Staying Sharp – NYU
Tape NYU
THE DANA ALLIANCE FOR BRAIN INITIATIVES

CS: Good afternoon everyone and welcome to the Staying Sharp, Ask the Experts Forum. I am Camy Sleeman and I lead the Marketing and Communications Program at NYU's Comprehensive Center on Brain Aging. I will be your host for this afternoon. At this time I'd like to start by just thanking our sponsors for their generous support, so thank you to the Dana Alliance for Brain Initiatives, the Met Life Foundation and AARP New York. Their generous funding has provided this program to us free of charge today.

In a few minutes we will begin our panel discussion, but to start we have something special planned for you. It's a mini exercise program and it's led by a certified personal fitness trainer, Linda Meyer. Thank you, Linda, for being here.

LM: You're welcome.

CS: Linda has a Doctorate in Education, as well as a Master's in Public Administration. She's a certified personal fitness trainer and consults with public and private schools,

agencies and families on fitness instruction and community inclusion for adolescents and adults with autism. Welcome.

LM: Thank you so much. (Applause) I saw your faces when she said exercise. I want to see some smiles. We're so lucky to be here and I'd like to personally thank the Dana Alliance. That's my connection to being here today, so thank you so much. I'm the warm-up act. Actually, I am the brain warm-up act, to be more specific. And I get eight minutes of your time to try to get you ready to hear the wonderful presenters today who will talk about the relationship between mental health and physical fitness and brain health. But before they get you I get you. And the first thing I want to do is remind you, you've got to use it or you're going to lose it.

[BRAIN WARM-UP - NOT TRANSCRIBED]

CS: We're going to start with your panel discussion and there will be ample time after the panelists talk to ask your questions. So please, if you could hold your questions until the end. I'm going to introduce the panelists, Dr. Melanie Shulman, Dr. Stella Karantzoulis and Dr. Milton Biagioni. They're from the NYU Comprehensive Center on Brain Aging. And if you

could spend a minute giving the audience a little background on yourself and your area of focus …

MS: My name is Dr. Melanie Shulman. I'm a neurologist here at NYU in the Departments of Neurology and Psychiatry. I've been at NYU for almost 15 years. I spent the first half of that, actually, in the NYU Epilepsy Center, and I was always studying memory. And as time went on my clinic increasingly was exclusively memory, people who had memory problems. And so I shifted over to the NYU Alzheimer's Center, and there I wear two hats: half the time I see patients privately in a faculty practice called the Barlow Center, and the other half of the time I run part of the clinical core at the Alzheimer's Disease Center, which his a research center where we study aging and have people come in as part of a research program every year, checking on seeing how people get older in healthy and sometimes not-so-healthy ways. So that's what I do.

SK: Hi everybody. My name is Stella Karantzoulis. I am Assistant Professor of Neurology here at NYU. I'm also a clinical neuropsychologist at the Barlow Center for Memory Evaluation and Treatment. And in my practice I get

people who are primarily concerned that they're experiencing some memory loss. And they come to see me to get an evaluation done in which I give a whole bunch of different tests, and I look to see if, in fact, there has been a change in that person's memory. And then we try to figure out some ways that we can help improve their memory. And we're going to talk about some of those later on today.

MB: Hello everybody. My name is Milton Biagioni. I am a neurologist. I'm doing research at NYU, the Neurology Department. My main field of interest is dementing conditions and other degenerative diseases, and specifically Parkinson's disease and Alzheimer's disease.

CS: Dr. Karantzoulis, let's start with you and how the brain functions. I think the best way to discuss this would be to help us understand how brain function is represented in the brain and how aging alters the brain and the processes.

SK: Please feel free to let us know if you can't hear us. Camy, in answer to your question, really, the human brain has mystified people throughout history. I mean if you think about it, it weighs a mere three pounds and it's small enough to hold in

our hands, but it's really our body's most vital organ. Its complex network of 100 billion or more nerve cells actually orchestrate every aspect of our thinking, our behavior, our emotions, our perceptions. It really does define who we are. And so to talk about brain function it's really represented in our brain as patterns of electrical and chemical signals that travel between nerve cells. And it's these nerve cells, or these neurons, that are really the work horses of our brain and their fibers, they form connections called synapses between the neurons in our brains. When activated, a neuron sends as ort of low level electrical current that goes down the axon, or the cell body, and it releases these brain chemicals called neurotransmitters. Some of you may have heard of that. And these neurotransmitters, they diffuse across the gap between where the one neuron meets the other neuron, and they latch onto the receptors of the receiving neuron, and that's where it sets off this sort of cascade of changes in the receiving neuron, and it continues to send a signal throughout the brain. And if you think about it, it's like relay runners in a race where the one runner passes the baton off to the other. And that's how the signals really get transmitted.

