Danny Lennon: Hello, and welcome to another episode of Sigma Nutrition Radio. This is episode 447 of the podcasts. My name is Danny Lennon and alongside me of course is Alan Flanagan. Alan, how are you today?

Alan Flanagan: I'm well, yes, I'm still in my post doctoral phase of wondering aimlessly around the world, knowing what to do with myself.

Danny Lennon: Yes. And in the last episode of the podcast, people had a treat where you would've walked through some of the stuff around climate change in your very optimistic, rosy outlook on society, as you usually do.

Alan Flanagan: I've said something optimistic. I'm still wondering, you know, how I feel about that statement? It's definitely odd. To feel, hope for humanity. Yeah, I don't like it. Yeah. I don't like how it makes me feel. Yeah.

Danny Lennon: Well, you're one optimistic sentence in the course of an 80 minute podcast is more than I thought you would get to. But yes. Good job on that.

Alan Flanagan: The only other alternative was I was, you know, obviously left with telling people that we're just all gonna burn, especially if you live in Australia. So maybe I just felt bad for our Aussie friends. Yeah. I want them to feel like I want them to feel like maybe they can stop the burning .

Danny Lennon: Well, speaking of burning, that is actually a perfect segue into what we are going to discuss today. Today, we're going to do essentially a analysis of a particular study in focus, but much of this will then maybe move out into a more broader conversation towards the end, but it comes off the back of a question that one of our Premium subscribers had sent in to us.

This came in from Vern who asked: what are your thoughts on the recently released study "in the us linking. Two servings per week or more of fish to a 22% increase in risk of developing skin cancer? From what I read the study, didn't take into account some key confounders, such as history of sun exposure and severe sunburns."

So that was the question that Vern sent in. And this is in relation to a study by Li and colleagues, 2022, that looked at fish and intake and risk of melanoma in the NIH -AARP Diet and Health study. So we're gonna dive through this study in a bit more detail to try and disentangle it from some of the headlines that you may have seen if you've seen this.

So if you've been on Twitter or if you've seen many of the mainstream news sites who do some reporting on nutrition and health studies, you may have seen headlines talking about skin cancer risk. And if you eat two portions of fish or more per week, this is gonna increase your risk of melanoma. And indeed this is reported a number of places it's being covered across many news sites.

And so it's worth diving into this both as a way of tacking this particular question, i.e. Does increasing your fish consumption to beyond this certain amount lead to an increased risk of skin cancer? But hopefully much of our discussion will also serve as a secondary purpose of how we can disentangle headlines from actual what is in a particular study. So like I said, this study that we're gonna discuss today is using data from the NIH AARP diet and health study. So this is a long term study with a over 3 million US citizens. And within this particular study that we're focusing on this particular data set and this paper it was around half a million adults in the us age between 50 and 71 at enrollment.

And there's a follow up period of about 15 and a half years. And it tracked cancer diagnosis among that group. And there's a few interesting kind of elements we'll look at in particular when it comes to the tracking of cancer diagnoses. And then they also looked at diet. This was collected in the form of a food frequency questionnaire.

We can talk a bit about that as well. And they essentially looked at the intake of fish, looked at the different amounts of someone has a high intake or a low intake. And was there a difference in skin cancer? So that's the kind of setup for this. Now there's obviously bits of detail we can get into here.

So maybe as a way in where might be the best place to start working through some of this Alan, in terms of the study set up that kind of initial study design. Are there any notable elements of that, that we should flag for people before we dive into actually the results of the study?

Alan Flanagan: Yeah, I think when it comes to interpreting a cohort study and a prospective cohort study, there's a couple of like questions that we want to ask as a way of working through its quality, overall as a study. And these characteristics of the study in terms of its design and dietary assessment are obviously going to be very relevant then for the interpretation of the actual findings and the wider context of the, those findings themselves. So as you mentioned, I think one of the real strengths of the NIH AARP cohort is the sample size, and then a lot of the analyses of diet come out of the NIH AARP cohort which I'm just gonna call "the retired person's cohort." , because saying out the acronym is actually a bit of a mouthful. So in this cohort is it's sample size for a lot of the nutrition studies has often been up around half a million participants. Okay. So that's a real strength of the study. And we wanna also think about then the duration of the cohort overall and how much follow up.

Is in the particular study that you're interested in. And in this particular study there's a very long follow up period. An average follow up period of about 15 years, 15 and a half years. And in these participants, if you factor in the. Number of years of follow up, you have relative to the sample size of the study that gives you a metric, which in observational research will be called person years of follow up.

And what that really means is not everyone in the study will be in the study for the average of the 15 year follow up period. Some people might die. It's an older cohort. They were 62 years of baseline. Some people might have an event in which could be is where their data then terminates as far as for the particular analysis.

So say someone has a primary outcome at three years and another person has it at seven years. So they're all different, right? So this all comes into your calculation of person, years of follow. and in this case it was basically six and a half million person, years of follow up. So in terms of the size and the follow up duration of the study, these are all positives.

