Younger You - Aging is Optional

Heather Sandison, N.D. interviewing Kara Fitzgerald, ND, IFMCP

Heather Sandison, N.D.
Welcome to this episode of the Reverse Alzheimer's Summit. I'm so excited to introduce you to my friend and colleague, Dr. Kara Fitzgerald. She's the first-ever recipient of the Emerging Leadership Award from the Personalized Lifestyle Medicine Institute in recognition of her work on DNA methylation. She received her doctorate in naturopathic medicine from the National University of Natural Medicine. She lectures globally on functional medicine, is on the faculty of the Institute for Functional Medicine, and is an IFM Certified Practitioner with a clinical practice in Newtown, Connecticut. She runs a functional medicine clinic immersion program for professionals and hosts the podcast "New Frontiers in Functional Medicine." Dr. Fitzgerald is also actively engaged in clinical research on the DNA methylome using a diet and lifestyle intervention developed in her practice. Her first study was published in the journal "Aging." She's published a consumer book, "Younger You" and an application-based program, 3YY, based on that study. She lives with her daughter in Connecticut. Kara, welcome.

Kara Fitzgerald, ND, IFMCP
It's great to be here with you, Heather. I can't wait to dive in.

Heather Sandison, N.D.
I know. So I was telling you as I was reading through your materials, I was just so excited to see that one of the things that you suggest to help with aging is cuddling.

Kara Fitzgerald, ND, IFMCP
Yeah.

Heather Sandison, N.D.
Tell me where that comes from. It surprised me and it brought a smile to my face. And I was telling you that it's one of the things that I recommend to my patients. So tell me how it ended up on your list of lifestyle practices.

Kara Fitzgerald, ND, IFMCP
So I love to sort of joke about how we didn't include cuddling as one of the variables that we measured in our study. I mean, it's really funny 'cause we did a randomized controlled trial. So group A, no cuddling. No cuddling for eight weeks and then group B, you guys need to cuddle in this structured, measurable way. I just find that so funny. But, no, so we didn't research it, but two things that we thought in hindsight and actually in our app that you mentioned will bring some of these things in are community, the importance of community in longevity that's been demonstrated clearly, and cuddling. Like both of them are huge. And so we're building this community component into the app. And our app is actually, we're continuing to research our program and as I'm suggesting here, refining it. So cuddling has longevity-promoting features to it beyond what I'll be able to say. I mean, we could write a whole book on it I think. But the two top things that come to my mind are cuddling and the decrease in glucocorticoid, so the decrease in stress hormone. Sort of the balancing of this hyper type A driven sort of affect, you can wind back with some cuddling, with some connection.

And it doesn't have to be a human, a spouse, a significant other. It can be a pet. It can be just a loved one of any shape or form. So on the clock that we used in our study, the 2013 Horvath Biological Age Clock, I know we're gonna talk about this in a minute and define it but it measures how fast our bodies are aging, our biological age. A full 25% of this clock is influenced by glucocorticoid response. And for me as I wrote in the book, it's like stress is gasoline on the fire of aging. And that is just one example. Like, this clock is locked into the stress response. There's no other variable that shows up with that extent of involvement in the aging clock. Stress is just a big player. And then we can look at stress across the board. Early life stress, stress changes that can be inherited across generations. And you can see that they just promote aging and they promote all of the chronic diseases of aging including Alzheimer's and dementia. So the stress phenomena is massive. And anything we can do to change that is extremely important. And we

can change it at the level of gene expression. The other piece with cuddling which I know you likely tell your patients is the whole oxytocin release. And oxytocin is a longevity hormone. And so we've seen there are studies showing an oxytocin association with longevity like with more muscle mass and with important components of healthy longevity, health span and life span. There are certain conditions that can be associated with hypermethylation of the oxytocin receptor. So what that means in plain English is that we don't get a oxytocin response in the same way we should. So it's not a genetic mutation of the oxytocin gene, but the gene is inhibited at the level of epigenetics which again we're gonna define again. So our thinking is that employing components of the study that we're gonna dive into could help, I shouldn't say will, but could help shift methylation of the all import oxytocin hormone, the feel good hormone. So for that reason I think cuddling would have been a nice variable to measure in our study but not realistic. Yeah, we can't control for it though.

Heather Sandison, N.D.
So you describe basically two different types of aging. So I think in our minds most of us go into this aging topic. Like when we're thinking about getting older and think, oh, there's nothing we can do about it. I've been on this planet for this many years and that's just the way it is, I can't go back and be any younger. But your book is called "Younger You." So tell us what you mean by that and go into the differences between biological age and chronological age.

Kara Fitzgerald, ND, IFMCP
Sure, yeah, absolutely. So chronological age is the number of birthdays we've celebrated, the number of trips around the sun. And despite the fact that my sister says every year that she's 29 again she in fact is not. We can't change our chronological age and scientists really today say it's not the most important number by a long shot. Your chronological age is not your your destiny, your health destiny. It doesn't speak to how long and well you're going to live. It's your biological age or how fast your body is actually aging that's where the rubber meets the road. We've all seen people who are the same age as our ourselves and they don't look like us. Either they look a whole lot older and a lot more damaged perhaps or just a lot of changes of aging are present on them or perhaps they look wildly young and amazingly youthful and are living in a really powerful space. These people clearly demonstrate different biological ages. And what's pretty cool about science these days is that we're able to measure with increasing reliability this process, this biological age. And I would imagine in the not so distant future, this is a number we're all going to know. You go and you get your chem screen or your CBC, you're gonna also get

your biological age, you're gonna probably care more. It's gonna have more meaning for you that you're 50 but your bio age is 40. I mean, you're doing things right. And so you'll have this tool to base some of your life choices and the plan you might design with your physician on. I think it will just become standard of care. In fact, probably at some point we'll have wearables, like I've got my Oura ring on that might give us snap shots into bio age and what's good for us in the immediate. I think that's probably where we're headed and I think it'll be really exciting. So biological age measures how fast our body is aging. The way that that is done is by looking at gene expression and this is called the field of epigenetics. So epi above genetics the gene. So we're not looking at our genetics, we're not looking at our DNA, but we're looking at the biochemical marks that regulate what genes are on and what genes are off. And let me just stop there Heather and see if you've got any defining questions in that.

