Diet Doctor Podcast
with Dr. Ethan Weiss
Episode 56

Dr. Bret Scher: Welcome back to the Diet Doctor podcast. I'm your host Dr. Bret Scher. Today I am joined by Dr. Ethan Weiss and I've got to be honest this is an interview I've been looking forward to, because he's a preventive cardiologist. I can't help it; I like talking to another preventive cardiologist, especially when they're low-carb friendly preventive cardiologists. Because, let's be honest, we are kind of a rare breed.

But before we get into all the details, first Dr. Weiss... He got his medical degree and internal medicine residency from Johns Hopkins. He did his cardiology fellowship at UCSF where he is now on staff, both in a clinical role and in a research role. And I think that's something that makes him uniquely positioned to give great advice and think about things from a wonderful perspective.

Because he has that one-on-one interaction with patients... What can I do to help this patient in front of me today and now with what I know. And he has an understanding of what it takes to design these trials and run trials and do good science. And that's a big part of his message. Is sort of doing good science means separating the emotion from science. And we talk about that.

We also talk about the article he wrote with Nicola Guess about low-carb tribalism. And he has some interesting perspectives about reflecting on how he wrote that and the reception he got and how he would do things differently. I think that's very interesting. And as you'll notice as we start discussing things... this thread or this topic of LDL of course comes up multiple times. I tried to drag it out and save it for the end to get through a lot of the stuff first before we opened up. Well, it can be a can of worms, let's face it; LDL can be very controversial.

But I do appreciate his approach to it and even though everybody listening isn't going to agree with his approach or agree with his conclusions, I hope you can recognize his thought process and what he goes through to reach his conclusions and why he believes what he believes. And I think it's a lesson we can all learn, again trying to separate emotion from science. I think that's sort of the take-home message here. So I enjoy this. You can probably tell just by my enthusiasm of talking about it now. I hope you enjoy it just as well.

Dr. Ethan Weiss welcome to the Diet Doctor podcast. It's great to have you today.

Dr. Ethan Weiss: Thank you, thanks for having.

Bret: Yeah, it's my pleasure. But I've been looking forward to this for a while. I mean, in my mind you're one of the most sane and logical voices in preventive cardiology... and I almost made you

choke on your water there. Sorry about the timing of that comment... caught you off guard.

But I guess the sad thing is when it comes to nutrition, when it comes to medications, when it comes to trying to combine the worlds of healthcare and nutrition. There are a lot of voices out there on the extremes and it's sort of rare to find educated voices in the middle. I guess that's sort of how I see you. But we will see in this discussion if that's true or not. It's that how you see yourself?

Ethan: Well, I do... probably have an affinity for trying to be relatively moderate. I like to please everybody, so there's that. But I hope just to keep an open mind. I think I'm trying very hard to keep an open mind with... with all this stuff throughout my career.

Bret: Yeah, do you think that's a rarity in what you've seen from your colleagues, from Twitter, from the way you were trained... Do you think it's rare for a doctor in your position to really say I'm keeping an open mind and I want to be objective about this and admit what I don't know and explore things for their own merits?

Ethan: It's hard to quantify how rare it is. I think that people unfortunately... And look, it's hard... We have been taught for the past 20+ years to be evidence-based... And I aspire to be as evidence-based as possible. The problem is that there's a whole lot of stuff out there for which there really is no evidence basis. And then do we just ignore it?

You know, this sort of question for me has always been how did we incorporate some of these areas for which we don't have data yet or the data where the quality of it is pretty poor, how do we incorporate that and what do you do for the people...

You know, their clinical situations where I think there are really important questions that are not answered and may never be answered... We may touch and some of those later, I think we're doing our patients a disservice to just throw up our hands and say, well, there's not enough data, so we're not able to even weigh in.

Bret: I think that's such an important point. I think we're going to get into some details about that for sure. But you are a preventive cardiologist with your own practice at UCSF. You are an educator, teaching fellows and working in the hospital and the CCU and you are a researcher actually working on designing and working on research projects and publishing papers. So you sort of are a combination of three different versions of a healthcare provider and a scientist.

And I think that probably gives you a more unique perspective than many in terms of like you said the quality of the science and where the evidence exists and where it doesn't. So from that perspective, since you've seen drug trials, you prescribe medications, you take care of patients... what do you think the state of nutritional research is, the quality of nutritional research as it applies to helping that patient in front of you, having an intervention to help one person in front of you? Is it strong? Is it weak? Is it absent? Like how would you kind of qualify that?

Ethan: Well, don't think it's absent. I think it's not the strongest in the world. I think if you want to identify what is the gold standard blah-blah-blah, all would aspire and want to have to make a clinical decision, it would be something like a randomized controlled trial. And there are few of those in the nutrition world, especially when you start to look at outcomes that are so-called hard outcomes... heart attack risk or stroke or... death.

You know, there's really a small number. And partly I think that's because there hasn't been sort

of the financial incentive to pay for such studies, they are hard to do, it's very hard to untangle the specific nutrition intervention from the real world prescription and there are, you know, multiple other obstacles to doing, you know, well-done, robust and rigorous clinical trials in nutrition. It doesn't mean it can't be done.

I think they can and will be done. It's just they... we're sort of lagging there. I think a lot of the evidence basis in nutrition these days is derived from epidemiology and small sort of un-randomized and uncontrolled studies and the quality of that is... it's hard to make much of that.

Bret: But, clearly you've made some sort of a break from what we could say is the standard dogma of preventive cardiology teaching. Because, you know, I was trained in an Ornish style program and it's the low-fat plant-based diet is what is promoted most often with plenty of grains by the AHA, by most preventive cardiology societies, but you're sort of broken from that and gone more towards the higher fat lower carb versions.

So, give us a little bit of your background on how you got led down this path and why and if it was difficult to do that break from what you've been taught for so long.