And before we go on to some of the other, how this relates to say the number of cases of your actual endpoint and the breakdown of those cases, I think when it comes to the size of a cohort study and its follow up period. What becomes particularly relevant obviously is both the baseline characteristics of the cohort in terms of your relevant exposures, how much in this case fish intake do they actually consume.

And then what's the balance of other factors like alcohol education, physical activity, other dietary factors, because these are all going to be relevant to the type of analysis that's being conducted. And one tab that I'll just open at this point that we'll come back to is the photo type or a person's actual skin pigment, which also been referred to as the Fitzpatrick skin types, there's six across the board.

So you want to have a look at them to see how they're balanced across your different exposure groups. And to make sure that these relevant factors have actually been included in the analysis and adjusted for. But the main thing then is obviously the robustness of any cohort study will, will relate to its dietary assessment method.

And you want to ask questions like, well, what method was used? Was it a food frequency questionnaire or was it say a 24 hour recall? And then you want to be concerned about the validation of that particular instrument that's been used. And again, the NIH AARP cohort or the retired person's cohort has the strength of using a very well-validated food frequency questionnaire.

So this was an FFQ that was developed by the national cancer Institute. It was validated in the population that the cohort the, in a subgroup of the total cohort it's a 124 food item, food frequency questionnaire. And with the validation of the FFQ. The correlations between measured foods in the food frequency questionnaire and the calibration dietary assessments that were used to validate the questionnaire were quite good.

As far as nutritional epidemiology cohort study goes, they were relatively strong for a lot of macronutrients and foods of interest. You know, we can say at the outset that it's a very large study, there's a lot of strength and power in the overall sample size in the number of per years of follow up in the follow up period.

And it does use a well-validated food frequency questionnaire, which would be the best tool to use as a instrument of measuring diet in a prospective cohort study. But these factors are going to be relevant again, particularly the size of

the study. When we come to discuss. The actual outcomes, as far as say, number of events in the different groups goes and how that relates to thinking about relative versus absolute risk and some other factors.

Danny Lennon: Yeah. I think that's really useful. And this is where a bit of nuance is worth noting for people that at the outset we can see, okay, we got really good sample size in terms of dietary assessment, you noted, we have this reliable, well validated food frequency questionnaire, and that kind of takes away some of the concern people have around food frequency, questionnaires of what we mean by validation.

It's actually being validated or checked to see does this actually line up with actual intake. And so if we have a validated questionnaire, we can have a bit more faith in it. So we have these positives, but as you noted, that's only really half the story related to these two things. So on the side of say that the size of a study.

One of the other parts of that tells us how useful this information will be, would be number of cases, which we can get to in a moment. And in terms of dietary assessment, another aspect in terms of just not the only the food frequency question that's used, but then how that gets used. I think that's something we're gonna revisit a bit later on.

So maybe let's talk about exactly. Let's talk about the cases that were reported here and how that might fit into the picture of how robust a set of data this is. So within this particular study, we said that they're tracking cancer diagnoses among amongst the group. They classified melanomas either as in situ, so meaning on the skin surface, or malignant, which is meaning they had spread deeper. And within that you have about 5,000 cases of malignant melanoma being identified around 3000 of melanoma in situ being identified. So with that type of case number, how does that fit into this picture of how robust this data set might be?

Alan Flanagan: Yeah it's not enormous. It sounds obviously if we say the word 5,000, 3000, that sounds like a lot of cases, but we have to make it, we have to think about that number relative to the half a million people in the total cohort and the number of person years of follow up within that cohort. And this then is important to think about the actual outcome of interest, right?

It's always really important that we think, well, okay, this is the exposure. Obviously in this particular case, we're going to discuss fish intake. And they divide fish intake into fifths of intake in their cohort. And we have to think

about the nature of the outcome of interest and what we know about that outcome.

And in this context, we know that melanoma is a obviously form of cancer. Like you said, you there's two types. The in situ melanoma is stage zero of melanoma cancer. and there's three layers of the skin that we're typically concerned about. There's the epidermis that outer layer, the dermis, the inner layer, and then down to subcutaneous tissue.

So melanin cells are in the kind of deeper layer of the epidermis, but they're in that they're in that top layer of the skin in situ melanoma will be essentially characterized as stage zero. So it's there's cancer cells, but they have not, they're localized to that area and they have not spread other areas.

And then obviously, you know, melanoma itself can spread as the cancer develops. And so exposure to skin is of particularly UVB light is of enormous relevance to thinking about this particular cancer type within that. We have to think about what are the base rates of incidents in the population.

And this differs. According to essentially Fitzpatrick's skin type, right? According to skin pigmentation. So the overall lifetime risk in white Caucasians is 2.6% or about one in 38 it's 0.1% for people of African ancestry and it's 0.6% for nonwhite Hispanic ancestry. And this reflects the fact that for different skin pigmentation types, there are differences in the concentration of melanin in the epidermis layer.

