DANNY LENNON: So thank you very much for joining us on the podcast. It's a pleasure to have you here.

DEIRDRE TOBIAS: Thank you so much for inviting me. Happy to be here.

DANNY LENNON: Yeah, this is a topic that we're obviously very excited to talk to you about, and it's one that regular listeners of this podcast will have heard us explore on a previous episode of the podcast, where we essentially put forward a case for the importance of nutritional epidemiology. So it's kind of a perfect situation here to be able to talk to you about some of that, given your work. So maybe just to give people some background on the work that you've done and the positions you've held, and why that is so crucial to today's topic, can you maybe give us that quick overview of some of your work – although trying to do that quickly might be a challenge, given all that on your CV.

DEIRDRE TOBIAS: Sure. So briefly, I have my doctorate in epidemiology as well as nutritional epidemiology from the Harvard Chan School of Public Health. My mentor there I stuck around and did a postdoc with, so I spent quite a while in the nutrition department there with Frank Hu. And then now, the last five years I've had a faculty position at the Brigham and Women's

Hospital as an epidemiologist in preventive medicine. So those are, I guess, my titles and my research interests along the way. I have really run the gamut of looking at diet lifestyle factors, mostly diet for obesity, type 2 diabetes and other obesity related complications overall, and among women who are at high risk with a history of gestational diabetes. More recently, I'm interested in really diving into Epi methods more and seeing how we can kind of combine what other facets of epidemiology have done really well for diet data. So that's kind of a topic that's always been on my mind, but I'm actually trying to put pen to paper there now. And then I also am academic editor at the American Journal of Clinical Nutrition, which is an exciting role as well.

DANNY LENNON: One maybe point that we'll probably revisit later on, but I think is an interesting start point, is while we'll be discussing a lot of the usefulness of nutritional epidemiology, how to do that correctly, what it can tell us, as we have discussed in this podcast, it's unfortunately one of those areas that gets sometimes misrepresented by others and painted in a bad light by maybe some that don't really understand some of the nuances of it. Is there any particular misrepresentation of nutritional epidemiology that ends up being most frustrating to you, or, what is the first thing that comes to mind that you faced?

DEIRDRE TOBIAS: It's so much. I think the ecological study design where the seven country studies or anything where you're comparing populations who eat this, and they have disease rates of that, I think that's what a lot of people think Epi and nutrition Epi is, and that's really like the weakest bottom of the barrel kind of evidence you can drum up. So if that's the impression people have of nutritional epidemiology, I can see where they're coming from. And there's just so many large databases out there, and you don't have to be an expert in the methods or even the exposure outcome to really get your hands on data and try to publish something

these days, for better or worse. And so, I do think that in addition to kind of like the obvious, really limited study designs, even just your basic cohort studies are kind of really being exploited with a lot of – I don't want to use the word garbage, but there's a lot of it out there. So I think that probably contributes to this perception that the whole field is useless, but I would argue that that's not a very fair judgement.

ALAN FLANAGAN: Yes. In terms of then maybe flipping the coin and putting the best foot forward for nutritional epidemiology, something we've spoken about before is the logistical issues that nutrition as a subject faces investigating chronic diseases with long latency periods, where the exposures that may lead to a particular outcome are influencing disease processes earlier in life. And that places various research designs sometimes at a disadvantage from a biomedical standpoint. What, to your approach are the most important or the best features of epidemiology – and you mentioned kind of the hierarchy even within epidemiological research there – so in terms of designs, the strengths, limitations and the best characteristics of cohort studies?

DEIRDRE TOBIAS: Yes, I think there are some strength of cohort analyses that really set them apart from other just cohorts that are doing nutrition, diet-disease relationships; and having repeated measures of diet, for example, is, particularly if you're looking at a diet-disease outcome that is 10, 20, 30 years into the future, I think is incredibly important. And having a single baseline dietary assessment and following that up for risk of some outcome 20 years later is probably a little bit of a stretch. So I think that cohorts themselves can have strengths in the data that have been collected, but as a field, I think you alluded to the limitations of probably clinical trials not really being able to feasibly randomized people for 20 years to one diet or another for a variety of logistical and cost reasons. But even if you could do that, I think

there are certain advantages of cohort studies that really get to look at those, get to look at the full spectrum of how do we realistically consume the foods that are of interest, and I'm translating a randomized trial to observational setting isn't always obvious, and it's kind of like, oh, the trial must be the gold standard, and everything else is trying to get as close as it can to the trial, but I do think they're also asking inherently very different questions often, and so one strength of cohort and observational analyses is that ability to really ask questions somewhat differently than trials can, particularly when it comes to duration and looking across the spectrum of doses.