Ethan: Yeah, for me it's even more complicated because not only have I sort of grew up in the era of sort of low-fat Ornish style cardiology world. My Dad is also a cardiologist, so I literally grew up in the home of somebody who bought into that, you know, like 1970s and 80s, and I always told people that we didn't just have low-fat in the home, we had no fat in the home, we had eggbeaters and margarine-- I mean everything you can think of that sort of today makes people cringe, but we had basically replaced the entire macronutrient category and what we replaced it with, of course, was carbohydrates.

So I could have almost anything as I wanted as long as it didn't have fat in it. So that's how I grew up. Now how did that change? Well, for one, I probably just became more curious, but, really where it changed was I was introduced to the folks at Virta health and I have ultimately asked to join their advisory board. And I've done that for three years.

And when I did that I, you know, came in pretty skeptical, I did a lot of reading, got to know the data as best I could and started to think, oh gosh, this story is definitely more complicated. And that was sort of the beginning of the journey for me and that was probably four years ago, five years ago.

Bret: That's so interesting. I assume they brought you in specifically to be the skeptic. That you weren't low-carb and they wanted you to be the skeptic, but then you turned into not to be the skeptic after all. You turned out to be the believer in the end.

Ethan: I don't know why they brought me, but I did give them credit for bringing me in as somebody who is not a true believer. And again I think I cringe of the concept of being ever called a true believer anything.

I mean, that is one thing I would never aspire to do, is to just become overly religious or dogmatic about anything. I tried to follow the data and follow the science the best I can. That's what I did with that experience from Virta... was, I was looking, you know, both their data and historical data and seeing that this picture that had been painted was not necessarily as it was, which happens a lot in medicine.

Bret: But, what do you think about people who have yet to sort of recognize that in fact so

stealthily believe the opposite, that no fat is still bad, carbs are still good, the whole grains are still necessary and saying otherwise is crazy? I mean is the term keto is almost like a bad word among cardiologists. So how does that react with you internally to maybe have colleagues look down on you because of that or look down on the concepts?

Ethan: Yeah, I'll just start by saying, I haven't really gotten a lot of pushback. I've gotten remarkably little pushback from my colleagues. And I do think that one of the things that is different about me from sort of the regular sort of conventional keto low-carb world is that I still, despite my very strong affinity and personal experience with it... with keto and low-carb diets, I still believe that LDL is a problem and that is an important risk factor for developing clinical cardiovascular disease.

And I do think that allowing for that has left me in a different position with my colleagues, where they might feel that some people who advocate for low-carb or keto diets do so, while rejecting the lipid hypothesis, rejecting that LDL is an important causative risk factor in cardiovascular disease. So I think that's probably part of the difference.

And in fact, I mean, so the proof is in the pudding. I mean I have developed pretty good relationships with a number of prominent plant-based or vegan cardiologists. And we have, obviously, different ways of eating, but we found a lot of common ground on the way we think about things. And I think the important overlap in sort of how we think about things is that we trust each other on some of the basic facts. Now, there are some of them out there who believe vehemently that any fat, even olive oil, even a few drops of it, are toxic and poisonous.

Bret: Right.

Ethan: I'm probably never going to see eye to eye with those people, just as I think, you know, somebody who believes that vegetables are poisonous, probably I'm never going to see eye to eye with them.

But I think we have found-- I think there is enough evidence in this mess of nutritional evidence that we all look at, there's enough evidence, I think, that they can see, that really comes down to, from their perspective, that they can see that unsaturated fats and plant-based fats, so, you know, oils and fat that come from plant-based sources mostly, seem to them to be relatively benign. And I don't know why or how this all happens, but it does seem like we actually agree more than we disagree.

Bret: Yeah, that's interesting. So you talked about not getting much pushback from colleagues. How about from your dad? Has he given you some pushback?

Ethan: Not at all. No, he and I eat very differently, but he's also almost 80 years old and chooses to eat how he wants and I don't begrudge him that. No, but I think she is very differential to me. He wasn't an echo guy during his heyday, so I would never argue with him about, you know, read on echocardiogram. And likewise, I think he is not going to argue with me about nutrition science. I mean I know him.

Bret: Makes sense. And now tell us of what are some of the-- you mentioned briefly about your personal journey with low-carb. What's changed for you when you made it personal for yourself? What did you notice?

Ethan: Well, I never really saw myself as anything other than the way I saw myself when I was 18.

It's interesting, you get up in the morning every day and look in the mirror and you look relatively the same to yourself, because the changes are happening relatively slowly. Anyone who hasn't seen you for a while might feel differently.

But, you know, as I got into my mid-and late 40s I definitely put on more weight, especially in the midsection, and I started to find... and when I get blood work done I would have an, you know, increased fasting glucose or my A1c was creeping up... And again I found ways to kind of rationalize all that and ignore it and I was busy and distracted and... you know, trying to parent two girls and keep a job and be a good husband, all the stuff that I'm supposed to do, so I was able to kind of dismiss all that.

When I started eating low-carb it was really somewhat of an accident. But the results were so profound and so fast that it was impossible to ignore... I mean, I lost-- I'm 6 feet tall and I probably at the time that I started weighed about 180 pounds. And I lost 15 pounds within five weeks. And again, I wasn't even really trying to do it. And distinct day, I remember at the end of the ski season, and I just remembered not only was I feeling better, having more energy, but I was performing better and I was able to stay out with my kids until late in the afternoon and, you know, not fall apart physically.

So I think it was really a physical transformation and the people couldn't help but notice. Like it was people came up to me and occasionally I had people say things to me or to my wife like, "Does Ethan have cancer?"... Because I lost so much weight so quickly. So, yeah, it was a pretty rapid transformation. And then, of course, you know, I got blood work done and saw improvements across the board and so for me I think it was kind of a no-brainer. And I basically... Oh, no, never go back.