And there's an inverse relationship between that concentration and cancer risk such that the higher, the concentration of melanin in the epidermis, the lower, the lifetime cancer risk. So the Fitzpatrick scale. Is one may way of quantifying what they call like a phototype or the type of skin and thus the interaction, the concentration of melanin and the interaction between sun exposure and cancer risk.

And one would be Northern European. Two would be European Scandinavian three would be Southern European, central European; four would be Mediterranean or Latin; five would be native American or African ancestry. And then six would be African or Aboriginal or 'first peoples', as I think now that the appropriate term is. So these are gradings of pigmentation and this is highly relevant obviously then to the incidence of this.

And so it's important to note that overall there's a low lifetime risk but that risk is higher, much, much higher in terms of absolute lifetime risk in white,

Caucasian skin types, than it is for other phototypes. And so this is going to be particularly important when we think about both a there's a low kind of base rate in the population.

Although that low base rate is much higher. It's one in 38 for people with white skin. It's like I said, one in a thousand. For people, black ancestry and it's one in 167 for people with say either Southern European or Latin ancestry. So these differences matter when it comes to thinking about both the demographics of this cohort and the number of actual cases, which is not particularly high, although five to 3000 sounds high, when you break it down by the different groups that are stratified, according to fish intake, for example, you have say 802 cases of malignant melanoma in the reference group and 1,100 in two cases.

So 300 more cases in the highest fish intake group. And of course the relative risk that's derived from the analysis is comparing. These rates of incidents relative to the numbers in that group between these two groups. So these are not particularly high numbers of cases, and that reflects the fact that the actual base rate of this outcome in the population is not high, although it is higher for people with white, Caucasian skin phototypes.

Danny Lennon: So if we have low base rate in the population generally, but of that, the highest is going to be in white Caucasians. And then we look at the demographics of this particular study, where the majority is of white ethnicity. So we could say then even if someone was trying to extrapolate this beyond that to other populations you'd have even lower than maybe what's being identified here.

So within that let's talk about fish intake and how that was quantified because as you've outlined already and something we've tried to impress upon people in many previous episodes is we wanna look at, okay, what are we comparing? What is the fish intake we're actually looking at? And what is that exposure contrast? So within this particular study, you see quite a wide range of fish intake anywhere from an average at the lower end of around 20 grams, up to 300 grams on the higher range. And for the main findings, at least the main study findings that we'll discuss here, where we look at this positive association between fish intake and melanoma, you have this comparison between the top and bottom quintiles. So if again, to, for people, if we're breaking that into chunks of 20% each as, or break it into five and we compare the highest 20% to the lowest 20%, and we're looking at the top versus bottom quintile of fish intake, and then we're seeing, okay, what is the difference in the hazard ratio or what is the risk for being in the top versus bottom level of fish intake?

So I was just wondering, can you comment on a couple of things of first of all, what. Do we actually see in terms of, again, those absolute amounts or the, I should say the average amounts of fish intake that was seen in these different quintiles, and then when we're comparing them, what does that actually tell us in the context of this study?

And so maybe just as a reference for people, again, I think it was referenced in our question, but for malignant melanoma, we see a hazard ratio of 1.2, two comparing top to bottom. So that'd be a 22% increase in risk. And then for melanoma in situ it's about 28% increase in risk when we're comparing this top versus bottom.

So can you maybe just talk about what levels of fish we're seeing in those quintiles and and again, maybe a more broader point around thinking about exposure contrasts of, if someone is reading this paper themselves what should they be looking out for when they start seeing comparisons of low intake versus high intake and what we define those as.

Alan Flanagan: As you said, depending on the kind of spread, so to speak of an exposure in a cohort study you, a group of researchers might decide to split that exposure into different quantiles and that could be thirds of intake. It's commonly fifths of intake. And that was what was used in this study. And so that means that you now have a different total number of people within each of these, and that's relevant to the actual incidents of your disease outcome as it relates of course, to your exposure of interest.

Yeah, like you said, they divided total fish intake and that included fried fish non fried fish and tuna specifically. And that total intake ranged from three, an average of three grams a day, basically up to about 43 grams a day. And so you can, like you said, extrapolate that up to weekly intake.

You'd get as little as maybe 20, 21 grams to over 300. And within that, then you have in each of those groups that are divided, you have your cases, number of actual outcomes, melanoma, malignant, melanoma, or melanoma in situ, and you have the number of people in each of those groups. Right? And so the relationship between those cases and those numbers goes in, and then for these types of analysis where it's divided, according to quintiles, in this case, it's you do the main outcome of interest is the high versus low comparison, quintile five compared to quintile one, but actually they'll calculate hazards in this case for each of the other quintiles compared to that very, the low intake or the lowest intake reference category. And that allows you to see how as you go across

increasing levels of intake, how that ultimate risk changes, and this can be quite informative in and of itself because you can see trends in how that changes.