ALAN FLANAGAN: Yeah. Well, on the question of dose, because I think this is a really crucial aspect of yielding findings and strength of association and epidemiology is the concept of having an appropriate contrast and exposure. And you can have cohort studies where the high versus low comparison is either not particularly wide or high. And then, you can have, as you said, this ability to then if you do have a spectrum of dose to look at these kind of dose response relationships. I wonder if you could maybe dig in a bit more on that and the importance of having an adequate contrast in the exposure, and how that might relate, if there isn't that presence to sometimes null findings that may not actually reflect no association, but may actually reflect the lack of a sufficient contrast in the exposures of interest.

DEIRDRE TOBIAS: That's such an important area and something that myself and colleagues have been thinking a lot about lately, like, just simply defining the exposure and the causal question, which includes what this contrast or your comparator diet is, whether it's having someone maintain their course as the competitor, so this kind of usual control group, or, a direct head to head comparison, looking at the comparative effectiveness of two diets, for example. But in the observational setting, but even in trials, this, I think, does get rather vague, where you

have this kind of categorization of your dietary exposure, where you have low, medium, and high intake; and to say, okay, the participants and the high intake versus low, what's the risk of heart disease, for example, I think that's probably 90% of nutrition Epi, I think really doesn't define the exposure well enough to be able to really answer the question the researcher probably set out to answer to begin with.

And what I mean by that is, if you, like, to sufficiently define your exposure, if you say something like, okay, a randomized trial even, like Women's Health Initiative, let's have our participants achieve a low fat diet. So if the exposure is a low fat diet below 25% of calories from fat, for example, you're assuming it doesn't matter how you get to 25% calories from fat, whether you're eating graham crackers that are fat free and muffins, or vegetables and healthy proteins, it doesn't matter. The assumption that's inherently there is that the percent of calories from fat is the only thing that matters. And we know that that's a poorly defined exposure, because it does matter what the composition of the diet is to get there.

And similarly, with the observational data, if you're saying two servings per week of red meat versus none, if you're consuming red meat, doesn't matter what you're excluding; if you're not eating red meat, doesn't matter what you're eating instead. And if that's not explicitly defined in your exposure of interest, and then your causal comparator, the contrast, this reference group, then it's just too vague, and you don't even really know what your effect estimate at the end of the day represents. So it could be the exact same analysis repeated across a number of populations. The background diet of that population will be what this kind of reference group that's at low intake of red meat is eating instead of red meat. So it's red meat versus this kind of food, but you might not even explicitly know what that is.

And that comparison, if those non red meat calories matter at all for your outcome, then your causal exposure is poorly defined, because you don't know what it is that you're even comparing it to. So high versus low intake, every single time, if it's not an explicit substitution, really is just, I think, running the risk of this vague assumption that all calories behind the scenes are created equal for your disease outcome, which maybe you're comfortable with that assumption, maybe you're not, but I think it's most of the time hardly even acknowledged.

DANNY LENNON: It's obviously the case that there are better and poor studies that we can look at and the importance of looking at the methods and how a certain study was done. But I'm wondering in terms of the prevalence of seeing some of these issues come up, and specifically from your position as editor at the AJCN, obviously, one of the more prestigious journals relative to many others that are out there, but I'm just wondering, in terms of some of the – and this is an impossible question probably to answer, but in terms of the amount of epidemiological research that is submitted from different areas, how common do you think it actually is where groups are just not having appropriate exposures defined, that would lead to a study that's maybe problematic or at least not as useful as otherwise could, if it would have been properly defined, how often are we seeing this?

DEIRDRE TOBIAS: I mean, so in my editor role, it's daily, there's submissions that are just this kind of run of the mill high versus low, pick a food, pick a disease. And this open access movement with data, I think, is incredibly valuable. But it does kind of put at people's fingertips, this vast quantity of data, and when it comes to exposures like diet, where just a single FFQ can give you kind of an infinite number of papers, if you really wanted to, maybe there's more risk of this happening with nutritional Epi compared to other fields. So there's enhancers available, UK Biobank is available, and submissions from all over the

world using enhanced data or biobank data, because you can just download it with a click are very common; not to say that there isn't some utility in some of them, but you can tell when it's not a hypothesis that they started out with; sometimes there's red flags when it's just kind of this food and that disease and the subversion of the disease, and in the next paper, they submit or whatever, but it's unfortunately common. And then as far as what I see in the published literature, in my academic role, not so much as the editor, of course, the worst offending cases are when it makes some big splashy headline in the news, and then it's just so cringe worthy to read the paper underlying it that really didn't ask or address anything related to what the headline made it out to be, and that's always frustrating, I'm sure for everybody.