And I think a lot of things have changed in sort of the way I perceive food and think about food and the rewards I get from it and how I tasted and things like that. I've now gone from probably preparing myself or, you know, having somebody in our family prepare maybe 25% to 30% of our meals a week to now at being close to sort of 80% to 90%. So it wasn't just a replacement of carbohydrates, especially refined carbohydrates with fat. It was changing the fastest food I was eating, preparing more food, spending more time-- you know, doing all the things that sort of generally make you healthier.

Bret: So, it really changed your whole relationship with food, which is so important. And now where does it rank in terms of interventions with your patients? Is it a go-to? Is it sort of something you look to put your patients on? Is it fall back when other things don't work? Like how does low-carb fit into your practice scheme? And I know every patient is different, so it's hard to summarize. I'm sort of putting you on the spot, but--

Ethan: No, it's an interesting question. And I am... I don't know if "afraid" is the right word, but I'm really acutely aware of the potential conflicts of interest that I have. You know, I have this company... So, I really want patients not to feel like I'm pedaling my latest gimmick or trying to sell them something. And so I have a lot of patients coming to see me, because of my stance and my sort of experience with low-carb.

I mean the vast majority of new patients that I see these days are coming for that reason. Historically the patients I had before, if they bring it up with me and want to introduce it, I'm more than happy to have a conversation with them. I have not been pushing it. And I think that's mostly just sort of this... you know, fear of conflict that I have that I don't want them to feel like I'm trying to

profit off of them.

Bret: Yeah, that's an interesting position. I mean if you feel like it's something that could benefit them, but you're holding back because of this fear of conflict of interest, that's sort of an interesting wrestling match within yourself I guess.

Ethan: It's a hard one. I think what I've grown to, maybe particularly over the past year, is I've grown to being able to make general recommendations to educate people around sort of the relative merits and the merits of-- So, our foods and each macronutrient class, without making a specific prescription or a specific recommendation-- Definitely, not a product recommendation.

So, I would never-- On the rare occasions, where I've actually suggested that somebody use a product that we sell I've given it to them. I wouldn't feel comfortable, I think it would be-- Personally, given where I am and sort of what I do, it would be hard for me to sell my patients a product. Now, many of them have bought it before they come to see me and that's... I can't do anything about that.

Bret: Integrity over profit. That's also something that's a little rare in the nutrition field nowadays.

Ethan: Yeah.

Bret: It's good to see though. But when it comes to I guess your version of low-carb, or your version of keto, I've heard you say that you propose-- Or you personally-- And your beliefs are more on the lower saturated fat versions. Is that an inaccurate statement?

Ethan: Yes, and... I would say... I think if you go back to the first question you asked me about sort of the evidence basis for nutrition science, I do think and I mentioned to you that there were a sort of a handful of well-done or somewhat well-done-- There are no perfect nutrition studies, but there are a handful of randomized controlled trials in nutrition science, where the outcomes are hard. And I think the majority of those, if not all of them, demonstrate benefits of the Mediterranean diet.

Now, you can argue about what do you mean about Mediterranean. And it was about really... Mediterranean wasn't really a trial of olive oil and nuts or was it even really a trial? It was retracted and then republished... I mean that are all these questions. But I do think there's something to the-- I've always been intrigued by the Mediterranean diet.

And so, what I tell people when people are saying like, how you eat, I say I do Mediterranean keto or effectively I do the Mediterranean diet, but I take out the pasta, the bread, the grains and basically replace that with, you know... the healthier fats. Like this is the way I would put it. What I consider to be healthier fats.

Bret: Yeah.

Ethan: So, yes, in net-net, I do aspire and I've had conversations with people all the time about this, including groceries with Ron Krause, who I think has made a lot of news in the last couple of months with his stands on saturated fat. And I think my goal is not to get people to eat no saturated fat.

I certainly don't think that's necessarily required. I say probably eat less than more. And so... And I hate this concept of like putting numbers on things, because I don't think even I can deal with numbers. I'm not very good at tracking anything, so I think to expect our patients to-- you know,

sort of punish them on-- -What does 10% saturated fat mean?

Bret: Right.

Ethan: What do all these different numbers mean? So for me it's all about trying to put together a sort of an average of sort of what do I typically eat and so that's how I kind of communicate with my patients.

Bret: Man, you know, I think the saturated fat question is so interesting and recently there was a Cochrane review that came out looking at RCTs, looking at the randomized controlled trials with heart outcomes for saturated fats. And what they found was there was a very slight decrease in the incidence of cardiovascular disease for eating less saturated fats, with no difference in who lived or died or who had cardiovascular mortality.

But then when you control for whether there was a change in cholesterol in response to saturated fat, then the benefit sort of went away. So it seems like at least by that study it was a direct saturated fat affecting your cholesterol. And even then it sort of in that population eating a high carbohydrate diet and a high saturated fat diet and what are the versions of saturated fats... because let's face it, we eat food, we don't eat saturated fat... so was it, you know, 6 ounces of steak or 8 ounces a steak or was it a Philly cheesesteak sandwich with the big bread?

You know, there are different-- pasta with meat... So there are different versions of saturated fat. So it seems like that... even the best data we have, it sort of weakens as you peel back the layers of the onion. Now, do you think that's sort of a fair way to look at it? Or is that overly complicated? How do you respond?

Ethan: I do think that's mostly fair. I think, you know, this is where the conversation often turns in a direction where it sort of becomes just a bunch of people yelling at each other. But I think if you could approach it in a way where-- Let me put it this way.

If I had a patient that came to me who was eating, you know, a low carbohydrate ketogenic diet, and they were eating 40% of their daily calories from saturated fat and their LDL cholesterol through whatever reasons, genetics, whatever, or if they happen to be taking drugs... and their LDL cholesterol was in a range where I would, you know, be comfortable, I'm fine with that. I don't have any problem with that. I think the point you've raised about the effect of saturated fat on LDL-cholesterol, not HDL or ApoB, it's one that's been described for ages and that relationship is real.