And in this particular study, mostly the hazard ratios increased across a range of say 7% of an increase. So comparing the people with an average of seven or well, nearly eight grams a day. So you know, 50 odd grams a week or more, there was a 15%. Increase in risk of malignant melanoma that went to 18% in quintile three 24% in quintile four and 22% in quintile five.

So actually quintile four and five in terms of their estimate of effect, the hazard ratio and the confidence intervals were very similar as far as the overall estimate of effect and the precision of that estimate went. But when we look at then the incidence rates in the reference group the number of cases relative to the number of total people in that group, which was 98,147.

So that's about the, this outcome of melanoma in this is occurring in 0.8% of those participants and in the high group it's occurring in 1.1% of those participants. So factoring in a number of different things that were adjusted for age sex, education, attainment, body mass index exercise. And then they did look specifically at what's called the erythemal UV light measurement.

Basically, it's a way of using estimates of the average midday UVB exposure, given a certain latitude and longitude. And they did adjust for that as well. And you get this between these comparison groups, you get this 22%. Increase relative risk increase in the high fish group compared to this low fish group.

And then we have to think about that finding in terms of the, again, these, this is why I keep repeating like number of cases relative to the number of people that you have in your groups against the background base rate in the population. So in this case, the actual absolute difference between the low group and the high group is not enormous.

And when we think then about the absolute risk are the lifetime risk, the change in risk, I is not in any way overwhelming or particularly strong in, in this overall cohort. It would change if we're assuming. That this would be in people of, for example, white, Caucasian ancestry, which the majority of this cohort were and their baseline absolute life, lifetime risk is 2.6%.

This would change it by about 0.2 or three of a percent. So it's really important that we always bring these things back. The strength of those findings in any given study could change obviously relative to the number of events in a group and otherwise. But I think we have to be cautious here that there's not a

particularly huge amount of cases against a condition that doesn't occur or that has a low lifetime risk in the population and where that lifetime risk is higher.

It's higher in the participants that we would assume. were the dominant participants in this group. So 90% to 92%, depending on the quintile that was broken down of participants in each quintile of fish intake were classified as non-Hispanic white, and this analysis did not adjust for phototype. So I think that they've left a potential crucial factor in the relationship between particularly UVB exposure in skin cancer incidents that was not adjusted for in this analysis.

So I think in terms of the ultimate outcomes, they're the kind of top line things. I would say that the number of cases are largely low. The actual incidence rate in each quintile was very low. It was 1.1% in the high group. The relative risk estimate does seem high, you know, 22% increase in risk is something to pay attention to.

And there was, a relatively consistent direction of effect across these quintiles of intake. But again, with the number of cases in each group, if we're looking at these absolute changes against the background lifetime risk, then the actual change in absolute risk is minimal and where that ultimate outcome was not adjusted for.

Although they did adjust for race in a general sense, which is often common in these a. I think not factoring in the relationship between phototype and pigmentation and skin cancer risk is probably a big missing potential confounder in this study.

Danny Lennon: Yeah. So maybe let's linger on that point related to adjustment here, because I think this is probably where most of the kind of limitation here might come in or might give us more pause about what we actually do with these particular results.

So as you've already outlined, there was indeed an adjustment analysis done here for a number of different factors. The typical ones we think about physical activity, smoking family history of cancer alcohol intake race. Now it's worth noting that the retired person's study where this data comes from was designed to track many types of cancer, not necessarily melanoma specifically.

And so therefore that might give us some reason as to why maybe some of the adjustment isn't as robust for melanoma as we might like. Now there's a couple of elements within that. You've already mentioned one of, okay, there might be

an adjustment for race, and ethnicity, but not necessarily actual skin pigmentation.

So that could be one, a second one that could be brought up is in relation to the adjustment for UV exposure, which there was this daily UV exposure that was adjusted for, like you said, but this was based on the average UV index for a suburb that person was living in. And they would use that as a way to get a gauge of their daily UV exposure.

But that is different for adjusting for someone's actual UV exposure or particularly their lifetime UV exposure, which becomes important to consider when we know about typically melanoma and how that is oftentimes driven by say, sun exposure, or maybe exposure to tanning beds and how it's a lifetime risk of if people have had severe burns in the past, that can increase risk.

And that is one place where maybe this measure for daily UV exposure was adjusted for, but it's again, it's for this average UV index in the suburb that they were in. And then there's a number of things that maybe weren't adjusted for that are very melanoma specific. So in addition to that lifetime UV exposure, we could think about, well, what is their history of having severe sunburns in the past?

What is their individual, sun related behavior? Not just what area do they live in. And then other aspects like a mole count, or as you say, skin pigmentation. So I think the adjustment here. Could be a place where people could point to and say, well, yeah, there was some adjustment made, but here's some other places where if we had the luxury of being able to adjust for all these things, would we still have the same results that were observing here.

