



Danny Lennon:

So let's dive into it from the very start. I mean, the best way as we usually do is to lead off with some definitions of some key terms that will be coming up throughout the rest of this conversation. And I'll maybe start here with Niamh given as, as we talk about throughout this conversation, you have a number of publications in this area. And so when we're about things like cognitive function and then cognitive decline and any other terms you think are important, what are some of the few definitions that you'd want people to be most clear on?

Niamh Aspell:

Sure. Yeah. I think it's really important in, in this area to distinguish between all of these, because in a lot of the publications, they don't really distinguish show what exactly they're trying to target. And it's also becomes really important in terms of recruiting particular participants or patient groups, and then the types of assessments that are conducted as well. So when we talk about cognitive function, this refers to a lot of different brain functions and processes simply put it's just the ability to receive information, how we process that information and then how we respond with a particular behavior. So it covers a wide range of different mental abilities. I'll go with the American Psychological Association definition for cognitive functions and, and they state it to be the performance. So this is cognitive perform of different mental processes. That includes things, our, like our perception, learning our memory, understanding comprehension, awareness, reasoning, judgment, intuition, and then language.

Niamh Aspell:

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So if we think of the broad range of functions there that becomes quite complex, we try and evaluate it in intervention studies or look at it through observational studies as well. I, I want to distinguish then as well between cognitive decline. So there's two different types of cognitive decline. There is this normal cognitive decline that we'll all experience. So this which is age related. So JUST like any other system in the body, as we get older, we'll start to see certain declines. And then there's also neurodegeneration based on having with the presence of an illness or a disease. So things like a dementia or Alzheimer's disease. I think most people, when we talk about cognitive decline will initially jump to things or associate it with memory loss, but it does relate to all of those other cognitive processes that I'd mentioned before.

Niamh Aspell:

So again, sticking with the American Psychological Association definition, which is the most widely used, they would define cognitive decline as a reduction in one or more cognitive ability. So not just memory and it happens across the lifespan. So typically we start to experience some form of cognitive decline in midlife, and that's a part of our normal, healthy aging, but if it's more severe or if it's a more rapid decline, that would be usually when there is also a disease. So some neurodegenerative disorder in place as well, and that's more prolonged degeneration of those neuronal pathways or processes. And that would be things like mainly, I suppose, there a lot of the literature that we probably discuss today would be things like dementia. We won't go into, I don't think any of the other neurodegenerative disorders, which also have some elements of cognitive decline.

Niamh Aspell:

So things like Parkinson's disease or Motor Neuron disease and the gradient losses of cognitive decline are quite different between all of those different disorders as well. But essentially the consequences are quite similar. So typically this would have, this would present in a person as a loss in their ability to who perform routine tasks or ADLs. So things like being able to manage your home life shopping, managing household, budgets, doing your work as normal. And that then continues with a decline in your overall quality of life. And then ultimately at later stages leads to loss of independence where you require supports in terms of caregiving. There is just differences between things like Alzheimer's disease and dementia in terms of how they, how they might present. And I can get into those a little bit, I think in terms of cognitive decline and, and nutrition research, this has changed quite a lot as the area of dementia and Alzheimer's disease has been better understood over the last 20 years.

Niamh Aspell:

So I can talk a small bit if you like around the current strategies for dementia and Alzheimer's and how that's managed: quite simply, there's just been a lot of failed drug trials. So there's been about over a hundred drugs at this stage that not been able to show efficacy in terms of reducing the symptoms or changing the course of Alzheimer's disease and dementia. So a lot of trials now have started focusing a lot more on the prodromal or preclinical stages of Alzheimer's and, and dementia, where they're trying to prevent it. And then in the last 10, 15 years there of nutrition,

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interventions are looking at prolonging or supporting cognitive resilience or cognitive health with aging. And I think that's a lot where a lot of the research has focused on at the moment. I think since 20 2003, only one drug was approved for Alzheimer's disease.

Niamh Aspell:

And that was last year. And there's a lot of controversy around that one particular drug because it's based on two conflicting clinical trials. So there is like a desperation at the stage of, in terms of drug development for Alzheimer's and dementia. And most of the research is really, really focusing now on, on midlife where before symptoms begin to present. So I think when we talk about some of the literature later on in nutrition search, it's really good to consider at what stage the participants are at, whether they're healthy and don't have any signs of cognitive impairment, whether there's early cognitive changes, whether it's been diagnosed or whether it's late life. And what also makes it really complicated is there's no strong diagnostic markers for things like Alzheimer's disease. It's usually confirmed on autopsy as well. So in terms of recruitment and managing progression of the disease and seeing biomarkers of change, it gets quite it's quite complicated I suppose. And it's not clear.

Danny Lennon:

Yeah. And I think that's something that you echoed on our podcast, Alan on polyphenols and, and cognitive health, this real focus on, on the potential value of some of these nutritional interventions in light of just a lack of positive interventions we have to treat these in a pharmaceuticals sense. And then also noting where we're actually going to be intervening with these. And I think that that point actually sets the stage nicely to think about some of the pathogenesis of some of these diseases, because if we're considering, if we're going to intervene in a preventative sense versus when something is already established is going to obviously be our large difference. And so before we think about the mechanisms by which say nutrients or diets or supplements may have some degree of, of impact.

Niamh Aspell:

Yeah, I suppose dementia itself is an umbrella term for lots of different pathologies. And the main dementia that is investigated is usually Alzheimer's. And the pathogenesis of that has some quite distinct features. So it's things like a buildup of amyloid plaques, which lead to these, these tangles essentially of your neurons in the brain, which result then in your neurons being unable to communicate with each other amyloid, be like this quite like a sticky substance. And typically the way your neurons work is they send, they send messages to each other and that's how they remain healthy and remain active and alive. If they're unable to communicate with each other due to this buildup of amyloid beta, then the neurons start to die. And if they die, then you'll have a loss of brain function, brain volume. And it depends one particular area of the brain that this occurs and that will then result in which cognitive ability is then impacted.

Niamh Aspell:

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So the primary for that would be this, this imbalance in the production and then the clearance as well. So typically you clear that the amyloid beta as well, so there shouldn't be an excessive amount. And when you see later stages of someone who's got Alzheimer's disease, they do have this accumulation of these neuro fibrillary tangles in the brain as a result of having an excessive amount of amyloid beta. But there is a cascade of events that happen there as well. So when you have that loss of synopsis or communication between the neurons, there's other knock on effects. So you've got impaired glucose utilization, oxidative damage there's reductions in metabolic activity in the brain, and these are all associated then with these tangles or formations that then reduce the size and the functioning of those, those neurons as well.

Niamh Aspell:

Things like Alzheimer's disease, there's other con there's other risk factors for it. But one of the most prevalent forms of dementia is vascular dementia. So things like secondary vascular dementia would be when somebody has a stroke or an ischemic event, or there is a, a specific injury or to a certain area of the brain, which is usually due to a blockage or, or a stroke. And then that results then in brain damage as well. So I think a lot of the nutrition research focuses that maybe targeting or supporting vascular health as a way to reduce the risk of some sort of vascular event that would be lead on then to brain changes or, or cognitive decline as a result,

Danny Lennon:

Keeping on that topic. And as I mentioned a moment ago to Alan, one of the things that you noted in our poly episode specifically was we can look to certain nutrition interventions, and we're in a current state where there's maybe lack of good pharmaceutical inter interventions. And so with the initial hypotheses, we might put forward on a nutrition front, where does some of that emerge from, well,

Alan Flanagan:

As as a point of departure, there's possibly a couple of important factors. So Niamh touched on the age factor, right? So we, we, we see this quite substantial difference in the accumulative incidents of dementia and Alzheimer's with increasing age. So within the, you know, 70 or 65 to say, even 75 bracket, it's less than 10%. It jumps to 20% around the 85 to 90 bracket. And by the over 95 bracket, it's, it's up to four, you know, 40 plus. So there's a huge age related component to this. And so within that, as Niamh described, there's this like progressive deterioration that can occur in cognitive function. I use that term in the broader sense, you know, learning and or sorry, memory and other aspects of cognition. And so from a nutrition standpoint, first and foremost, this is very much something that is related to the stage of intervention.

Alan Flanagan:

And that's going to be particularly relevant when we come to consider some of the potential disconnect in the omega3 fatty acid research, for example, as it relates to the, the current health status of whatever study group. So do they have mild

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cognitive impairment already? Do they already have a diagnosis of dementia or are we talking about healthy, older adults? So 65, 70 plus, but otherwise healthy or are we talking about people more in the mid stage of life? And so that's a really important factor to consider, and there's a couple of other, I think, important points that relate to what we've seen from some of the cardiovascular research that actually translates over. So for example, there, there has actually been a reduction in incidents in, in the last 20 years. And that has primarily been attributable to the statin era of cardiovascular treatment.

Alan Flanagan:

So there was a meta analysis a number of years ago on the use of statins and the risk of dementia Alzheimer's and mild cognitive impairment. Respectively was reduced by 1528 and 26%. So what you can see here is related to the first point I made in stage of intervention. So the greatest magnitude of risk reduction is observed in people with MCI, mild cognitive impairment and, and the lowest is observed in people already dementia. So stage of intervention is going to be really important. There's another critical factor that Warren's mentioning as it relates to potential dietary considerations, which is an individual's APOE status; APOE is a gene, and there are two types that are particularly relevant for neurodegenerative disease and they have oppositional influences on risk. So APO E 4 is a significant risk factor for dementia Alzheimer's APO E2 is associated with reduction in risk.

Alan Flanagan:

And the reason that this may have to do with is cholesterol metabolism. And so there's evidence for disorderED cholesterol metabolism that relates to the development of the neurofibrillary tangles and the accumulation of amyloid beta protein that Niamh was discussing. And there are certain pathways that, that in relation to the processing of those proteins, that disordered cholesterol metabolism may relate to. So there's you know, a consideration that will play into some of the nutrition related research, as far as lipids and cholesterol and cardiovascular risk factors, you know, having, having a big impact potentially on someone's neurodegenerative disease risk. You know, finally, obviously Niamh has mentioned that, you know, 96% give or take, or, or 99% failure rate of drug therapies, and it maybe one approved FDA approved since 2003. And so, you know, this occur in the context of a population generally living longer.

