How to Slow Cognitive Decline | Dr. Peter Attia & Dr. Andrew Huberman

What is the story with neurodegenerative disease Alzheimer's in particular how can we offset it And perhaps as importantly how can we all slow our own cognitive decline Irrespective of whether or not we get what is called Alzheimer's dementia So Alzheimer's disease is both the most prevalent form of dementia and the most prevalent neurodegenerative disease So it occupies that unique spot Uh We're talking about roughly 6 million people in the United States have Alzheimer's disease That's one in uh let's see I mean about 2% of the total population Ok But that doesn't include those with mild cognitive impairment or predementia or other forms of dementia And of course the right metric is not what percent of the population which of course includes Children things like that It's you know so the function of age is age the major risk factor for having Alzheimer's we stay with glaucoma a disease I'm much more familiar with because my lab worked on it for many years The biggest risk factor for getting glaucoma is age Yeah the the greatest risk factor for cardiovascular disease is age The greatest risk factor for cancer is age Um We tend to not spend a lot of time talking about that because it's not a modifiable risk So you know we we tend to focus on modifiable risk factors Um So what else can we tell you just to give you kind of lay of the land So the second most prevalent neurodegenerative disease would probably be Lewy body dementia followed by Parkinson's disease Although the rate of growth of Parkinson's disease is the highest So I think we'd probably be most you know we those three diseases we want to really be paying a lot of attention to As you know there are a lot of other neurodegenerative diseases Every one of these things is devastating like multiple multiple sclerosis Uh A LS hunting disease these are awful awful diseases Um There are also other kinds of dementia vascular dementia is not Alzheimer's dementia but it is it produces comparable symptoms Each of these things by the way are slightly different Lewy body is a dementia It's a dementing disease but it also has a movement component So it sort of sits on a spectrum that's sort of you know I mean loosely halfway between Alzheimer's disease and Parkinson's disease Um we talked obviously about age being the number one risk factor Kind of not that interesting because you can't do anything about it So the real goal is as we age what are we doing to reduce risk Um well let's start with an important

gene the gene that everybody's heard of certainly uh came up a lot on the limitless special where Chris Hemsworth was um you know made the decision to reveal something that none of us expected when we started that whole series which was that he ended up being homozygous for the A OE four isoform So um maybe folks understand we have two copies of every gene So for gene X you have copy that you got from your mom and copy that you got from your dad And the A OE gene is kind of a unique gene and that it really it has three different isoforms that are all considered normal None of them are mutations So you have the E two isoform the E three isoform and the E four isoform The E four isoform is the og isoform That's the one that we have historically had as as far back as we can go We actually think the E four isoform offered a lot of advantages back in the day It's a bit of a pro inflammatory um isoform and it certainly offered protection against infections especially parasitic infections in the CNS which would have been a really important thing to select for 200,000 years ago How do parasites get into the CN Si mean we have blood brain barrier a thick skull I mean I'm not calling I'm not telling you you have a thick skull but but I mean it just seems like parasites and other tissues Would be an issue because what we're talking about here is brain disease but it also could have predicted it probably offered some protection outside of the brain as well Um Anyway the um the E three isoform I think showed up God I think 50,000 years ago and the E two isoform showed up very recently about 10,000 years ago Now today we realize that there's a clear stratification of risk when it comes to Alzheimer's disease that tracks with those isoforms So because you have two copies you basically have six combinations of how you can combine those genes It could be 222324333444 Um The prevalence of them is basically as follows 33 is now the most common three is the most common So double three is 55 ish percent of the population The next most common is the 34 which is about 25% of the population And then after that most things are kind of a rounding error So uh two threes and two fours uh would be the next most common Four fours are very rare and two twos are the rarest of them All two twos are less than 1% 4 fours are about 1 to 2% Um Very important point here is that the E four genes are not deterministic So they're highly associated with the risk but they're not deterministic There are at least three deterministic genes in Alzheimer's disease Uh One is called Psen one another one is called Psen two and another one is called A PP Those genes collectively make up about 1% of cases of people with Alzheimer's disease So they're fortunately very rare genes But sadly they are deterministic meaning if you have those genes

you do get Alzheimer's disease And what's perhaps most devastating about those genes is how early the onset is of the disease These are people that are usually getting Alzheimer's disease in their fifties Um So we do have a patient in our practice Actually she's spoken about this very openly um who's whose mom had one of these genes Um And she you know got Alzheimer's disease in her early fifties was I I think she might have made it into her sixties before she died But you know absolutely devastating consequences here Why do people with Alzheimer's die Because I know about the hippocampal degeneration hippocampus of course being an area of the brain important for learning and memory Uh but is their brain stem degeneration do they lose breathing centers or cardiovascular Usually what happens is it's sort of failure to thrive aspiration things like that Yeah So it's usually they just stop eating Um or they can't control secretions they aspirate they get a pneumonia or they really lose the ability to even sense like pain in their body and therefore like they'll get an ulcer and they don't realize it and it'll become cellulitic and they'll develop a horrible infection in response to it I see So it's a body vulnerability The reason I ask is yeah every once in a while a news report will come out and based on a legitimate um case study where um they'll do a scan on some person and discover that they're missing literally half their cerebral cortex like huge chunks of brain and they're functioning relatively normally And so here we're talking about a neurodegenerative disease of relatively it's widespread but there are a few hotspots of course in the brain that degenerate more profoundly than others and and the people dying So that makes sense It it extends to lack of peripheral awareness or control and then some some acute injury or infection got it Um You mentioned earlier some of the controversy right So what what what are we talking about here Well it it it's and I I do write about this at at at length in the chapter on Alzheimer's disease because I think this is a very important point right Which is the index case for Alzheimer's disease There's always an index case right You know there's there's the the quote unquote patient zero The index case was a woman who you know 100 years later we realized had an A PP mutation I was either A PP or PSEN one but she had one of these deterministic genes that led to a very early onset of disease which by the way without which we may not have come up with the diagnosis because had she just got Alzheimer's disease in her seventies it would have just been referred to as senility which is you know was not interesting enough to pay attention to Um But I think it probably set the field on the path towards an overemphasis on amyloid beta Um And it's not really clear how important