ALAN FLANAGAN: One probably research design that, and this is something Danny and myself have spoken about before, that in nutrition, particularly as it relates to epidemiology is, I think, most guilty of this is meta-analysis of prospective cohort studies. Because this lack of a clearly defined exposure and high versus low comparison, in a meta-analysis context seems to assume that the high versus low holds true invariantly across every population, but high in one study in particular that I can remember that was saturated fat and stroke, but it was mostly Japanese cohorts. And the mean high was like 20 grams a day of saturated fat versus low, which was seven grams a day, and suddenly people are extrapolating that to kind of European or US population. So it seems that meta-analysis of prospective cohort studies has really become a place where you could throw paint against the wall and see what sticks as far as your varying high-low comparisons go.

DEIRDRE TOBIAS: I totally agree. So my first job out of undergrad was this meta-analysis consulting company, and I had no idea what meta-analysis was, I was just out of undergrad, not even really sure what to do with my life. But for two years,

literally, all I did was meta-analyses, from the search terms to the data extraction, and reading through each individual paper, and the topic I kind of got – I worked with most was bariatric surgery. And so, that kind of sparked my interest in obesity. And so, even before going to school, like, meta-analysis has always been really interesting to me. And over the last decade, everything you just said is so true, it's completely become this sort of like, let's garbage in garbage out everything and draw conclusions. And because it's a meta-analysis, it's like the culmination of everything, and this is what we ultimately have to believe. And so, I think that's really unfortunate how they got really just misused. And on top of that, it's a single line of code to actually do the meta-analysis and all the data is free. So anyone can do a meta-analysis that requires absolutely no expertise on the subject matter. And if you look at the individual models and estimates that are being included from studies, like, when you have confounders in your model for dietary exposure, they completely change the interpretation of your dietary exposure. And we all know that calories is important because it's a confounder, but I think many people still don't appreciate that, you know, that makes it now an isocaloric substitution. And then when you start controlling for, say, saturated fats' exposure, you add carbs, you add red meat or whatever it is that you think might be related.

Now, what does your beta coefficient even mean? I don't think there's thought – so when you have a meta-analysis, and you're pulling across all of these studies probably 20 different ways, with different background diets, different doses and exposure, like you mentioned across populations, I think they can be really misleading, kind of crunching, distilling down of data into a single estimate, that doesn't always really mean much. What can we do to move forward from that? I don't know. I think it's a really good question to ask because they'll only continue to be published. If there's ways we can have them be more transparent in the

methods but having a lack of comparison is probably one of my biggest pet peeves. So you see like red meat and colorectal cancer, but red meat compared to what, because you know that that's, if you were to do a trial, that you would have to have some sort of control group then. What that comparator is probably, is very important for what the effect of estimates on that are,

ALAN FLANAGAN: Yeah. One thing that comes to mind there that I think would be really helpful for listeners, because I know we do have a lot of people that are quite interested in epidemiology and understand that it's likely to remain the mainstay of nutrition science for the foreseeable is one of the kind of straw man arguments that gets put forward about nutrition is well, there's x exposure, for example, let's stick with the red meat example, high red meat, AND people with high red meat had higher BMI, higher prevalence of smoking, low fruit and vegetable consumption, etc. And the straw man is that these potential confounders are somehow just kind of brushed under the rug and not even factored into account. Whereas a well conducted cohort study will have run through a number of statistical adjustment models to try and account for non-dietary confounders and potential dietary confounders. I wonder if you could just dig into that concept of adjustment models and epidemiology, and how they relate to maybe the concept of control in a trial, and how they can be used well to try and elucidate an effect estimate that is, has accounted for some of these common confounder, potential confounders.

DEIRDRE TOBIAS: Yeah, so that’s like all of EPI 201 in one question. So let's see. If you have a randomized trial, if you think of kind of the typical table one, let's say you have a binary treatment exposure, okay? You either get this drug or you don't, or, let's stick to food, meat or don't. You look to table one to make sure that the column of people assigned to know me and the column

of people assigned to me are identical. That assures you that randomization worked. And that's because the investigator is deciding the individual participant's diet there with the flip of a coin saying you're eating this, you're eating that. Now, in an observational cohort, same baseline, recruit a bunch of people, but now instead of assigning you eat meat, you don't. You go around and you ask everyone, do you eat meat, yes or no.

