Danny Lennon:

A big, welcome to the podcast to Dr. Kevin Klatt. How are you?

Kevin Klatt:

Everything's good on my front. You know, it's hard to beat, but Berkeley, California weather especially this time of year, it's nice 60 degrees Fahrenheit every day. Don't ask me to do the Celcius for your non-US listeners, but things are good.

Danny Lennon:

So before I get into any of the questions I have on today's topic, can you maybe give people a bit of an introduction to your own background?

Kevin Klatt:

Sure. I have a bit of a weird path. I guess my undergrad is in biological anthropology and I realized early on I wanted to do nutrition and metabolism stuff, but I had a nice scholarship. I couldn't leave. And so I took all the prerequisites I needed to, to like kind of head towards a path to become both an RD and then do my PhD in some area of metabolism. And then I did some dietetics coursework after that for a year and did some teaching and research with it. And then I ultimately did my PhD in molecular nutrition at Cornell. And I did my dietetic internship at the national institutes of health clinical center here, which was a fun dietetics training, I guess. It's, it's an interesting all the patients we see around research trials and whatnot and kind of have rare diseases.

Kevin Klatt:

And so it's a different way to do clinical dietetics for sure, but it was a good experience with lots of time spent in metabolic kitchens. And I had done some controlled feeding work in my PhD. And so it's a nice, I

guess in my PhD work, I really set out intentionally to do both human intervention work, but also basic science, so transgenic animal models and a lot of experimental work cell culture. And I actually had co-chairs with Marie Caudill, who is a PhD RD who's really well known in using stable isotopes and doing controlled feeding studies, particularly during pregnancy, and just broadly in human nutrition. And then I worked with a professor at the vet school, Mark Roberson. Who's a hypothalamic pituitary gonadal axis kind of guru. And broadly it kind of gave me good training in reproductive biology, both in preclinical approaches, but also clinical approaches.

Kevin Klatt:

And I try to do translational research as much as I can. I know it's always a little bit challenging. And then I did a postdoc at the Baylor college of medicine, and my first postdoc mentor moved out to UC Berkeley, which is where I'm at now. And that, that lab work is much more in nuclear receptor biology. It was half of my dissertation was on some of the stuff we'll talk about today, probably with dietary choline and its requirements in pregnancy and how it influences metabolism. And that's really relying. It was a focus on one half of the way our bodies make phosphatidylcholine through the liver through the PEMT pathway, which we can get into. And then the other half of my dissertation was on the other pathway that most, basically all nucleated cells have to make PPH lipids of phosphate choline.

Kevin Klatt:

And I focus more on lauric acid and generation of nuclear receptor ligands. So my dissertation title was some people didn't get the joke, but it was "a tale of two PCs" kind of a riff on "the tale of two cities", but really looking at, you know, I guess back in undergrad when I heard about phospholipids and phosphatidyl choline, I was like, ah, stuff that sits in membranes that, you know, some biophysicists still study and perturb and I don't really care about. And they're actually quite important reservoirs of things like omega-3 fatty acids and they're also producing nuclear receptor. Ligens probably on site. And so lots of from the choline molecule that I was initially interested in Dr. Caudill's group you know, I quickly got into nuclear receptor agonism and an avenue of nuclear or nutrigenomics and fatty acid biology there, and then also methyl transferase and methylation activity and all this kind of fun stuff that choline brings you into. So it was a fun experience, but I've had this long winding path through some clinicals, some preclinical it's been fun.

Danny Lennon:

A and much of what you just mentioned are things that we will touch on throughout this, this conversation in particular. And before we get into some of those, those details which I do wanna explore later on, maybe as like a very ground level to, to get everyone on the same page before we start, we're gonna be talking quite a bit about choline, which you've just referenced. Can you maybe get, let people know, well, what exactly is this nutrient choline that we're talking about, maybe where wemight find it? What are some of the very basic roles that we know that it, it may play? What, what's the first introduction you would tend to give people to this nutrient?

Kevin Klatt:

I would tell everyone it's a trimethyl ethanol ammonium compound <laugh> which it is, but that tells you nothing <laugh> but it is, you know, I think most people have probably heard of choline before, cause they've heard of acetylcholine. And so that's a neurotransmitter that folks I think hear about in probably early biology classes. And so that sort of puts choline on the map, but actually historically it was first isolated as a component of depending on how you look at the history, it was either found in, in

brain or bile. It was, you'll see, lethicin still being used as an emulsifier on food product labels and a component of lethicin is phosphatiylcholine. So early work, trying to discover the that they named a compound lethicin, that was basically a phospholipid lipid mixture.

Kevin Klatt:

And then ultimately could isolate choline from that. But the roles of choline then are really as supporting neuro transmission. And so acetylcholine binds both nicotinic, which are sort of ion channels and muscorenic receptors, which are G protein couple receptors that are found all throughout the neuronal physiology. And there's also a non-neuronal cholinergic system as well. And then choline is a component of phosphotidylcholine, which has all these important roles and membrane stability, both of plasma cell membrane, but also different organelles. And you know, more recently phosphotidylcholine have these other described roles like nuclear receptor agonism and those reservoirs anti acids. And so it's pretty complicated there. And then also cholines really important as a methyl donor. So it's got three methyl groups. And just because, you know, folks might have heard of methyl metabolism from thinking about folate.

Kevin Klatt:

But folate, we eat and microgram amounts. We eat a lot of it as folic acid, which doesn't come with a one carbon unit, whereas choline we're eating and milligram amounts and it comes with three methyl groups. And so choline ends up being a quantitatively, very significant source of those methyl groups in the diet. So for quickie on methyl metabolism, we're trying to thebody is trying to regenerate the universal methyl donor S-adenosylmethionine or SAM-e. You might see it in products is like SAM in all caps and then a lowercase e, but that's the universal methyl donor that's used by hundreds of methyl transferases in the body that have all sorts of roles in creating synthesis, hormone synthesis catecholemine neurotransmitter synthesis, and degradation, just like the list goes on and on and on of all the things that of all the reactions that methyltransferases can be involved in.