And I think that that is to me where this becomes the issue that if you're one of these people who does have a robust response in increasing the LDL cholesterol, and in proportion how much saturated fat you eat, then I think that can be troublesome. In fact I saw a patient just this week who had an LDL of 375. And now he came to see me... I didn't go out to see him. This was not interaction on Twitter, this was not me, you know, trying to sort of have a conversation. This was somebody who came to me and so I always start these conversations with, well you came to see me for a reason.

What was the reason? And he said, "I'm worried about this." And so, I think that's probably fair. Now, if you're going to make some sort of-- There isn't one right diet for everybody, but again I'm just telling people, the sort of the diet I aspire to eat and just for me personally what works best it's sort of more, you know, fish-- It's not that I don't need any meat; I do. I eat meat a handful of times a month. But more fish and less meat.

Bret: Well, and it's helpful to hear that with your patients is not the meat per se as long as the LDL is in an area where you're comfortable.

Ethan: That's right. I think that's fair. I think the evidence supporting the independent harm of saturated fat in the absence of effects on LDL is probably really thin and so I don't think it makes sense to sort of hone in on that point.

Bret: Okay. And I want to get into more LDL, but I guess I'm sort of purposely letting it slide and drag it along to the end here. We will finish with the Big Bang with LDL at the end and a couple more things in between. So before we dig a little deeper into the LDL... and actually this might be related... you and Nicola Guess wrote a an article about low-carb tribalism back in May.

And it was a very interesting article, basically on the one hand sort of talking about the benefits of keto and talking about the benefits of low-carb, but talking about the dangers of how we can get carried away and how we talk about it. And specifically you sort of compared it to guns and climate change and abortion and religion... And I am curious of what motivated you to write that one and what was some of the sort of response you got after writing it.

Ethan: Yeah, so just to be clear, that article, you know, got... ...portrayed as being focused on the low-carb world. That was meant to be about troubles in nutrition in general. In fact, although maybe we didn't flash out as much of it, we certainly made the same claims about the plant-based or vegan world.

That they were as extreme-- from my experience, it's definitely true that there are as many extreme opinions in that world, as there are-- if not maybe more-- in the low-carb world. I think what we are trying to do is to try and take emotion and religion out of science. I think that was one of the things that-- Frustrating to us was that it felt like we were relying not as much on data or science but more on opinions and it became very much of a team sport, that there were people who were self-identified, you know, vegans...

They put a little plant in their Twitter handle and were people who were carnivores, they put a little "c" in their Twitter handle. And it was becoming this sort of team sport. So I think the general purpose of that article was to try to get people to focus on the science and less on the sort of competition or sport of it all.

Bret: Yeah, you got a good way to say it, as a team sport. That's an interesting... I hadn't quite thought of it from that perspective. But I mean that's part of human nature. People like to be part of a team, people like to belong, people like to feel included and you find your team. That's sort of the way we teach teenagers... you find your crew where you feel comfortable and where you feel like important and validated. And that's part of human nature. But I guess what you're saying is that has no part in science. Science should not have any role there.

Ethan: Right, and I think it's actually even one step beyond that. I think that we-- Look, we talked at the beginning about what I was taught as a kid, you know, with my dad as a cardiologist-- we were all taught as young cardiologists, and how a lot of the information we were given was wrong. And the reaction to that can be, "Oh, my God, science sucks, science is terrible, science, as they are telling us, they're trying to poison us and kill us."

Or can be, "Hey, you know what? Science is about actually data." And data evolved and evidence changes and, you know-- Whereas, you know, in the 1970s and 80s we focused on the potential danger of fat and probably didn't recognize the dangers of carbohydrate. The evidence has

changed now. And people are sort of seeing things differently. I think one of the things that bothers me or bothered us and motivated us to write this was that one of the reactions to people discovering low-carb is that they then also dismiss nutrition science as being biased and poisonous.

And so I think-- Not just nutrition science, but sometimes even the whole science. And I think that particularly kind of whirrs its head with this story about cholesterol which we keep pointing back to. So, that was sort of one of the... one of the things.

Bret: Yeah, sure is the elephant in the room that's not going away. So, we'll get there. But it's interesting that... I'm glad to hear you say that it was about nutritional science. The tribalism article was about nutrition and nutritional beliefs in general. Because that's right, it's just as strong in vegan, if not stronger. And it's interesting... so if the nutritional epidemiological studies fit your narrative, then you sort of double down on how important they are.

And if they don't fit your narrative, you sort of double down on how poor they are. And I guess that's where I am. I mean I actually truly believe they're very poor studies and the quality of the study doesn't back the strength of the recommendation by the ACC, by the AAJ, by the dietary guidelines.

The nutritional epidemiological study shouldn't inform a decision of how the world should eat, but if it fits your narrative, you sort of believe that. So it's interesting how you can sort of twist the same science to sort of fit your narrative. And I guess that maybe plays into this tribalism as well.

Ethan: Well, in fact the twit that I pinned to my profile on Twitter is almost word for word what you just said. It's a quote I took from Michael Lewis who wrote The Undoing Project, which was about Amos Tversky and Dani Kahneman. And I don't remember which one of them said it, but the quote was, "This is what happens when people become attached to a theory.

They fit the evidence to the theory, rather than the theory to the evidence." And I think that's sort of what's happened in nutrition science. And again, I'm not saying it's only unique to low-carb nutrition at all. It's not, it's everywhere. And Nicola and I both agreed that that was... there was no place for that. That we should be-- We don't need to dismiss it and disparage all of the science because there were some things that changed over the decades.

Bret: Right, that's a good summary and a good sort of simplistic way to look at it. Say, look, it doesn't have to be more complicated than this other than science changes and we need to be able to change with it.