Alan Flanagan: And that's really important when it comes to then thinking about wider context.So you highlighted that, yes, they took this kind of average exposure you know, essentially what they called the the kind of average noon time dose of UV exposure in the month of July. And that average served as a proxy that they then used based on levels of that UV exposure in that month to adjust for in the analysis.

But as you say that doesn't take into account any sort of. Oh, yeah. And they did this average between 1978 and 2005, but it doesn't account for someone's actual variation in overall sun exposure. And this becomes important when we then come back to, as we always have to, when we're thinking about these outcomes and we're working through, okay, this is this outcome.

This is this 22% increase in risk, 28% for melanoma in situ. How do we work back to test essentially the robustness of this outcome relative to the characteristics of our cohort. And remember that in, and this is really important, the actual incidence of cases, which we discussed before the vast majority of them were in the ethnic categorization that they designated as non-Hispanic white.

There were only two cases recorded in the black participants in this retired person's cohort. And in terms of each division of intake, they represented only about 3.5 to 5% of the total study cohort. But yet within that, there was only two cases. There was 15 cases in Hispanic participants and then three who had identified as other ethnicity; there was three cases. So the thrust of these cases and this, so that was melanoma in situ in the same pattern was observed for malignant melanomas. There was like 13 cases in, in black participants, 21 in Hispanic participants and 11 in people who had reported other ethnicity. Clearly the bulk of this is driven by white participants in this cohort.

And we also know that they were older, so they're they carry a higher risk that we could infer just based on what we know about this particular outcome. But they were also 62 at baseline. So to give the researchers credit, they did do a number of analyses where they looked for example at excluding early follow up, which is always a really good sensitivity analysis to do in a cohort study.

Because if you exclude an early period of follow up, what you're allowing yourself to potentially rule out is that there was a kind of a latent disease just about to be diagnosed in your participants. and by excluding a certain amount of early follow up, you try to account for any of that potential that could have influenced the outcome.

Now they only excluded cancers occurring within the first 12 months. I've seen some analyses for example, and this is a common approach in many different studies that would exclude the first four years of follow up. I think that would've been a more robust way given what we know about lifetime exposure to sun ultimately being the biggest risk factor for this particular outcome.

And given the fact that participants were 62 at baseline, I think a wider exclusion of the follow up period would have allowed for a more robust. Consideration of whether there was people that were already high risk at baseline in this cohort. But they didn't show the data for the exclusion of 12 months because they said it didn't change the outcome, but 12 months might be too short of time if we factor in the lifetime exposure and the nature of that risk.

And also the fact that they were baseline age was 62. And I think one more thing to think about is this there's a concept. There is a quantitative method to report the amount of U B UV exposure. And it's called the minimal erythema dose, or MED. And so that's basically a quantitive metric to quantify the amount of UVB exposure needed to induce sunburn in the 24 to 48 hours after sun exposure.

But this is not something that really can, probably, be easily determined in a cohort study because it actually requires an examination of erythema of redness and swelling as endpoints on skin. But you can use it for intervention trials on skin and a number have, but the reason this concept's important is because we know that a low Fitzpatrick phototype correlates both with having a higher MED response to sun exposure and with melanoma and other skin cancer risk.

So again, factoring in the demographics of our participants in these cohort, in this particular cohort and factoring in the fact that over time, a low Fitzpatrick phototype is always going to correlate with a higher level of MED and with melanoma risk, the inverse relationship between epidermal, melaninconcentration and cancer risk. I, I think when we think about that factor, When we think about the age of the participants at baseline there's. And we think about the lifetime risk element of this there's it's, there are too many factors potentially influencing the ultimate outcome that perhaps. Are not necessarily included in this study and that's not necessarily a criticism as much as it's a critique; i.e. There's no perfect study and you can't measure everything. And certainly some of these are measurements that actually require methods that would probably not be feasible for a large scale epidemiological study of half a million people.

Danny Lennon: Yeah. And especially like we said, when you counter that most of that original data comes from the larger umbrella study, which is not a specific melanoma study. Right. That could give some credence to that with relation to these limitations that we've discussed. We've talked about that on the side of the kind of skin cancer part of the equation, or certainly related to the UV exposure, which obviously the connection is that for most skin cancer, one of the primary causes is this.

UV light exposure. So we've looked at some of those limitations in relation to the kind of skin cancer, UV side of things, but there's also one that could potentially crop up on the diet side and this relates to that dietary collection. So we've started at the outset by saying, well, we use this food frequency questionnaire.

There's actually, well-validated it's a really reliable questionnaire. However we need to consider then. Well, how is it used here? And when you look at this particular study for assessing fish intake, it seems that dietary assessment was done once at baseline. But when we consider the type of this study and the degree of follow up, I'm sure people can connect some dots as to why that might be potentially.