Kevin Klatt:

And so choline is oxidized to betaine, which ultimately partake in the re methylation of homocysteine to methionine. And then the generation of s-adenosylmethionine via a pathway that's sort of either complimentary or alternative to the folate mediated. So folate and B12 participate with methyionine synthase to regenerate homocysteine to methionine and then betaine homocystine methyl transferase is a separate enzyme that can use betaine to donate a methyl group to regenerate that homocysteine. So choline very readily supplies, a lot of the one carbon units. And from that you get links to everything from neurotransmitter synthesis, but also those are the metyl groups that are tagging CPG dinucleotides and histone proteins as well. So there's lots of interest in choline and epigenetic function and how modulates gene expression there. And then I guess the, so those are the major metabolite pools, so acetylcholine, betaine, and then phosphotidylcholine, but then there's also been recent interest because it's been known for a while that choline has metabolized to trimethylamine.

Kevin Klatt:

And so you might hear a bit called TMA. So choline's metabolized by the gut microbiota to TMA, and then it's absorbed and the liver converts it to trimethylamine oxide, but the activity of an enzyme called FMO3, and it's been, that's been known about to generate TMAO. And that's been known about for a while to, as a sort of in inborn error of metabolism or very genetic syndrome where you have lacking FMO activity and you get a buildup of TMA and it comes with like a fishy body odor. And so it's a classic

medical nutrition therapy to restrict things like choline and carnitine to reduce TMA buildup. But recently, gosh, pretty much every chronic disease pretty much has elevated TMAO. And there's lots of debates about the sort of causal role of TMAO and disease and what mechanisms, why, which it might affect disease. And we can kind of touch on that, but there's been a lot of interest in choline's health benefits, but then also like every nutrient, at some point it comes up that it might have health detriments and at what dose and what intakes the yada yada yada but the TMA link was really first with cardiovascular disease and it's kind of expanded to diabetes and chronic kidney disease. And thelist sort of goes on and on

Danny Lennon:

As a focus point to start, because we're certainly gonna mention your recently published trial, which has looked at the potential for choline alongside DHA, particularly in, in pregnancy. And this is something that on previous episodes of this podcast, regular listeners will have heard us discuss around. andit's probably more widely known generally of the benefits of DHA status andtherefore, maybe even a direct source of that during pregnancy for fetal development and a number of areas. But this connection then with choline is probably much less at least maybe recognized or even heard of before. So maybe to try and connect the dots for people. Can you maybe talk about where this potential hypothesis comes in around choline and how this is inter weaved into this story around DHA and particularly at the time of pregnancy.

Kevin Klatt:

So to time travel, if we go back to around the 1980s I guess even you can go further than that back to like the fifties, sixties time, it was recognized that there's two pathways to make phosphatidylcholine in the body. And so phosphatidylcholine, those don't know has a glycerol backbone. So three carbons, the first carbon you have, one is fatty acid esterified. The second carbon, another fatty acid esterified. And then the third carbon, you have a phosphate and then a choline as the head group. And that's just the general structure of phospholipids and that head group can change. But so phosphate choline you'll often hear as a singular, but it's actually should be said as phosphotidylcholines because that fatty acid composition really dictates the, you know, biochemical structure of that phosphate choline species. And it was in the eighties kind of in early nineties, there was experimental work to show that these pathways are not necessarily functionally redundant.

Kevin Klatt:

And so the one pathway is the CDP choline, or you might hear it called the Kennedy pathway that is possessed by nucleated cells. And this takes a choline moeity and in the cell it's, phosphorolated, it's activated to CDP choline condensed with diacylglycerides, and then you get a phosphotidylcholine from that, but the alternative pathway, which is an enzyme pathway, that's almost exclusively restricted to the liver is the PEMT pathway. And so this takes a different phospholipid phostidylethanolamine, and methylates it in a trimethylation process. And so PEMT does all three of those methylation steps. And from that you can create phosphotidylcholine. And so you often hear that called a Denovo pathway to make a choline moeity wasn't until the early nineties that people accepted the humans had a likely dietary requirement for choline because this pathway exists to make things Denovo and like everything in nutrition, you have to prove that you need it in the diet.

Kevin Klatt:

So like vitamin D, for example, we can make in our bodies and you have to, you know, there had to be deficiency, feeding studies showing that you needed some dietary level to maintain adequacy for whatever health outcome they set. And so choline, you have these two pathways to make phos choline one in kind of all cells and then one in the liver. And you get an early PEMT knockout mouse in the two thousands that sort of confirmed this, where you knock out PEMT in the whole animal's body. And one of the biggest changed factors in the circulating plasma or serum, whatever they isolated was they did fatty acid profiles on it. And you see that omega-3 fatty acids, the circulating levels in phosphatidylcholine fraction and the cholesterol ster fraction have just like plummeted that added some in vivo evidence. This the integrity of the PEMT pathway is really important for the sort of export and circulating levels of DHA or Docosahexaenoic acid.

Kevin Klatt:

That seemed to be the fat acid that took like the biggest hit. And so it's suggested there's this in vivo relevance to the PEMT pathway for likely getting omega3s out of the liver. There was also some work using those animals that in the context of pregnancy. So looking at PEMT, knockout, mice, and looking at the brain fetal brain concentrations of DHA in their offspring and noting that those were low, which sort of opened up the likelihood that there's this maternal hepatic PEMT kind of placental fetal DHA access, which is, you know, not a, not the most fluid or eloquent way to say it, but there's something, yeah, there's a lot of research in DHA happening at this time, highlighting that like feeding zero to primates and feeding zero to rodent models are compromising the alpha linolenic acid precursor intake is impairs neurocognition and whatnot.

Kevin Klatt:

So folks are accepting that DHA is important, at least some degree for brain and retinal development in the, in the fetus. And then there's big debates. So DHA is circulating in different pools within the body. So you can have it as a nonsteroid fatty acids, or just the DHA bound to albumin. You can have it as lysophosphotidylcholine DHA, bound to albumin, and then you can have it esterified phosphotidylcholine and other phospholipids, and cholesterol esters sort of circulating lipoproteins. And I think there's all, I think this is pretty accurate to say that there was a good bit of literature kind of saying that the natural insulin resistance like adipocyte level insulin resistance that occurs during pregnancy that allows for more fatty acid spill out from the adipocyte was a major source of the DHA for the fetus. And so you've got basically, it's been argued for a long time that the normal physiological insulin resistance of pregnancy is there to kind of push nutrients to the fetal compartment and support growth. And that, that spill out of lipid and free fatty acid from the adipocyte would allow for, for DHA accumulation.