Ethan: Right, I mean the same conversations are happening these days in real time in warp speed with Covid. Everyone loves to point to the fact that Tony Fauci went on 60 Minutes in March saying that no one needs to wear a mask. And I'm sure he really regrets saying that, but does that mean that Tony Fauci is a terrible scientists or that everything he said should be dismissed, you know, out of hand?

Of course not. I mean, we all make mistakes, we all learn from mistakes and I think the mark of a great scientist is to be able to say, "I made a mistake. I now can look at data and see how I saw it wrong and we need to move on." Which is, I think, you know, back to the sort of the way I evolved into the world of low-carb myself. Was to, you know, be able to say, actually this is different than the way I used to see it.

Bret: Yeah, I think that's important. But again going back to sort of rare features in a lot of physi-

cians who've practiced a certain way for 20 or 30 years, or who've made their career on a certain way of research or, you know, a certain guidelines, it's hard to say, you know what? I now recognize the science is changing. And maybe what I've done for the past few decades was wrong. I mean that can be very challenging for people to do.

Ethan: Yeah, right, so anyway, that was the spirit. Yes, and we did get a lot of pushback and I think people focused... And in retrospect we should probably not have made these inflammatory statements about guns and politics and stuff. It was really probably an attempt to get people to pay attention and of course all they were doing was paying attention to that and they missed the greater message.

So, it's a lesson then how not to write, I think, you know, whether to do it or are we going to do it differently. But, it's interesting, you know, we're both now involved in this movement to try and find common ground in nutrition science that has people from all areas of the spectrum.

So, getting back to your quote, then, about the matching the evidence to the theory. You know, some people in the plant-based community are now saying HDL doesn't matter because frequently the diets that they recommend can lower or certainly don't raise HDL in their drug trials, showing that raising HDL doesn't help, so it fits their narrative to say HDL doesn't matter. People in the low-carb world would say, well HDL does matter if it can happen naturally.

So that's sort of if you can raise it naturally, not with drugs. And so that's sort of fitting the narrative. And then of course the same thing happens with LDL. And that's sort of the elephant in the room here that I knew we were going to get to eventually.

So the question of does LDL matter for heart disease is different than the question of is LDL causal for heart disease? Is different from the question of could there be areas where elevated LDL is not concerning? And those are three completely different questions that when you have a patient in front of you, can be kind of hard to answer, can't it?

Ethan: Sure. And HDL is even more complicated. Or maybe less complicated, I don't know. HDL is hard to talk about as well, they're both hard.

Bret: Yeah, but HDL doesn't get the attention because HDL doesn't have the drugs and the guidelines and it doesn't have the same sort of immediacy to it that LDL seems to have. So, do you think we should be focusing on HDL as much as we are on LDL?

Ethan: No.

Bret: Okay.

Ethan: Well, and I think, again, you know, following the evidence when we were coming up-- I'm probably older than you are, but when I was being trained as a medical student, resident, fellow... we were taught that LDL was, you know, bad cholesterol, that you wanted it to be as low as possible, that HDL was good cholesterol and you wanted it to be as high as possible through whatever mechanism.

At that time there were no drugs available. That would have been nice, but there was exercise and alcohol. And there was sort of this idea that if you exercise more and drink, the alcohol might raise your HDL. Now it's thought to be a good thing. And we were told to ignore triglycerides largely unless they were really elevated.

Now, mostly through the work of human geneticists, like my friend Sek Kathiresan, who now has moved on to a company, but Sek showed through really elegant Mendelian randomization studies that that was likely wrong. And this was before the drug trials. So, this was before either drug trials on HDL or triglycerides existed.

We had tons of drug trials on LDL. That's the same. So what Sek showed was that, yes, LDL looks to be causative. That is a genetic, the multiple genes controlling LDL levels are very strongly associated with risk of cardiovascular disease. That nothing changed there. But what he showed in advance of all of the HDL drug trials, was that it looked like HDL wasn't playing a role in the causal pathway, that it didn't look like genetic regulation of HDL levels had any effect on outcomes and that in fact it was the opposite, the triglycerides seemed to...

The thing we were told to ignore for all these years. So now we have drug trials showing that HDL... Multiple drug trials showing that raising HDL doesn't do anything to impact risk. And we had sort of a drug trial showing the drugs that impact the cholesterol... the triglyceride pathway may decrease risk, although that is complicated. But I think, you know, getting from what I look at the evidence I tried to assimilate evidence in all four phases...

So, for me those phases include preclinical models, basic science, right, what do we know from animal models, whatever animal model you like, through epidemiology, through human genetics, both single gene defects as well as multi-genic or polygenic diseases and then interventional drug trials.

And again the value of interventional drug trials-- and, you know, we get into this all the time, but the value for interventional drug trials, especially in prospective randomized trials, is that that is the scenario which is easiest to control the baseline population and make sure that they're matched.

In all these other trials it's much harder to do and introduces all sorts of potential bias. So that's sort of the way I look at things, you know, the four different kinds of evidence, and that's how I form my opinions today that I reserve the right to change tomorrow.

Bret: Yeah, and I think that's what makes HDL so interesting is that the whole concern of HDL started because of the observational studies that showed if you had low HDL you were at higher risk of heart disease. So, the logical conclusion is you don't want to have low HDL. Well, how can you not have low HDL is different than saying you want to have high HDL.

That you want to do things to purposely raise your HDL versus not have a low HDL. And it may sound like the same thing. Because low HDL is associated with metabolic dysfunction and type 2 diabetes and insulin resistance and other things that confer other risks. So if you can use HDL as a marker more than a causative effect, then having a lifestyle to raise HDL could still be beneficial, because you're no longer in that pool where you would be identified as a higher risk. Does that sort of make sense?

Ethan: I think it's probably much more that low HDL is a marker of high triglycerides. That those two are linked together. And that the risk we are attributing to HDL is probably a risk that should be attributed to triglycerides. That's my bias. I think HDL is an independent... It certainly is a marker, but it's probably a marker of insulin resistance and high triglycerides.