When we talk about the aging brain, we do know a lot more about how it changes, or how brain function changes as we age. And this is a lot, in part, due to all these fancy neuroimaging techniques that have come out over the years, things like MRI – magnetic resonance imaging – or PET scans or diffuse tensor imaging, all these are fancy labels that we hear a lot in the news. Well, these have allowed us to take pictures of the brain and see how the brain works both when it's resting and when it's active. And what we've seen is that in fact there are changes that occur as we age. So, for example, starting in the sixth or the seventh decade of life, the brain starts to shrink. There are changes in brain mass. And this is especially true in the frontal part of the brain, what we call the frontal cortex, and in the temporal lobes. And this is important because the temporal lobes are where the memory system of our brain is housed, in something called the hippocampus. And in the frontal part of the brain, this is where we have our executive functions. So this is higher order thinking skills, like decision making, planning, organizing. And these are really where we do see changes from a thinking skills perspective in older people.

We also see changes in neurotransmitters. As we age, the brain starts to generate fewer neurotransmitters, so things like dopamine or acetylcholine – you may have heard of some of that. And that does correlate with changes in memory. It may also be the reason why we see a little bit more mood disorders, things like depression, in older people. We see changes in the density of the – I talked about earlier – the synapses, these connections between the neurons. We see changes in the cortex, this ridge-y, outer layering of the brain. It becomes thinner as people age, and that also has to do with changes in the synaptic density. And all of these changes do correlate with changes in our thinking skills, especially things like processing speed, which may explain why some people, as they age, become slower. So hopefully, Camy, that has answered at least some of the questions about brain function.

CS: Leading onto the next question, which is about forgetfulness, when is forgetfulness not a natural part of aging? And how can one differentiate the signs between normal forgetfulness, let's say, and a more serious condition.

SK: Abnormal aging, sure. I think, Dr. Shulman,

you wanted to start with that and then I can jump in with that.

MS: That, essentially, is my most common complaint of people coming into my office. They say that they are forgetful. And then it's up to me to try to distinguish between whether this is in keeping with the natural changes of getting older or does it signal something a little bit more significant? What are the red flags of changes or complaints about memory? So, forgetting the name of an actor when you're talking to friends, forgetting the name of the book that you just read or the author, those are things that really do occur commonly as we get older, and don't really signal anything particularly sort of significant. If there's no troubles in really being able to communicate well, that's a little bit more a significant thing.

Perhaps the most common telltale problem that I hear when people who accompany individuals who have memory complaints come into the office, they say they keep repeating themselves. You had this conversation, I told you we're going at two o'clock, and they keep asking me over and over again. That does raise a little bit of concern to my ear because it really does sound like that's loss of recall of having had that

conversation at all, so repeating things a lot is a little more significant than just perhaps misplacing a key one day or misplacing your glasses, that not so much. Other things that kind of raise red flags, if people come in and say their whole personality has changed, it's just not the same kind of person that they were. They're not interested in going out, they're not animated, they don't show the same amount of affection. That, again, is more of a concerning issue rather than just normal changes related to aging, related to others, more functional troubles. If people keep missing payments and they're having their electricity turned off, well that's obviously a more significant problem than simple forgetfulness or missing payments once or twice. Misplacing your car, forgetting where you parked your car, well that counts as a significant problem. So there's a spectrum of things. But, of course, and this is obvious, the more severe the problem, obviously, the more suggestive of a more significant problem.

SK: One of the things that I would like to add to that, and I think you will hear that repeatedly from all of us, is that just because you're getting older does not mean you're going to have memory impairment. It's not an inevitable consequence of

aging. Many people go into their 80s and into their 90s staying as sharp as they were. You're not necessarily going to forget things like Dr. Shulman talked about forgetting names or where you parked your car. It does happen to many people, but it doesn't happen to everyone. So just remembering that there's a lot of variability when we're talking about aging and in terms of our thinking skills. Okay.

CS: Speaking of being forgetful, you lead a very successful cognitive remediation program where you help your patients with learning strategies in terms of memory retention. What are some of those tips and strategies you could share with your audience today?