Danny Lennon:

One of the aspects is that you mentioned that when we have a DHA and let's say someone consumes DHA that can then get incorporated into different physiological pools within the body. And some of those you noted, then the connection with how that's related to choline. The, a second element that you mentioned is in relation to this PT pathway. And I think one of the things that was noted, or at least as a kind of basis for the hypothesis of thetrial mentioned, maybe in a moment, is that not only is this a, an important pathway in everything we're discussing, but particularly in pregnancy, there might be an increased activity of this pathway. Can you maybe just touch onthat a bit and just really solidify for people this connection between the PEMT pathway, choline, and then DHA and how those connect together, particularly at pregnancy?

Kevin Klatt:

PEMT and pregnancy is not only you have the knockout studies that show that it's important, but that's like complete loss. So then you go to, what do we know about PEMT? And there is an estrogen response element within the promoter of the PEMT gene. And so this is a way that estrogen is able to, you know, binds the ER, the estrogen receptor, and then translocates to this region of the DNA that then recruits transcription factors and promotes the transcription of PEMT, which as its mRNA turned into protein, then you have high enzyme activity. So a major determinant PEMT enzyme activity is just the transcription of it. And so estrogen binding is super important for upregulating PEMT activity. And so this has a lot of implications for human physiology and nutritional requirements. So that estrogen binding is the underlying basis of why males, basically people with low estrogen state are much more susceptible to calling deficiency in general.

Kevin Klatt:

So you'll look at the 1991 trial that first done in humans by Steve Zeisel's group. That showed that there was, it basically fed less than 50 milligrams of calling a day to folks and saw elevations in liver functional tests, and then went on to do work. And there's some folks present with fatty liver and elevated liver, functional tests, indicative of liver damage, but then some folks present with a more of a muscle damage. And you see elevated CPK part of, I guess, theconfusion here about like "isn't choline a nutrient?" Is that like, depending on your estrogen status, you need a lot more choline or not. And I should also add into that, that postmenopausal women then are much at higher risk of choline deficiency as well. And estrogen replacement therapy influences the risk of choline deficiency, but in pregnancy that estrogen becomes really important because if you look at like first trimester pregnancy, estrogen levels longitudinally across second and third trimester, it's just a steady increase in estrogen.

Kevin Klatt:

And it's, it's almost about tenfold higher with some variability in there. And so, you know, estrogen's high in pregnancy for a lot of reasons, but one of the things that it's doing is that it is driving PEMT. Activity to produce phospholipid, but also a lot of that phospholipid is getting cleave. The choline's getting cleaved, and then that choline is heading to the fetal compartment as well. And so this is just a way for the body during pregnancy, particularly during the you know, during fetal growth takes a lot of choline, everything from the choline that you need as a phospholipid to incorporating into cell membranes, to grow a new baby, to the methylation that is being established on DNA and his stones neurotransmitters, that this is so much stuff is happening. And the choline moeity is really important. Choline's actually quite concentrated.

Kevin Klatt:

If you look at its concentrations in the fetal cord blood versus the maternal blood, there's like a five to 10 fold differential there. So the placenta's concentrating it against a gradient. And so choline super important for the fetus and the estrogen levels that increase in pregnancy allow for the body to produce a bunch of phosphotidylcholine and choline. And so just a reminder, PEMT stands for phosphel ethanolamine and methyl transferase. And so that's a methyl transferase, that's utilizing the methyl groups. And so that SAM and so choline, it has, it's kind of wonky where it, and this is like a very philosophical question I had that like, when you eat choline, choline can be phosphoralated and go through the CDB choline pathway and make PC that way. But it can also be oxidized to betaine and participate one carbon metabolism and fuel PC production through the PEMT pathway.

Kevin Klatt:

So through a much more direct route choline can make PC through the Kennedy or CDP Choline pathway, and then through a much more elongated, one carbon metabolism mediated route, you can make PC through the PEMT pathway. The question then becomes is PEMT activity potentially well, is, is one carbon metabolism and choline metabolism stressed in pregnancy? And at what intake? And does PEMT get compromised by that? So pregnancy increases PT activity, and you have to ask yourself whether PEMT's activity becomes limiting based off of the supply of one carbon units to fuel its activity. There was collectively enough evidence for us to suggest that choline is so important during pregnancy, that it's probably entry into one carbon metabolism, a slightly compromised, and we hypothesized it. If you supplemented it back, you would increase the availability of choline to support one carbon metabolism, these methyl transferase reactions, and that you would support this dramatically increased rise in PEMT. Activity that occurs during pregnancy because of that increased estrogen.

Danny Lennon:

We're going on. The presumption that DHA is important in pregnancy. This is a nutrient that is, is important. And whether that's someone taking it from the diet and or supplementation, which is often advised at this particular time, then you mention that in pregnancy, we tend to see this kind of linear increase in estrogen, maybe getting up to like tenfold higher. And with this increased estrogen, we potentially have this increased PEMT activity. And then we can hypothesize that this increase in PEMT activity could have a knock on effects. One, one of the other things that we have a suggestion could be happening that you noted is this, that choline metabolism is pushed to its limits. There's this stress on choline metabolism at this time as well. And these things collectively then could theoretically limit one's response to DHA coming in from the diet or supplementation. And so from that position, then we can set up this nice hypothesis that you had for your trial of, okay, if we add choline back in via supplementation alongside DHA, can we get this improved response to the DHA because we're taking care of all these potential issues we've mentioned in relation to increased stress on choline metabolism, potential increase in PEMT activity. And therefore, could we see a benefit? I, is that a relatively accurate overview of some of what we've discussed to this point?

Kevin Klatt:

Yeah, definitely. Good job.

Danny Lennon:

That sets the stage nicely to actually get into this trial. And there's some really nice elements to this. andI think people who are really love getting into the details will note just thehigh quality of how this trial was laid out. So in relation to the study design, do you want to introduce people to basically how you set up the trial and from an overview level, and then we can dig into details as we go.

Kevin Klatt:

Yeah. I'm glad you think it's nice because you know, when you design these trials, there's like 8 million things you want to do that you don't have the money to do. And so I guess a high level thing to note is that dietary choline intakes are below the adequate intake, which is what you would expect adequate intakes despite their name are not. Because at least there are a DRI value that is a set when there's not enough dose response data to set an estimate, average requirement, an RDA. And so coin intakes are lower than that. And then, you know, they vary per life stage and whatnot, but the average American and Western populations typically eat like 300 to 350 milligrams of choline eggs are pretty rich source of

choline, end up being a determine of where you fall. But from a nutritional perspective, I would say that compared to something like DHA, which is lipid soluble, you're retaining it in membranes.