Alan Flanagan:

And so there is a prevalence increase predicted to be quite substantial by in the next 20 to 30 years. So the emphasis really is unmodifiable risk factors. And so there are certain things that are non-modifiable. So gene you're born with APO E two or four is non-modifiable, but factors like dietary intake, exercise maintaining cognitive challenge so like, you know, learning new languages or playing your Sudoku in the paper, and then other factors that are behavior really related, like social participation and things like that are, are also associated with reduced risk. But obviously our emphasis today is going to be on dietary intake. So I, I think before we launch into the dietary interventions or, or the, the dietary evidence, epidemiology and intervention, I think the important things to consider are, you know, wider

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background characteristics, particularly for cohort studies where things like education are associated with lower risk.

Alan Flanagan:

It's important that, you know, well= conducted cohort studies adjust for some of these other factors like exercise and education level to ensure that any association that we have is, is independent of those potential non-dietary related confounders. I think that's one important factor, the actual age and stage and health status of the population group. We're looking at whether epidemiology or an intervention is really important. And I think some of these other factors, as well, as far as your genetic risk and the related pathways in the brain that relate to some of the mechanisms by which the nutrients will discuss act, I think is probably better left, or when we start to hone in on some of those particular nutrients or food groups.

Danny Lennon:

So, so with that, let's maybe start looking at some of these dietary components. And maybe before we look at any specific nutrient, maybe we can look at some of the evidence related to general dietary patterns to see what that tends to show us. So maybe if I, if I ask you to start us here Niamh what we know from an overview level of the impact of various different dietary pattern on associations with cognitive function. And is there anything that is that we're consistently seeing that we could say is a good evidence base to?

Niamh Aspell:

Yeah, I think so. I think, yeah, the, I suppose the evidence here is very much so split between whether it's dietary patterns are specific nutrients and a lot of the nutrients I think that we really focused on are usually the main contributing factor to the dietary patterns that we've also investigated. So one of, you know, the most commonly one in this area, or, you know, usually that's investigated when we talk about aging or healthy aging or longevity, which we've mentioned in previous podcasts is the Mediterranean style diet it, and that's been the predominant focus, I think, in this area, in terms of cognitive function, cognitive health. When we look at dietary patterns, there is other strategies which have focused on overfeeding or high caloric diets, low dietary fiber diets, or consumption of like real diets, really low in antioxidant nutrients as being poor dietary habits.

Niamh Aspell:

So the opposite, essentially really of the Mediterranean style diet. There's a couple of different, there's been lots of association studies and there's been a lot of association studies that would usually categorize this as a Mediterranean style diet. So where they've taken cohort studies or longitudinal or national studies and assess them to see how much they fit the criteria of a Mediterranean style diet. There was one published last year. That's a really, really good example, which I think will reflect, you know, will highlight the limitations of a lot of the others through a paper published last year in, in urology called the Mediterranean diet Alzheimer's disease biomarkers and brain atrophy and old age, where they wanted to determine if

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following a Mediterranean like diet. So the typical features of a Mediterranean type diet related to cognitive functions specifically they were testing this based on biomarkers of Alzheimer's disease.

Niamh Aspell:

So most of the nutrient based studies looking at dietary patterns and outcomes and cognitive health have used very crude measures of assessing someone's cognitive health to determine their where they're at their baseline, and then following them up over a number of years or whatever it might be. And that can vary widely between studies. It makes, it makes it really, really hard to determine if there is an association at all, but in this particular it was a cohort. It was a German study. It's a longitudinal study, but this is just the first instance of it. And it's a cross section analysis, it's they, they have an average age on this group of just about 70, so 69.5 years. And there's very little variation and that's, so they're getting them at this very good point, I suppose, in terms of the aging process, where you might expect to see some change, it's a mixed cohort.

Niamh Aspell:

So it's broken into people who have, who are normal in terms of cognitive status. And then they also have individuals who have a high risk of Alzheimer's disease. So this is things like the genotypes specifically, or they have relatives or familial history of Alzheimer's disease in their family. Then they have another group who have subjective cognitive decline, which is a really good measure that a lot of studies don't include. So this is where you would ask the participant at the beginning of the study. Do you feel like your memory or your cognitive ability have changed in recent years or they're not as good as they used to be, which I think is a much better marker than say something like a very simple screening test where somebody might score, you know, in the normal range, but for them it might not be their normal.

Niamh Aspell:

They might feel like there's there's differences. And then they've got another group within this study that have of mild cognitive impairment, but essentially they defined, they looked at the Mediterranean diet, they looked at a food, they used the epic food frequency questionnaire for this, but their endpoints were changes in brain volume. So they did MRI studies. They were able to assess different sections of their brain so that then they could correlate cognitive performance based on also objective changes in brain volume at the same time. So they did like a neuropsychological battery, which is quite extensive. It included lots of domains of cognitive function, not just memory, which most studies typically focus on. And then they also looked at Alzheimer's disease related biomarkers. So they were able to look at amyloid beta. So this is a very what is the word I'm thinking of extreme, I suppose, assessment on these patients, they did sign up or they were in patients, they were just participants, but they did sign up to these examinations.

Niamh Aspell:

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So they looked at tau, as well. So phosphorylated tau, and also amyloid beta. They took cerebral spinal fluid in all of these, in all of these patients that enrolled in this as well. So they analyzed essentially the associations with those who adhere to the Mediterranean diet compared to those who didn't follow that typical based diet. And they just did some really simple linear regression models to if there was any associations between them all. And they showed that those who adhere quite typically to the Mediterranean diet had larger gray matter. So obviously gray matter in your brain is just made up of neurons. So it's how, how tightly and the number, I suppose, the volume of neurons in your brain. So the more you have, the more that you're healthy, as you see with cognitive change, you'll see deterioration of gray, of gray matter volume, and that's the main feature of an Alzheimer's disease.

Niamh Aspell:

They also then correlated that with having better memory and they also had less amyloid beta plaques as well. So they were able to use really specific markers of pathology and relay it to somebody who would follow Mediterranean style type diet as well. So I think this is a, a really strong example of probably one of the first, I think really good examples of how we've tried to evaluate nutrient status and cognitive health, because it's in a very early stage it's in that of looking at those different cohorts and they were able to detect these early changes, which in neuropsychological battery typically wouldn't be able to detect. I think, you know, obviously it's only cross sectional and it is going, it is a longitudinal study, it's just at its very early stages. So it would be very interesting to see over the next few years, whether certain groups, particularly those who say follow Mediterranean diet, whether that's pre neuroprotective and they have less decline or a decline that's just relative to normal age related decline.

Niamh Aspell:

And if they are less likely to maybe go on and have cerebral vascular events as well. So that supports a lot of the cross-sectional studies that we have in terms that are, and even the intervention studies that are presented in some of the meta-analysis. So there's a lot of meta-analysis that show greater adherence, like give people a adhere to the Mediterranean diet during a adult older adulthood, but they have a lower risk of poor health outcomes, not just neurodegenerative disorders, but things around cardiovascular disease, which then as a proxy then to your risk of, of brain health or, or poor effects on your brain health. So I think from there there's, there's lots of meta else. I think a lot of work has been done in this area. And there's lots of published studies showing that people who adhere to this particular diet.

Niamh Aspell:

I think the main thing about this diet is the things that are, they're trying to explore. What's included in the diet. You will present lots of, specific nutrient studies as well. But I think what a lot of them don't really conclude it is the fact that what this diet eliminates. So think foods that typically aren't consumed, if you follow a Mediterranean diet. So I think we'll probably go into it, but there's lots of studies then where you look at specific, very specific things like blueberries and how if you

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eat blueberries, you're less likely to get Alzheimer's and dementia, which is an extreme extrapolation of maybe what the, the real basis is, is

Danny Lennon:

One thing that I don't want to circle back to Alan is because you did bring up someone's APO E status and, and quite clearly something genetic like that is, is not modifiable, but what is maybe not modifiable of course, is the, the diet that someone has that could have an interaction with APO E. And I think this is something people may have heard of. So what, what we know about actually, if someone let's say does is, has APO E4 as their status, what does that possibly mean for maybe certain dietary choices or the interaction with diet that puts them maybe at, at more risk than it would for someone who has say the APO E2 alleles, for example.

Alan Flanagan:

Yeah, I think that the lowest hanging fruit and the most important in terms of magnitude would be saturated fat in the diet animal fat generally, and concomitant high saturated fat cholesterol foods. And this is going to be because of the impact that, that has on blood lipids. There is, you know, what's good for the head is good for the heart, you know, is somewhat of a truism, but as it relates to these related areas of research, there there's increasing validation for that being the case. And I alluded to the statin reduction, neurodegenerative disease risk at the outset. So what this tends to relate to is the potential disordered cholesterol metabolism that occurs. And, and this is, you know, this is quite an, an important consideration because it relates as well to the pathways that Niamh was discussing. So there's, there's essentially two pathways through which the protein amyloid beta is produced essentially right.

Alan Flanagan:

There is the alpha and gamma secretase pathways. One of them would be called the amyloidogenic pathway. I E when substrates are processed down that pathway, it leads to an accumulation of amyloid beta. And then the other pathway would be the non-amyloidogenic pathway. So it's the opposite. So it's, it's, it's effective metabolism in the brain, diverting, substrate away from it, it being ultimately coming out as a byproduct of amyloid beta, right? And so the mediating protein here is known as amyloid precursor protein, or APP. And there's a relationship as there is for cardiovascular disease. There is a relationship between saturated and polyunsaturated fatty acids in particularly mediating this risk that may relate to APOE. And so a high saturated fat diet might ultimately, and, and we know that that this is what primarily influences blood lipid levels in humans and increases blood cholesterol levels.