Heather Sandison, N.D.
Yeah. Well, I think what I wanted to talk a little bit more about is unraveling how we measure this, right? So we know how to measure our biological age, we count the trips around the sun, celebrate each year, and then hopefully, and then when we talk about sorry, that's chronological age, I'm saying the biological. Now, biological age. So I think there's still some discussion in the field if I understand it correctly that DNA methylation is one way to look at that, but like telomeres were very popular for a long time as another way to look at that. And I think there's several other ways that we can asses like how old our system is. But why did you choose DNA methylation? And then please describe the Horvath clock and who he is. And give us a little bit of context about how we're measuring this.

Kara Fitzgerald, ND, IFMCP
Sure. So telomeres are sort of looking at the caps of DNA and these predictably get shorter after cell division, cell division after cell division after cell division and they've been associated with aging. They've been demonstrated to not be as reliable as we once thought. In fact, you can actually measure telomere changes using DNA methylation patterns. So you can look at the telomere genes and look at methylation patterns on that specific telomere gene and have a more reliable tool of what's happening at the level of telomeres. So it's just kind of interesting. But DNA methylation, biological age clocks have supplanted I think telomeres. Although it doesn't mean that we're throwing them out. Likely they will be a useful biomarker and we're just kind of rethinking whether or not they are the biological age tool we once thought that they were. Especially interestingly enough that you can get a better job looking at the methylation

pattern on the telomere gene versus looking at telomeres directly. So I think there's just changes upfront. This is a rapidly, rapidly evolving field. I should actually say that. Like, the clock that we used in our study is the flagship 2013 clock. And we're up to three generations later. So we used a first-generation clock and we're already up to third-generation clock. So it's such an evolving field. There are biomarker collections that different scientists have pulled together to look at like standard biomarkers, and describe these as biological age clocks as well. I don't know that they're... I think that they're useful and I think that they're important. I can say specifically, standard biomarkers used in an AI model, so plugged into artificial intelligence and sort of crunched with chronological age formed the basis of a methylation clock. So again, using these bio age markers plus chronological age, were used to train a DNA methylation clock called the PhenoAge clock. But this DNA methylation clock actually outperformed these biomarkers. So it was more predictive of health span and lifespan, morbidity and mortality. So isn't that fascinating?

Heather Sandison, N.D.
Yeah, and so the other thing it's like, what exactly does this biological age mean? Is it the length of time between now and when we're predicted to die or when we're predicted to have illness?

Kara Fitzgerald, ND, IFMCP
Good question. So yes to both of those, and it depends on what clock you're using. So for instance, there's a clock called GrimAge and just as the name implies, it's predictive of time of death amazingly enough. So whereas the PhenoAge as the name implies phenotype, this is more predictive of morbidity. So health span and the robustness or lack thereof of health span. Whereas the Horvath clock that we used in our original study is trained against chronological age. So it is much more correlative of chronological age than telomeres, like far more reliable. But it's not a one-to-one relationship. So if it were 100% predictive of chronological age, it would only be useful for that. So there's this wiggle room within this clock that actually is more predictive of morbidity and mortality than your actual chronological age. Does that all make sense?

Heather Sandison, N.D.
Yeah.

Kara Fitzgerald, ND, IFMCP
And we're now looking at clocks that will measure age of various tissue like brain, mitochondria, immune system. So it's an extraordinarily rapid, evolving and interesting field. So as we're into our second study, we are using a next generation clock that's more predictive of health span. So it's a little bit more malleable than the Horvath clock that we used in our original study.

Heather Sandison, N.D.
So I wanna go into the design of your study and what people can be doing like today to reduce their biological age. But before we go there, I wanna just talk about kind of like setting the context. You're looking into aging. And because for so long we've accepted aging as inevitable and something we really can't do anything about, there hasn't been a whole lot of emphasis on it. And yet dementia and aging have this huge intersection, right? The National Institutes on Aging, we've heard of one of the institutes out of the NIH, the National Institute for Health, 2/3 of their budget goes into Alzheimer's and dementia. I mean, this is just a radical number of dollars that are being spent on understanding dementia. And yet, does 2/3 of aging mean dementia? Not really, right? And like the overlap it's like maybe if what we were looking at was aging, then by default, we would be preventing dementia.

Kara Fitzgerald, ND, IFMCP
Exactly. Yeah, that's right.

Heather Sandison, N.D.
Yeah, I'm glad you agree. Because I'm kinda like, I think this is backwards we are like we're looking at the final steps instead of looking at like what-

Kara Fitzgerald, ND, IFMCP
The number one, the root cause, right? The root cause of dementia is aging.

Heather Sandison, N.D.
doctor.

Kara Fitzgerald, ND, IFMCP
I mean, really, the root cause of dementia, Alzheimer, cancer, diabetes, cardiovascular disease, the root cause of these is aging. In fact, a really interesting and crazy statistic but it kinda gives

perspective, is that what's the bigger risk factor for lung cancer? Let me ask you, pop question. What's the bigger risk factor, smoking or aging?

Heather Sandison, N.D.
Well, I have to say aging now, but I would have said smoking years ago.

Kara Fitzgerald, ND, IFMCP
100% smoking. Yeah, of course. Yeah, no, it's aging, it's aging. So the breakdown of the lung tissue over the lung haul increases vulnerability to lung cancer more so, more profoundly than smoking itself. Yeah, I 100% agree with you and I think that the paradigm is changing. So now that we're starting to build these rather extraordinary tools to be able to measure aging we can begin, and they're sensitive, 'cause otherwise you can't really research aging in humans because we live a long time. I mean, it's just prohibitive to be able to pull together reliable studies, we just can't get them. But now that we've got this building, this suite of surrogate markers for aging, these clocks. And they're really more than surrogate markers so I wanna circle back to that. Aging appears to actually happen at the level of gene expression. So, again, going back to root cause of aging, it may just be sitting right there in the epigenome and I'm gonna park that put a pin in it and we can come back to it.

Heather Sandison, N.D.
Well, and you just mentioned, it's hard to measure this in humans because we live so long. And so we'd have to be waiting decades to get--

Kara Fitzgerald, ND, IFMCP
Yes. So we need life measures so we can do reasonable length studies. That's right.

