANAGAN: Yeah, if I have high cholesterol, and I'm starting to get medical management of that condition, I may be given a statin. I don't habitually have statin floating around in my bloodstream. I don't have a minimum amount of statin that prevents me from having some deficiency, from not having the statin. What differs to biomedical sciences, fundamentally is that the absence of a drug as a remedy is not the cause of the disease. I don't develop atherosclerosis because I didn't have enough statin in my life, in my diet, or I wasn't taking a statin from the age of whatever. So preventative interventions or interventions designed to, specifically, from a medical perspective manage or reduce a risk of the disease or reduce it progressing, are completely different exposures, for which we don't have an equivalence. Right? Because we've eradicated nutrient – certainly in the developed world – nutrient deficiencies are largely eradicated. We have certain population subgroups, certainly, that are exposed to more of a nutrient insufficiency or even a deficiency, and so we know that vegan diets do take some thinking about planning in order to manage, but some of them are particularly well known, like B12, some of them are becoming more well known, like iodine.

And outside of population subgroups though, just to stick with this conceptual point, I have sufficient vitamin C, because I don't have scurvy; I have sufficient vitamin B1, because I don't have Beriberi. I don't have these single nutrient deficiency states. And it means that I constantly have a certain amount, likely at least adequate amount, of a given nutrient at a given

time, whereas with a drug, I can give me a statin, and you don't take a statin, and that means there is a clear difference between us. I am on a satin, and you are not, and it's a comparison between an exposure versus zero exposure. Whereas if we both go into an intervention study looking at calcium and bone health, and I get the calcium supplement, and you don't, you still have calcium, you still have probably adequate calcium in your body. So I'm just simply getting more of something I already have, and you're getting nothing but you still have something that I already have a baseline level of.

So we're not comparing calcium to zero exposure, even though trials are often set up with we compared calcium to a placebo. It's like, no, you didn't, you compared more calcium to a certain level of calcium, and that's because nutrients exist on a bell curve of distribution of intake, from deficiency to adequacy, to excess potentially. We say toxicity and toxicology, but I think excess is a better word for nutrients. And so, most people are probably within a range of adequacy, and certainly from an RCT perspective, most ethics committees won't allow people to go into a study with insufficient levels of a given nutrient. So that means it's very difficult then to detect an effect, if more of a nutrient does not necessarily mean better, if more does not necessarily make the biological activity, or the mechanisms through which that nutrient acts or works, then most of what makes nutrients show a benefit is when you're increasing levels of that nutrient from states that are low already or insufficient. And this means that the difference in the levels of intake in nutrition becomes crucial. We're not comparing, I have calcium, you don't have calcium. We're comparing, I have a diet with 1000 milligrams of calcium a day, and you have a diet with a 100 milligrams, for example. And if we have that contrast, where you're getting under what we think is optimal, then we might see a difference between these levels. But if we both go into that

same study, and my baseline diet has 1000 milligrams of calcium, and yours has 600, which is probably sufficient, and I'm given extra calcium as an intervention, there could be no difference between us in the outcome; and then people would conclude, well, that supplement doesn't work or calcium doesn't work for whatever outcome we looked at; when in reality, we were simply comparing the exposure to a supplement, giving more than adequacy, but there wasn't simply a comparison between us.

So this is one of the limitations of randomized trials in nutrition. In epidemiology though, the same issue occurs, however, if a cohort study, and because people in the fields are live to this issue, if a cohort study is well thought through, it can actually design itself to try and deliberately, through its screening process and recruiting and various other factors, deliberately try and have a wide contrast of whatever, of nutrient intake in that cohort, so that you get more meaningful comparisons. So you're not comparing, let's take red meat for an example – I'm consuming a 100 grams a day, and you're consuming 60 grams a day – is that really going to yield a meaningful difference? Probably not. But if I compare someone eating over 180 grams a day to someone eating less than 20, on average, then we've got a wide contrast in that exposure of interest, that would allow us a more accurate representation of the comparison in levels, in the risk of that particular exposure.