Alan Flanagan:

But we, you know, cholesterol metabolism is obviously then an important part of this picture. What can happen is you get increases in free levels of cholesterol in, in brain membranes, in central nervous system membranes, and that inhibits the non-amyloidogenic pathway, the alpha secretase pathway. So excess levels of cellular

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cholesterol end up inhibiting that pathway that we want functioning to properly metabolize substrate away from beta amyloid. And so this, what you end up with this increase in membrane cholesterol, decreases membrane fluidity and this also contributes to this abnormal processing of amyloid beta plaque, conversely, and this is, again, a lot of this is mechanistic evidence, but we know that DHA in particular has a civic role in diverting amyloid, precursor protein down through the pathway that you want to channel through, which is the non amyloid Egen pathway, reducing amyloid beta levels. There's other effects that DHA might have on this pathway which again, this is going to be relevant when we discuss the omega three fatty acid literature, but, but the, the main point as relates to diet and that particular pheno or genotype APO E4 in particular, would be that saturated fat in the diet would want to be kept to a minimum.

Alan Flanagan:

And certainly the replacement of that with polyunsaturated fat, it appear to be particularly with polyunsaturated fats of the long chain marine omega3 variety would likely be the most efficacious step that someone could take if they did present with that genetic predisposition.

Danny Lennon:

One more, maybe macronutrient for us to, to consider before we get into some of these other micronutrient is the impact of alcohol. And there's some interesting and possibly counterintuitive evidence in this area Niamh that, that you've highlighted. Can you maybe touch on some of what we've seen with the associations with alcohol intake?

Niamh Aspell:

This is really interesting, cause I think this can really get exploited quite a lot, but it, again, it follows that one component to the Mediterranean diet where moderate alcohol consumption seems to be protective. But I think there, and there is, you know, they have proposed some mechanisms of action so that alcohol can, can protect or precondition different effects on some of our, essentially our microglia. So this then goes in and back down to neuro inflammation. These cells essentially are macro masses and that help protect the, the brain, but they, they believe that alcohol, there is a component in alcohol that helps up regulate some of the proteins and helps support the survival of cells within the brain. Okay. But I think what's this , there's two different when we think of alcohol behavior and alcohol consumption, and we, this should be assessed in all of the studies as well.

Niamh Aspell:

It's where it's moderate drinking or there's, I suppose, poor behaviors around alcohol, the the history around the, on moderate drinking and cognition can be separated based in a much, much earlier research in the, in the eighties and nineties where they didn't do neuropsychological evaluation and related it to alcohol behaviors. And they looked at that particular period in time as well. They only Sur looked at people's alcohol behaviors and neuropsychological function and

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neuropsychological outcomes, things like depression and anxiety in people of midlife. And that was expanded then, and little bit later on in the last like 20 or 30 decades to look at alcohol intake, whether it's impacting neuropsychological outcomes as well. And then whether that's linked to cognition too. So there is a lot of research in this area it's quite complex, but I think what it comes down to is the, is the social aspect or the aspect of drinking certain types of alcohol with meals.

Niamh Aspell:

So it's , it's around alcohol behaviors that I think needs to be really much, you know, very much distinguished here. They haven't been able to divide or show or a reduction, I know there's a lot of research around research on wine and different components in wine and their antioxidant properties and how that might be one supportive factor. But the, the basis of the research is the light or moderate drinking behavior has been shown to reduce cognitive risk. But I think that this doesn't usually get explored in enough context, because when you look at it in the group of people who typically drink light to moderate drinking behaviors, it's usually either with meal times, it's, it is that level of moderation as well. So if they've moderate alcohol behaviors, they might have other moderate approaches to maybe their diet and lifestyle.

Niamh Aspell:

Well, and typically they have, there's a couple of studies as well, that look at moderate and light drinking behavior and the environment in which that takes place. And it's typically around social behaviors and goes back to that Mediterranean lifestyle, as opposed to the Mediterranean diet where it's having a small number of drinks with food and with social interaction and social interaction is being shown to really mediate that relationship between dietary behaviors, alcohol intake, and cognitive health with aging, which is, you know, directly related then to quality life and other factors. And that goes into, and more the area around cognitive resilience, neuroplasticity, and a lifestyle preventative strategies, these more multimodal interventions. Whereas they haven't been able to show, well, you know, am I better off drinking a certain type of drink if I drink moderately, you know, a certain spirit, there doesn't seem to be that relationship or they haven't, haven't shown that yet anyway.

Niamh Aspell:

And then we obviously no excessive alcohol. So anything over what you should be consuming has very negative effects on, on cognitive health and related neuropsychological process as well. So I think that one really needs to be, because it's be always been presented as a, as, you know, drink wine to help your memory or, you know, you'll live longer if you drink wine. But I think that's been really that's obviously really misleading, but in terms of the research, it's still very correlational. And when you're also talking about, again, these genetic components, there seems to be a, when you, when you think of things like binge drinking, that if fact of binge drinking on people who have that APOE4 allele type, that they have a much, much greater risk of dementia if they're also binge drinking as well. So the drinking

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behavior, when it's a poor behavior, the it's the impact of that is much greater on people who have these additional risk factors as well.

Danny Lennon:

Right? So it's not okay. So of having a, a shot of pure ethanol a day as a health benefiting strategy, it's more so around number one, these behaviors. And then you also mentioned that there's some speculation around the potential role of let's say polyphenols in something like a wine. I think this is something that, that you and I touched on in the alcohol episode Alan of, of why current guidelines around not advocating for someone to start taking up alcohol consumption as a healthy behavior, if they don't currently do so, is because it's not really backed up by by much, but the well maybe circle back to the, the behaviors around things, but on the polyphenol issue, another component or food, or actually beverage in this case where this gets brought up is in relation to coffee consumption.

Danny Lennon:

And we did mention this on, on both the polyphenol episode and in the coffee specific episode as well for a number of different health outcomes. And really there's probably two components here. There's one where you can look at the polyphenol content of coffee, but then there's also the caffeine content of coffee, which has some mechanistic basis. And each of those seems to, again, differ on different outcomes and maybe even different types of neurodegenerative disease. So maybe I I'll ask you Alan, on, on the area of coffee and again, there's these maybe two different roots. We can look at caffeine and then maybe the polyphenol content. What way would you summarize some of that data that we may have discussed previously that in this case specifically relating to cognitive health?

Alan Flanagan:

Yeah, I think, I think coffee overall fits quite well into the umbrella consideration of polyphenols. Although like you mentioned, it does contain caffeine as well, which independently exerts you know, neurological properties as a, as a psycho stimulant. And indeed having, you know, cognitive boosting effects certainly acutely. So there is the caffeine component. And then there are the quite range of compounds that, that coffee contains that would for all under the polyphenol umbrella, chlorogenic acids in particular. And there are some other components to coffee as well, depen and these other, these other minor constituents that would be, you know, phytochemical compounds that exert biological activity, most of the emphasis would be on chlorogenic, a acid as regards the protective associations that are observed for caffeine. And in relation to neurodegenerate sorry for coffee in relation to neurodegenerative disease, the strongest associations for coffee, which we discussed, I think on that episode were are in relation to Parkinson's disease.

Alan Flanagan:

Although there are positive associations i.e. a reduction of risk associated with regular coffee consumption and dementia Alzheimer's. But as far as strength of association, there may be something going on in relation to the path of physiology of

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Parkinson's that coffee or indeed component parts of coffee appear to have a beneficial effect on. But I think this is probably a good point of departure to, to tie in some of the mechanisms by which some of these non-nutritive bioactive components that we would consider when we discuss coffee or where we go on to discuss certain polyphenol. And flavonoid in particular rich foods, the irrespective of the subclass that we are talking about in relation to polyphenols, we appear to be able to distill their potential mechanisms of action down to a, a number of potential mechanisms.

Alan Flanagan:

The, the most consistent across the board, maybe enhance cerebrovascular blood flow. That sounds quite broad, but the enhancement of cerebrovascular blood flow appears to relate to a number of other related processes in the brain. And so what you tend to get is that these compounds end up being digested and processed and absorbed and the parent compound gets converted into a secondary metabolite and those secondary metabolites act in the brain at very low physiological concentrations. And this is actually quite important to their mechanism of action because to study only the parent compound could, could actually miss this potential activity. So they act through influencing brain cell morphology, viability vascular effects and inflammation, but the enhancement of cerebrovascular blood flow appears to be a unifying mechanism. So polyphenol compounds and have beneficial effects on multiple aspects of vascular function. So they act as vasodilators, they activate an enzyme known as endothelial nitric oxide synthase or ENOS that in turn regulates, angiogenesis and vasodilation.

Alan Flanagan:

And then there also may be a relationship between enhanced vascular dilation in the brain and cerebrovascular blood flow and activation of what's known as brain derived, neurotropic factor or BDNF. So you get these at the first level, this activation of, of pathways is that increase blood flow to the brain, essentially that in and of itself influences other factors like neuron function survival repair and synaptic plasticity, the ability of these cells to remain responsive and adapt and grow and develop over time. And then neuroprotection from inflammation which is possibly if, if not with increased cerebrovascular blood flow, just as important to mechanism. So polyphenol compounds broadly speaking act through various pathways in the brain that influence inflammation in the brain in a positive sense. So they, they down regulate inflammatory processes. They act through specific anti-inflammatory pathways as well.

Alan Flanagan:

There may be some relationship with omega three fatty acids, although that's less well understood as far as interaction effects go. And these mechanisms then. So if we take, we've got better blood flow to the brain that in turn influencing other processes that may be involved in learning and memories such as BDNF, we've got the down regulation of inflammation in the brain and then we've got other pathways that affect the actual survival and, and health of brain cells of neurons. We have this three primary mechanisms by which polyphenol compounds in particular may have a benefit on neurology within the coffee consideration, chlorogenic acids exert a

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number of these effects, right? And so they're associated with quite a benefit and mechanistic research shows benefit towards the vascular endothelium from chlorogenic acids. They appear to also then enhance nitric oxide production and potentially again through that eNOS enzyme.