Heather Sandison, N.D.
But there's a lot of information that comes out of labs like David Sinclairs where they're looking at yeast and mice and other things that procreate quicker and die quicker and age faster. And those things can be applied at some level to what's going on in humans.

Kara Fitzgerald, ND, IFMCP
Yes, you can definitely translate some of it to an extent, but we need to... You can't 100% translate it. Like there's just no way. And we shouldn't kid ourselves to say that we can look at the

rapamycin data or some of the other really impressive data or the Yamanaka factor data and say, oh, yeah, we can do that in humans. No way. You can't translate that into humans at this point and time. Those are preclinical studies.

Heather Sandison, N.D.
Okay, so let's try and have a clinical study.

Kara Fitzgerald, ND, IFMCP
But we have learned a lot, I wanna say that we have learned a lot though from those guys and going to Sinclair's lab in particular, they've shown that aging happens in the epigenome and specifically I think in DNA methylation and demethylation. So they've driven aging forward in an animal model via disordered epigenetics. And then they've reversed it using something called Yamanaka factors which are transcription factors. So these guys turn on, they change gene expression. And so they alter epigenetics these transcription factors. So what they're starting to show is that aging is happening in the epigenome and I just think it's profound. We've had these ideas that aging is increased free radical activity, increased exposure to toxins. Like it's just breakdown of our ability to efficiently fold protein, it's damage to DNA, it's more mutations. Like we have all these pillars or hallmarks of aging, but we're starting to see that perhaps up above these downstream effects is this change to gene expression. So, we've got these clocks that are measuring changes to gene expression and they're doing that specifically via DNA methylation. But in fact, maybe these clocks are more than just a surrogate marker of aging, maybe these clocks are reflective of aging. We don't know that answer and it's probably beyond just the clocks. But it's ridiculously compelling that this might be like root. I just think it's extraordinary. It's so interesting.

Heather Sandison, N.D.
So fascinating, such exciting stuff. So tell us why you designed your trial. How many people were in it? What did they do?

Kara Fitzgerald, ND, IFMCP
Yeah. I wanna just give you a little bit of the backstory because I think it's just interesting. Like how the heck did I end up designing a methylation diet and lifestyle study or program. Back in 2016 we published an ebook on the methylation diet lifestyle. This was before any human trials looking at biological age clocks had ever come to pass. And it was before understanding what

we do from Sinclair's lab, we started to think about it in about 2013, I was reading the literature on cancer epigenetics. And it was a game changer for me as a physician in clinical practice. So cancer takes over, cancer hijacks epigenetic expression. So it takes over gene expression very efficiently, the tumor microenvironment takes over from us what genes are on and off to drive its own life. So it turns off genes that protect us from cancer, it turns on genes that cause cancer. That's what happens. That's been very well defined. And that was our entry into that. And I wanna say that these change, this abnormal gene expression phenomena that's been so well defined in cancer, appears to be happening in the other chronic diseases. So you see this abnormal change happening at the level of genetic expression. I didn't know this back in 2013, I was simply aware of what was happening in cancer.

And it occurred to me so we're seeing increased and decreased methylation. What they call in science, aberrant methylation, aberrant DNA, abnormal DNA methylation is happening. Some genes are way on and that means they don't have a lot of methylation groups on them. Because the methyl groups block gene expression, just think of them as a bunch of cars parked in the parking lot, you can't get out. So when they sit on the gene the gene is not able to open and be transcribed. Or conversely there's no methyl groups or very few, then that gene can be opened up and turned on. So I was looking at it through the lens of cancer and decided that well, in reading the literature and it was apparent to me that the safest way that we could move forward with this information in functional medicine where we're thinking about methylation all the time, we're measuring homocysteine and other intermediates in the methylation cycle. We're giving loads of B vitamins and choline and batten and so on and so forth.

Like we are very savvy around methylation. And it occurred to me that the safest way to do this given the research on cancer would be through a diet. You can bathe the body in methyl donor rich foods. So folate rich foods, choline, B12, and so forth. All of these nutrients you can within the food matrix, within a whole food diet, you can just load them on and there is no negative outcome there. In fact, they're protective, there's no study out there showing that greens cause cancer. So we started this program anchored in diet and then we expanded from there and saw the influence of exercise, of quality sleep, of meditation. All of these sort of upstream influences on DNA methylation as well. So we're moving outside of manipulating the methylation cycle itself to variables that are upstream and influencing favorably methylation. The other piece of information that we learned that was a huge aha for me was phytochemicals. Plant polyphenols seem to drive traffic of where methylation happens on DNA. And our study appears to

corroborate that. So our participants DNA was rearranged in such a way as to, DNA expression, excuse me. So their methylation patterns were rearranged in such a way as to appear younger. So we didn't net increase methylation in our participants. We did measure that and there was no net increase in methylation, but there was a rearrangement of gene expression towards a more youthful pattern. Which to me is extraordinary. So we poured in the methyl donors and we gave all of these plant chemicals to sort of direct where it was happening, at least that's my hypothesis. That's what I think happened. And then on top of that exercise, which really kind of acts like a phytochemical, it sort of acts like a polyphenols. When you look at DNA expression and DNA methylation exercise is amazing. But taken all together we sort of rearranged towards a more youthful pattern.

Heather Sandison, N.D.
So how did you design the trial? What did it look like?

Kara Fitzgerald, ND, IFMCP
Yeah. So, I'm jumping around a little bit. So this is what we created in our office. And we used it for quite a few years. We anticipated we were changing gene expression. We wanted to study it though. But at that time there were and still really to this day, we don't have access to a lot of assays, at that time there were none available to us in clinical practice where we could measure DNA methylation. And we were given an unrestricted grant through Metagenics. They covered the funding of our study without dictating either ownership of the findings or the design, which is extraordinary. And I'm just beyond deeply grateful to them as a company and to Brent Eck their visionary CEO for supporting us. I mean, these were many conversations that I had with Brent on what I was learning and he was as riveted by it as I was.