So this idea that there is no nutrient free state, that we're constantly in a process of taking in nutrients, most of us have at least adequate amounts of nearly all micronutrients, you know, specific populations, subgroups aside; and so how we tease out the effect of that is a different methodological consideration to comparing people on a drug versus people not on it, where you could be certain that the people not on the drug simply aren't on the drug, and they don't have any of that drug in

circulation, and they're not exposed to whatever mechanisms of action that drug is doing. Whereas we all have vitamin C, we all have some B1, we all have some folate in our system. So how do we go about actually comparing whether there's a difference in high intake of one or inadequate intake of another, we need a sufficient contrast between different levels? To do that, we need prior knowledge of different levels.

And just to maybe kind of wrap that up with an example of how this plays out, an example, I like using is with the epidemiology of vitamin E – and two outcomes, vitamin E is typically, the interest in vitamin E focuses on is cardiovascular disease and neurodegenerative disease through similar mechanisms. But with vitamin E, you have a couple of cohort studies, which found a benefit to quite significant in terms of relative risk reduction, reduced incidence of dementia, reduced incidence of cardiovascular disease. So you scrutinize those cohorts, and you realize that the group consuming the highest at over 18 milligrams a day on average – in fact, there was a subgroup within that, who were consuming over 27 milligrams, and that was being compared to a group consuming less than 10 milligrams. So we saw this big contrast in exposure where the group with the highest levels of intake had a significant relative risk reduction against the group consuming the lowest. Right? Then you look at other cohorts, and you see, for example, no finding at all and no finding. And you scrutinize the levels of the exposure contrast in that study more, and you realize that the highest group now was consuming only 6.4 milligrams a day, and the lowest group is consuming less than one.

So the idea of high versus low doesn't mean anything. It has to be defined. And in this group, there was simply everyone existed in the cohort, under 10 milligrams. Right? So, of course, you find no effect, because you either have too narrow a contrast to determine a

difference between the two groups, or, all of those levels are simply insufficient. And you go to look at other studies like the Chicago Health and Aging Project or the MAP study, and again, you see similar or the Sweden Kings Health Project, which was another cohort study in Sweden, you start to see these similar thresholds emerge, where you've got the highest quintile or group. If they're over 15 milligrams as a minimum, you're starting to see that, if you compare them to people with less than 10 or less than eight, there's a benefit. Okay? And then people would say, oh, we can't trust the epidemiology because this study found nothing, or, we can't trust it, because it's inconsistent findings. It's like, well, okay, let's think about some of the RCTs, because the RCTs on vitamin E largely found nothing, they found no findings, no difference between intervention and placebo group.

And so, there was two consequences to that in terms of people's thinking. One was, people start going, ah, you see, the epidemiology that found a benefit is obviously wrong, because this study was an RCT and therefore it's right. That's methodological prejudice, and it's ludicrous thinking. But the second consequence is, well, what was the study testing. Going back to this nutrient-free state, maybe people just had enough vitamin E. And actually, if you look at some subgroup analyses from one of these interventions where the overall study was a null finding, people were supplemented 400 milligrams of vitamin E a day, but you do a subgroup analysis of that study, and you look at people whose baseline vitamin E intake – because they measured baseline vitamin E intake, thankfully, because we were able to tease this out – was under six milligrams, and there was a significant benefit in them. That's entirely consistent with what we see in the epidemiology.