Alan Flanagan:

So they're, they're having this effect that we broadly associate with polyphenols. Then there's the potential synergistic effect of coffee in particular because the associations tend to be for coffee as consumed as a , if we consider it as a food exposure, so to speak because of the the matrix of nutrients within it, then, you know, we, we tend to see stronger associations for coffee consumption than you might just for caffeine alone. But this, this would appear then to relate to these mechanisms as described as far as beneficial effects on the Cerebra vascular blood flow and reductions in neuroinflammation.

Danny Lennon:

Just while we're on this topic and we've brought up flavanoids and I think we don't really need to go into much depth here because for the real details and specifically on some of the studies that we could mention here, I'd refer people back to the episode on polyphenols and cognitive health, where we walk through these in quite some, but just for those who maybe didn't hear that episode and just to keep some consistency on the topic of, of the flavanoids. And I suppose there's these, I suppose, short term interventions where we're looking at something like a, a grapefruit or a grape juice extract. And then we also have larger cohort studies looking at things like blueberry intake, as Niamh mentioned, what is the quick overview we could give people of the literature in this area? Do you think, Alan that would be a, a decent summary of that, that episode?

Alan Flanagan:

Yeah, so I think, you know, the first thing is in, in the epidemiology and Niamh alluded to this where we have these dietary patterns, and then there's an emphasis on Pacific nutrients. And what, what certainly the, one of the real pioneering nutritional epidemiologists focused on dementia; Martha Clare Morris had really pioneered was, was then working backwards from there. Okay. We have these potential nutrient associations and mechanisms, where do we find these nutrients in food and what's effect of these food based exposures? So there's a number of the us cohort studies that have found associations with specific what we would consider flavanoid rich foods whether they're blueberries in particular or strawberries. And we know that they're rich in a number of flavanoid compounds that have effect that have been demonstrated in short term intervention studies.

Alan Flanagan:

And those associations are not necessarily confined to the us. So there's been positive associations in some European cohorts and indeed in the UK with broadly speaking flavanoid or polyphenol rich foods, and then specific foods then within that, like citrus, fruits berries red wine chocolate. And, and these have, these have

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typically been associated like when, when analyzed as individual foods, there are a number of factors that then play into the epidemiology, like, you know, baseline education, status, and socioeconomic status. And some of these studies after they adjust for those factors, don't find a significant association anymore, but it gives us enough to think about, okay, we've got these polyphenol compounds, we know that they are rich in these foods. Can we parse this down with interventions and, and largely the intervention studies that we have to date are, are congruent with what has been observed in epidemiology.

Alan Flanagan:

There's a number of interventions that are both acute over six hours or over 12. So these are short term interventions. And the one limitation to be fair is that the majority of these studies, although a range of polyphenol, rich foods have certain associations in the epidemiology, the interventions of really narrowed in on blueberry anthocyanins because they're very rich or Concord, grape juice, and they haven't really expanded out. Although there are a number of studies that have looked specifically at cocoa flavanols as well. And overall, the direction of effect in this body of evidence is, is good. Now, there are a number of like additional factors that need to be considered then as we relate the potential effects of interventions to long term protection and prospective cohort studies, because as some people have rightly argued, well, if you're seeing an effect in a six hour post ingestion study, that's an acute improvement in things like reaction time or, or verbal recall, or, you know, so how, how are we then to extrapolate potentially an acute effect to chronic effect?

Alan Flanagan:

And that might come back then to this relationship between vascular function and BDNF because BDNF is typically not considered to be an acute response. So the short term effects appear to relate to enhance cerebrovascular blood flow, and a number of short-term intervention studies that have looked berry anthocyanins specifically have shown that the peak improvements in cognitive function have occurred around 90 minutes and six hours after ingestion. And actually then if you look at the peak improvement in cognition, in those studies, what you see is that correlates with the peak in Cerebra vascular blood flow in that period. So that might underlie acute benefits, but as far as chronic benefits go, it may relate more to this relationship between this enhanced blood flow and then brain derived neurotrophic factor increases, and BDNF also increases through polyphenol and flavanoid intake through other mechanisms.

Alan Flanagan:

And that might explain more chronic benefits. I.E. sustained activation of the BDNF pathway providing some explanation of some of the protective effects against memory degenerating conditions like dementia and Alzheimer's, and also providing an explanation for synaptic plasticity, this process, we just discussed this strengthening of learning and memory processes. So, you know, yeah, again, overall, you know, we do have this temporal discord often in nutrition science, where we're dealing with associations in epidemiology over seven, 10 plus years. And then we're kind being asked to like, relate those observed effects to interventions that might be

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over one day or over 12 weeks. But I think the important thing here is to realize that there's quite a strong biological plausibility based on the mechanistic work that we have and based on the short term intervention studies and the studies that have actually looked at circulating levels of metabolites, that these compounds specifically Anin citrus flavanols and cocoa flavanols exert these effects and all of these cognitive effects have been demonstrated. And yes, they are. Short-Term interventions up between the mechanistic research that we have on the pathways that these compounds work through to the intervention studies. It is congruent with the observations that have been shown in longer term perspective, cohort studies overall,

Danny Lennon:

A at this point, maybe let's turn to vitamin D. And this is one that no matter what the health outcome is, is always carries some degree of, of debate around it. But in particular relation to cognitive decline, there's probably no better person we could ask about this than, than you Niamh given as you've actually published in this area. So there's a lot that we could potentially walk through. What is a good starting point?

Niamh Aspell:

When you think of the basics of it, when we talk about brain health, what we want to do is reduce neuro inflammation and protected the blood brain barrier. Also going back to the, the basis of vitamin D and the vitamin D receptor and it's present, it's also been, you know, established it's present in the brain, whether it's actually active and exerts effects, there is, is unknown. But we do know that vitamin D is, you know, it's a steroid hormone. It does have that ability to exert some really potent effects in terms of inflammation and have a impact on the immune system. So that has sparked, I suppose, a lot of interest in vitamin D research and, and brain health. There's a lot of correlations. There's a lot of associational studies around this, and that's because typically a lot of these vitamin D studies are just looking at associations between vitamin D levels and cognitive decline.

Niamh Aspell:

But one thing with vitamin D is obviously our risk for vitamin D deficiency increases quite a lot as we get older. So older adults will have a reduced ability to metabolize vitamin D they'll have less sun exposure if you're in a residential facility and not in a community dwelling, you're going to have really low levels of vitamin D and supplementation use isn't that high, even in, in people who are living in a nursing home or that facility. So typically when you look at like population levels of vitamin D and correlate that with cognitive health, you'll see that there's a market increase in, you know, cognitive decline in people who have vitamin D deficiency, but it's not looking typically at the bigger picture in terms of the, the ability to metabolize vitamin D and how old high of vitamin as you get older.

Niamh Aspell:

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So I still think there, there was, you know, a lot of base, there's a lot of observations on studies. A lot of the, especially the large US studies and the Nurses Health Study, where they've focused a little bit more on like vitamin D supplementation at like a very low level and calcium. And they've extrapolated that to show like different novels of cognitive health and cognitive decline. There's very little done in terms of intervention studies. And there, there was a, a couple of studies, one of the largest studies. It was a post hoc analysis done by Anne Wheeler. Their group is one of the most known, or, you know, if you look at vitamin D and cognitive research, a lot of the intervention studies come from this particular group. There's so many flaws in the vitamin D supplementation research when it comes to trial interventions.

Niamh Aspell:

And this is based on all of the stuff that we know about vitamin D research already in that there's no standardized way of determining deficiency. Well, there is standardized ways, but everyone defines it slightly differently. So the criteria for deficiency is very, very different. I remember doing a lot like a meta analysis years ago, looking at prevalence of vitamin D deficiency globally in different countries around the world. And it ranged from zero to a hundred percent prevalence of deficiency, vitamin D depending on what criteria they use. So when you look at vitamin D studies and their correlation with cognitive decline, it can be, there's a lot of freedom, I suppose, in the researchers, in defining what their cutoff is for vitamin D deficiency, some would define it as less than 75 nanomols. I think, you know, most people will say something like less than 30.

Niamh Aspell:

If you look at, you know, some of the recognized boards around bone health, maybe the international guidelines I'll say less than 30 is deficiency. Whereas a lot of the researchers in this area will say things like less than 75, less than a hundred for cognitive help, but there's no real basis on that. So they'll say that anybody who's older, who's got like a low level, which isn't particularly low is more likely to have a cognitive more likely to present cognitive decline. But I think there's a lot of other factors that need to be considered in that with the study population, for that initial, the the main intervention study that they'd looked at this was looking at patients or participants who were deemed to be cognitively healthy. So they had no mild cognitive impairment at baseline, however, in this particular study, they recruited all of the participants in a memory clinic.

Niamh Aspell:

So there had to be some basis for these patients or these people to be presenting at a memory clinic. So I think that was one of the initial flaws on that one. And then they gave them bolus doses of vitamin D, which we, in terms of looking at mechanisms or they exerting their effects. We typically the studies that give bolus doses. So really, really high levels. It can be up to 150,000 international units and as a monthly dose, typically don't exert effect. So what we would assume is that it's continuous maintaining continuous levels of vitamin D might be protective to some, to some extent. So I think for my own PhD, I took some of the, the cross-sectional analysis and tried to understand well, at what level should we be trying to target

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people if they're vitamin for their vitamin D level and a lot of these come to studies as well, it's where we should be targeting the groups that we should be targeting are those who are deficient not trying to boost people to extreme extremely high levels or giving them massive doses to boost their cognitive health.

Niamh Aspell:

It's getting people here at a, have a low level of vitamin D measured in their blood and seeing if we can Inc increase that where we're looking at in terms of preventative strategies, particularly for vitamin D, you're wanting to group people at a period of their life where they should be maintaining their cognitive functions. It's just typically in midlife, which is challenging. So none of the intervention studies or the longitudinal studies have really been able to do this to much of a degree in the sense that it's quite difficult to follow up. Somebody for could be 30, 40 years. Before you see cognitive changes, even in with disease like Alzheimer's disease, the progression of that is decades. It's not over a couple of years, so it can be a little bit difficult. And the intervention that I conducted, it was a feasibility study would give them 2000 units every day for a period of six months.