So now your table one looks completely different. You have a column of people who don't eat meat, and you have the column of people who do eat meat, and they are not eating or not eating meat at total random, like, there are very strong correlates of people who eat meat and don't, whether they're causal or correlated or whatever. So it's almost the complete opposite now of this table one from a randomized trial, where everyone looks exactly the same, because the investigator decided and now it's smoking, BMI, prevalence of type 2 diabetes, every other dietary factor. You can see that very clearly. The people who eat and don't eat red meat, of course, are very different. And as epidemiologists, we know that. That's why we're using the tools and models that we do to try to address this really important limitation or concept that I think maybe gets brushed under the rug, because you can't, you know, there's only so much space in an abstract and that's pretty much all that people read. But I can guarantee you that behind the scenes, this is probably one of the most intensively kind of like thought through components of developing an analysis.

So you have these two groups. So in this observational setting again, now you have a baseline. Okay, so we recruited people, they were either randomly assigned or we asked them what you ate. And you follow them over time, say 10 years, and then tally up who had a heart attack over the 10-year period. So if this was a trial, you just do like this intention to treat analysis. You just say what's the incidence

in group one versus two, and that's the effect of red meat that we randomized that baseline. In the observational setting now, okay, we have all these other reasons that meat eaters are different, that we have to account for. If any of these other factors are related to their risk of developing type 2 diabetes over this next decade, we need to do our best to account for that, because we want to isolate the contribution of red meat itself, not all the other lifestyle behaviors and foods that correlate with the red meat.

So that's what these models or other methods and approaches are attempting to do is to really kind of break it down so that we can say, okay, these meat eaters, it's because of the red meat, or not, that they're at higher risk of heart disease. I don't know if that helps clarify somewhat. But how you choose what to put in the model is really kind of these characteristics you think not only would differ by meat intake, but also be related to your outcome. Right? Those are confounders.

ALAN FLANAGAN: Right. And it seems that while an adjustment model cannot necessarily erase the effects of say a lifetime of smoking in an individual, what I think, again, is often underappreciated or simply just dismissed, depending on the kind of diatribe we're talking about and what the analysis actually is finding is that if you have a point estimate that has survived all of that adjustment for dietary and non-dietary lifestyle factors, which are known, and you have a strong summary point estimate and relatively tight confidence intervals that couldn't necessarily just be explained away by potential residual confounding, unless it was a residual confounder with quite significant effect size itself, well, then it's a finding that warrants taking seriously. But what we tend to have is a lot of sophistry when it comes to nutrition, and you'll say people will be like, well, it's a relative risk of 1.4, I don't care. I wonder if you could give us just a little, yeah, kind of insight in terms of how we think about risks and

exposure effect sizes in nutrition, because we don't tend to get relative risks or hazard ratios over two. So how do we contextualize the effect of an exposure that might have a 1.2 to 1.4 hazard ratio or relative risk?

DEIRDRE TOBIAS: Yeah, I think that this is so unique to behavioral lifestyle interventions, and especially nutrition, where, really our exposures are continuous. Right? There's no kind of like dose versus no dose. And we all eat our entire lives from the day we're born to the day we're dead, so it's not only what we ate today, but if it's a chronic illness, maybe it's your exposure over the last several years or decades that matters. So this kind of continuous exposure, that we either force into categories or model as a continuous variable, but then end up with these teeny tiny effect sizes, I think, really need to be interpreted both in the context of, okay, what's the distribution of this exposure in the population. So if it's servings per day is associated with, and it has – you know, we get this relative risk of like 1.4 which is pretty modest – but if in this population, people are consuming two, three, four servings per day, then you take this continuous variable, and now see what the dose where most of the population lies, and that might change your interpretation of an otherwise modest effect estimate.

Similar to the other extreme where you have like a contagion that has, or a gene that has like a really high effect estimate, but it's incredibly rare. Right? So with that, it's similar, something that's a common exposure, but with maybe not as drastic of an effect estimate, particularly when you're looking at a continuous kind of grams per day or servings per day that isn't really comparing extremes. It might look less than from an effect estimate size than it really is, given the entire population's exposure to it.

And then you mentioned kind of adjusting for confounders and seeing what that does to the

effect estimate, I think that's what a lot of reviewers might ask for like, oh well, what about adjusting for this; and then you say, oh well, we did that it didn't modify the estimate, so we left it out because it's not measured well or whatever. But I think that really kind of having that knowledge going in, so the kind of like what's my exposure, what are my potential confounders that are really important because my team is expert on X, Y, and Z, so we should know, like, these are strong risk factors for heart disease, really that's subject matter expertise, I think this also can be underestimated and I think a lot of the criticism comes from, oh well, what about this, you didn't adjust for that, or, that really may not understand its relevance that it's not maybe that strongly correlated with the exposure or whatever.