So in people who were low into this insufficient range, there was a benefit to additional vitamin E, in people who were low at the start. In

epidemiology, you compare people with those levels of low to those levels of truly high, and you do get significant effects. So suddenly, it's not all of this inconsistency and hocus pocus, there's actually a way that we can reconcile this against each other, and certainly, the analysis from looking a bit closer at the epidemiology coupled with looking a bit deeper at the levels in an intervention, marries up. And we actually do have more consistency between these findings. So we've two kind of take home points there. One is that this idea that an RCT is right, by default, because it's not an observational study, an RCT in nutrition is just as likely to yield findings that are kind of inconsistent or potentially unreliable as an epidemiological study, because of this key issue of the contrast and exposure and baseline levels of a nutrient that we're discussing. So it's not sufficient to just dismiss it.... And then the second one is, it's critical to determine what these levels of intake actually are. Cohort studies will simply say we compare high versus low. Right, what's high versus low? Because that could be 27 milligrams versus under six in one population, or it could be six as the highest versus under two. And they are not in any way comparable.

DANNY LENNON: Yeah. And I think so much of this is not only crucial, but I think for people who regularly listen to this podcast, hopefully, it should start connecting some dots have a number of topics we've discussed in the past, whether that was red meat, whether that was saturated fat, whether that was sodium, etc., whether it was dairy that we covered in the Sigma statements. This kind of issue comes up all the time when we're trying to evaluate, well, what are these studies telling us in which ones are good or not. So the fact that there's no such thing as a nutrient free state, there's some amounts of them, how we divide that up and determine what is low and high is crucial, and then really importantly of that contrast in low versus high needs to be sufficient in a certain study, and I gave some great examples. And I think, particularly, when we're looking at saturated

fat and cardiovascular disease, we've often talked about this 10% of calories or less being a kind of recommended intake for saturated fat. But if you were to do a study, and we were to compare 11% versus 9%, and expect to see a difference, we probably obviously...

ALAN FLANAGAN: Right, find nothing, yeah.

DANNY LENNON: And, in fact, it seems to be like 16%, probably maybe 18% plus, where we start to see these really good contrasts between low and high. So knowing what we're comparing to what is crucial, and I think you've probably heard Alan mention that a number of times in our previous episodes, and in our statements of what are we comparing to what in this context. And then related to that, the fact that when we have nutrients in the diet that are not acting in one way, they can have many different effects in many different tissues, in organ systems, and then they can also interact with one another.

ALAN FLANAGAN: Yeah, absolutely. And that idea, the term polyvalence, like, what you mentioned there, a drug acts, generally has a very specific or targeted mechanism of action; it's not to say it doesn't do other stuff, but generally, it's quite a targeted mechanism of action. Whereas the idea that, let's just say, omega three fish oils, for example, and we might be talking about them in the context of a specific outcome, oh well, heart disease, okay, they reduce triglycerides, that's just not what defines their action. Right? So a nutrient is providing substrate for multiple tissues at the same time. And the term that describes that is polyvalent. It's acting through multiple pathways, multiple tissues, multiple organ systems. It's influencing the brain, it's influencing vascular function and it's influencing postprandial triglycerides, amongst other things. So we have these very complex exposures that are sometimes difficult to tease apart. I think it's what makes the science so interesting. But a misunderstanding of these kind of unique aspects also makes it

vulnerable to some criticism that is often misplaced, or certainly misconceived.

DANNY LENNON: That second issue that makes understanding these relationships difficult was the temporal relationship here, and most notably, the latency period of some of these chronic diseases. Now, you at the outset had referenced that, of course, with nutrition, we can have a true nutrient deficiency, where that can be corrected, kind of, in an acute manner. But really, that's not really a concern most of the time for us right now. We're really looking at these relationships with chronic disease, which are characterized by this long latency period. And there's also the impact of diet on that at any one time, make relatively small differences that just accumulate over this longer period.