Niamh Aspell:

So that was deemed to be the shortest period of time where you would expect to see a change in cognitive performance in how healthy community dwelling from that. Then we looked at different cognitive performance metrics. Most of the literature and vitamin D and cognitive health will focus on one particular domain. So as I'd mentioned previously with cognitive functions, that they fall in different fears of ability and different processes, a lot of always focus on memory, but memory typically isn't the, especially the preventative early stage, isn't the first thing that maybe you should assess. It can be things like executive function. So ability to , I suppose, multitask or things that might have more subtle changes that you might be able to pick up on at an earlier stage. A lot of them focus a lot more in memory.

Niamh Aspell:

We went beyond just looking at cognitive assessment. So we would want to determine whether somebody, what their perceived level of stress was on day of the actual cognitive assessment their alertness, their sleep behaviors, all of these things that very much would influence your cognitive processes, or if you're to be, you know, if you had an exam one day, your performance on an exam is really going to depend on what your previous week maybe looked like. So for this study, we looked at everything and then, because it's a healthy cohort, we standardized the scores and looked at population averages to see if there's any, any difference. It was obviously the vitamin D levels improved over the course of the study, that those who were taking the vitamin D supplement, it had to be conducts of vitamin D research. Obviously you have to be quite careful in terms of seasonality because you don't want the placebo group to spend, you know, the summer months outside in the sun.

Niamh Aspell:

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And then everyone comes back with an increased vitamin D those, so that can be quite challenging as well. But what we showed is like an early in some indication towards changes in executive function and memory, which was measured using both pen and paper type tasks, but then also computer computerized tasks as well, which are a little bit more specific to pick up smaller changes that you wouldn't be able to detect in like a pen and or based assessment. There was significant differences between the two groups after the six months, however, when we adjusted for those other neuropsychological factors that most cognitive studies in research don't typically adjust for. So we, we looked at perceived stress, quality of life. We did an automated computerize alert task as well, sleep quality and sleep over sleep patterns over the previous week. And we factored in, I know we'll probably talk about cognitive assessments a little bit more, but we factored in other important things like pre-morbid IQ. And once you factored those in this, the effects were no longer observed. So I think in terms of the, the plausibility for vitamin D it's, there's quite strong evidence there, the correlations are all there, but I feel like the correlations are very much related to the, you know, vitamin D status. If you've got a good vitamin D status, you're likely to be of overall good health,

Danny Lennon:

There's so much on vitamin D. And, and what you said actually is a great example of a number of different issues that we could probably spend a lot of time talking about. And indeed, in the past, when we've brought up vitamin D we've discussed some of these. So for example, the, this interesting recurring theme that we see of this disconnect between what we see from this plausibility of having a sufficient vitamin D status over an extended period of time. Then when we look at intervention trials of vitamin D supplementation tend to be very underwhelming and oftentimes don't really show much impact on a variety of different health outcomes to the point where some people will then conclude, oh, there's just no point in looking at vitamin D at all. Which is different from what you're saying of, well, look, we have this plausibility and someone's over time could have an impact which becomes much more relevant.

Danny Lennon:

Then when we consider a disease process, like we've outlined here where it could take multiple decades we're also considering this as a preventative intervention we're looking at when is that intervention happening? So rather than supplementing someone over a short trial late in life, if we're looking at someone's vitamin D blood levels for multiple decades, because of either supplementation and or behaviors, that may be two very different things. And so all these different issues are wrapped been this one example that you've talked through. And it's just interesting how this tends to be a theme, I think with vitamin D and other nutrients, indeed. When we see this disconnect between overall status for extended periods of time versus maybe acute interventions of a, a supplement.

Niamh Aspell:

Yeah, I think so. I think it's important to look at the, the, on all of these papers is looking at the, where the baseline population are actually at when they begin and

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how much you can really expect to boost, particularly when it comes to cognitive performance. And it, it's, it's something that sometimes isn't really very clearly described in some of the cognitive papers, as well as whether they're trying to, are they trying to maintain current cognitive levels, they trying to boost people and try and get them to improve on some of these cognitive tests, which is probably you know, I, I'm not sure that should be the target or the aim necessarily there's other things like looking at neuroplasticity and looking at cognitive reserve and how we can maintain that function as we get older. And what we need to do with these studies is to make sure that we're maintaining levels.

Niamh Aspell:

I, I don't think the aim here is to make, you know, to make people improve in terms of their cognitive performance. And then when we come to improving cognitive performance, that goes to people who already have pathological changes. And you're either trying to, you know, if we're trying to improve somebody's cognitive, who has pathological changes, that we have been unable to this point to find a drug, to help improve like nutrition in terms of vitamin D status, is it that potent that it's going to have that much of an effect that it's going to reverse? These neurodegenerative changes that we're unable to find any pharmacological substance that is able to, to do that. So I think that should be typical. I think that should really be the focus in terms of it's it's long term preventative or long term supportive strategies and a lot of these interventions, like I think all of the interventions that I'd looked at in, in my thesis and all of the cross section or longitudinal analysis, just didn't follow people up for a long enough period of time, which is usually the, the issue with these studies as well.

Niamh Aspell:

It just comes down to practicality and retention of these participants as well. But yeah, I think it's it's, especially that things like seasonality and those changes and a lot of them as well only assess this at baseline. So they, they might follow them up for 20 years, but they don't also follow up to make sure that they follow this same behavior that they had when they were 55 60 to see if they still have that same behavior at 80. So extrapolating something a way that you live 20 years ago and saying, well, that's the reason why you've got protective effects, neurologically it's quite a, it's

Danny Lennon:

A jump. And it's also then noting, well, what is the actual outcome we're we really care about in, in practice, in, in the real world, versus which proxy measure are we going to then pick? And the importance of selecting that appropriately as, as a, I guess we might touch on a bit later, okay. With that then we'll that maybe sets us up for the omega three fatty acid, because I think some of the issues related to vitamin D supplementation could also apply here in, again, a number of health outcomes, but in, in terms of what we know about a omega threes can you maybe, again, recap for us Allen of why this may be looked at what is the plausibility or the hypothesis of, of why this might be an intervention that could have some degree of success?

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Alan Flanagan:

Yeah, so, I mean, we know that basically nearly 60% of the brain's dry weight is lipid is fat and of the fat that makes up our brain 50% of that. So half of the fat that makes up our brain is comprised of polyunsaturated essential fatty acids. And in that regard, there's DHA and EPA. Now I know that they're not technically considered essential fatty acids because ALA is considered the essential fatty acids. We won't get into why that is not sufficient for brain health. But suffice it to say it's to do with the level of conversion and the primacy of DHA. So while we can get conversion and we can increase bodily EPA status from ALA alone, we can't seem to do that with ALA for DHA. In fact, there is indeed some evidence from interventions that DHA depending on the tissue compartment that you measure can actually be, be displaced if ALA is taken in really high amounts, you know, 14 grams of, of omega three ALA the precursor.

Alan Flanagan:

So of the fatty acids, DHA EPA, and then arachidonic acid AA would be of most interest to cognitive function and brain health generally. And they take on respective levels of importance depending on the life stage. So a Raonic acid is primarily considered of importance during the infant brain growth spurt from around the third trimester, 20, 24 weeks gestation onwards. It's really important in preterm infants to ensure, you know, proper achievement of like body weight and cognitive development and otherwise. But if we're looking today at the other end of the lifespan, so to speak and protection or preservation of cognition and, and brain health into aging, most of the focus then is on DHA. And the reason is that EPA in particular and ALA the precursor are actually quite low in brain tissue, right? So less than 1% of total brain fatty acids are ALA and EPA DHA comprises over 90% of the omega three fatty acids that we have in the brain.

Alan Flanagan:

Now that's not to say that there is no role for EPA in terms of preserving cognition. So EPA may itself reduce neuro inflammation. So EPA acts through these compounds, and DHA as well, which are anti-inflammatory mediators, and they're known as resolvins and docatrions, right? So EPA acts through resolvins and resolvins literally does what the term sounds like. It, they are mediators of resolving inflammation in the brain. So that's primarily how EPA appears to act EPA. There is some evidence from prospective studies that EPA can for example, lower risk of depression associated with dementia. And there's also evidence that there can be prevention of atrophy of the Amy amygdala with higher cerebral plasma levels of EPA. So there appears to be a role for EPA and that role may be in plasma. And this is very distinct from DHA, which I'll go into and we have intervention studies that corroborate the, certainly the antidepressant effective EPA there's been certainly more recent meta analysis suggesting that around a gram of EPA is a supplemental intervention.

Alan Flanagan:

Now, how that, how that depression, how we extrapolate that to infer, you know, protection against dementia Alzheimer's is a different question. But the plausibility

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of EPAs potential role in the brain appears to be via this reduction in neuro inflammation. And the reduction in depression that appears to be through influencing central nervous system, and sympathetic nervous system activity. So, but EPA, like I said, is relatively low DHA is, is really the primary polyunsaturated, you know, fatty acid in the brain. I mentioned earlier, this two divergent pathways associated with amyloid beta plaque processing. And that one was non-amyloidogenic, and that metabolizes this protein, this amyloid precursor protein and reduces beta amyloid levels. And then we've got this other amyloidogenic pathway, which results in disordered processing of APP and the buildup and accumulation of amyloid beta protein fragments.

Alan Flanagan:

And so when brain phosphate membranes are enriched with DHA, it appears to divert amyloid precursor protein through this non amyloidogenic pathway away from producing amyloid beta protein and, and consequently plaque. It may also directly suppress. So it's, yes, it's, it's influencing the, the dive, the processing pathway of this APP but it might also directly suppress the amyloidogenic pathway itself. And then it also, like I said, as it acts through an anti-inflammatory mediator and then there's a role for DHA in membrane fluidity or increasing membrane fluidity or decreased DHA concentrations associated with membrane rigidity and that inhibition of appropriate cholesterol metabolism. And so DHA appears to have a number of protective effects against the cholesterol mediated, amyloid, beta processing and plaque production. So at this mechanistic level, and we, we know that DHA at various stages you know, certainly in the is rapidly incorporated into the central nervous system and has these neurological mechanisms.