SK: That's a question that I get asked all the time, "What can I do to improve my memory?" Camy asked specifically about memory retention. What is important to know is that people have memory failures for a lot of reasons. So, for one, in order to remember something we have to learn it, we have to take it in, in the first place. So some people experience a change in which they're slower to take new information in. Other people, they're really quick to get the information in, but they can't hold it over

time, it just doesn't stick. Other people, it gets in there but then when it comes time to get it out they have trouble. They have trouble with retrieving the information there. And sometimes a little cue is what they need to help get it out. So when I see people I do like to think about where does this person have the problem? Is it learning, taking it in? Is it holding onto it? Or is it retrieving it? And that becomes important because when I try to come up with a strategy to help you improve your memory I need to know, are you not paying attention? Because I'll tell you, if you don't pay attention, at any age, you're not going to take the information in. So one thing is minimize distractions when you're learning new information. Turn the radio off. Turn the TV off. Don't listen to your conversation on the phone, don't talk to others. Focus and pay attention to the information so your brain is able to take it in.

If you want to retain something an excellent thing is make the information more meaningful. So repeat the information over to yourself many times because that is going to sort of help it get a deeper level of processing, so it does stick in your brain. Make an image. Use visual imagery somehow so that your brain can form a deeper connect. I always given an example

of when you're at a party and someone says, "My name is Robin," for example. How are you going to remember? I can't remember all the people's names that I meet. So what I do is, "Oh, Robin is wearing a red dress," and I think of a Robin, like a bird, that's red or wearing … associating with the color red, and so I think, "Robin with a red dress." And so that helps, for me, to make this association more meaningful in the brain. Anything you can do to visualize, to make it more meaningful, even writing it down – that's repeating it, but that's also making some sort of a visual cue for your brain.

That's some of the things. It's hard to do that in a nutshell, but there are simple things like that, that you can use in your every day to help improve your memory. And even, Camy, just some simple things like at your home, you know, we all, or many of us, have a tendency to come through the door and throw our keys somewhere. Organize your life. The less stress you put on the brain the more it's going to hold onto information. So always keep maybe a bowl or a key chain, somewhere where you can hang up your keys when you get home. Always put things in the same place. Just simple organizational stuff that will help

reduce and make things more efficient for your brain will go a long way.

CS: Thank you. Those are very helpful tips. One area that we haven't discussed is cognition. Are cognition and memory one and the same?

SK: This is a question I hear a lot too in clinic, and that is, "What's the difference between my cognition and my memory." Well, there really is no difference. The word cognition is really just this umbrella term that we use to talk about our thinking skills, so memory is one aspect of our cognition. Other things that, when we talk about cognition, that includes your attention, your concentration, your language, your ability to communicate, your ability to understand things, your ability to remember things. All of that, things that we call executive functions, like I spoke about before, are planning skills, are organizational skills, are decision-making skills. All of that we are talking about our cognition, so there really is no difference. Most people that do come to see us are concerned about their memory but that doesn't mean that there aren't other changes in your cognition that you can be concerned about.

CS: Occasionally, Dr. Biagioni, we hear about the term ‘cognitive reserve.’ What exactly does ‘cognitive reserve’ mean?

MB: Basically the term ‘cognitive reserve’ is used in a broad way to say how good is your brain to cope with damage. You know, people usually have neurodegenerative diseases, or what we are discussing now, of memory problems, when they are old. That means that that brain has gone a long way, 60 years of many things going on, like vascular problems, maybe some traumatic brain lesion, maybe some Alzheimer’s pathology. So it reached a point when the person starts having problems. Specifically for Parkinson’s disease we know that the specific changes that defines the diagnosis of Parkinson’s the specific pathological damage that we can see in the brain starts many years before the symptoms, so it’s not a night to day thing, it’s a progression and it reached a point where the damage accumulates and is more spread through the brain that you start having problems. That point is different from one person to another, and that’s the ideal basic concept that defines what is cognitive reserve. A researcher who studied patients with Alzheimer’s

disease, and he decided to see how much damage were in the brain autopsy studies and he tried to compare the mental function of these Alzheimer's patients, one to another, after they passed away, and the anatomo-pathologist did the autopsy, couldn't predict how good they were meaning, for example, they were patients with a lot of Alzheimer's disease pathology in the brain, but they had mild dementia at the time they died; and the opposite also they found, for example, brains with a lot of damage, mild demented; and patients with almost no damage, like a few specific Alzheimer's disease damage, with a really a lot of impairment in the cognitive functions. So this gap between what I see in the damage and what I see in the function, it is called like cognitive reserve, and we try to study these kind of things to see what makes a person to perform better regardless of the damage they have. And what they found, at least at that time, was like three major factors that define this concept, that the patients that did better, meaning that with more damage and good performers, they did have more leisure activities by the time they passed away. These people also had more years of education, so they studied longer. And these patients also have highly occupation attainment