ALAN FLANAGAN: I think the biggest misconception that I see is how what you just described, adds up to risk. Right? And I'll often see someone say, oh well, it's a relative risk of 1.4, it's a 40% increase in risk relative to the lowest group or relative to the comparison group. I don't care, I'm not interested in hazard ratios or relative risk unless they're over two. And that's ludicrous thinking on many levels. One, it just seems like it's just a willful dismissal of a finding because, hey, I don't, you know, I'll just choose to not address what might be explaining this finding. But two, if we were talking about an exposure that you encountered once in your life, if you drove your car once a day, and you were told that the relative risk of an accident was 1.3 or 1.4, and you only drove it once a day, you might be like, okay, I'm factoring that in, but it's probably maybe something that I could accept.

But the relative risks for nutrition might seem small, but they're really important because the prevalence of the exposure is so high, you're exposed all the time. So when people say that, relative risk of 1.4 or 1.5 to 2, it's irrelevant, just like that's really not a correct way to – it's not a good heuristic to think about this, because you're talking about the cumulative effect over

time of a particular exposure that might be daily for someone. Multiple, you know, and we eat multiple times a day. So this can add up. You're not just doing an act for 10 minutes. People's dietary intake is really only limited in Western societies by when they go to bed, for the most part, and it's constant. And people's diets tend to be, like we said, day to day variability, superimposed on an underlying pattern of consistency, relative consistency and intake.

So what we're talking about is a complex exposure, interacting with a disease, whatever the outcome is, that has the potential to be developing silently for some years before a diagnosis or an event. And it's influenced by diet before that event occurs, and that interaction could be something that is going over 10, 20, 30 years. That means that relative risks or the risk reduction, for example, on the other hand, people will say, well, it's a 30% risk reduction, just doesn't really matter, doesn't make that much of a difference. Probably doesn't make that much of a difference if you were only exposed to it once. But if you're exposed to something over 30 years, then that relative risk is not necessarily – it might seem small, so to speak. But actually, it's important because the prevalence of the exposure, the exposure to whatever that diet or nutrient or food is, is really high, and it's mostly continual and constant for people over time. So I think that's the most – I think that's a really important point to try and think about the long term relationships between diet and disease. And the practical implications of this sometimes is that don't be too quick to reify all RCTs, because, yes, it might be a 8 to 12 week, maybe it's a one-year RCT comparing X to Y, whatever those kind of comparisons or exposures are. But I think what I see a lot in conversations around nutrition and science and risk is this assumption that a really short term study speaks to what is happening over the long term, and I think we need a bit more care and appropriate extrapolation, and I'm

trying to contextualize findings in RCTs against what we see in epidemiology.

But this temporal relationship is crucial, because we have the potential to influence disease outcomes that may only occur when someone is 50 or 55 or 60 or 65. But the interaction with diet, as a whole exposure, could be influencing those processes 30 years before that. And so, that can add up to a cumulative lifetime exposure and risk, the actual relative risk or hazard ratio for which doesn't seem like it's enormous as a magnitudes. But actually, if you factor in the duration of exposure and the prevalence of that exposure, it is a relevant outcome that deserves to be taken seriously and thought through and reconciled against other lines of evidence.

DANNY LENNON: And I think some of the dismissal of relative risks often comes from this quite false dichotomy of relative risk versus absolute risk in the sense of using absolute risks as a way to dismiss the usefulness of relative risk. And this is typically the narrative people, I'm sure have came across before, of someone points out, news headlines are sensationalist, they use relative risks; and if you look at the absolute risk, it's actually small. So they might give a hypothetical example of new study reports a 100% increase in your risk, but that's actually moving you from a 0.1% absolute risk to a 0.2% absolute risk. So your absolute risk increase is tiny, but it's reporting a relative risk increase of 100%. And then they'll use that as a way of saying the only thing that matters is your absolute risk in the sense, so don't worry about any relative risks, and again, painting this picture of they are wholly unusable.

ALAN FLANAGAN: Yes.

DANNY LENNON: And so with this kind of narrative, because it's so common to see, and as with some of the most problematic narratives, there's, of course, some grain of truth in it, in that, yes, some headlines can be really scary because of this

large number in terms of relative risk changes, but I think it kind of relates to a point earlier that we made of knowing when and where things like this are useful. So if someone is kind of confused because they've heard that narrative, how do you think is a more nuanced, useful way to consider absolute risk and relative risk?