Kevin Klatt:

There's quite variable intake in foods and conversion of ALA to DHA and how much supplements you use. And so if you recruit a random population of people with to do a DHA study, you're gonna get a huge variation of baseline status in choline we're slightly more protected in that. And that's actually, I think part of the impetus for making sure we do the trials well during this early time where you don't have a lot of choline supplementation occurring during pregnancy and choline is too big to put into prenatal vitamins. So because it's a milligram amount you'd have to knock out. Prenatals are already too big and people complain about them. And so you'd have to convince the calcium people to take out calcium and put choline in instead. And so basically background intakes are lowish. So we did screen folks based off of their choline intake just to make sure that they weren't like, you know, I "I'm on a carnivore diet and eat seven eggs a day" or something.

Kevin Klatt:

And so that allowed us to know that we can make a significant differential and even using a single dose, likely see more of an effect. Whereas if you use like a single dose of DHA and some population, you're just shifting the baseline distribution and some of the high people are gonna stay high and some of the low people are gonna get not that high and it's a whole mess. And so we randomized and we designed it to randomize people to standard of care, which would be a prenatal vitamin and a 200 milligrams of DHA omega3. And then they either got, they were either randomized with the control, which got 25 milligrams of choline, which came entirely from D-9 choline. And that was the isotope tracer that allowed us kind of track metabolism across pregnancy, or they got 550 milligrams. And so that came from 500 milligrams of choline as a water soluble salt, and then 50 milligrams of choline as the D-9 tracer.

Kevin Klatt:

We had previous data to suggest that intervening in choline with choline really late in pregnancy, like by the third trimester already was probably too late to see a big DHA effect from some post hoc analyses we did, whereas non-pregnant women with choline supplementation did see it change in DHA status. And there was some animal data that we had to maybe suggest an effect as well, if you supplemented for the entire duration of pregnancy. So we planned this to go as early as we possibly could in recruiting women and getting them into this study while also being past the window where you have sort of a spontaneous abortion. So we got gestational, we recruited gestational week 12 to 16 pregnant women got, you know, screening. So we had ada, we had a DHA screener and a choline intake screener and got all the health and demographic information.

Kevin Klatt:

And then they came in, they gave fasted blood draws and then got loaded up with their choline supplement that they were randomized into whichever group. And then they came back every eight weeks. So 12 to 16 was the baseline. A lot of them were around gestational week 15, but then so they came back either gestation week 20 to 24 or 28 to 32. And then we also got delivery blood and delivery is not, you know, a structured thing. These were natural births. And so delivery blood came at whatever time of day, which was a lot of 3:00 AM. I can talk to you about cutting up placenta at 3:00 AM and how that is not fun. But yeah, so we have these four time points, basically a baseline. And then we have three

time points where they were in the intervention. Two of them being structured, fasting visits at the metabolic research unit at Cornell and then delivery blood anddelivery.

Kevin Klatt:

We also get placenta and fetal cord blood. And I should say at the structured visits, we also got 24-hour urines as well. So we have repeated 24 hour urines across this study. We did eliminate, we wanted to get relatively healthy as representative as of the general population, as you can in Ithica, New York, which is not that much like the general population, lots of you know, relatively healthy folks. It was a predominantly white ethnicity or self-reported race. People were relatively young on the leaner side that wetried to exclude based off of like an excessively high BMI just to reduce the risk of gestational diabetes and preeclampsia development. And other than that, I think that's, that's pretty much the design.

Danny Lennon:

You, you noted that in the intervention group, the total amount of choline was 550 milligrams per day. And I think previously you've, you've just mentioned that the average intake, maybe in a us population was somewhere around 3, 3 50 milligrams per day. Something like in, in that area. And that is typically below theadequate intake. Is there a potential risks at going very high dose with, with choline andthis is probably something we'll maybe discuss later when we're talking pragmatically about what people might do with their individual choices. But is there risks that may occur at higher doses? Or what do we know about the actual dose response and safety of choline supplementation?

Kevin Klatt:

Oh, dose response. I would love for the NIH to fund dose response data don't blast us for having more than two arms. That's my little rant on the side. So the dosing, I should say that was informed by previous literature, some from Marie's group, but in, in general, everyone tries to get like at least 500 milligrams into pregnant women with the goal of the improving of infant cognition measures. And so that was asimilar this dosing scheme, mirrored, a lot of Marie's previous controlled feeding trial, at least theintake differential between the groups, although the previous controlled feeding trial was the control control, low intake arm was fed the AI, which is higher than habitual intakes. And so we have a more habitual intake group plus a doubling of that. And so Marie's previous trial did show cognitive benefits for the infants across the first year of life.

Kevin Klatt:

And so it was a safe dose to go with to try and match that intake. So we wanted to go with a dose that was known to support not only plasma choline levels, but also plasma one carbon metabolism levels that we thought was, you know, give it our best shot to increase the flux andproduction and utilization of SAM. It's there. I will say that the human studies are using a dose that is relatively safe and likely achievable. And so it's sort of a two X like usual intake and something that would be likely to occur via supplementation with choline. There is like decades of animal literature looking at maternal choline supplementation in pregnant animals, but they typically used four X of what is in C relative to the one X amount choline's thought to be relatively safe. And so the UL, so the 3,500 milligrams per day is set at the UL.

Kevin Klatt:

So choline is thought to be like relatively safe. The doses we're using are sort of a two X in animal models. They're giving up to a four X to see a lot of cognitive benefits. And I should note, that's a really interesting literature base for people who want to go into it. The cognitive benefits are not short term. They're like as you age out the animals, the effects become really pronounced and just maternal choline supplementation only during pregnancy. And really only during specific windows of pregnancy influences the whole neurocognitive aging phenotype that you see in animals afterwards. And so it's this like critical developmental window where choline supply is really influencing the SEPTA hippocampal circuitry and age related, cognitive decline. It's, it's fascinating. It's nothing you'll ever repeat in a human, unless you have an 80 year RCT. But nevertheless is really cool.

Kevin Klatt:

The TMAO thing always sits in the background here. And so if you, if you follow the TMAO literature, TMAO and prospective studies in non-pregnant humans, you know, it's associated with cardiovascular disease and there's some mechanistic work coming out that it does all sorts of bad things to dyslipidemia. And so really high choline supplementation. I think most clinicians would tell you, like, hold off until there's like a clear benefit risk ratio. And it's a, like everything in nutrition you setting policy is really hard and you're working in a, in a great degree of uncertainty, but there is from the trials that exist. There is not a risk signature for gestation diabetes or preeclampsia from like the amount of choline that we are supplementing with.