So, again if you control for insulin resistance and high triglycerides, then the effect of HDL goes away. Which is fortunate, because there happens to be a dietary intervention that's very good at

lowering triglycerides and raising HDL. Doing both, right, which is the low-carb dietary intervention. Now, in that dietary intervention the majority of the patients who are studied in the research trials do not have elevation in their LDL.

So I think the concern by most cardiologists when they hear keto or low-carb is, oh, your LDL is going to go up. No, stay away from it, because this is going to happen. But it actually likely happens in a minority of the patients, certainly based on the data we have. But it can happen.

So when it does happen and when it happens with normal HDL, with low triglycerides, when it happens with an improvement in metabolic health or, you know, reversal of metabolic syndrome and low inflammatory markers, all the things that-- I wish I had that... to put up with that diagram in the European Society of Cardiology... their article of how LDL is causal for heart disease, had like 20 different points coming in.

You know, hypertension and inflammation and glycated in products, which I think is a little humorous if you're saying it's causal, but it's still dependent on all these other interactions. So if you can control the majority of those other factors, and LDL is the one elevated abnormality, is there a spot in your brain that says, okay this could be different than all the evidence we have today and maybe does deserve a special lens to look at rather than looking at all the other populations combined.

Ethan: Yes, and it's a fantastic question and needs to be answered. But... There's the 'but'. It's not answered right now. So, then what do we do in the meantime? And in the meantime we have a choice, right? We have to wait until the experiments are done, whenever they're done. Which is going to be a while. So what do we talk patients in the meantime? And for me, personally... I put together the whole picture of evidence.

I have a hard time telling people that they should ignore HDL... sorry, LDL. I think the question of doing the net effects of low-carb diets, including weight loss, including metabolic health, insulin sensitivity, you know, HDL for whatever it's worth, lower triglycerides... all the different things that we see... lowered inflammation, you know, improved fatty liver... all these other things that we know are risk factors for cardiovascular disease. Does that actually... net out whatever potential negative effects of LDL?

That is a spectacular question. And I guess from my perspective, if you can get all of that stuff that we just talked about, that's yummy and good and great and that we all want without the rise in LDL, would you choose that for now even though we have uncertainty? And so, that's how I ended up in this sort of Mediterranean version, substituting a lot more unsaturated fats.

Because I found personally and I think, of other studies that have been done I think there's pretty strong suggestion that if you can replace, not in everybody, but in some people, if you can replace a lot of that saturated fat with unsaturated fat, you will move the LDL back down. So then you get all the benefits plus you don't have to worry about the LDL. That's sort of the way I look at it.

Bret: Yeah, I think that's interesting. And that's where is this sort of disconnect between looking at the question, looking at the evidence we have, pointing out the holes in the evidence and then saying, look, there are all these holes, but then here I am sitting across either the room or the computer from a patient and what do I do with this patient?

And I don't know that it's an automatic, you know, you have to lower your LDL or it is not automatic;

you can ignore your LDL... right? It's somewhere in between and like you said with a patient who came to you. You said, "Why are you here?" He said, "Because I am worried about this." You have to get to the beliefs of your patient sort of plays into it as well as much as the beliefs of yourself.

So it's actually good to hear you say that because I think so many doctors would do sort of like a knee-jerk that has to be taken care of as opposed to, well, let's explore other options potentially and talk about the risks and the benefits and that's harder. That's harder than writing a prescription, isn't it?

Ethan: It is and that is why when I see a patient who comes to me with this question, which happens a lot these days, I have a prepared speech. And my speech goes like this. I say, there are four things we can do with these news that your LDL is up. In response to you going on a low carbohydrate diet. Well, most of it is people say, my LDL is sort of fine, and I'm on a low-carb diet and at once it gets skyrocketed.

So I say, there are four things you can do. And I start off by saying no matter what you choose, I'm going to support you when I will see my practice. I'm not going to kick you out of my practice and reject you and tell you that I can't, you know, see you anymore if you choose to do something that may not be exactly what I would choose. But I say, by the same token, I'm going to give you what I would do without making it sound a real judgment.

But here are the four things you can do, and number one you can ignore it. You can say there's this sort of potential netting out and without the evidence it is harmful, and so until there's evidence, it is harmful. Even though there may be too... So that's one option. Option two is to take... Is to say, all right, well, maybe you don't do low carbohydrate anymore.

Maybe you decide you're going to go back to eating more carbohydrates, which I think-- You know, some people in the low-carb community discussed, as a potential way to mitigate this, is to not go completely back the other direction, but to add in some more carbohydrates in the form of berries and other... Option three would be to do what I typically do, which is to kind of trying a moderate saturated fat intake and replace that with unsaturated fats, mostly monos and omega-3 polys... So fish oils. And the fourth option is to take a drug.

And again, the drug gets the most attention in this conversation as always. Drug classes always stand. But there are other choices and for people who are uncomfortable with or can't tolerate statins, that's what they choose to want to do, I present them these options as well. So that's sort of the way I approach this clinically with patients. I will make one other editorial comment. And I run the risk of offending people, but I can say this to you.

Because I do think that there is a different world that we live in, you and I live in... When you sit in front of a patient or across a computer with the patient and have to make clinical decisions... Then it is the world when you can pontificate broadly and widely, but don't actually have to interact with patients.

I do think it's a different experience and it's not as many people want to say. It is not driven, at least in my case, by fear of a legal response. I cannot get too-- I don't want to get your podcast-- I cannot get too you know what about-- I've never been sued, knock on wood, I hope I never will be sued, but I think as long as I continue to do what I've been trying to do, which is convey to people recommendations that are based on evidence, I don't think I am going to get sued. I think for me it's about wanting to do what's right for my patients and what's best for them.