So he allowed us to study it. We did it through Research Institute. I don't know where you went to school, but it's my alma mater, National University of Natural Medicine. Ryan Bradley is the director there and they're just a great clinical research center. I mean, they're just really doing top tier work and I'm so thrilled. It was Brent Eck's idea for Metagenics that we work with Ryan and team over there. And I couldn't be happier. I think they designed a really highly quality study for us. The intervention was eight weeks. So again, diet, a modest exercise prescription, nothing too crazy, 30 minutes, minimum five days a week, a perceived exertion of 60 to 80% of max. So this could be walking, this could be gardening. This could be a little an easy bike ride, et cetera, nothing too crazy. And that was by design. We wanted people to be sleeping well and so we

supported them with sleep hygiene chips, et cetera. A basic meditation program, we wanted them to do twice daily, a minimum of 10 minutes twice per day using "The Relaxation Response" by Herbert Benson. This is a tool that's been used in many trials over the years. What else did we do with them? They took a probiotic, lactobacillus plantarum. There's some evidence that lactobacillus plantarum may help increase microbiome production of folate. And we did significantly increased circulating folate in our participants. And then we also gave them a greens powder. So another concentrated hit of these all important phytonutrients that I've mentioned a couple of times. Extremely important was the fact that our study population met with a nutritionist. They were required to meet with a trained nutrition somebody from our team, at least weekly for the first month to make sure that they had the basics of the diet down.

Now, this wasn't a cheerleading session. We actually had to have an IRB approved script. It was really dry and you know Ryan Bradley he was like, he's a stickler for making sure all your Is and Ts are very correct dotted and crossed. So our nutrition team were not doing motivational interviewing with our population, they were just confirming that they do you have questions or don't you have questions. And then they would also just make sure they were getting exercise in and brainstorm on sleep hygiene and so forth. I do think given the complexity of this multimodal intervention that our nutrition team was the difference between success and failure. Otherwise, I mean, it is an involved protocol. And I knew I had one shot. I mean, where are you gonna get six figures gifted to you basically for something like this. And so, I really wanted to do the best I possibly could with this opportunity.

Heather Sandison, N.D.
Yeah, it's so incredible. So just to listeners know, I also have been working with Ryan Bradley on our clinical trial here in my office where we took 25 participants through our approach to cognitive decline and reversing that. And so, we'll publish our results in the next six months or so. But Kara and I have been on these, I've been behind her, I've been trying to catch up but not running fast enough. So she and Ryan worked together to publish your paper in aging and get this done. And all through my trial, I was hearing, oh yeah, on Kara's trial, they did such a great job keeping participants engaged through this and that. So we'll have to use what we learned from that trial. So our participants benefited from so much of what you guys learned.

Kara Fitzgerald, ND, IFMCP
Awesome. Oh, geez, that's great to know. Wow, I'm so thrilled to know that. I mean, Ryan was like we're gonna study you guys in actually executing this trial because it's very involved. And I think he was dubious that we'd be able to pull it off to be honest.

Heather Sandison, N.D.
He is a skeptic by nature and so it's fun to kind of be showing him what's possible. But yeah, you guys did it first. So then what did you find? And how many people were in the trial?

Kara Fitzgerald, ND, IFMCP
So it was a pilot study. There were 18 people in the treatment group and then 20 controls, so 38 total. We found a handful of things. Of course, what kind of got us a ton of attention right out the gate was as compared to our control group who received no intervention, our study participants got over three years younger as measured by DNA methylation again using the flagship Horvath clock. The within group comparison. So looking at the study participants themselves at baseline and then at the end of the eight weeks, they got two years younger. So both within and control group comparison showed some impressive changes.

Heather Sandison, N.D.
Very good.

Kara Fitzgerald, ND, IFMCP
Yeah. And this is like me being sort of a stickler, but we actually redid our calculation where we included the eight weeks as 1/16th of a year. We didn't publish this in our study. But when we included the eight weeks we achieved we were almost at statistical significance originally with the within group comparison at a 0.06. But when we included that little chunk of time in the study we actually achieved significance at 0.04 and it was over two years younger. So both measurements showed a significant biological age reduction. We also showed that our study participants were increased circulating folate as I mentioned before. Their LDL cholesterol dropped, their triglycerides dropped, their total cholesterol also dropped. And I wanna underscore because people always always ask me. In fact, I was just having a really fun conversation over at the Cleveland Clinic Center for Functional Medicine with those doctors and providers there. And they said, well, did you measure CRP and did you measure insulin? And did you measure other markers? And did you see big jumps there? And we didn't do a lot of other

standard biochemistry. And in hindsight I probably would, but we used healthy participants. We had to use a rolling enrollment. It took us a while to recruit a really healthy cohort. So, no, blood sugar wasn't elevated at start. Homocysteine was not elevated, A1C was not elevated. These were healthy guys. So we didn't see changes in those numbers.

Heather Sandison, N.D.
Interesting. Okay, and I think that's also really important here 'cause if you're talking to somebody who's not healthy, you might even expect more of a change, right?

Kara Fitzgerald, ND, IFMCP
That's right. And that's been demonstrated. So if you take diabetes for example, or are you guys using biological age? Are you looking at DNA methylation in your population?

Heather Sandison, N.D.
We didn't, no, not in our trial. I do for patients sometimes if they're interested but we didn't use them in trial. Although I talked to those guys recently and it was like, when we do our follow up--

Kara Fitzgerald, ND, IFMCP
You'll do it. And if you've banked specimen, did you bank specimen by chance?

Heather Sandison, N.D.
No, we didn't.

Kara Fitzgerald, ND, IFMCP
Okay. Understand. Well, and Dale Bradesen is going to be looking at DNA methylation and I hope to just consult with those guys on that, that's very exciting. I'm really glad they're doing it. And I think we're just gonna be using it as a tool especially in the research setting 'cause we have so, so, so much to learn. And I can actually remind me, tell you about some of our other findings outside of the biological talk which I think are as interesting and as important. Anyway, what was I just saying when we digressed?

Heather Sandison, N.D.
There's so much here to talk about. One of the things I wanna get into for sure is, you already mentioned this intergenerational--

Kara Fitzgerald, ND, IFMCP
Oh wait, it came back, the train reentered the station. So we were talking about accelerated aging when you have a chronic condition and yes, in fact that is the case. So all of these chronic diseases are both accelerating at the, biological age is accelerating. And when you turn around the condition you can see a deceleration. And I think that's been best characterized in diabetics where they're six to nine years older biologically than their healthy counterparts. Now within an eight week timeframe, will we see more of a bio age change or does it take longer? I mean, I think that that's something that has yet to be demonstrated.