Danny Lennon:

So, so with that, let's, let's get into the results. Obviously here were primarily concerned with DHA status and you took a few different measures. Can you remember maybe talk through the main findings and main results of those different measures and what are the most significant ones to bring to people's attention?

Kevin Klatt:

So this was a very like physiological trial and like nutrition mechanism trial, but we still did the typical clinical trial thing, primary outcomes and secondary outcomes and all that kind of stuff. We had phosphatidylcholine, DHA levels in plasma. And we had phosphatidylcholine DHA levels in the red blood cell and the previous data that we had suggested that unsurprisingly the red blood cell levels were more stable. And so we powered off of that. And so we have measures of red blood cell PC DHA, and we have measures of plasma, PC DHA. And then we also wanted to add onto that to have the more robust validated markers of omega-3 status. So RBC, total DHA. And so and then our plasma total DHA. And so PC DHAs are a sub-component of the total DHA pool. And so we wanted to look at PC DHAs because we had pilot data for it.

Kevin Klatt:

But because we also think that the PT pathway is producing PC DHAs, but the definitely the PC DHA can be metabolized to other things that DHA can be liberalized and incorporated into other lipid pools. And so you capture that all those dynamic processes much better in just a total DHA measure. And so we have all of those measured, all four of those measured at all the time points including in the placenta, in the fetal cord. And so the pattern that we saw was, you know, you very rarely run descriptive statistics on your data and go, oh shit, like there's a very... like I didn't need to run stats. I was just like, oh, at the third time point in that we measured. So that was like in the third trimester at the 28 to 32 gestational week window. And I should say, as I was, I did all these analyses blinded.

Kevin Klatt:

I had no idea whether this trial would work out or not. It was very possible that you could choline give choline supplement and you would like fuel the CDP choline pathway and not the PEMT pathway and like a lower DHA status for all. I knew like that wasn't out of the realm of possibility for me. So I was blinded and had a zero in one grouping. And all I saw was that there was this dramatic difference between the groups and DHA status. And I was like, oh goodness. So I was very happy when I was unblinded to the analysis and saw that it was the choline supplementation group that at that third trimester time point when PEMT is activity is at its highest that there was a big obvious difference in the plasma PC DHA, the plasma total DHA and the red blood cell DHA.

Kevin Klatt:

There was an obvious magnitude change in the red blood cell PC DHA, which was our primary outcome. But in the models we had all the time points. So we a priority said we would include delivery time point, even though our pilot data didn't have that. And the delivery blood was just like wonky. It was very weird for red blood cell DHA, for some reason, total red blood cell DHA stayed the same between the third trimester time point and the delivery blood. But the red blood cell PC DHA levels like plummeted between the two. And so there's like adelivery. We don't know if it's like a partition stress or some weird thing that happens across the rest of the third trimester prior to delivery that DHA is getting reorganized around from different fossil lipid compartments in the red blood cell. But nevertheless, it, like if you leave the delivery data out everything, statistically lines up for the most part, with all the other outcomes.

Kevin Klatt:

But if you leave the delivery data in, and there were like outliers that were like multiple standards of deviation going in the opposite direction as themeans for all the other time points. And so just from a good trial design perspective, our primary outcome did not reach P is less than 0.05 for, but it was like P 0.1. And then when you, you know, do the post hoc things where you look at the, without the delivery time points and without the two outliers, it's like very significant and all the other measures are like very significant as well. So we still feel quite confident that like choline is influencing DHA status and the red blood cell DH total DHA, which is the major marker of red blood cell or of omega-3 status. So it's sort of the generally considered to be the most stable and it's the most well validated that was like a very consistent effect.

Kevin Klatt:

So basically the control group and the trial was started at 6% red blood cell DHA, which is pretty high. And we can talk about that which I think has some interesting points to it, but they went from basically around 6% at baseline to around 7% at study end. And at that third trimester time point with the red blood cell total DHA at which we'd expect, we gave them a DHA supplement. There's some, you know, background, dietary, DHA intake. So we weren't surprised that it went up, but the choline supplemented group, despite having similar self-reported dietary DHA intakes and got the same 200 milligram per day supplement ended up at like 7.9% DHA. So like almost a doubling of the effect. And so without changing intake, you altered metabolism to better get DHA into tissues, basically with choline supplementation.

Kevin Klatt:

And so the fasting plasma levels supported an increase in plasma, PC DHA, and total DHA, which very much supports our hypothesis that choline supplementation was fueling the export of PC DHA. And that

was increasing the total amount of DHA circulating available for tissues to uptake. And then you obviously see that reflected in the red blood cell levels as well. So it was like all the points kind of line up. We also had lipoprotein levels as well. And so total LDL increased, particularly at that third trimester time point and so consistent with supporting just hepatic lipid export as well. It's very, I should say we talked a lot about PEMT, but it, there's not there's other mechanisms that might have potentially contributed to this DHA effect, just like a greater total lipid export in general might be a factor which could also be facilitated by higher PEMT activity itself.

Kevin Klatt:

So these things are really hard to like tease out, but our icy took tracer data was also pretty consistent. There's more nuance in the interpretation of it, but we're quite confident that we increase PEMT activity. And so, and which sort of in the inverse, you can think of it as habitual choline intakes, don't support maximal PEMT activity. And you need supplementation of some amount in our study with 500 milligrams to support its full activity and the most efficient handle, or at least more efficient handling. I'm not sure if you gave higher, if you would get even higher DHA status, I kind of doubt that, but to get this more efficient DHA handling within the hepatic compartment andgreater facilitating that export and out incorporation to tissue.

Danny Lennon:

Yeah. Fascinating. So some of these findings based on something you just said towards the end, there could be very important. So you discuss that. This seems to be suggested that with, through choline supplementation and getting a higher intake than people typically have, is able to support a more efficient handling of DHA. And that is from going from the pregnant mother's liver and being able to allow that to get at least into the bloodstream and then delivered to various tissues. andas you noted in the placenta, and so it's able to support that at the same DHA intake, let's say. And so there seems to be a benefit there. And then I suppose one of the big things that people can take from that is then when we're thinking about something like the role of DHA and its importance in pregnancy, it's no longer just a consideration of DHA intake. There there's other things going on with methyl metabolism that are important to consider and much more, I suppose, questions that are probably gonna come from that that would like to be teased out.