DANNY LENNON: Just as you bring up that point of almost that decision making process, when one is putting together a study design, I wonder if we can maybe talk specifically about some of the dietary collection methods. And earlier, we've referenced food frequency questionnaires, and you talked about the importance of maybe repeated measures of diet, and, of course, there's a lot to get through here, and we could maybe mention some of the various dietary collection methods that are most common, some of the pros and cons of those, but really, ultimately trying to get to that question of in that decision making process for researcher looking to decide what is the best collection method for this particular study, what that thought process looks like.

DEIRDRE TOBIAS: Yeah, so that's a great question. And I teach my nutrition epidemiology course, and the first half is just assessing diet, how do we do it, how do we validate what we just measured even, is measuring what we want. And I think one of the most important questions, first and foremost, if you're designing a study, is what is my exposure of interest; and the answer isn't, oh, it's red meat, it's red meat like habitually

over my life, or red meat right now today and I'm interested in like do I get foodborne illness tomorrow, like, how acutely or chronically or habitually, like, what is the time window for your exposure, and where you think the outcome falls into that. So for chronic diseases, of course, we're not interested in having one steak on January 1, and then who cares, it's your chronic habitual, are you eating a lot, are you eating a little.

And so, with that in mind, something like a food frequency questionnaire which ascertains from the participants, okay, think over the past year, here's a 150 foods, tell me how often you eat this, this, this, this. So you know cheese, do you have cheese, never, once a month, once a week, whatever. There might be eight categories that you can answer up to five servings a day or whatever. And then it goes through like a handful of vegetables and section by section food groups and covers for that population, what the researchers included on the questionnaire as probably the most important at capturing kind of variation and diet for this study population. And, of course, there's error in that. It's not going to tell you what you ate yesterday, and we know that as researchers, and that's not what we're even trying to measure anyway. And I think that's where a lot of the criticism comes from. It's, I don't even know what I had for breakfast yesterday. Like, did you have a roasted pig for breakfast? Probably not. If I asked you, did you have a bowl of oatmeal? No. Okay.

So we can like narrow it down pretty well what you actually ate and then people tend to somewhat be creatures of habit, so do you do eat pork or not. And so, I think for the most part, people do pretty well. That's not true of every food. It's not true of every nutrient. And some of it's because of the participants remembering, and a lot of it is just because of the questionnaire doesn't capture it very well, like, sodium, for example, terrible on a food frequency questionnaire. Because at the end of

the day, we don't know which brand or type or how much you're adding or whatever, and so the composition databases that we use to take your responses on a questionnaire and crunch it down to how much protein, carbs, dairy, whatever relies on this kind of database to make those translations. So there's opportunities for error every step of the way, but it's not just kind of people can't remember like, I think, a lot of people think.

And then there's these other methods that, on the flip side, capture what exactly did you eat today, or what exactly did you eat yesterday. And the assumptions there are, if you're really trying to measure again, this habitual long term diet that if I get one or two days or maybe three days of diet collected on someone that on average does, like, captures pretty well what they tend to do. So the NHANES, the national US health statistics survey is a single 24-hour recall, I think they added a second one that are subset to. But if you told me everything you ate yesterday, or even today, and we had a picture of it, and we were exactly precise, and we weighed it, and we knew exactly what you ate, like, how representative is that of your habitual long term diet?

So, the FFQ, while it doesn't have the precision some people think you need to be able to study diet, it really probably captures the exposure we're more interested in, which is your usual intake. And then when we go to say, okay, how much of red meat are you eating, who's high, who's low, the FFQ probably doesn't say, okay, on average Deirdre you're eating 40 grams a week or a month or whatever – that estimate that it crunches out, there's not a lot of precision in that gram amount, but there is the ranking relative ranking of participants, it does very well. So the people who intake a lot of red meat are going to, if we ranked everyone based on their food frequency questionnaire responses, will rank people pretty well. The precise quantity of a dietary component or nutrient has some error, and we know that.

People underestimate, overestimate, and that random noise or non-random noise on a population level does impact your actual estimates of grams of carbs, for example. But the ranking, like I said, is usually very well preserved. So then when we go to compare across categories or a dose response or even continuous, the trend across the population with a disease outcome for a dietary exposure is usually something that I'm personally, you know, believe in and that can be validated.

ALAN FLANAGAN: Yeah, there's two things that I think are really helpful for people listening to dig into. One is the validation process itself. I think that again, people have this straw man idea that researchers come up with some random questionnaire and hand it to people and off you go, and well conducted cohort studies, the validation process is such an important part of their integrity. And then from the validation then, we get our correlation coefficients between the instrument and FFQ and the validation study. And when people say, oh, nutritional epidemiology is so inaccurate, well, it seems to me that the answer to that is always, well, it depends on, again, what your exposure is. So for sodium from an FFQ, correlation coefficients are quite poor. But for major macronutrients, like fat and carbohydrate, seems like some of the well validated cohorts, you get correlation coefficients of upper ends, you know, 0.7, 7.5. So that's as good as homeostatic model of insulin resistance, but I've never seen someone published a paper saying Homa-IR is pseudoscience. So I'm not sure why nutrition comes in for a special bashing.