ALAN FLANAGAN: Yeah, I think, and you're right, because almost both get misused, I think, absolute risk is important to contextualize the relativity of the risk. Right? But it's almost used sometimes as like a dismissal of the – well, your absolute risk is x, therefore, this is not a relevant finding. And that's not really a useful way to kind of think about this stuff. The first is the reason risk is relative is because relativity of the same exposure is not the same across populations. Right? We can't say that the effect of yogurt consumption in a Swedish population extrapolates and is equivocal to yogurt consumption in a US population, or in a resilient population. So the risk of the same exposure is not the same from population to population. And so, relativity is a really important way of defining that risk. Right?

So, with an example for that, which we used in the red meat Sigma statement, which people can refer to, is if we look at, if we're thinking about red meat as the exposure of interest here, we would – and we're thinking that relative risk has no value, well, then we wouldn't be able to look at comparisons between populations, because with the relative risk in European cohorts, we wouldn't really find any associations or any increase in risk. Now, if we looked a bit closer at the dose coming back to this contrast and exposure, we'd often find that actually, they're not really that high of a red meat intake in a lot of the European cohorts. So the highest group might have 90 odd grams a day on average or 80, and the lowest group might have kind of less than 20. So we could be getting null findings, because either the contrast isn't sufficient in the exposure, or

there simply is no change in risk at that dose. Now, we could point to those studies and say, ah, there is no risk for red meat consumption, for example. But that wouldn't be accurate, because we can't assume that that holds true invariantly across all populations.

And then we could go over and look at the US cohorts. It's like, okay, now we're looking at some cohorts where the highest group of – and bearing in mind food frequency questionnaires will underestimate intake, you could be looking at a minimum of 170-180 grams a day compared to less. And so, now we've got a... oh now, we've got a relative risk increase of 43% increase relative to the group not consuming it. Okay, so you have two choices at that point. You say, I don't care about relative risks that big and you walk away. Well, that's ignoring the fact that there's a relative component to this risk that's important, because you're saying that this change in this exposure has a material difference in the outcome, and the exposure itself may not be large, 180 grams a day is not a huge amount of money. But someone's eating it, on average, daily. Then that's adding up over time, and so, the relativity there is important. Even if we're going to reconcile that study against the European population, and we could say, okay, cool, in the European populations, we don't tend to see any association with these levels of maybe 80-90 grams a day. But we double that, and we go to the US, and we do see.

So relativity in risk is a really important component of quantifying risk. But then to go from there to the absolute risk issue, yes, it can be helpful then to think about absolute risk in closer detail, just to give us more context to the relative risk, not to dismiss it in entirety. And where absolute risk seems to get misplaced in these conversations, is in thinking about how this relative risk, and this risk generally from this exposure might apply at the whole population level. So in the example we used in the study, in the Sigma Statement was

addressing the NutriRECS study that came out, the meta-analysis in red meat. And they reported both relative and absolute risk, and it's easy to say, for example, that okay, well, the absolute risk here means that per 1000 persons reducing red meat by two thirds would result in one less diagnosis, that's not worth caring about. Okay, but look a bit closer at the findings, and what you see is that, well, for overall cancer incidents, the difference was 18 fewer diagnosis per 1000 people; for cardiovascular disease it was 10 fewer diagnosis per 1000 people. And those numbers are really important when we scale that up to the whole population.