Kevin Klatt:

Yeah. I mean, I think it puts on the map, a clear synergy between dietary coin availability and the achieved DHA status when consuming a DHA supplement. Yeah. I don't think people really appreciate a ton necessarily like the one carbon metabolism, the integrity of one carbon metabolism is a determinant of, you know, is a big determinant of what fatty acids are getting out of the liver and are available. And for these very important ones, like omega threes, it's alink that has gone relatively unappreciated. And I think like, as I reflect on the literature base in omega threes, it's like infuriating <laugh> because it has like abandoned all the first principles of nutrition science. Like you just have these trials that have like done nothing to assess baseline DHA status or background intakes, they've randomized a single dose to a pregnant population and then assess some outcomes.

Kevin Klatt:

Often the outcomes for like neurocognitive suffer like a bail scale, which is not even like an instrument tuned to detect subtle changes. It's really, there. It is like validated to detect cognitive delay, not like slightly improved cognitive benefits. And so there's not a lot of like functional outcome testing. But

basically these trials have like not really tested any real hypothesis. And this is like a big issue for the DHA world of you're intervening on DHA intake. But actually what you're trying to do is increase DHA status or tissue levels. And so much of the hypotheses coming from like epidemiology are saying like higher versus lower status is better, but then we've just sort of, willynilly recruited people with like probably variable baseline status, there's variable achieved status whether people achieved the levels associated with neurocognition is not clear. Some people had them at baseline already and had no potential to benefit.

Kevin Klatt:

Some people probably needed higher doses than what was given in the intervention to receive it. And so the literature is just like a mess and this applies to the cardiovascular disease, literature and all, but when you look at think our study ads that like part of the, one of the determinants of the achieved DHA status upon supplementation is your methyl donor supply and the activity of the PEMT pathway. And that you can definitely support that more. It means a lot, but it also, it just adds to another determinant of the achieved DHA status upon receiving a DHA supplement, which you could just measure with red blood cell DHA already. And I think it's I hope our trial adds to further impetus that the DHA literature, like supplementation, literature and pregnancy, which if you look at all the systematic reviews, they're all like no findings.

Kevin Klatt:

And it's like, well, yeah, if you don't account for background intake, you don't account for baseline status, you don't account for achieve status and all the modifiers of it, then you're probably just gonna get a hodgepodge. There's a very like explicit word I want to use, but I'm trying to think of a scientific <laugh>, but yeah, so I, our, our study basically suggests an analogous thing might be if you had a big calcium supplementation literature, and you turned out that you didn't know about vitamin D being a determinant of calcium, like a major modifier of calcium metabolism. And then you have to look on that entire literature and be like, oh, well this is actually calcium intake in the context of suboptimal vitamin D. And so we kind of, I don't wanna speak for the other authors necessarily, but the way I kind of think of it, and it's not totally analogous, there's a lot of differences between minerals andsteroid hormone vitamins. But we basically should look at the DHA literature as not only not having really tested any true hypothesis other than shifting baseline distributions of status, having intervened on DHA in the context of choline stress and likely everybody across the board because of that choline stress achieved a suboptimal DHA status at the end.

Danny Lennon:

But what is clear is that not only is there large uncertainty, but now you touched on where we are in terms of the DHA literature, this under-appreciation of choline that has, has been around for period of time. So if we were to just park some of these questions that we could ideally wanna look at and research for people who are currently listening that are dieticians health professionals who tend to work with some of the, these populations and advise on diet, what are maybe some takeaways? Is there anything that we could translate here? And again, this might be where we need to take a step away from being very conservative in, in some of these conclusions, but even if this is just something that based on a, any of the work you've done, but including this trial, is there anything you would tend to, or that you would like to see more get translated, or at least communicated to those who are working in practice that could have decisions?

Kevin Klatt:

The we're looking at like DHA outcomes here, which if you're intervening on DHA status, for whatever reason I mean, DHA itself is the cognitive stuff is wonkier, there's actually better data kind of looking at prevention of preterm birth. And so if you're trying to like up DHA status in somebody, you could consider utilizing choline in some the way we have, but I would caution that like DHA status is a metabolic outcome, and it's not that it's not important to itself, but I think it's very important to like policy member, policy makers to consider and things like that for the individual, as much as our trial is about choline DHA interactions. Choline is like, I don't want it to get lost in the sea of DHA. Like choline is quite important on its own. It, it, then the previous work that's been done that there is an increasingly robust body of evidence, although it's still mixed about choline supplementation in the general population, it's influence on infant cognition across the lifespan choline itself is important in something that should be thought about in pregnancy and pregnant, pregnant persons that are in someone's clinic might be reading the literature.

Kevin Klatt:

And I think you should have a patient-centered discussion with them about risks, potential benefits, and whether choline supplementation is something that they might want to consider. Based off of there's a large body of animal literature, there's some human trial evidence. There are not authoritative guidelines. So like the American college of obstetrics and gynecology, which recommends DHA supplementation has not said anything about choline and the American Medical Association said something kind of in passing in 2017 or so about getting choline into prenatal vitamins. I would encourage healthcare practitioners to encourage their representative societal bodies, to like do systematic reviews, look at this evidence base and make some sort of recommendation on it because it's definitely on more pregnant people's radar. And it's something that dietitians don't really have like an evidence based guidance to go off of. They have to kind of look at the individual trials and decide whether it matches their population they're working with per se.

Kevin Klatt:

And so it it's something that like, you know, you could say there needs to be like hard evidence, like super hard evidence for calling supplementation, like clear evidence of benefit, because it's like too big to fit in a prenatal supplement. You're asking somebody to take a second pill. Like we put everything in prenatals. There's no like trial data on manganese to say that it's like OUS and beneficial, but we just like throw into the prenatal vitamins cause it's small and tiny. And so choline becomes this, like there's a higher bar of evidence I think, needed to recommend taking, unlike, I guess, unlike every other nutrient, which they just put the RDA amount and the prenatal vitamin, regardless of whether there's robust trial evidence to indicate doing so we don't do that with choline just simply, because it's too big. If it was like a microgram micro yeah.

Kevin Klatt:

Microgram amount intakes needed, it would be in the prenatals. And so we have this like now very high bar of evidence. So you know, you can, there's different ways. I think healthcare practitioners can approach this. You can just try to achieve at least the AI, which most people are not consuming. The AI for pregnant persons was derived from a study done in men. So high uncertainty value there. So it's a body weight adjustment for from men down to non-pregnant women and then an additive amount of like 25 milligrams a day to support the amount of choline within the fetal compartment in placenta. And so it's like atypical almost like a nitrogen balance approach, but like a choline balance approach based

off of no functional data. And so, but that's like a, it's a relatively safe thing to be doing to say, let's work towards achieving the AI, particularly for people with very low choline intakes.