Bret: That's incredibly well said. And I agree 100% with everything you just said. And I think it's good that there are people digging in the literature and pointing out inconsistencies and bringing things to attention that previously haven't been talked about; I think that's so important. But you're right, that's very different than sitting across from a patient and needing to make a decision of what's right for this person in this moment with what we know and we don't know.

Ethan: Let me ask you this. I have a little sort of anecdotal not very well controlled experiment going among people that I interact with in the low-carb community. I tried to sort of stratify clinicians, people who are taking care of patients, and non-clinicians... Just forget whatever else they might do. And I do think that there seems to be a different approach to managing cholesterol among the clinicians. Do you share that?

Bret: A difference among the clinicians... the low-carb clinicians versus the non-clinicians... yeah. Yeah, I think that's true. And I think that's exactly because of what we're talking about. Because it's not black and white. And because you need to discuss things with the patients and see what their fears are and see what their hopes are and what their desires are. And that plays a lot into it.

And... yeah. I mean... the other thing is though what else is going on, right? Because at least in my practice I find that I get a number of people come to me and say, "I am a hyper-responder. So, my LDL is the only problem, right?" But then they have a high LP(a) or their inflammatory markers are still high and they have, you know, a chronic autoimmune condition or something, or something else that muddies the picture.

So maybe we see a lot of epic expenses that aren't so cut and dried either. I think that's important to not just boil it down to that the one thing and that's it, but really look at the whole picture and all the other risk factors. Because you look at the ACVD calculator - there's no LP(a) in there, there's no CRP in there.

There's a lot of things that aren't incorporated in that calculator that we should be incorporating in the cardiovascular risk. And this is a situations no different than that.

Ethan: True, although I guess in theory you capture LP(a) in the HDL fraction, but yes, you're right, there's no information there. There's no family history...

Bret: Right.

Ethan: ...which is also interesting.

Bret: Right, that's interesting as well. I think that's a good perspective. And some people in the low-carb community obviously give you a very hard time for having that perspective. But I think it's perfectly reasonable and so much better than the perspectives of people who won't even listen to it and won't even open their eyes to the potential that there's something different about this situation.

Ethan: I guess what I don't understand is why you in order to sort of believe in the benefits of the low carbohydrate nutrition, you're also forced to dismiss the role of LDL in the pathogenesis of coronary disease. That's what I've never understood. Is why are these two things getting together. I think I understand psychologically or sociologically how that happened, but I don't understand when you're just sitting here, you know, having a conversation, why the two have to be linked together.

Bret: Yeah, it's interesting. I think part of is that narrative that we were talking about. You want

to fit your narrative. But also to be low-carb you sort of have to question the norm. You have to question the authority of what we've been taught for the past 30 years. So if you question in one area, you likely question in other areas too.

So I think it's the personality of the people who are drawn to this way of living, that makes you a little controversial... or contrarian I guess I should say. But as you said we sort of don't know and it's a great question that needs to be studied. Now you are a researcher. You know the ins and outs of health research, nutrition research. Can this really be studied? Can we prove this to the point or investigate it well enough to appease people on both sides that it has been studied? What do you think the chances are?

Ethan: Yeah, of course, it can be done. It will require a lot of resources. I mean we're looking at doing some trials, not in coronary disease, but in other areas in cardiology that keto is going to sponsor. That I think are really exciting and potentially practice changing. So, I think it can be done.

That is an area of medicine that is notoriously difficult to study in clinical trials because of the events that link to the trials and the power that you need, the ability to detect meaningful difference. So, we know from drug trials that these are thousands of patient trials, which I think it's going to take an enormous mobilization of resources to be able to do that.

But I certainly do think it can be done. I think the threat is, as you described, that there could be a bad outcome. That to me is sort of more theoretical and would potentially obviously be, you know, devastating, but it's probably a long ways away before we have something real that we can hang our hat on. When I'm talking about threat, I am talking about sort of going back to-- I guess the very last talk I gave at a meeting before Covid, was in February.

I went to DC and gave a talk at CRT, which is an interventional cardiology conference. It was organized by Kim Williams, who is a very prominent vegan cardiologist. His also very prominent in the American College of Cardiology. He's an old-timer, he and I had gotten into some things on Twitter before, because he's usually involved in writing guidelines and he's been very unfriendly to keto. But he invited me to come give a talk on low carbohydrate nutrition at CRT, a session that he organized and moderated. I was the only--

Bret: That's impressive.

Ethan: Not only was I the only low-carb doctor there, I was the only non-vegan among the group. There were like 10 vegans and me. And I have no idea what the audience makeup was, but I imagine it was a little bit more balanced. But it went incredibly well. And I think what they saw was... it was somewhat demystifying and making keto less scary, because to them keto is about eating slabs of bacon and whole cows and everything else.

And once they could see that there is a way to do keto that was maybe not exactly how they would eat, but in their sort of mind a little cleaner I think it became a little much less threatening to them. And this is a group of people who like lobby Congress to try and block keto studying. I mean this a group of people who have been historically very unfriendly to keto.

So I think we were able to find a common ground, a middle ground, where they saw this is not only not threatening, but also potentially something useful. And again what I did was focus on the data and focus on shared areas of belief. And one of those areas of shared belief was obviously over the role of... certainly in cardiovascular disease. So it did change.

Bret: Right.

Ethan: And again I think you asked me early on about my colleagues. My colleagues, I think, are very open to all this, because I think they know that I have not lost all my marbles. And so I think they trust that this is something that I thought a lot about and again making the most informed decision I can with the data we have.

Bret: Right, so first of all that was incredibly brave of you to step into the lions' den like that, you and the panel of 10 vegans... that could be intimidating. So kudos to you for taking it on and stepping up. But, secondly, that makes sense. So when you talk about the danger of LDL it's more of the... if mainstream doctors or contemporary doctors see keto as necessarily giving up on LDL or ignoring LDL and don't ever even consider it, yeah. So you have to separate those two for it to become more adopted.