Problematic. Right. If we consider that there could be some change in time,

Alan Flanagan: You know, this is one of the aspects of epidemiological methods that, that has been the subject of a lot of discussion, which is when you do a baseline measurement and you only have a baseline measurement, there are a number of additional assumptions that go into the interpretation of your findings.

One of which is that diet was constant over time in a group of elderly people that might be a reasonable inference, but it's always preferable. And this is becoming increasingly acknowledged to have repeated measures. because if you do have repeated measures of dietary assessment over time, you're able to determine the reproducibility of your dietary assessment method.

And you're actually able to quantify the degree to which there is consistency in the maintenance of a particular dietary pattern in your cohort. And so the fact that wasn't done here over a 15 year follow up period, is a potential limitation. The other factor is when we think about the exposure and how we relate that back to validation.

If you look at the validation studies for the NIH, a R P cohort for nutrients micronutrients they were, many of them, depending on the nutrient of intake were good and better than some cohorts, but they were really around the average of say 0.5. point between 0.4 and 0.6 macronutrients and certain foods were much stronger.

They were sometimes, for example, dietary fat, if I remember was, point nearly 0.7 which would be a very good, correlation, but I haven't seen the correlation for fish specifically reported and they don't mention it in this particular study. most of the other publications I've seen from the retired person's cohort will actually mention what the correlation coefficient of the exposure food or nutrient is from the validation studies.

And I don't see a mention of that in this study. And I have looked at some of the other validation studies and I actually haven't seen anything specific for fish. So

we don't really know how well this particular measurement instrument actually assessed this particular exposure of interest in terms of fish and the types of fish intake in the actual study.

Danny Lennon: At this point, acknowledging all those potential limitations and why we maybe shouldn't read necessarily too deeply into this. We can start thinking, okay. Even if we take this at face value and again, we're acknowledging that this isn't a study, that's set up to demonstrate causality or anything like that, but that we do take these results.

And let's say we were to. That we accept that there's an increased risk. We then lead on to the natural question of, well, well, why is there an increased risk? Why would increasing fish intake cause and increase potentially in something like melanoma risk and within the, this study itself, the authors give their own kind of speculation.

And of course this study, wasn't set up to assess why and there's no way of knowing from this particular study, but their own speculation could be well, rather than fish per se. It's probably some sort of contaminant in fish or whether that's PCBs whether it's arsenic, whether it's mercury, there's these number of contaminants that we know can.

Detrimental to health. And some of these we actually discussed in our previous episode on is fish bad for you. And we looked at some of these claims around contaminants and indeed you can point to different areas of research where there's negative health consequences of very high fish intakes with let's say heavy metal content of mercury or arsenic, particularly at certain life stages.

Or we could go and look at some of the day that's shown potentially increased risk from like drinking water that is contaminated with arsenic, right. Can increase risk of skin cancer, potentially. And other types of cancer. So there's this mechanistic kind of plausibility to, well, if there's a high load of these contaminants, and these are things that we find in fish, this potentially gives us an explanation as to what is causing this increased risk.

Now, if we start thinking about that question, well, well, could it be contaminants? Could it be PCBs? First of all from this study, we clearly don't know level of contaminants weren't measured in this, but when we think of that kind of broader beyond that, and I think this will maybe get into some of the issues that we raised in the "is fish bad for you?" episode itself.

What kind of questions should we give listeners to, to think through when trying to assess these questions of, okay. Here's something that could make sense. How do I actually now weigh up whether this is a problem? Do I need to stop consuming fish because of. Levels of contamination what is a kind of maybe a brief checklist of questions we can start asking?

Alan Flanagan: So I think because this is epidemiological, we need to think more in terms of Bradford hill criteria, as far as a number of questions we could ask if we're trying to determine causality, and we can think about wider research that lends itself to one of those criteria, which is biological plausibility, the authors in their discussion mention, well, we saw this kind of linear trend and that trend was statistically significant, but, and that is one test within the overall Bradford hill framework.

As you would look to linear trends. Now, the actual change is not enormous, so it's a statistically significant linear trend, but the actual. Difference in risk as we go up. Those categories is not enormous. So I would say yes, technically that box is ticked, but I would have a caveat as to, it's not a particularly strong dose response relationship as it pertains to kind of change between increasing quintiles of fish intake.

The second thing is we would say, okay, is if we've thought about strength of association and potential biological plausibility or sorry, and potential linear trend, how strong is the relationship? And typically a criticism of nutrition research is the magnitude of relative risks that are deduced from comparison studies.

And as we've discussed before dismissing a relative risk, because it might seem in this case, a 22% increase for malignant melanoma, 28% increase for melanoma in situ. Dismissing that because it's, less than some arbitrary value, that's decided as being worthy of consideration is shortsighted.

However the strength of that relative risk has to be considered in the context of the particular outcome relationship like we've discussed in the background level of intake and the lifetime risk. And so overall we would, know as we've discussed that actually the strength of this association isn't particularly overwhelming and the absolute change in risk is really minuscule.