Kevin Klatt:

There is some choline epidemiology, which, you know, that's a people, the role of observational data in individual dietary planning is like hotly contested thing. But there are some evidence from neurocognitive outcomes to suggest that like, you know, quartile four of intake relative to quartile, one is associated with improved neurocognitive outcomes too. So the collective body of evidence would support kind of achieving closer to the AI and then the supplementation literature, there's three general population trials, two of which show neurocognitive benefits to the infants. But the third, which is also the largest had kind of neutral findings and two of those trials utilize a phosphotidylcholine supplement. One of them uses a choline chloride supplement. So that's a lipid soluble choline versus a water soluble choline. They have different pathways of metabolism. So you get into, this is a pretty practical factor that comes in of how do you supplement choline if you are going to supplement choline?

Kevin Klatt:

So just keep in mind, phosphate choline is only like 7 to 13% choline by weight. And so a big concern in a lot of the supplement trials that we're like trying to get 500 milligrams or so intake choline from a PC supplement is that participants would need to take like nine pills a day, depending on which brand they use. It's like quite burdensome. Whereas our choline chloride, we deliver in like a little juice cocktail of 15 ml, like a shot to take back and you can more readily because the choline salts are close for like 40 to 50% choline by weight. You can just more readily have it in a typical capsule size thing. It's like not as burdensome. The metabolic fate of those things is probably a little bit different. There's not a lot of like head-to-head comparison studies in animal models or humans, but thelipid soluble forms are a little bit different than the water soluble forms and there's debates in the literature about which should be the best to use.

Kevin Klatt:

But the animal literature that has like dozens, one of the most reproducible things in animal nutrition to maternal choline supplementation, like doing four X choline versus one X produces cognitive benefits for the infant, they're all using choline salts. And that sort of informs why we've utilized calling salts apart from just how much easier they are to deliver. I just wanna emphasize there are no authoritative guidelines. I think you'll look at the systematic reviews and they sort of say like, you know, there's suggestive evidence of benefits from maternal calling supplementation, but like a larger definitive trial is needed. And then outside of pregnancy, it gets to be even less data pretty much.

Danny Lennon:

It's interesting if you wonder around the internet for long enough, you'll see no shortage of different choline supplements, whether that's acetylcholine, alpha GPC, these are kind of commonly seen andtouted for all sorts of different things. And so it's interesting to note that there's differences that we would potentially see there, but then also the other thing you notice is a potential difference between some of the supplementation, particularly like the water soluble salt version that you used in this trial versus getting that from food. And when we're looking at any type of trial noting where we're getting that source from may lead to kind of different outcomes, is there anything you would want to add before we wrap up on any of this related from like food versus supplements or different types of

supplements, levels of confidence we can have amongst those things? Or just any uncertainty you would like to convey to people?

Kevin Klatt:

Yeah, there's, I think there's big uncertainty in equating supplements to food. I know a lot of dietician are trained in training to have this kind of like knee jerk, like food first approach and not supplements, but supplemental choline is just, it's a water soluble salt. The little data we have suggests that it's, you know, entering the portal, vein oxidized a lot to bean different kinetics and a little bit of a different metabolic fate than a PC version, which in food is mostly PC. And so not to say, to ignore dietary choline and not to maybe use that as a focus, but if you're relying on supplement evidence, then trying to back translate to food one, you're gonna be telling people to eat like four or five bags a day, which is just not sustainable. And two, it's not really an evidence based thing.

Kevin Klatt:

So it'd be great if we had a food based, you know, two egg, a day supplementation trial, looking at neurocognitive benefits, you couldn't isolate it to choline, but it would at least be a dietary approach, but we don't have any of that. So if you're, you're trying to make recommendation to folks to like, well, just up your dietary intake I don't think that is at least in line with our trial and thepredominance of the supplementation literature. I also just like, think it's interesting to throw out that like betaine is in the diet. Betaine is not a nutrient, but dietary betaine does the same thing as far as we know, as you know, when choline gets oxidized to betaine. So like betaine is a big factor that I guess more for researchers who are thinking about this and might be listening like it's in choline epidemiology, for example, betaine doesn't always get considered, but be, I would love to repeat our trial and have a betaine arm and see if betaine can do the same thing to support DHA status as choline did, because it's going to be you know, we think the mechanism is relatively the same as providing methyl groups where choline's oxided to betaine, and then partake in one carbon metabolism. You could just provide the betaine directly and similar portal, vein route of metabolism and hitting the liver. So it's possible that it's not, and that they're not bio equivalent, but I think it's kind of interesting to think about when you there's a lot of, like, you find lots of things on the internet, but there's a lot of like people being like, oh my God, like these choline trials are showing clear evidence that we've not eaten eggs and ruined babies cognition and all sorts of stuff. And like, we need to eat animal based diets and all this kind of stuff. But like there's animal evidence to suggest that at least some of the choline requirement can be alleviated by dietary betaine and plant-based diets would have more dietary betaine and so much in the same way that like beta care routine can be converted to vitamin a and sort of alleviate the requirement. betaine has some role here. We just can't really put numbers on it. And when you look at choline's association with whatever outcomes and cohort studies, you should also look at dietary betaine intake as well, because it has the metabolic potential to at least compensate for choline to some degree.

Danny Lennon:

Brilliant. first there's gonna be people that are gonna want to reach out andcontact you. No doubt. So first of all, where can they find you on the internet and social media, places like that?

Kevin Klatt:

Sure. I'm on Twitter where I talk more about science just @KCKlatt, and then I'm on Instagram and I don't really talk about much science there other than to make stupid memes as a way to <laugh>. I started during the pandemic to not go crazy in my house with all my, what I think are witty thoughts, but

you may not find them as witty. They're very niche memes. I will caution you about that, but it's an outlet for me to get my thoughts out. I'm also on the editorial board of the American Journal Clinical Nutrition as their young career editor. I host a podcast for them called AJCN In Press, which is sort of recently published articles. Author interviews gets pretty wonky. There's a little something for everyone and try and make sure that, you know, it's not all metabolism, it's not all epidemiology.

Kevin Klatt:

And so you may not be interested in every episode, but if you're a nutrition wonk, and I think the folks on Sigma nutrition radio are, you will get some like author details. I intentionally gear it towards being heavy on the rationale, the instruction and the methods, and pretty light on the results to one, stimulate you to go read the paper and look at the results yourself and get those clicks for AJCN, but also just to kind of humanize the scientific process a little bit more. We also started that during the pandemic, and I think just hearing researchers talk about their research, not constrained in the way that you are in the introduction and methods section of paper is kind of fun and freeing and, you know, just ask whatever questions come to mind.