Heather Sandison, N.D.
Yeah. Future trials.

Kara Fitzgerald, ND, IFMCP
Yeah.

Heather Sandison, N.D.
So I do wanna talk about this kind of intergenerational impact. So whether it's trauma or what you were exposed to in utero, what you eat, if you're of procreating age, right? If you're in that age group. What you're eating even before you're pregnant or before you are a procreating, how that can have an impact on your offsprings genetic expression. So tell us about what we know there. 'Cause I think some of us kind of intuit this and there was data out of highly stressed populations that shows that three and four generations later, there's an impact. But tell us kinda how that applies here in your work.

Kara Fitzgerald, ND, IFMCP
Well, what do I wanna say? I get into it in the book. I get into it in the book. So what would I say? Like, we were looking at post conception, we're looking at middle aged guys and changing DNA expression in this population. I mean, each cell division is another generation, you can think of it that way. So when we put time in and this is an important understanding. Because when we put time into our good health habits, it's going to spread to more cells with more and more cell divisions. So you can just look within your own self and your own many generations of cells to see that an investment, a consistent investment is going to yield best results. So we know that one meditation actually can show favorable changes to DNA methylation, but people who are practiced meditators are biologically younger. Likewise, we can see that in four hours time of

exposure to pollutants, you will see negative DNA methylation changes. Conversely, if you're around this or more so if you're around a toxic exposure for long term, you'll see further damage to DNA methylome and gene expression. So heritability in humans. There's a good body of literature showing heritability in animal studies. So the very famous journal in Waterland, agouti mice study. They gave to pregnant agouti mice. So these mice are blonde and they're very distinct. They're obese and blonde. These mice, you see them once and you'll never forget what an agouti mouse looks like. That agouti gene is on an expression and making them blonde and obese, and also vulnerable to cardiovascular disease, et cetera, in this mouse model. Waterland and Jirtle showed in actually the most cited his paper in the history of all science, their paper, their 2003 seminal paper. Showed that giving the pregnant dams methyl donors, so B12, folate, choline, inhibited hypermethylated the agouti gene and they gave birth to agouti mice that were, they call them pseudo agouti because that gene was hypermethylated and therefore, they were brown, wild type, slender.

Actually, it was a continuum of that but they changed very visually, they changed phenotypic expression. And they showed this actually, they didn't conduct the studies but other labs conducted longevity on the influence of this generation zero methyl donor exposure and showed five generations out. So five generations, generation zero pregnant dams received these methyl donors and five generations out they're influencing methylation of the agouti gene. I mean, is that crazy? If that doesn't show you, suggest how powerful our nutrients are in this era of being able to look at gene expression and measure it, oh my goodness. Humans, we've got some interesting data. We've got cohorts like Dutch Hunger Winter and over calyx. And these were generation, these were populations that either had profound food scarcity as was the case with Dutch Hunger Winter so this was World War II.

They were isolated by Germany and they were starving some of them. Women who were pregnant in during that time gave birth to offspring who had higher risk of really what we see as diseases of over consumption. So cardiovascular disease, obesity, diabetes, et cetera. I think schizophrenia as well. And different from siblings who were either born then or born later. So they had to be within this exposure to the profound caloric deficit. It altered their gene expression towards something that we call the thrifty epigenotype. So every calorie is really hung on to. Now, in the over calyx cohort what's really interesting about these guys is they just kept copious records. And so some farming seasons were lush with lots of food and other farming seasons there was a deficit. They weren't starving but there was less availability. So they so

showed similar negative outcomes with over consumption. But interestingly, they showed beneficial outcome with less consumption. So not starvation but a little bit you're not pigging out all the time either. Circling back to your question, what I think is extraordinary is that they showed the benefit of this lower intake of food in pre-pubescent boys. So pre-pubescent boys they're engaging in spermatogenesis like they're sort of defining epigenetically what's happening on during the spermatogenesis journey, this pre-adolescent journey. And that influences their later offspring through multiple generations. I mean, so when we talk about preparing, when we talk about thinking about eating for our genes, there's really no time and no sex, like men are in this. So we can see that adequate nourishment with what we call epinutrients or the nutrients that influence gene expression and decent lifestyle factors, I think can influence at any time. And it can be surprising. In the book we include a preconception and pregnancy programs.

So what we think are the smart nutrients and we've got amazing data and this is for men and women. I can't underscore enough. This is where the rubber meets the road for men. So if you think it's all on women and during pregnancy, you're simply mistaken. We see the heritability of stress from both sexes and likewise with exposure to nutrients or nutrient deficits influencing both sexes and offspring. So we included that information and what we thought would be a healthy program in our "Younger You" book. And we also write about Grow Baby Health. I wanna give them a shout out, Leslie Stone and her daughter, Emily, run a program called Grow Baby Health, and they're engaged in research. And they use our methylation diet and lifestyle program with their pre conception program. And their birth outcomes are absolutely extraordinary. So they published on a cohort of 200 and they've got like zero incidents I think in their population of autism. Very low allergy rates, preeclampsia, virtually non-existence, gestational diabetes like non-existent. I mean, their birth outcomes are extraordinary.

Heather Sandison, N.D.
Wow.

Kara Fitzgerald, ND, IFMCP
Yeah, and it would be interesting actually to track that through the generations.

Heather Sandison, N.D.
Through the generations. Yeah, absolutely. So this is I think just to underscore your point, right? There's no time that this isn't a good idea.

Kara Fitzgerald, ND, IFMCP
Exactly.

Heather Sandison, N.D.
And you don't have to wait until you have dementia or you don't have to wait of someone in your family has dementia. Even though this is the Reverse Alzheimer's Summit, this is really great information for absolutely anyone who is concerned about the effects of aging or the risks associated with aging.