Alan Flanagan:

And so then we get to the the epidemiology and in terms of dementia, Alzheimer's one of the most consistent associations across populations is in relation to fish and specifically oily fish consumption. And we've seen reductions, there's a number of cohort studies over periods of seven to 10 years, depending on the, the cohort study that have various. So there was the one of a French cohort that was based around Bordeaux, Southwest France. There was a 34% lower dementia risk over seven years in that cohort. Now, again, coming back to the importance of other related factors in dementia, Alzheimer's risk, high fish consumption, correlated with education level, higher education tended to correlate with higher fish consumption. And once they adjusted for education, that association with Phish was no longer significant. But again, we've seen in other cohorts, there was a Dutch cohort where fish, they looked at fatty fish specifically that was associated with lower risk for cognitive impairment.

Alan Flanagan:

But when they did the fatty acid analysis, what was interesting is that DHA was associated with the 19% lower risk, but actually there was no association for EPA or ALA, right? And this is important when we're thinking back to the mechanistic processes that each of these may act that I just described. And then we have, again, Martha, Clare Morris's research. So two major cohort studies. So the MAP study the Memory and Aging Project, Chicago based, and then the CHAP study, the Chicago

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Health and Aging Project. And both of those studies cohorts found associations with Phish consumption at a minimum frequency of once a week. That seems to be the minimum effective dose. And then two might two servings a week of oily fish may confer that maximal benefit. And again, when they separately analyzed fatty acids, DHA specifically was, was the one associated with reductions in Alzheimer's disease risk, whereas neither EPA or ALA were. There's another, a number of observational studies some born out of RCTs.

Alan Flanagan:

So sort of secondary analysis, subgroup analysis based on RC and some others that have used various MRI outcomes based outcomes to look at some of this. So one was at the Framingham offspring study. So that's a cohort study, but what they looked at in a subgroup of this study was red blood cell DHA levels a more reliable tissue compartment for looking at DHA compared to say, plasma or serum where DHA turns over really quickly and what they looked at, and that was total cerebral brain volume and cognitive testing. Again, what they found was that the people with the lowest had lower cerebral brain brain volume and performed worse on those cognitive tests. And then there was the women's health initiative intervention study. And there was a component of that study where they had a brain MRI component in the research.

Alan Flanagan:

And this was looking at MRI the MRI scans eight years after their baseline omega three red blood cell analysis was conducted. And what they looked at was the omega3 index, which we've discussed about before, which is the combination of both EPA and, and DHA and red blood cells. However, it primarily reflects DHA for a couple of reasons that we discussed previously. I want rehash, we can refer people to that. And what they found was that higher of omega3 index status or your red blood cell status for these fatty acids was associated with a 2.1 centimeter larger brain volume. And that was assessed by MRI. So th they're, they're the the body of the epidemiology, or indeed the secondary analysis or specific study components of interventions like the w HHI, you know, all really points in this direction of effect where we get to this discord is in relation to interventions, the interventions that have used DHA specifically have been really inconsistent.

Alan Flanagan:

And again, the lazy interpretation of all of this, that critics of nutrition science are fond of is just a hand wave off and say, aha, well, the interventions show something different, or they're disconnected from the epidemiology. Therefore the epidemiology is wrong. It's like, no, bro. Like we can try and work a bit harder to reconcile why we might be seeing this disconnect. And there's a number of things that may play into it in relation to DHA. The first is that in brain tissue, DHA turnover time is, is really slow. So the average halflife in brain tissue is 2.5 years for DHA. You contrast that to serum where the turnover time is a matter of minutes. And then there's also the baseline status of the participants, right? And then there's also the supplemental dose. So each of these are factors that play into the inconsistencies that we've observed with the interventions.

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Alan Flanagan:

So for example, one study conducted over two year in a UK population was looking at 500 milligrams of DHA, 200 milligrams of EPA. And that showed in otherwise healthy adults, older adults, no effect on cognitive function. Right. But what was, what was interesting is that the control group in that study didn't show any signs of cognitive decline because these were older adults. So it could be that the duration of the intervention was too short. Given the turnover time in the brain, it could be that the supplemental dose of 500 milligrams was too low and it could be the stage of intervention in the lifespan. A critical component of this research from the intervention perspective is that a lot of the studies don't control for fish intake. And so you you'll have control and intervention groups that often may still have background fish consumption, right?

Alan Flanagan:

It's, it's an absurd oversight, but it's one that unfortunately is present in a lot of these interventions. There's been a couple of more recent studies that have bumped up the dose. So 900 milligrams a day, which was in older adults, free from dementia, but with some evidence of age related, cognitive decline, they're otherwise healthy, but some evidence of age related, cognitive decline. And that was a 24 week study in which 900 milligrams of DHA did a improve cognitive function assessments. And then there was another study which looked at a combination of 800 milligrams DHA with another carotenoid called Lutein about 12 milligrams. We can come to Lutein later. There is some evidence of a benefit for Lutein for cognitive function. And that resulted in improvements in learning and, and memory rate. So obviously the latter study is slightly different because it's not a DHA alone study.

Alan Flanagan:

And so there may be, there may certainly be the fact that Lutein contributed to that outcome, but what's, I think notable about those two studies is the dose of DHA, right? Eight to 900 milligrams. And interestingly, if we were to parse what the levels of omega threes that you might get from two oily fish meals a week are that 900 milligram level is more what you would average out at in terms of that. So it may be that some of the other studies have, have gone too low. There's also just a general lack of wider interventions in this area. So there's a, there's a really a short pool of studies at this point. But I, I wouldn't be dismissing the observational associations and the brain MRI associations just yet on the basis of the inconsistent interventions, because I think there's a couple of, you know, very nutrition, specific issues we've discussed about in terms of methodology for intervention studies that are, that are influencing the purported inconsistencies in these, in these outcomes.

Danny Lennon:

Yeah. And especially as you may mention some of the aspects of the, the nature of this relationship that we're trying to evaluate in this particular case may actually be set up really well for epidemiology to answer some of those questions better than at least certain types of intervention trials, depending on how they're set up. And so

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yeah, to dismiss them based on the limited interventions that are there as seems a bit of a, a misstep, but is common as we've discussed during this, this,

Alan Flanagan:

There is one study that has just been published that I haven't had because I literally came across it yesterday and I haven't had a proper opportunity to dig into it, but I'm quite interested in it because what it was is a food based intervention. So it was a group in South Africa, it was 12 weeks long, but it wasn't using supplemental omega three fatty acids. It was in an elderly population average age of like 72 at baseline. And they specifically got them to increase their fish intake used like, like basically anchovies and, and sardines. Whereas the control group just had like meatballs and soy. And they used a couple of cognitive tests while also looking at red blood cell fatty acid status. And what the findings of the study are, or that there was an improvement.

Alan Flanagan:

And this was in the context of the, the modified the DASH diet, the modified Mediterranean/DASH diet called the MIND diet. But yeah, like I said, I, I'm not going to comment too much on it because I haven't properly dug into it, but I, I, it just, it flashed across the screen and I thought, well, this is interesting because it's shown obviously a benefit, but specifically this was a food based intervention targeting increasing omega three levels rather than a supplemental intervention trial. And that may be something then that is more congruent with. Obviously the observations we're seeing in epidemiology are not for supplemental forms of therefore food based specifically oily fish intake resulting in DHA and EPA status in the participants.

Danny Lennon:

And for people listening, we'll link to that study. So you can go and check that out. In addition to all of the other studies that we're, we're mentioning here. So given the, the time that let's, let's continue on here and, and try and wrap this up with the last couple of things that we did want to mention, I think it would be Remis not to finish off without referencing some of the B vitamins and some of the trials in this area. So I might ask you to discuss some of this Niamh because you did bring up the B vitamins earlier.

Niamh Aspell:

Yes, there's, there's a lot of work in this area and it was actually a big part of my studies; I studied in the University of Ulster and they've got the One Carbon Group there, which do a lot of research into, into B vitamins and across the life cycles. So from early age and this is around cognitive development as opposed to cognitive decline. So at during early life and then later life, so it's effects are wide spanning in that sense in terms of what they're extrapolating the mechanisms too. But essentially again, it's looking at either, you know, cell production in early life and cell growth. And then again in later life, it's the protective side of things, neuro protection looking at different, because B vitamins gets a little bit complicated because some of these studies are looking at specific B vitamins.

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Niamh Aspell:

Whereas, you know, obviously B vitamins all work in a, in a, in a process together. And it's more so the, I suppose the levels of some vitamin, if some, B vitamins compared to other components that, that becomes more important. And I think Alan you've mentioned this study, there's been a lot of research in that Rush Memory and Aging Project. And I think you also mentioned Martha Clare Morris has done a lot of the vitamin research in, in she's in the human nutrition research center in, in Boston. And she's done a lot of the research around dietary components of vitamin B. She had published a paper quite recently. I think it was only in the last couple of years, but she was looking specifically at food intake. So looking at green leafy vegetable intake, which I suppose, you know, it's directly related to, I suppose, vitamin vitamin B status and they wanted to look, she wanted to look at look, you know, consumption of green leafy V but then also looking at the specific nutrients that were contained in green, green leafy vegetables as well, and whether they had an impact on cognitive health in this particular cohort.

Niamh Aspell:

I think this particular cohort there's so many studies published on the rush memory clinic or the much their rush memory study. I think one thing, one of the, the biggest studies come out of this was looking at the social construct around the participants of this and the other religious order study. A lot of them were nuns and they were living in these shared cohabitation. So they had a lot of cognitive stimulation, a lot of social interactions and they showed that the, I think some of the strongest evidence from these studies around the cognitive health of these participants was around cognitive reserve based on their lifestyles. There's lots of lifestyle factors there. And then also based on the living circumstance in, in a lot of these participants as well, I don't think that discredits then, you know, the, the dietary side of things and might also support it in terms of, they had very similar dietary patterns giving their, their lifestyle behaviors then as well.