DEIRDRE TOBIAS: I'm not sure either, but that's okay. At the end of the day, the criticisms that are, well valid points of someone's perspective on the field, I think will only help us do better. And if we took the FFQ at face value, then it would have never been validated and improved upon. So I'm okay with valid criticisms, helping the science do better or demonstrate that we've done okay.

And validation studies, for a lot of the large cohorts for the different methods or a questionnaire are incredibly important to be able to say, okay, we've been able to estimate reasonably well, this is probably less reliable and so forth. And I think biomarkers or something like Homa-IR always get a little bit of a free path, but there's error in those as well. And again, if you're exposure of interest is long term intake, then the most precise biomarker on a single day may have nothing to do with your long term exposure and therefore have a ton of error, if long term was what you were validating, but biomarker again.

So what is it that you're trying to ask if your data is something that I think researchers should think of, and then also if, for the casual reader too, like, what's the exposure of interest, what did they actually measure and does that reasonably well – and it's also a tradeoff at the end of the day too. There's a tradeoff of precision for sample size, and part of that is just restrictions and constraints on logistics. Right? Like maybe someday we'll overcome that, and I think there are a lot of like, omics feeding studies and ways that we might be able to get better measures of habitual dietary intake from a single biomarker, from a metabolomics pattern score or something like that. I'm not – the diet assessment, I think is not what I'm most worried about when it comes to people's criticisms of the field, because I think it does pretty well, and a lot of it is just the limitations of our current tools that I'm hoping someday are overcome anyway with being able to ask more questions, because it's online, and not a piece of paper, and things like that.

ALAN FLANAGAN: Yeah. In terms of validation, the kind of historic, I mean, if you look at, say, the Nurses' Health Study and the process of validation and the repeated, the reproducibility of that FFQ over time and the validation was again seven day food records, taken at different points in the year and different seasons. Now, you'll see

large cohorts, Epic being one example, the NIH ARP being another where they've used, for example, for the validation, two 24-hour recalls. And I've seen Victor Kipnis and others argue that actually the kind of gold standard designation of the seven-day Wade food diary possibly isn't as warranted, because it seems like validation against multiple 24-hour recalls can result in similar levels of correlation, what are your thoughts on that?

DEIRDRE TOBIAS: Yeah, so this kind of like triangulation or comparing across a number of different collection methods of the same person responding on their diet, but in different ways, I think is one of the main approaches to a validation study. And basically, what you want a gold standard that, if it has any error, that type of error is not correlated with your tool of interest. So an FFQ requires memory and thinking back, so does a 24-hour recall, so some of the error of those two methods are correlated. So if you're looking to validate the FFQ having something like the way diet records, which is prospective, and the errors are more related to the scale and your diet composition, and if you ask for people to do it for too many days, then they start changing their diet, that sort of thing. But not so much recall, because they're not remembering anything, they're doing at all in real time. So that will give you some differences between methods, what types of errors are correlated, when you look at the correlation between the different types of tools used to assess diet in the same person. And then if you look over time, like reproducibility a year later, and have everyone do all of that all over again, there will be real changes in diet too. Right? So you'll have reductions in the correlation between two measures a year apart that are random noise, because there's always random noise and relatively blunt tools like that. But also people's diet do tend to change slightly, not drastically, for the most part. And that's also a contributing factor to a lower correlation.

DANNY LENNON: Yeah, I think one of the crucial points here that seems to be coming from much of the discussion on dietary methods is for people when they're reading studies, not to immediately fall into that trap of dismissing a certain paper or a piece of research, because diet wasn't captured well enough. Right? And it's often this thing of people saying, oh well, what can we take from this study, because if people didn't weigh and measure their food every day, then this is just all kind of guesswork. Again, on the first layer, that's just misunderstanding the validation of some of these other measures, but also beyond that, it also doesn't take into account the logistics that you mentioned, and some of the constraints of a certain study, but also then just what the study is trying to achieve. So coming back to what is the actual research question, and if it's to look at the differences in a certain group between those with the highest and last exposure. So in the red meat example you gave, then it actually doesn't really matter how precise we are with that number of grams we're looking at, because it's going to still be that top quarter, and the bottom quarter are still going to be the same, despite the slight differences in the precision. So I think it's just realizing what is that research question, and then working from there to see is this tool appropriate in this context, as opposed to having some black and white rules on what is good and what is bad.