Kara Fitzgerald, ND, IFMCP
And I mean, just to go beyond that DNA methylation gene expression is doing stuff at every life stage. So an important really sticky point that Davidson Claire made on my podcast was that DNA methylation in embryogenesis and pregnancy in early infancy is just wild. So the fate of all our pluripotent stem cells, an embryo when we're negative age is defined by methylation and demethylation. So it's wildly important that we are consuming enough methyl donors. So we're not thinking about aging we're just thinking about development. And likewise, newborns early infancy, infancy, toddlerhood, and a time of extraordinarily robust development. And DNA methylation needs to be happening really pristinely. And we can see negative fallout when it's not, and these are the developmental delayed. So they're actually aging more slowly. And in this cohort, in this young group it's unhealthy.

So DNA methylation is playing a fundamental role in directing developmental traffic I think throughout the lifespan. And there are different time points where I think we understand it a little better. And these radical changings happening early on are as powerful and important and impactful as aging. So actually to state Sinclair, he put it in the opposite, that changes to DNA methylation that are happening with aging are as potent as what's happening very early on. So there is no time like the present to be eating for gene expression. I would say that that's what we can conclude. And if we are doing that and adopting some of these habits early on, then yes, I think that we can influence the aging journey and also keep our health span and lifespan robust.

Heather Sandison, N.D.
So this is great because I often will have conversations with people saying autism is just the flip side of the Alzheimer's coin, right? Like when we're talking about brain health, there's very similar things going on. One just from the developmental stage and the other is just in the aging stage. So this is speaking exactly to that what we're seeing clinically. So I want people to have really great takeaway to be able to take this incredible information and put it into practice. What foods and simple swaps in the daily routine can add years to our health span? So not just our lifespan but to our health.

Kara Fitzgerald, ND, IFMCP
It's such a good question. And as we're gonna be giving people a freebie of what our diet is. I would love it. I mean, if you want the rubber meats road, grab our book, grab the book, "Younger You" because it's all in here. And the program for preconception and pregnancy is in there. And then the program that people can transition to after they finish this intensive is in there. But important foods, so what not to eat. And I know Heather, you talk about this and I'm sure a lot of the other people you're interviewing talk about this. We don't want a lot of garbage, like the standard American diet is not gonna allow you to live long and prosper, period. It just isn't. So we wanna move away from sugar. We employ a gentle time restricted eating, this diet is higher in fat. For the eight week time period it's grain free, it's lagoon free and it's dairy free. You can transition back into those foods after you're off but maybe a little bit more modest.

I'm not anti lagoon at all, I think that they are a longevity food, but just within the eight weeks we pull people off of it. So what not to eat is as important as what to eat. Your methyl donor rich food. So simple swaps, have some green tea. This is actually what we call a methylation adaptation. So this is the phytochemical I was talking about. The catechins in green tea are wildly important for gene expression. And we know they're also important for cognitive health and inflammation, et cetera. So have some green tea. Coffee is okay. Coffee has some important phytochemicals in it. So you don't have to kick coffee to the curb, but switch your afternoon coffee out for a nice, strongly brewed green tea. Have a piece of liver folks if you're open to it. Liver is a methyl donor in a food matrix. I can't even tell you how extraordinary it is. If you're willing to eat it, I will admit I don't cook it and I have in the book there's a bunch of recommendations for liver capsules if you're open to doing that. Mushrooms.

Heather Sandison, N.D.
Can I stop you on liver? Because I've never eaten liver.

Kara Fitzgerald, ND, IFMCP
You've never had liver?

Heather Sandison, N.D.
I've never had liver.

Kara Fitzgerald, ND, IFMCP
That's so funny.

Heather Sandison, N.D.
I'm a little haunted even thinking about it. And then when I think about taking capsules, I'm afraid of like, and even when I think about eating liver like where that animal raised? Because liver it's gonna concentrate nutrients but it's also gonna concentrate toxins. So let's break down like when you say liver, what do you mean? How do you do it? Why are they so helpful?

Kara Fitzgerald, ND, IFMCP
Yes, so you wanna get clean source liver clearly. And it seems to me that the most pristine we can get is from New Zealand and it's available and it's not. It's not wildly expensive. So you can do that. That's what I do. And I wanna say Heather, you should know this as an ND, actually, maybe you do know it. I just find it so funny you've never had liver. You didn't grow up in the Midwest. It's what we prescribed back in the day for pernicious anemia, for peripheral neuropathy, for macrocytosis, et cetera. I mean, it's what we were using before we synthesized B vitamins. And now we can give B vitamins in really high isolated doses. And arguably, there are smart reasons that we wanna take it in that food matrix. And I talk about some of those in the book. So you get choline, folate, you get a day's worth of B12 in a serving of liver, all of these guys, plus minerals and so forth. But indeed you're 100% correct that you need to get it really clean source. And we can, I mean, funny enough, that was of the conversations that nutritionist would have with the team. The study cohort, like where are they sourcing their clean liver? And in Portland, Oregon, it was not difficult. Here in Connecticut I think it's also not difficult but perhaps a little bit harder but some parts of the world.

Heather Sandison, N.D.
Say you find clean liver at the butcher and then you just like fry it up. Like how do you make liver?

Kara Fitzgerald, ND, IFMCP
Well, one of the guys in the study loved making what he called the new chicken McNugget. So he would sort of bread it. I think he used a little bit of almond flour or something like that and fry it and he absolutely loved it. Famously since you haven't had liver, where did you grow up?

Heather Sandison, N.D.
I grew up on O'ahu, so like, I've eaten ahi heart, or like tuna heart fresh out of the ocean. So I've eaten plenty of weird stuff.

Kara Fitzgerald, ND, IFMCP
Okay. You've eaten more than me. You know what, I think Oregon meats in general are really dense with those nutrients. I guess if you had grown up in Alaska with the Inuit, you would've probably had polar bear liver or maybe perhaps a little bit of that. We have an awesome pate. So probably the easiest way to eat liver at least for me is just a really nice pate. And you can put that on a cracker that's legal, like a seed based cracker, or you can put it on a celery stick or something like that. It's just really delicious and flavorful. We have kids like have no problem consuming liver in this really beautiful farm. I grew up eating liver worse which is sort of like a poor man's pate and loved it with mayonnaise. But again, I don't cook it either, I'm not gonna tell a lie. So unless I can buy some prepared clean source liver product which I can, I can actually get some nice pate around here. I just take it in caps.