Danny Lennon:

Fantastic. for everyone in this thing, I I'll link to all those things in the show notes this episode. So you can click through immediately and check all of that out. And with that, we come to the end of the episode. So that means I will leave you with this final question, Kevin. And it is simply if you could advise people to do one thing each day, that would have a positive impact on any area of their life. What might that one thing be?

Kevin Klatt:

Oh, is this like not evidence based? It's just my like, opinion, but like stress less about food. Like if you were at the point where you were like micromanaging, every little thing, like I can't thedetriments of that in the long run for your mental health and your relationship with food, I think are a lot more than people like weight them as, and I see this in the patients, I still do telehealth on the side and people would be like, yeah, like I spent five years, like just worrying about every little thing and diet matters and diet's super important, but that like, it's the totality of diet. That's super important. I think we come back to over and over again, and as love as I much as I love a myopic fight about like, what percentage of calories from saturated fats or what vitamin D level is like optimal.

Kevin Klatt:

Like these are all population scaled debates talking about shifting population health, relatively marginally, so that the totality is quite big. And you know, you're not gonna die from a sugar sweetened beverage or a day of high sodium intake or whatever. But the way that I think our, the like, <laugh> our, I don't wanna get too political, but like our society is very interested in selling you things and nutrition ends up being a great way to sell you lots of things with the promise of extremely magnanimous benefits, where I think a lot of researchers look on those promises and are like, okay, maybe like, even for choline, like prenatal choline supplementation might be. I think of it always in the context of like, oh my, if you didn't choline supplement during pregnancy, you didn't just like harm your baby necessarily you're. But like on a population scale, the shift in the distribution of IQ and other neurocognitive outcomes would be meaningful, would prevent X number of cases of down syndrome diagnoses, all these sorts of things that would be magnanimous on a societal scale. And on an individual level, we have like no predictive capacity to say what it means for you. And I think folks should keep that in mind as

they tailor their diets and integrate them into their social lives andthat sort of thing, because diet has become quite toxic and it, it really lines the pockets of a lot of people. And as a poor person who is not selling these things, I'm out to get those people. So, right.

Danny Lennon:

<Laugh> it, it's funny that in a, in a world where there's so many self-proclaimed nutrition experts, there's a very small number of people who I actually think fit that title and those people when, when I think of them, I I'm yet to meet one who I actually think has expertise in the area of nutrition or nutrition science that actually does micromanage their diet or stress about these things or promote peop other people doing. So it's people that I think have no real understanding of what they're talking about, tend to promote those messages. So it's an interesting kind of paradox or an irony that I think will, is probably lost on most people in, in the general population that are just not aware of this, that presume that the people that are talking about tracking everything diet wise and making every perfect decision are the ones that know what they're talking about when it's actually usually theopposite. So yeah.

Kevin Klatt:

I wanna plug the, the, these people are not just benign making money. They're actually quite harmful. And a lot of my time clinically, like at the NIH clinical center, you know, people don't get there until they failed for other trials or for other drugs and they're on a trial treatment and it's, it's quite often it's like a dire situation, you know, cancer diagnoses and whatnot that you're doing in a experimental immunotherapy for. And it's sort of a last ditch effort. The number of supplements people were on like 51 was my, my highest that I saw. But like, there is just a lot of people are selling false hope, even if they're not intentionally doing it, the exaggerated claims and the extremely conditional stuff that you see like, well, if this is true and if this is true and if this is true, then this should be true.

Kevin Klatt:

And it's like, okay, well you just did A to B to C to D to E to F and you told everyone that A goes to F and it's like, okay, now there's actually like quite a number of things that we don't know about in that pathway, whether it really works out that way. But it things that seem like benign wellness, capitalism that like rich people just spend their money on to be like, oh, maybe this will be helpful. Maybe it won't, whatever often ends up being false hope for the most vulnerable in society. And you know, we're talking about pregnant populations, which are quite protected, but anybody with any sorts of disease sees these things. And, you know, you might think it's benign to say, oh, like the diet's anti-inflammatory or whatever, but like, you know, people with rheumatoid arthritis and all sorts of autoimmune diseases are gonna see that and spend tons of money and chase down all these things and all these diets.

Kevin Klatt:

And it's often like, I see them after years of having done this. And they're like, can somebody just tell me, like, what's real, what's not real what we know what we don't know. That would be my plug for healthcare practitioners that are listening. Yes. Social media drives you to make exaggerated claims near. I understand the struggles of trying to have a business and make it all work out, but like lying to people is still against your professional ethics and you might have good intentions, but that doesn't make lies, not lies. And over exaggerating, the evidence is still a lie and your patients have a much more profound capacity than you often give them credit for to understand that we don't know everything

there's uncertainty and having a truly patient centered counseling approach is letting them know the level of impetus, medical impetus for things versus when it's just an option.

Kevin Klatt:

If you think the data is suggested, you should be very forward about this is my personal bias. I think this based off the data, but there is no guideline that says this and being much more honest with patients, I think I would, I would love to see a big tide shift, because it's not just the alternative practitioners who are making this stuff up online. We've got MDs and RD and NPs and everybody across the spectrum that like, I don't even say anymore, oh, go see a dietician because I'm just like, oh, if you do that, you're gonna type into Google. And the top hits you're gonna see are a bunch of crap. And so the everyday dietician working in the clinic is amazing and doing wonderful stuff to save lives. But the forward facing components, the profession are are very concerning to me these days. So that's my, my little diatribe <laugh>

Danny Lennon:

Yeah, man, I couldn't agree more there things that, that they're certainly not benign. And I think the people with the largest audience then are even another step removed from seeing that harm. Right. They can say things and they don't actually see the consequences of that. So they can maybe delude themselves into thinking they're not doing harm, but in reality, like you said, the harm is very real. So yeah, I very much echo that. With that we will leave it there. You've been far too kind with your time as it is Kevin. I wanna say thank you so much for taking the time to do this and for coming and talk to me about your work. I'm sure people will have got a lot from this and will probably be hitting you up with questions or comments and a ton of nice things, hopefully over the next couple of days. So thank you for doing this. I really appreciate it.

Kevin Klatt:

Cool. It's my goal to have another publication and make it back on sometime <laugh>.