So if I take cardiovascular disease, and I take the UK population, I'll just scale it to 67 million, and I take 10 fewer diagnoses per 1000 people, well, that's 67,000 less cardiovascular disease incidents than without that exposure. That's not immaterial as a risk across the population in terms of burden of disease. So then the question becomes, does changing that exposure reduce the incidence of that outcome? And if we factored in the lines of evidence and considered the dose, we could come to a more reasoned conclusion on what level of dose might be a risk. And we could say, well, in that cohort or in this synthesis of evidence, then yes, for groups consuming over 180 grams a day, could we look at them then at that point, and say, you have no risk. And this, it seems to me that people try and do is get to a conclusion of there is no risk. Right? And it starts with that relative risk size doesn't matter. It progresses to, well, the absolute risk difference is X; and then it gets to, well, the epidemiology is obviously wrong, because it's epidemiology, therefore there is no risk associated with this fighting. And it's just like, it's a bizarrely illogical way of thinking through from a scientific perspective findings and how we reconcile them.

DANNY LENNON: Yeah, interesting, I think that line of thinking tends to most often correlate with people who

have dietary recommend and policies that kind of are basically butchered by good quality epidemiology we have.

ALAN FLANAGAN: Yeah. So I think one final thing to, just as a way of thinking about this, because I don't want to say that every relative risk just has equal weight. And I also don't want to say that we can't put a hard and fast line on what type of relative risk, for example, is important versus unimportant. But I would say, a way to kind of try and think about this, there is some discussion in epidemiology, on how to better quantify this, and it's a subject of ongoing debate. So I won't labor too much, like E values basically where you mathematically use the relative risk and the lower bound of the confidence interval to determine effect sizes that could explain your finding of residual – effect of potential residual confounders.

Now, it's got issues, but as a concept, I think it's quite important, because what they're saying is, how do we think about the potential for a finding to be explained by residual risk. Right? So if I have an 8% relative risk increase from one egg a day for cardiovascular disease, for example, and I'm really thinking that through, and I'm like, okay, well, what would be the mechanism, how would that egg impact on blood cholesterol levels, okay, that doesn't look particularly plausible. Then I might be inclined to think, well, the relative risk is so low in that context, and the biological plausibility of the relationship is questionable, so that's something where you could be more comfortable thinking, residual confounding could explain this association. I'm not going to take this as seriously as a finding as others. But if I've got a 43% increase in risk or 53% is one of the European, the subcohorts of the epic group found in relation to their highest red meat group and ischemic heart disease, which I think in that subcohort, the highest was over 150 grams a day.

Again, one, I'm seeing a consistency in the dose at which risk is observed with this cohort from the US cohorts, now I'm seeing it in the European population; two, 53% increase even if I tinkered with the idea of residual confounding or multiple, they would have to be enormous to shift that risk to null, to eliminate that finding, so to speak. And most confounders, potential confounders, as it relates to diet or certainly non-dietary lifestyle factors, we are aware of, and can control or adjust for. Now, we can't eliminate their effect, obviously entirely, but we can certainly try and think through some statistical adjustment models that might help us get more kind of – and if your relative risk is still that high, factoring in – and I say, high, factoring in the cumulative nature of the exposure – if it's still about high, after you've adjusted for these things, then you need to come up with some combination of plausible confounders that we don't know about, that could influence that finding, and that's when you might be left clutching at straws. And when you marry that particular finding up with some biological plausibility, which we would have in that context with our understanding of things like heme iron and nitrates, etc., well, then you're at a finding where you're like, I can't dismiss – now, does that mean I'm never going to have steak? No, it's more about actually just accepting once you've reconciled those lines of evidence that you can't say that the risk is zero. And that's seemingly what everyone tries to do in these conversations, is seemingly work their way through mental gymnastics to a point where they're saying risk is zero. That's not an accurate conclusion to come to.

DANNY LENNON: Yeah, it's not congruent with reality, essentially. But yeah, I think that's important, because, again, not only in the context of looking at the relative risk within a specific study, but even the fact that we've talked about how prospective cohort studies can be useful, I think the takeaway for people is not that go and find one prospective cohort study with a certain

relative risk, and there you go. It's like you said at the end there, like we say, with all these studies, it's taking these looking at is this study good quality, what does it actually set up to be able to assess. And then how does it fit in with all the other lines of evidence? And then that's what we're going to be basing actual hard conclusions on, as opposed to people that will just wave around one particular study.