And that would then lead us to think about, okay, even if it's a very kind of minuscule ultimate change in absolute risk of this outcome even if we've got this potential linear association in this, is there consistency in this particular

exposure outcome relationship in wider research? And that's actually where we start to get into a much clearer answer that.

No, it's actually not really that consistent of finding and, the body of evidence is not particularly strong. There are a number of, and most of the prior research is case control studies. These studies have typically not found associations with fish consumption and melanoma risk. Some have found a lower association when they have focused on fish that's omega three rich, which is a point I'll come circle back to. And so although the designs of the studies are different, the overall body of evidence is not necessarily consistent. There are some other prospective data, so there was the Swedish Mammography Cohort follow up was not as long as it was in the present study. It was four and a half years in the Swedish study. They found dietary EPA and DHA associated with lower melanoma risk. Now that was obviously looking at dietary EPA and DHA specifically, but, we know that fish is the primary source of these in most diets. And I think consistency is where we start to see some holes in the overall strength of making a causal kind of argument. And then we've got to think about, well, what's the wider body of evidence and interventions and potential mechanisms. If we actually look at some of the specific trials that have looked at EPA and DHA specifically, and they've used outcomes like MED which, like I said, is this minimum tolerability or minimum dose that someone could take of UV exposure without getting redness and swelling without getting sunburn, basically.

And typically what we've seen and I should say, look, the body of evidence for skin and nutrients is really poor. It's a really shoddy area of research methodologically in terms of the size of the trials, in terms of some of their outcome measures. They look at things like wrinkles and stuff like that. Like it's a really poor area of research, but in the available evidence, that's there particularly studies that have used supplemental EPA and DHA. We actually see improvements in some of these outcomes. So you see reduced UV induced redness and you see a kind of an increase in that MED so like a greater tolerability to that minimum effective dose of sun exposure that someone could take without getting redness and swelling in group supplemented with fish oil.

So I think if we look at we're thinking, what could these components in fish be? I don't think it's any of those nutrients that we typically associate with benefit from fish. It would be very difficult based on the available evidence, poor that it is to argue that actually it's related to those aspects of fish intake.

So I do think that the author's suggestion in the discussion that it may come back to contaminants is actually the author's kind of going with the, when you

hear hoof beats, think of horses, not zebras. I think they're going for a more likely plausible explanation for why fish particularly might be associated with this outcome.

And then that then leads into questions. Well, if we assume that it's these potential contaminants or environmental pollutants, if that's the issue, is there a way to mitigate that? And the answer to that of course, would be yes, that there are in terms of, purchasing type of fish or deliberately deciding to select for farmed fish or other mitigating factors that could be considered in this context.

Danny Lennon: Right. And I think then at this point then when we get away from actually trying to work out this specific question of let's say fish intake and melanoma risk, and we just think about, okay, pragmatically for someone, is this something that informs anything they need to do with practice? A kind of point we made in that fish episode was well, even with accepting that there are contaminants in fish and that there are certain high levels of that can be negative to health.

The bigger question is the levels that they're typically consumed within the diet. And then also in the context of the benefit that we know consuming fish gives based on all these other nutrients you've mentioned, for example, EPA and DHA, and knowing there is a benefit. What we are really trying to weigh up is not, is there any possible detectable harm from any component within fish?

It's when we consume fish regularly in the diet, is there a net benefit or net harm. And it seems from most of what we can put together. And this is why most recommendations fall in line with that, that if we think about if someone's consuming this one or two portions of fish a week, or this two portions, which was in this study associated with risk, that seems to be.

Benefit would outweigh risk from what we can tell, even if we accept these risks that are there, that seems the most likely right now, or certainly there's a lack of evidence to suggest people should stop consuming fish because of potential worries like this. And I think we, we mentioned some of the Mozzafarian research in that episode saying that, well, if people start doing that, it's causing a net harm, right?

If you try and get away from some of these problems by taking fish out of the diet, that could potentially cause harm. If there's a change in someone's overall nutrient intake. And I think weighing up the fish intake and health outcome data, that way is a way for an individual listening.

Maybe they can weigh this up for pragmatic conclusions for their own diet.

Alan Flanagan: I think with the findings of any given study, it's important that we don't just hand wave them off and you take a kind of methodological approach to working through if the findings hold up and if they potentially hold.

What then is the actual implication of that from a practical perspective? I think in this study, there are some factors that are positive in terms of, standing over the findings, which is that they did adjust for a lot of factors that could be relevant, like alcohol intake caffeine, which is associated with, so there was a number of dietary variables that were adjusted for fruit and vegetable consumption.

So these are all good, but knowing what we know about this particular exposure or sorry, this particular outcome and its lifetime risk and the factors that primarily influence it, then I think there are like, we've discussed a few potential holes in the ultimate veracity of the findings to put it simply, I think from a practical perspective, if you were given with the choice between.