Heather Sandison, N.D.
Got it. Okay, that's super helpful. Okay, then you said mushrooms. We can move on.

Kara Fitzgerald, ND, IFMCP
Yeah, mushrooms for sure. So mushrooms are really rich in choline and that's a incredibly important methyl donor. They're rich in a host of other really important nutrients as well including some folate. But particularly shiitake mushrooms, but enoki and mitake. So really important good players. If you can eat eggs, if you're not allergic, I know it's a common allergen, or if you're a vegan obviously you're not gonna be eating these. By the way folks, yes, we do have a vegan/vegetarian version of the diet but we didn't study that version. So it's there and it's available and we'll be collecting data on it in our new cohort in the app but we don't have publications. But if you don't eat animal products at all, you can still do this program. We lean heavier on legumes and beans and stuff like that. Yeah, so mushroom, super important. Your

greens, we list spinach in our dynamic dozen list, but really any of those super nutrient dense fresh greens. What else do we like? I said, eggs, just a superfood. What else do we have in there? Seeds, so seeds another really important player. And then you want good fats actually in the seed arena, pumpkin seeds, sunflower seeds. Omega 3 fats. So if you can do a fatty salmon that's gonna be an important methyl or epinutrient as well. And actually, let me just add in the book we have, there are many, many epinutrients. So if somebody was listening to this and going, I don't like any of those foods, which I hear from people, or somebody emailed me not too long ago and said, I can't eat any of those. I mean, she had a bunch of different sensitivities. Like just she was really hit with pretty profound sensitivities and allergies.

There's a 30 page nutrient appendix in the book of food sources of the epinutrients that we found in the literature. So there are a lot of foods out there that are epigenetically active. There are a lot, any of us could go into the back, the most finicky, the most sensitive individual could go into the nutrient appendix and highlight all sorts of stuff. That they're either already eating so you could go back there and look and see what are you already doing right. And then you can look and see what you can add. So if you need to enter into this conversation gently, I would say start at the nutrient appendix and see what you're doing right and see what you can add in. But if you are ready to be all in obviously I'm going to encourage all of us to do our eight week program as we used it in our study.

Heather Sandison, N.D.
So helpful, super, super helpful. And so then, do you also like suggest variability? Like eating with the seasons, or do you guys get into that at all?

Kara Fitzgerald, ND, IFMCP
Not in our study, no, we didn't. It has to be broadly accessible. So you can create something that you make unavailable to somebody who might be a little bit more in a food desert or somebody who doesn't have the funding to access organic. And we really wanted to be mindful of that. So we got our findings without requiring organic, without eating for the seasons. Clearly, if we want to engage in some of those practices, we may niche the needle a little bit more. But we didn't study it. Again, just with the intention of can we make this available to anyone?

Heather Sandison, N.D.
The masses that need it.

Kara Fitzgerald, ND, IFMCP
Yeah.

Heather Sandison, N.D.
So let's talk a little bit more about some of the lifestyle practices that were in there. You talked about some meditation, exercise and really the diet feels like the foundation. But there were other pieces as well. And do we kinda have a sense, I'm a complex systems thinker, right? So I'm like, no, we wanna do it all. Like it's a reduction and I think that we need to reject that at this stage. So it's not just about one thing, it's not just about one food or it's not just about diet, it's about everything. But do you kind of have a sense of like, how much was the diet, how much was the meditation or the stress. Like you said 25% of your biological age clock is just glucocorticoids. So that's a heavy lift, right? Like that means maybe we should put stress first not the diet first. But for somebody who is just kind of entering into this, what's the best easiest entry point?

Kara Fitzgerald, ND, IFMCP
Yeah. It's funny because I've talked to other people who have different opinions, I am with you and maybe it's our naturopathic background that we're like, yeah, the diet had to be doing the heavy lift here. Certainly it's complex and every nutrient on your fork can be information for gene expression. Like it's so powerful and all of the things that you're not putting in your mouth or how you're structuring your eating program, is so, so, so significant. So I agree with you that I think the diet is doing the heavy lift. But man, reading the science on stress like you just said, you can see stress inherited through the generations. I mean, it's extraordinary. But I wanna point out that it's the minority. So when we think about PTSD, the minority of individuals will actually have a true PTSD response. So you can have a very stressful event but it's gonna be an actual small minority of individuals who are going to sort of change gene expression so profoundly.

Heather Sandison, N.D.
Wait, we don't all have PTSD right now?

Kara Fitzgerald, ND, IFMCP
Technically yeah, technically, no, we don't. Thank God. I think that's important. I think we tend to almost overdiagnose PTSD. And I think that it's helpful to know that it's perhaps not as widespread. However, total life stress will influence gene expression as well. Stressful events or

lack of I'm thinking of in infants, but also the famous animal studies from who was our study advisor and author on the paper. But one of the highest regarded epigeneticist. He's out of McGill University. He did these early studies looking at maternal grooming in mice, in the pups. So the dams grooming the pups. And those didn't receive it had a lower stress threshold. So their epigenetics were wound to create a stress response at a much less stress exposure. And we see that similarly in infants who lack cuddling. So going back to your original cuddling point there you can see cuddling as almost, well, the lack of cuddling causing a developmental delay phenomena in humans. So stress is a big, big deal I guess, is my point. Stress is a big deal. But it looks like we can change things. I mean, it looks like we can change gene expression through things that destress us. Again, coming back to the idea that one yoga event or one meditation event, even one exercise event can favorably change gene expression. But then when you engage in something habitually, it can spread like wildfire, it can have more impactful influences when you can continue the practice. So people who meditate are younger, are biologically younger. Sleep, likewise. People who sleep well have a lower risk of all the chronic diseases of aging. We see really negative. We see a pro-aging phenomena in people who don't sleep well. You see changes to neuronal pathways like pretty profoundly in animal models who aren't with insomnia. Or not even insomnia just one sleepless event can change things in an animal model.

Heather Sandison, N.D.
I mean, it can change it in my model, right? Like, I fly across the world and I'm jet lagged and my brain is . I think we can all relate to that.