Niamh Aspell:

But in this particular cohort is it's a quite a large study. Their age range in this is quite broad, which I think is there should be a lot more subgroup analysis than there currently is, but it ranges from late fifties, right up until the cents up to 99, but it's a large population. So they can do subgroup analysis when they enroll the participants on this particular study, which comes back down to looking at these really extrapolating these findings based on cognitive outcomes and brain held outcomes is they all consent to be evaluated every two years, but they will donate their bodies, including their brain to to research at the end so they can identify. And they have identified the number of people with confirmed Alzheimer's disease, which is the only real strengthened way to really evaluate this.

Niamh Aspell:

So they did a battery of cognitive tests in this particular study, which is really important. So they accomplish a score of 19 different tests and this ranges across lots of different cognitive abilities. So depending on, on the person, you will have

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stronger abilities in different tests. So if I, you know, if, if they were to just look at working memory, it's very re it's very hard to say that everybody's going to have the same working memory ability at the beginning. And even though they obviously control for baseline cognitive status, their ability to change, that will depend on where somebody begins. For this study, they were a lot older. So the average age was 81 as with this study and a lot of the aging studies they're predominantly female. So this was 75%, almost 75% of of the population were female, again, really highly educated.

Niamh Aspell:

And they had an average green leafy vegetable consumption of very little, so 0.09 servings a day. So almost nothing to 1.3 servings per day. So it wasn't I suppose like an extreme consumption, this is just general daily consumption of green leafy vegetables. They did narrow it down to three particular vegetables. Let me think. What would, were collared greens as like, you know, cabbage essentially lettuce was another one and the third one has, has left my brain, but they essentially, they just did a, they looked at different quartiles of how much you were eating. And they did show that those in the highest quartile. So those who were eating on average 1.3 servings or day, or the median of 1.3 a day, had a slower rate, which they equvalate to 11 years younger in terms of their cognitive performance, based on these global cognitive scores, they had estimated how much they would anticipate somebody's cognition to decline if it was based on just age related decline. And they equivalent that to 11 years, they were 11 years healthier or more cognitively able than those who pretty much had no consumption. So that 0.09 consumption. What they wanted to do then was to try and understand well, is that related to particular components of the green leafy vegetables around vitamin B status, they looked at different different molecules or different components in regard to that. And they compared those compared those bioactive or nutrients against each other to see if there's any, the only one that they didn't correlate would brain function, that wasn't part of the B vitamins, was carotene. But they were able to show that there was a, an indication towards all of the B vitamin B components and better cognitive performance.

Niamh Aspell:

Another study, just to mention briefly in this, where they focus a lot, they focus specifically on B vitamin intake was published in that group that I mentioned a niche in the university of Olster a couple of years ago was about four or five years ago now where they wanted to look at B vitamin intake and bio biomarker status in relation to cognitive decline in healthy and older adults. And this is a four year follow up study. This one's I think quite interesting. And there's a lot of other similar researchers come out since where they wanted to look at vitamin B levels. In, in these particular, in these particular groups. Now they did use an MSC to test the content status, which is quite limited, but again, it just, they still were able to indicate that it had a protective effect in terms of cognitive to decline.

Niamh Aspell:

So maybe that was just underestimated slightly. And if they did some more complex testing, it would be a little bit stronger, but this is AF over a four, a four year follow

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up. They were able to indicate a small bit of a relation between that and homocystine levels. And this then follows on nicely, I think, to the fit cog study, where they, they showed that those beneficial effects for cognitive performance in participants with mild cognitive impairment who had elevated homocystine levels. So I think this brings in the complexity, particularly around the vitamin B research, is that the impact that different types of vitamin B are components of, of the B vitamins then influence others? So I know it's been shown quite a lot, obviously in cardiovascular health. We look at like B6 or riboflavin, and then it's not in all participants, which can mark results, but it can be in participants who also have an elevated homocysteine level. And that's been shown in a couple of different studies around B vitamin status. And that's why there can be a lot of confusion around, you know, when, when we see no effects. So potentially it's in certain responders or certain people who have got other attributes. So I, I think that's a, there's a lot of evidence there that follows quite a nice pattern, even though these are all separate studies, they've all investigated and an extended on our understanding, I think of B vitamin status and its ability to have impacts on neuro neuroprotective impacts essentially.

Danny Lennon:

So that leaves us with really one nutrient that we had planned to cover that we have not done yet. But in fact, probably what is one of the big topics or big issues to raise here and something, I think you've probably mentioned before, Alan, in relation to vitamin E is again, this concept of this disconnect. We see where we go and look at interventions and see null findings, and then people may be misinterpreting what that may mean. So in the context of vitamin E and cognitive decline and cognitive function, can you maybe touch on that issue of what we do see in those interventions and how you would more appropriately interpret?

Alan Flanagan:

Yeah, and this, this comes in the context of the, the range of epidemiology and vitamin E and neurodegenerative disease being very positive and, and often in terms of not just the effect size, but the robustness of the effect estimates in terms of accompanying confidence intervals in many ways more robust in some of these, in some of these studies than some of the other observational associations for the nutrients we've discussed. We typically see the benefits observed at a minimum over around 15 milligrams a day. And certainly there's evidence from some of the cohort studies that even higher than that up to like 26-27 milligrams a day will confer an even greater benefit relative to people consuming at least less than 10 and probably less than eight milligrams. We've got some cohorts that have had people in the entire cohort the Chicago, or sorry, the Washington Heights Inglewood project study was an example of this, where the demographic of the cohort, they all just had really low vitamin E intake, right?

Alan Flanagan:

So the comparison was the highest group had four milligrams a day. And the lowest group had like just basically little to no vitamin E intake and they saw no effect. And so we're seeing that there's this threshold in the epidemiology of what constitutes low, that will be a risk compared to higher levels. And it's at least under 8% or eight

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milligrams a day. And this has been corroborated by brain autopsy studies, which have shown that it's not necessarily alpha tocopherol, which is typically what's used in interventions that might have neurological activity, but gamma tocopherol. And that was again from the, the, the Chicago, the rush memory and aging project. They did a brain autopsy study of PE brains that died healthy with no evidence of neurodegenerative disease and brains that died with dementia Alzheimer's and looked at levels of tocopherols, total vitamin Totinos in the brain.

Alan Flanagan:

But specifically what they saw was the gamma tocopherol was the one that was higher in concentrations of healthy brains. Now. So you've got these associations that compare to very low levels of intake. Higher levels are beneficial. You've got associations in terms of biomarkers of vitamin E there's. There's no association necessarily other than the autopsy studies. If we're looking at plasma levels, the associations are not for any isoform of vitamin E, but are for total vitamin E total plasma levels of tocopherols and Totinos. And then we have these intervention studies and, and this, this, this vitamin E example has been used in multiple of the papers, knocking nutrition as a science, "this is why it's unreliable", but again, it's a lazy criticism because the low hanging reality here is that the interventions have asked the wrong research question and tested the wrong hypotheses, right?

Alan Flanagan:

The observational findings found apples and the interventions went and tested oranges. So the interventions, the associations in vitamin E epidemiology are for dietary intake, right? Whenever there has been a separate analysis for supplemental vitamin E intake, they have not found any effect of supplemental vitamin E intake. So what do the interventions do? They went and tested supplemental vitamin intake. The Associa are primarily for total vitamin E right, whole food vitamin E the eight isoforms, even though we primarily have alpha tocopherol as the major circulating isoform, but they've gone and used a synthetic version often of just alpha tocopherol on its own, even though based on the autopsy research that may not actually be great in isolation for cognitive health. And they've also tested people who are completely replete with vitamin E in both the intervention and control group. Whereas the epidemiology has found the benefits observed when people are consuming less than eight milligrams a day, compared to over at least 15 milligrams, even greater magnitude higher than that.

Alan Flanagan:

So they haven't tested the right comparison. They haven't tested the, the same exposure from the epidemiology, and they haven't even tested the, the same form of that exposure. And so ultimately you get this disconnect, but this disconnect is, is blamed by these methodological mishaps, essentially, that we've been discussing. And what I find quite interesting in that, in one of the intervention trials, again, this was the women's health initiative, which looked at 430 milligrams of alpha tocopherol and cognition in women over, I think this was maybe five years. They did. They actually did a subgroup analysis in this study relative to baseline vitamin E intake in the group. And while the overall analysis of the intervention was that there

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was no significant effect on cognition when you stratify people by baseline intake, they did find a benefit of supplementation in people with less six milligrams a day at baseline and women with less than six milligrams a day at baseline.

Alan Flanagan:

Now, if we think about what the observational findings have shown in their comparisons, that's a finding as a threshold of, of low baseline intake that is consistent with the epidemiology, but, but that hypothesis has not really been taken forward from that subgroup analysis and tested directly in its own intervention. So I, I think that the vitamin E example, as it relates to neurodegenerative disease and the, the purported discord between the epidemiology and RCTs, I is one of the best learning points that any student of nutrition can use to realize that there can be, you know, the same conceptual exposure. Yes, the RCTs have tested supplemental vitamin E right, but that's actually not really the right way to think about what they've tested. They, they quite literally have asked the right wrong research question. If we're, if we're te, if we're using epidemiology as a springboard to then ground the design and execution of an intervention, they've asked the wrong research question, and they've tested the wrong hypothesis.

Alan Flanagan:

They've tested a hypothesis of whether a synthetic isolated, single isoform of vitamin E in supplement form can improve cognitive in people, otherwise replete with vitamin E. That is an entirely different question and hypothesis to what we've observed in the epidemiology. So, yeah, I think, you know, the vitamin E question because of the intervention trials remains open, but I think there are very plausible methodological explanations as to the interventions came up with nothing. Because as I said, with the crude analogy, the observational studies found apples and the interventions went and tested oranges.