ALAN FLANAGAN: Right, Yeah.

DANNY LENNON: So yeah, I think that's an excellent point to end this on. I think we've got through most of what we were hoping to cover. Is there anything that you think we've forgotten or wanted to add before we kind of start wrapping things up here?

ALAN FLANAGAN: No, not really. I think for people that that do read research, so many listeners we know are nutrition professionals, or very interested lay people with scientific literacy, look, you're going to read cohort studies, you're going to read epidemiology, because it will be the coroner, the linchpin research design for nutrition science, for the foreseeable future until the nature of diet disease – diseases that we have changes. So I would say maybe a couple of kind of bullet point take home points to think about are consider validation, like, if you're looking at a cohort, it's the EPIC cohort, or it's the Nurses' Health Study, whatever the cohort is, always think about the validation process for whatever they use to measure diet, because that's an important point that relates to the findings, the accuracy. So think about how the study was validated, they'll always have a validation study.

The National Cancer Institute's just as a resource, by the way, has a database of all validation and calibration studies for nutrition, for diet studies, cohort studies. So that's a really useful resource. I would think a little more at this kind of level, we've been talking about risk, and try to not just look at the

relative risk and say, it's that and they are the confidence intervals, cool. But think through a little more in terms of biological plausibility of the finding the relativity of that risk. And whether the magnitude of the increase or decrease in risk is something that you think is worthy of kind of considering in more detail, whether potentially, it's a kind of a small effect that may be confounding could explain it if there isn't good biological plausibility. But just treat it like an important and valuable part of the evidence base, because it is, it doesn't have to be per – this weird standard that nutrition science seems to be held to in terms of the criticisms of it, relative to other fields of biological science, and this bizarre, like, knocking of nutritional epidemiology is absolutely worthless, is just strange. And it's not a good way for us to think about a cornerstone part of the evidence base. So no one's pretending it's perfect. No one's pretending measurement error and dietary assessment doesn't exist. The field has been working on this stuff for years and continues to. So just treat it with – and all epidemiology is difficult. Right? It's a hard science. It's a science that deserves a lot of respect, I think. It's a lot easier to set up an intervention and play around with that. So treat it as an important and valuable overall part of the evidence base that you can get valuable data and findings from, that you can use that in the overall assessment of whatever it is you're considering.

DANNY LENNON: Or alternatively, treat it with disdain, disrespect, and that's the kind of foundation for writing a bestseller.

ALAN FLANAGAN: That's it, yeah.

DANNY LENNON: So if you want to write a mainstream nutrition book that is going to sell out, use your disdain for epidemiology as the bedrock for that.

ALAN FLANAGAN: Right. Yeah, dismiss epidemiology in its entirety, and then fill in the blanks with

whatever you think is happening based on your own opinions.

DANNY LENNON: Yeah, if it goes counter to most recommendations, that's usually a good place to start.

ALAN FLANAGAN: It will, yeah, it will.

DANNY LENNON: So pick one of them.

ALAN FLANAGAN: Yeah, exactly. If you have found out the truth about why the experts were wrong, and why you've been lied to, and now you need to eat more of this food you were told were bad in order to achieve health.

DANNY LENNON: The added sugar solution is coming next.

ALAN FLANAGAN: Yes. Oh that would – you know what, no one's touched that. I think that...

DANNY LENNON: No. That's their next one, I think.

ALAN FLANAGAN: I might just do a quick eBook and see how it goes, just like a prelude...

DANNY LENNON: You could do that, you could just use the exact rhetoric that they use for all this stuff, and like swap in added sugar for the other stuff.

ALAN FLANAGAN: Right. Leave that one with me.

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