Ethan: That's right, and if you do that and you make it less scary, then it becomes an option, it becomes a viable option. It's not something that these folks would generally do for ethical reasons. Most of them. But they didn't see it as, you know, heresy and evil as I think they might have before. And I've become pretty good friends with a bunch of them. And I think, again, comes back to the same idea that we share more in common than not. And really what I tell them is that I'm a vegan, but I eat fish... and occasionally have some animal meat. But basically our diets are not that different.

Bret: Well, you know, the old story that eating meat is basically being vegan, because the cows turn the grass into proteins. So you're eating the "protein-ified" grass. That makes a lot of sense. Well, I know we've covered a lot more coming up on the hour. We didn't even get to your Covid experience. How you flew from San Francisco to New York specifically to serve on a Covid ward as a volunteer to help out. That must... and you've written about it, I encourage people to read about that.

And your experience with your daughter as well... You had a very well-written piece of should broken genes be fixed about that with... And I guess I'm lamenting here that we didn't get to cover these, but you want to make any sub-comments about either of these two topics? Pick one to sort of summarize your experience and what you think people can learn from your experiences?

Ethan: Sure, I think the story of my daughter is a great story and I think it has implications for all of us, maybe it's changed the way I think about things as a scientist in addition to how I think about things as a parent. But I think the main issue with Ruthie, so my younger daughter who is going to be 14 in a week or so, she has oculocutaneous albinism... So the colloquial term with that is that she is an albino.

People prefer not to use that terminology. So she's a person with albinism. And so, as you know, the main issue with that is that her vision is very impaired. She's legally blind. For people who don't understand what that means, her visual acuity is 20/200. But she is a kid who sort of makes the most of what she has and kind of doesn't know the word 'no' and is very active, and plays basketball, and skis, and does all those other stuff.

The thing that was sort of a revelation for us was this was a kid that we didn't want to have, right? This was a kid that if we had been given the opportunity to not have or to have without this mutation, what she carries around, we would've chosen that. And I think the sort of learning that I had was that that would've deprived the world of something important.

And then her impact on us, you know, here on our family, but on the community, on the peers... And hopefully, something in the world has been dramatic and positive... And, you know, more importantly-- obviously, no parent wants their child to suffer, but when you ask Ruthie, you know, sort if you can go back in time and unwind everything and edit out these gene and fix it and not have albinism, would you do that?

She's very consistently since the age of nine when I first asked her that question, she said no and continues to say that today. Now, she may change her mind and I have said, and again and again until I die, that if she comes to me someday and says, Dad, I don't want this, I want to be able to see normally... Can we explore an option... to use CRISPR or some other gene editing technology to try and fix this? I'll say, of course.

So, I'm not fundamentally opposed to her... you know, someday deciding that she wants to be able to overcome this diversity in another way, but as of now at least in her 14 years on this planet, I think she is more thrived... You know, almost because of her difference and because of her disability that she has, in spite of that, she's pretty special kid. Obviously she has a big impact on our family. Changes the way I think about a lot of things.

Bret: Yeah, big impact on your family and a big impact on probably just about everybody she meets and everybody's lives she touches.

Ethan: Yeah, and of course the question we all ask again and again, or I ask, because I like to think about these kinds of philosophical things, is would she have that impact if she didn't have this difference?

Bret: Yeah.

Ethan: Like it's an experiment you could never do. Is this just the force of her personality? Is she just this kind of person who would otherwise be this impactful or is it because of this difference? We will never know, but we like having her the way she is. It's been a really interesting experience for me, especially as a scientist and somebody who thinks of lot about genetics and gene editing and all these other things...

It's been kind of an interesting ride to come through this on the other side, sort of as a parent on a loved one, as opposed to a scientist or even a clinician.

Bret: Right, I found it on your Twitter feed. I don't know, is there somewhere you can direct people who want to read more about this? Because it's such a great human piece to read. Where can people go to read that specific piece?

Ethan: The original article that I wrote was for a medical journal that I think was called Perspective in Biomedicine... I'll send you the link. But the title of the article actually... Billy Idol. Which is the nickname that we gave to her when she was born, because she had white hair.

Bret: With the white hair.

Ethan: And I bet if you just google my name and Billy Idol, you'll see the link to this article come up. And that's a longer version of the article that was published in STAT news. And actually she's got quite a lot of press attention. She was... You know, a documentary film... And yeah, there's a lot there. She was recently quoted in a New York Times story about gene editing.

Bret: Great, that's wonderful. And I mentioned your Twitter feed. I mean, I highly recommend

anybody listening who is interested to follow your Twitter feed... It's a great feed. You get a little bit of sports, but not so much sports lately, you get a lot about medicine, and nutrition, and research, and then a lot of just about what's going on with the world and some really good perspectives. So I highly recommend Twitter... So what's your Twitter handle where people can find you?

Ethan: Thank you, that's very kind. It's @ethanjweiss So, it's my first name, my initial and last name. So, ethanjweiss.

Bret: And then where else can you direct people to kind of learn more about you?

Ethan: I mean, I guess you can... I mean, that's probably the best place... If you want to look at my academic, you know, homepage, you can just google me and say UCSF and that will come up and on there is all my contact information.

People don't have a hard time finding me, you know, my full number and email and everything... is pretty easy to dig up. So if anyone wants to find me, I'm not hard to... My DM's are open on Twitter. I don't spend much time on Instagram or other social media. It's hard enough to manage one, so it's kind of my go-to.

Bret: Great, well Twitter it is. Well, I can happily say you confirmed my suspicions that you are a wonderful person to talk to. I really enjoy your perspective on things, I really like how you see things in a balanced way and go back to the evidence and try and take the emotion out of it. So you confirmed all my suspicions, so congratulations.

Ethan: That's dangerous, Bret, but thank you very much.

Bret: Thanks for joining us, have a good day.

Ethan: Thank you.