Kara Fitzgerald, ND, IFMCP
That's exactly right. In fact, I remember, I'll never forget presenting this slide in Ireland some years ago before we did our study. Yeah, and being like, I'm so jet lagged you guys I can barely get these words out. So I'm experiencing this damage. I don't know that it's as far reaching as it is in the animal model for us to just have one lousy night's sleep. But it adds up if we continue not to be able to sleep well. So to your point, these are all incredibly impactful activities. I mean, they're incredibly impactful lifestyle habits. And okay, so you're eating a pristine diet but you're just wildly stressed out or you're always sitting in your desk day in and day out and stressed out without any exercise. I mean, is that person going to be protected from a heart attack because they eat wild-caught salmon but they're living a really difficult life? I don't know.

Heather Sandison, N.D.
Right. And for people who are in stressful events that maybe they don't have a lot of control over making--

Kara Fitzgerald, ND, IFMCP
Right, circling back to your point of us all having PTSD, yeah, right.

Heather Sandison, N.D.
Making sure that there are copying strategies and support that you have in place hopefully before that comes up. But things like meditation which you included. So can you talk a little bit more about the meditation that you guys included and how you chose that one?

Kara Fitzgerald, ND, IFMCP
Yeah, so this is going back to Ryan Bradley. It was his idea that we use Herbert Benson because he was a Harvard scientist who was studying the benefits of meditation like one of the first guys. And this was a basic program that he developed. It's super easy and turnkey. Anyone can do it. The instructions are in the book, the instructions are also on the paper which is available, it's open-source journal so anybody can get it and see what we were doing. It's just a simple, it's a breathing exercise to elicit what he calls the relaxation response. It has been studied as a stand-alone intervention using a different clock than the Horvath clock, but it was shown in healthy population to lower biological age. So it as a stand-alone intervention was shown to lower bio age in a healthy cohort. They also used it in a cohort of heart disease patients and it didn't reverse bio age. Just in that one particular study I think the take home is that we just need more research. But that gives an idea of how impactful meditation is.

Heather Sandison, N.D.
It's so exciting because when you start to think about like, wow, if we can show that one thing can change it, then when we start stacking these things on top of each other, the potential benefit is just so much bigger. And so many people are suffering unnecessarily. I think that's what gets me up out of bed in the morning, right? It's like just thinking about all of the people who are suffering today that didn't need to if they had the right information and the right resources, and could put these things into practice a little sooner. And so I mean, that's why we're here, right? Is to make sure that people are armed with information. They can start making

these great decisions and prevent and even reverse these complex chronic diseases that come with aging.

Kara Fitzgerald, ND, IFMCP
Yes, that's right. I mean, in our population we looked at middle-aged men, these guys were 50, between 50 and 72. So we didn't look in a young cohort and we were able to show improvement right in the heart of when age-related decline is kicking in. And we were able to do it. I think the massive take home and promise, also the responsibility of us being in this OMIX area where we can measure gene expression, is that our genes are not our fate. Our genes do not dictate our fate. And I'm sure that you talk about this given this close association of the and Alzheimer's. There are things that we can do even if we have these genes. So in this era, what appears to be the far more potent variable is those lifestyle choices that we make day in and day out. And we're really in the driver's seat of gene expression. And so it's up to us to choose it. We're the ones who get to choose quality of life. One of the statistics I cite early in the book is that our final 16 years in this country, our final 16 years are spent with at least one and often, more often than not actually, multiple significant illnesses. So just think about that multiple conditions.

All of our savings, our kids inheritance is going towards complex care, pharma, hospitalization, et cetera. We don't think about what's going to happen until it's upon us. And yet we need to be thinking about it now and changing it. I also cite some economics early on in the book. The potential cost savings for focusing on aging and putting some effort into improving health span is just astronomical. It's absolutely 100% astronomical. And as you said in the very beginning, if we look at aging and slowing aging down itself, instead of siloing out Alzheimer's, and then Parkinson and then cardiovascular disease and diabetes and cancer. Instead of siloing everything out in the National Institutes of Health and funneling billions of dollars into each of these isolated entities, let's look at aging as a whole and how we can slow that down. And the economic, the savings and suffering, the economics of it, I mean, I don't think we can overstate the potential benefits.

Heather Sandison, N.D.
Yeah, so compelling and also just like, why are we not already doing this? A little bit .

Kara Fitzgerald, ND, IFMCP
Well, I think a piece of it is that we haven't had, Heather, kind of the tools that we are moving towards now. And I think Sinclair's lab, like identifying the aging might be happening right here

in the methylome or in the epigenome. And, I mean, I think we're at a confluence of events today that's really shining light on where we need to be putting our energy. And hopefully science will just, and the government and funding, et cetera, will just follow up with focus here.

Heather Sandison, N.D.
Well, that is a hopeful message. And also, for those of you who cannot see this who are just listening, Kara's skin is a testament to how well this works. So I think that I read somewhere that you're 54. Is that right?

Kara Fitzgerald, ND, IFMCP
Yeah, actually 55 now.

Heather Sandison, N.D.
You look about 29.

Kara Fitzgerald, ND, IFMCP
Yeah, right.

Heather Sandison, N.D.
And so I'm gonna start eating liver today.

Kara Fitzgerald, ND, IFMCP
That is so funny.

Heather Sandison, N.D.
Yeah, if I didn't already drink green tea and eat lots of broccoli, then I would start that as well today. But, yeah, you're the best spokesperson for this because clearly you're living it. And so thank you for sharing all of this incredible, hopeful, empowering information with our listeners. I know that this is just insanely valuable, and also so simple and straightforward. And I hope that all of our listeners will get started and eat a little bit more of these great foods that you've talked about. Cuddle a little bit more, maybe meditate, exercise starting today. Thank you so much. I wanna make sure everybody knows. I know you've talked about "Younger You" the book, but I wanna make sure everyone knows how to get the app, everything else that you have.

Kara Fitzgerald, ND, IFMCP
Yeah. Just go over to youngeryouprogram.com and you'll find all things the book there, "Younger You" and the app, youngeuprogram.com app and book are there. You can also go to my website if you're interested in our clinic, our blog, our podcast, et cetera. And that's just drkarafitzgerald.com.

Heather Sandison, N.D.
Excellent. Kara, thank you so much for joining me today. It's been an absolute pleasure.

Kara Fitzgerald, ND, IFMCP
Yeah, likewise, Heather, I'm so glad to have this time to talk to you.