amyloid is uh uh which is not to say it's not important it is important and there's no ambiguity that amyloid is responsible for the um the changes that we see in the brain But it's not crystal clear because there are lots of autopsies that are done on people that are completely healthy and have died with no cognitive impairment and they're chock full of amyloid So what we don't fully understand is exactly what does removing amyloid do Um The other thing that complicates the story is there has been no shortage of drugs that target amyloid that have seemed unsuccessful And uh just to clarify when you say amyloid you mean people have died with their brains examining an autopsy and see that there are tons of so-called amyloid plaques um different than uh arterial plaques of course but within the brain so that the two hallmarks of Alzheimer's um uh histopathological would be plaques and tangles Um And even that now is of course coming under under question Um But for that's what we teach every neuroscience graduate student It's what we teach every undergraduate It's also what we teach every medical student Um and not just at Stanford but everywhere Uh So I have heard that the the link between A PP and whether or not one develops uh genes related to A PP and whether or not it's cleaved at one side or another this is what you were describing and and risk for Alzheimer's So it's basically a question It's a cleavage question right So A PP people with the A PP mutation I think have one extra cleavage site Um The the the the they result in one extra cleavage of amyloid and then it misfolds and the misfolding is is what the plaque is that's being created that also then predisposes them to the neurofibrillary tangles And um again but all this is under question now I mean this is what I was told and and when I look it sounds like there were some early there were some papers early in the chain of discovery Um and the research in Alzheimer's that um were either wrong because they were falsified intentionally There was there was an intentionally falsified paper on one particular amyloid uh variant and that clearly set the field back a decade because a lot of people went down that rabbit hole based on deliberately falsified data Um Then what happened to that guy I'm gonna assume I don't know why I assume it was a guy But what happened to that guy Yeah it's a good question Um I think I wrote one piece about it when it happened I actually reached out to the person who broke the story because I wanted to have them on my podcast and I I forget why he didn't do it I forget why he he wouldn't commit to it or something like that But I thought it was a little odd because I thought this would be a great way to talk about this Um I do not know what came of that scandal In other

words I I haven't paid attention to it for probably nine months So I don't know you know obviously the paper has probably been recalled but I don't know what disciplinary action was taken Um the field is I don't know I don't want to speak like I'm in the field because I'm not So I don't ii I wanna be careful what I say but I I think the field is probably in in a bit of a crisis because there's there have been so many bets placed on anti amyloid therapies and amyloid biomarkers and amyloid everything and we just haven't seen efficacy right So contrast that with cardiovascular disease where you know you have this a ob biomarker you you understand the pathophysiology of how it works You have drugs that target it So you have a biomarker So you give somebody a drug that lowers a ob you can measure a ob that's a really important and obvious thing to be able to do And then you have clinical outcomes which is oh when you take a bunch of people in primary prevention it takes this long before you see an effect in secondary prevention it only takes this long to see an effect right Different risk stratification all these different things We don't have any of that for Alzheimer's disease So we do use there are now serum amyloid biomarkers that we use and we do track these in our highest risk patients But only because we believe and I don't know if we're right by the way that lower is better And therefore if we make these changes to you and your serum amyloid levels come down that that tells us something about what's happening in your brain that's favorable But I mean I would hate to represent that we are practicing nearly the level of precision medicine there that we are in cardiovascular medicine when it comes to Alzheimer's disease maybe take a step back when it comes to brain health I think there are a handful of things that seem unequivocally true and there's a lot of stuff that is signal to noise ratio that's really low So the unequivocally true things for brain health are sleep matters Another unequivocally true thing for brain health is that lower LDL cholesterol and A OB is better than higher another thing that is unequivocally true is not having type two diabetes matters to having really being in being insulin sensitive insulin sensitive matters sleeping adequately matters having lower lipids matters Those three things are clear And the fourth one that is unequivocally clear is exercise matters specific form of exercise Uh Very I mean so I tried to answer this question on a recent A ma that I did because the answer is more is always better But if you if I I tried to have one of our analysts look at it through the lens of if you could only exercise three hours a week what would be the highest use case and our interpretation of the literature was if you could only spend three hours a

week exercising you'd be best off doing one hour of low intensity cardio one hour of strength and one hour of interval training