Danny Lennon:

So if we start trying to turn this into to some conclusions, and before we maybe summarize some of what we discussed, there's two different issues related to the actual research in this area that are interesting points for people to consider. Some that you have just summarized there, Alan of actual issues to do with nutrition research more broadly, that are well exemplified in some of these examples. And then there's also the other issue related to methodology that, that you've highlighted Niamh, of when we look some of the assessments for say cognitive health in this area. And this can be an important factor to consider when we're talking about this specific area. Yeah,

Niamh Aspell:

I think I suppose, and even just having those conversations to the last hour, I think that the most important thing is the eligibility criteria and their recruitment of participants with the, these making sure that they make sense in terms of the observational findings. So if you're looking at cohort, if you're, if we're seeing that people with deficiencies are the ones that are most likely to have poor count of

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health, and we should be recruiting deficient participants, then we need to go on and determine, well, what, at what stage are they in terms of their count of health? Is it, you know, cognitive health in middle in midlife, where there is very little change or is there early changes, or are we talking about pathological change in Alzheimer's and dementia when you decide which group that you're interested in, where you think the effect is going to be, then you can decide how you'll determine that.

Niamh Aspell:

So whether that's true a diagnosis, whether that's true, a cognitive assessment, the, and then beyond that, then you need to say, well, what are the endpoints that will really, really be able to test if there's an effect happening here as well. Things like cognitive assessments, if you're looking at very early stages and, you know, either preclinical or early clinical stages of my cognitive impairment, simple pen and paper tasks are not going to show much, unless you follow up that person for an extended period of time, the minimum period I suppose, is either three or six months for a repeated measure, but it should be repeated measures over a duration of, you know, five to 10 years. If you you're talking about early cognitive changes, if you're looking at reducing that time period, then you'll need more specific tests or you might need to focus a bit more.

Niamh Aspell:

And this then depends on research funding and the commitment of the not commitment, but how willing the research participants are to give cerebral spinal fluid, to take part in functional MRI and to do some more of these these more objective measures, if not, and if it's a, a research study that's maybe limited in, in funding, then at least has to include like multiple domain specific function tests. There's lots of tests that they have been validated to use to be used together. And they're accept by research participants, because again, you know, there's obviously going to be, if you're recruiting people for a memory study and they're 65 and they're cognitively healthy, and then you say you're going to present them an hour of tests that will assess their memory. That's a nerve-wracking process for somebody at that age to do those tests because it's, it's very, if, if you determine that they've at a low, a cognitive ability at stage, there's not much that you can do.

Niamh Aspell:

So there's a lot of, it's very, it's very difficult to recruit participants into memory, into memory based studies. So there is, there is that that component, but then you have to look at the broader aspect of who, who the participant is that you're recruiting and all of the interventions and studies that I've looked at for cognitive health, none of them have assessed to premorbid IQ, which is highly correlated to cognitive performance and how you're going to perform on, on these tests. So you can have somebody who's got really high, really high premorbid abilities. They've got a high IQ, there've got high educational attainment and they'll score really well within a normal range on a cognitive test, but it might not be their normal. So you should do some there's an assessment, which is essentially just a literacy test, which then can quantify people into their different IQ categories.

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Niamh Aspell:

And you can at least then control for that to a certain extent. But it's important to look at pre-morbid IQ as a part of that as well. Or if not to ask them about their subject memory to ask them, okay, you've done well on this test, but do you feel like your memory is the same as it was now as it was maybe three or four years ago, additional factors in terms of cognitive assessments, get beyond just looking at the certain domains is looking at other you know, cognitive health is directly related to other psychological processes. Okay. So there's like obviously sleep anxiety, depression, they should all be assessed as well to varying degrees. They will impact cognitive performance. They're all directly related to you know, mental fatigue when you're doing a cognitive battery, it's important in the what flow you do those tests.

Niamh Aspell:

So if you're going to look at something like attention, it's important to maybe do attention first before you spend another half an hour doing all of the other memory assessments. And if there's other assessments involved in the day, like taking blood samples if there's other parts of the test that they might be nervous about, or if they're waiting to do the memory test, do the memory test before you do the other assessments as well because anxiety on the day will also have an impact on performance. The final thing I'll mention is when it comes down to the statistical analysis is that there is measures that you can, there is tests that you can apply when being a reliable change index, which specifies the amount of change that patient must on a specific psychometric instrument or test between measurements. So if you're going to measure their cognition at zero months, three months, six months, that you would expect to see for it to be a reasonably, you know, due not due to measurement error or repeated measures, it's what you would expect to see as a result of either the intervention.

Niamh Aspell:

What I think is good, if you can't afford to do like an fMRI study, which are expensive and you can usually them in small sample sizes is there's loads of mobile technologies now, which are able to monitor things like changes in activities of daily living. And that's what we're really interested in. So somebody could have small memory changes, which don't have any impact on their daily today life, but you might be able to detect earlier things if somebody if it takes them a little bit longer to do certain tasks, if they're unable to do tasks that they were able to do previously, but then also to have input from people around them, like their family members to see if they have noticed a change as well. So a lot of these cognitive studies usually limit the interaction to just the participant, but there is newer studies that are enrolling participant participant caregiver and participant family members, which is important as well in terms of observing minor changes, which is what we see in early in early mild cognitive impairment that we can't really pick up on some of these other tests, which I think are the things that need intervening on as well. So supports in those.

Danny Lennon:

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So maybe the, the final thing I'll ask and I'll, I'll ask you Alan, and if there's any disagreement on, on your behalf, me, you can let us know, but I, in terms of, if people are now thinking, okay, there's these areas where there's still many open questions and certainly in relation to nutrition and cognitive function and probably more globally, just brain health. There's many open, interesting questions we could look at, but what can we relatively confidently conclude as it stands right now? What are some statements that we could make with a general degree of confidence? And that might even be just to say, we, we don't know, but what are the things that you think people should take away as, okay, what does this evidence in this broad sense of nutrition and brain health? What are some statements that we can make some conclusions about?

Alan Flanagan:

Yeah. Coming back to this idea, we, I mean, we started with dietary patterns and we can come back to dietary patterns. And Niamh had mentioned that study and looking at MRI and more advanced techniques as it related to Mediterranean diet adherence. And you know, what I'd be really interested to see is the effect of that on the MIND diet. So again, the MIND diet was the product of, of Martha Claire Morris and colleagues' research. And it was basically identifying that the Mediterranean diet had certain components that were cognitively associated with better cognitive health, but potentially missing some other specific food based recommendations. And similarly, the DASH diet had some components. And so they took both of those diets, but made it more specific to the wider research for foods. So for example, the DASH diet makes no recommendation for other than vegetables, generally speaking.

Alan Flanagan:

Whereas the MIND diet makes a specific recommendation for dark green, leafy vegetables. They make specific recommendations, the DASH diet makes specific recommendations for fruit. Whereas the MIND diet makes specific recommendations for berries specifically when, when we look at a lot of the nutrients we've just discussed and we work then backwards to food sources, what we tend to see are these foods that are dark green, leafy, veg, whole grain, nuts polyphenol-rich oils, like olive oil, flavanoid rich foods, whether that's a range of like berries, cacao and otherwise. And so, you know, we, we, we have this, you know, overall dietary pattern that is associated then with, with reduced risk. And some of the analysis is for example, have shown that, you know, you you'd get a protective benefit only with the highest level of adherence to a Med diet or a DASH diet, but even with average adherence to a MIND diet.

Alan Flanagan:

So I'd really like to see that level of scrutiny brought to the mind diet, but in the, in the interim, as far as like some of the more robust cognitive of brain based outcomes go largely the mind diet is confined to the us cohorts. Although there's been a recently published study from Australia, which found lower risk with a mind diet. So that was the first time it's gone outside of north American shores. So we look at a lot of these food groups and they are consistent with lot of the patterns in the Mediterranean diet. We, we think about those food groups at the level of say, for

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example, specific nutrients that we've discussed and they're food based sources. And, and there, there are, you know, aspects of a total dietary pattern that might be more specific within that.

Alan Flanagan:

So for example, oily fish specifically food-based vitamin E like avocado almonds oils, like vegetable oils, green leafy vegetables flavanoid or polyphenol rich foods like we've discussed coffee intake, mixed berries, anything with that dark level of pigmentation, high cacao chocolate and you know, moderate servings of red wine. The B vitamins, like Niamh said really mixed epidemiology, but the interventions have been positive so far, but again, you know, trying to, rather than trying to parse, you know, individual B vitamins it's, as likely as that, again, the component food based exposures give us, you know be complex, so to speak. And again, that's like foods like dark green, leafy vegetables, fish, other fruit citrus fruits as well. And, and then specific polyphenol, rich oils, like extra Virgin olive oil. So, you know, we, we can parse some broad general food based recommendations from this literature that fit within the context of a total dietary pattern.

Alan Flanagan:

And the evidence overall would suggest that that dietary pattern is associated with a, a lower risk. And we certainly have a varying degrees of intervention support for that, and, and certainly a lot more biological plausibility support. But yeah, overall, you know, coming back to the real top of the line theme that we started, which was, is the absence of effective pharmacological interventions for this condition. You know, I think anytime, and we've talked about some of these serious outcomes, I think it's, the caveat is, look, you can do all this stuff, right. You know, you can have this diet, you can exercise and do your Sudoka, and, you know, the unfortunate reality is the people like the, these outcomes still happen. And this is the problem with the, the lifestyle and diet approach and why we shouldn't evangelize it and moralize it is because you can do this stuff and the outcome still happens.

Alan Flanagan:

And that's not to say that diet is not effective, but diet is not drugs. So, you know, at this point, I think we could say that these characteristics of a dietary pattern and those specific food-based recommendations that I recommended are the best food-based evidence-based recommendations that we could make at this time. And hopefully, you know, like adherence to that type of diet over time can lead to a meaningful contribution to a reduced risk of neurodegenerative disease, alongside an adjuvant to all of these other lifestyle and behavioral characteristics that we know are positive as well.