Making sure you wear factor 50 when you're in the sun or excluding fish from your diet. I think when it comes to melanoma and skin cancer risk over the lifetime to choose the latter over the former would probably be fairly rash and not really majoring in the majors as far as mitigating this particular outcome goes, particularly for people that are at that kind of Fitzpatrick 1, 2, 3 end of that phototype.

So I think as far as the mitigation of risk for this particular outcome, focusing on the known knowns. Rather than really honing in too much on this specific outcome in this study particularly where there's a lack of consistency in the evidence base. It's highly unlikely to relate to EPA and DHA specifically, which are the nutrients that we typically associate with benefit with Phish.

And there's even in selecting fish, there's the potential to mitigate. If we assume that this finding is true. And if we assume that the mediating factor is. Contaminants and pollutants, there are ways to mitigate that particular risk as well. So I think sticking with the known knowns, as far as skin cancer, risk it's lifetime nature of that risk, the relationship with Fitzpatrick phototype and doing best practice that any dermatologist would tell you, which is make sure you have sunscreen every time you're going out into the sun, particularly at times of year, like this is where.

Put the focus.

Danny Lennon: Unless of course we are to listen to the anti-seed oil crowd. And if you remove seed oils from your diet, you can get as much sun exposure as you want. And it's actually good for you. So you will, you'll never succumb to any problems.

Alan Flanagan: Yes. I should have thought of that yet. Incapable of burning.

Yeah. Go low carb and don't eat seed oils. Wow.

Danny Lennon: So before we wrap up with the very final conclusions, I think it's also worth noting something we've talked about before when trying to address any diet cancer questions. And that is how difficult it is to come to really solid conclusions on this, that sure.

We can look at some of these associations and there is way of doing good work in relation to nutrition and cancer. And we do know certain things but certainly on an individual study like this it's very difficult to. Come away with anything concrete, but we can look at an association.

But I think it's worth knowing because of both the nature of looking at a chronic disease like cancer, but in also some aspects of cancer specifically because of how complex it is, there are real challenges there when we're trying to assess particularly a variable like diet because it has its own issues of trying to tease those apart.

And then if we look at melanoma, like you said, where we have these like really clear risk factors trying to then. Look at components of diet becomes very difficult to do. So getting that from one study is gonna be an impossible task. And so it's about maybe not jumping the gun or overreacting to one study we might see. At the same time, not necessarily dismissing it out of hand either.

Alan Flanagan: Exactly. And I think for this particular study, what we would want to see without dismissing it going forward is we would want to see more robust consideration of potential factors to do with, skin phototype and the relationship between susceptibility to burning we'd potentially want to see included like more potential direct consideration of environmental pollutant exposure, although that's really difficult to do.

So they're the open questions that a study like this leaves in terms of where to go to try and really tease out and further research, whether there is veracity in these kind of findings and whether it is something like pollutant exposure or toxin exposure that is related to that outcome.

Danny Lennon: Okay. So with that, maybe to leave people with a couple of a recap of what we've gone through. we said that in relation to the findings of this particular study in this reported increased melanoma risk, the reasons for that are basically unexplained or are, can't be explained by this particular study, there could be an effect, but there also might not be for some of the reasons that we suggested in terms of the very real limitations here.

And so there may or may not be, we don't really know. And if there is we're not really sure of what those reasons for it might be the kind of primary hypothesis that is being put forward by the authors. And as you noted, probably makes most sense would be, it's probably nothing to do with Fish per se, but it's probably some degree of a compound that is contaminating in fish.

So PCBs, arsenic, mercury, whatever it is rather than actually a nutrient we find in fish. And then we said, well, on the other hand, we know that there are clear health benefits to fish consumption. For most outcomes, we see a positive effect of that generally. And so there's still the recommendation that consuming one to two servings of particularly fatty fish per week is probably beneficial.

Or at least we certain change that recommendation. If that's something people are currently doing and noting that there's maybe some exceptions, for example, in pregnancy, where we look at the type of fish that's being consumed and maybe the mercury content there. But based on this study, and I think this is actually something that one of the main authors, Dr. Cho, said in an interview where she was asked about this study and she essentially said that; "I wouldn't discourage people from having fish, just because of our finding". And that's essentially, again, not overreacting to a study like this, and certainly not overreacting to headlines. You may have seen in certain news sites where they take a finding like this and report, oh, if you eat fish, you're gonna have an increased risk of skin cancer.

That's not necessarily the main pragmatic conclusion one should take from a study like this. And hopefully the reasons for. Have been explained what the course is, conversation, hopefully that aids you in being able to analyze questions like this going forward. Okay. Thank you everyone for listening.

Hopefully you found this useful and informative. If you have, please let us know about it and please certainly maybe share it with someone who also likes listening to conversations about nutrition science and share it around. Generally that's very much appreciated for anyone that is listening on Sigma nutrition premium, you'll get some study notes to this episode. And apart from that, thank

you for listening. We'll be back with another episode very soon. And in the meantime, I hope you stay safe and take care.