DEIRDRE TOBIAS: I think you summed it up nicely. I think really like what is your exposure and intent and how this ranking that questionnaires tend to do fairly well is really the biggest takeaway there. And then if you think, diet in general, I think is just incredibly complicated. I think a lot of people who criticize observational EPI and FFQs are the same ones that just bleed for RCTs. Everything RCTs say are the gold standard and diet RCTs are incredibly complicated, and I don't understand that kind of free path they tend to get, and I'm doing my very first one ever right now, and it's so hard. And even just thinking, okay, what is my

exposure, just like, if you had an observational dataset is incredibly challenging to think through, okay, well, if I'm asking – if I want to study red meat, then do I take people who are eating red meat, because what I really want to know is, is it good for people to stop. Right? So what's my clinical question, and if it's, okay, should I quit red meat to improve my heart disease risk, or does that like just confounding and blah, blah, blah, The observational EPI is junk.

So even if I'm doing a trial for that, then it comes down to, okay, so my question is really quitting. So then now, do I have to enroll people who are eating a lot of red meat right now, and randomize them to what, like, quit red meat or not? Okay, so then I have this or not group, which is kind of self-explanatory. And then if they're quitting red meat, and this is an isocaloric experiment, then they have to be eating something else. So do I just like leave that up to them or do I care? Because having that clearly defined exposure matters. So then it becomes this trial of, do I switch to fish, or do I keep eating red meat. But I don't think trials have even really started to get at that level of asking the precise causal question, let alone the observational epidemiology. And if you have randomization at baseline, you have absolutely no idea what people are eating even the next day. And how do we determine that? Well, it's usually questionnaires.

So if we are looking at adherence or if we look at a population – I've always wanted to ask this question – so if you have two populations, and one was randomized to meat or no meat, and the other just self-reported meat or no meat; and a year later you asked both of them, both populations, do you eat meat, yes or no, self-report, self-report, which population self-report would you have more faith in?

ALAN FLANAGAN: Both equally? They would be...

DEIRDRE TOBIAS: Both equally, maybe. I mean, if you have this intention to treat analysis of just based on their baseline assignment, but you really have no idea what they're eating at one year versus people who habitually eat red meat and are reporting it again a year later, I don't know. I think it's just really, it's complicated even for trials. But the free path that tends to be given is I don't really understand because I think it's just as difficult.

ALAN FLANAGAN: I think it's the fact, well, and this is just a – I've seen various commentators within the field of nutrition, the late Robert Heaney used to write about this all the time that nutrition is not medical science, it's nutrition science, but it evolved essentially using the biomedical model with this kind of very strict hierarchy where the randomized controlled trial is the gold standard, meta-analysis is the platinum standard, observational research you can't trust because, oh haven't you heard of this HRT example. And so, it's this veneration of an RCT, but actually if – and this is something we've talked about before was, if you look at the assumptions that underpin internal validity in a biomedical RCT exposure, zero exposure, one of the core principles of randomization is an assumption that there are no covariates introduced post randomization. So at that point, you're just having the only thing that's changed is exposure versus zero exposure. That's a practically untenable assumption for diet for the reasons you just outlined, because even if you randomize meat, no meat, the idea that everything about their diet holds true from the moment of randomization, unless you control every morsel of that food is untenable. So in a free living intervention, you don't know, there's too many moving parts. And what I think some critics of epidemiology who venerate RCTs maybe don't appreciate is some of those criticisms are contradictory because in that context, an RCT has achieved randomization, but doesn't have any more capacity for causal inference than epidemiology

would in terms of the exposure. But that kind of gets swept under the rug.

DEIRDRE TOBIAS: No, I think that nails it. I love that. I think this, like you said, this biomedical framework for assessing causality, the biggest benefit there is this double blind placebo control that diet doesn't have unless we're talking about supplements. But if you have anything happening post randomization and you don't know what pill you're taking, then you can assume that any non-adherence or quitting or whatever is unrelated to your treatment assignment. Right? That's like the big assumption that double blind placebo controls get away with. I don't know what I'm taking, but I'm the type of person who, you can tell me to take it and a week later I'll stop taking it. So those are equally distributed across your active drug in your placebo. So you know that there's some non-adherence, but it doesn't matter, because it's not related. The only thing that's going to do is dampen my effect size, kind of, work against my statistical power. But with diet, that's not usually the case, you know which diet you're on. And even if there's an attempt at blinding, you're still going about your day, and for living trials making choices for yourself. And if you're told, okay, I have to reduce my fat intake, or I have to reduce my carb intake, the palatability or how much you enjoy these diets or your usual background diet coming in, all of these things can influence your level of adherence. So now, all of a sudden, your treatment assignment, what group you got assigned to very much can relate to your ability to hear and especially with some of the interventions that are comparing something standard with something really extreme. So like, just stick to this diet or do time restricted feeding and don't, you know... So where if you have something where the intensity is different between interventions, that can really exacerbate this kind of different level of non-adherence between treatment groups, and it's very much related to the treatment. So now you do have what's basically

an observational study. So just at the beginning, they were told to do it, rather than [inaudible 00:52:04] themselves. So I'm really interested in this whole field though. I think there's so much work in this space that's been done in other substantive areas of epidemiology, really looking at this kind of like per protocol, rather than intention to treat effects for either trials or observational analyses. And I love this, I think this is going to be like a space to watch for nutrition Epi, at least, I hope, because I think it can offer a lot.

ALAN FLANAGAN: Yeah, it seems to me that even with the limitations, which – Danny had made this point before with some of the criticisms, even in the published literature, you would swear that no one in nutritional epidemiology is live to these issues at all, when, in fact, you've got an entire field that is not only conscious of the limitations, but has been actively working and continues to work to improve methodology and think at a very – I find nutritional epidemiology one of the fields probably why I kind of am so attracted to it, because it's fascinating, is it's a field where you get a lot of people thinking at quite an epistemic level, in terms of the ideas of, well, what is it, how do we know what we know, and what methods can give us more information on that. It seems to me that with advances in technology and new methods and this constant evolution of ideas and methodology in the field that it's only going to improve from here. And I thought on that, you mentioned, touched on earlier, metabolomics and biomarkers, for example, like, where do you see their utility moving forward, and the potential for their continued use or expanded use?

DEIRDRE TOBIAS: Yeah, so that's a great question. I think there have been a lot of really interesting kind of cross sectional analyses looking, can we identify from someone's blood sample, like a pattern in their metabolome that correlates with their self-reported diet. Right? So there have been a handful of these recently, like a

Mediterranean pattern, oh look, we found a Mediterranean pattern; metabolome, that sort of analysis. I think that's kind of like the step that I'm thinking of in that direction, where maybe, eventually, not necessarily replacing but very complimentary to self-reported diet would be this more objective biomarker version. And I think that would be helpful so that we can go back to stored blood samples and cohorts that never even assess diet to begin with, or have maybe a method that wasn't validated very well or that have kind of serial blood markers, but not serial diet data to be able to leverage a new version of assessing the same exposure, but maybe offering another way to look at the data. Because the metabolome isn't the same thing as what you're eating, we know that it's more downstream, and it's harder to maybe pick out like the food itself, it's more the overall composition. So its utility and its strengths and limitations are I think still really kind of in the infancy of being able to understand, but it's one area, and I think it's interesting to see what will come from that.

DANNY LENNON: Okay. So with that, before we let you go Deirdre, can you maybe let people know, if they're interested in finding you on social media or finding any of your work online or looking more into your background and your work, where are some of the best places on the internet for them to go and check that stuff out?

DEIRDRE TOBIAS: Yeah, you can find me on Twitter. I try to keep it professional. But I'll be honest, it's hard. So that's deirdre_tobias. I don't know how you can find my work, PubMed or Google something or another. Feel free to stock away, but it's not that, you know. But no, this was great. I look forward to anyone reaching out with any comments or questions. It would be awesome. It's not very often I get to like geek out on the methods themselves. It's always like, well, what's good for me, what should I eat. And it's like, I honestly don't really have an agenda

when it comes to the food. I want the methods to be right, and that's like my true passion. So if I had one last thing to say, like, I think everyone who has said in the past to like shut nutrition Epi down, just burn it to the ground, I think maybe it's just my naive junior faculty take on all of this, but I'm so excited. There's so many promising avenues in this field from Epi methods to omics and precision nutrition or trials merging with observational data, I don't know, whatever. But I think that there's a lot out there, and I'm looking forward to it. So don't burn it down.

DANNY LENNON: Yeah, we're lucky that our audience is a pretty nerdy bunch, so I'm sure there will be plenty of them hitting you up with questions following this.

DEIRDRE TOBIAS: I would love that!

DANNY LENNON: Yeah, and then on a bigger note as well, there's plenty of our audience that are nutrition science students or who are working in academia or doing active research, so I think this is hopefully another movement forward to spread the good news of nutrition epidemiology. So I think you've done a fantastic job on that.

DEIRDRE TOBIAS: Cool. Thank you.

ALAN FLANAGAN: Thanks.

DEIRDRE TOBIAS: A lot of fun. You guys asked very good questions too.

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