(sic). This is like more complex, but one of the questions in this discovering was how many people work for you and how demanding was your job while you were actively working. These things show us that in some ways the brain can shape the way to cope with damage. A brain can be better prepared and can function better regardless the damage we have. And after this, many other studies came out, functional studies, functional imaging, that we call functional MRI, showing the differences between a young brain, an older brain, an Alzheimer's disease brain, and just to mention, a very brief and very easy way to understand, for example, they give the same task, a very easy task for the three populations, and the people that was really young, they performed the task and they activate a few areas on the brain, so like they were more efficient. So people older activated a larger part of the same area, so they needed to recruit more help, more neurons trying to work altogether. And when they compare it with an Alzheimer's brain, it even activated areas different from that area because it got more help from other parts of the brain. The three persons performed the task as good, but it's showing that the brain still has the possibility to compensate for damage, and that's

what's going to resurface.

CS: Dr. Karantzoulis, I'd like to get back to you for a second. One of the things that we hear about are computer games and that there are certain computer games that can help us with memory. Is there any validity to that?

SK: That's a great question and one that I hear all the time in practice, "Should I go out and buy one of those computer games that I see on the TV all the time, that they advertise?" And my answer to that is there really is, at this point, no good science to support me telling you, "Go out and buy one of those programs." So right now I think there are more than – and this may be an underestimate – but at least 40 programs that I know of that have been developed by different companies, with a lot of money, and they're trying to make a lot of money. And so they've come up with all kinds of fancy programs that promise to improve things like your memory or your attention. I'm interested in these programs. I think that there is potential, but I do want to see more science behind it. So there's one very popular company called Posit Science. They do have, in fact to the best of my knowledge this company is the only one that has a randomized,

controlled trial to support the efficacy of their programs in older, healthy adults. So what that means is that they partially funded a study that included many researchers from very big medical centers, including the Mayo Clinic, and they looked at does their program improve memory, both do they show improvements on their tasks over time? And can we see these improvements in other tasks?, so unrelated to the computer programs. And in fact they did show some improvement, so people that took their program benefited more than those who had no access to the programs. It wasn't a huge effect, but they did show some positive findings related to their programs. And when you look at the … I do run some research that's actually looking at this program, and it does have an appeal to me. It gets you to sit on the computer to work on these programs and to really try to do something new and engage your brain. And the way that they did it, their study, was one hour a day, for five days a week, across eight weeks. So it's really getting you to focus on this. And so I'm running a study that's using the same paradigm, the same time frame, and I'm hoping that we're going to get the same results, independent of that company, that shows there is some benefit. But right now,

would I tell you all to go run out and buy this program? No. Do you want to? I don't think it hurts. But there's really no good science at this point to show that it is something that you should go run out and buy. Hopefully, by this time next year there will be some studies that do support their efficacy.

CS: We've talked a lot about normal brain functioning and touched upon the aging process and the brain. Let's talk now about Alzheimer's and dementia. Dr. Shulman, is there a difference between the two?

MS: I think this would be a good opportunity to just review a few definitions. What is dementia? I usually say that there are three requirements for the definition of dementia. There has to be a loss of intellect, meaning there had previously been skills in memory, attention or language, but over time they were lost. The second thing is that it can't have occurred overnight, or over a week ago. It has to have been chronic, that it has to be existent for more than six months. Sometimes people say the definition should be greater than a year. And then the third definition is really not a medical one, but I often say it's something of a social one in that it has to interfere with your everyday

activities. And by that I mean it depends whether you're an astrophysicist or somebody who is not as intellectually challenged. Does that make a difference in their definition of when they attain dementia? The answer is a little bit ambiguous, but that's the third requirement, that it has to affect you in an everyday way.

Now, one of the most common reasons to have a dementia, but not the only reason, but one of the of the most common reasons, is neurodegenerative disease. So, within that very large category we've come to recognize that certain parts of brain, certain systems, certain neuronal populations, are particularly vulnerable to change dependent on what the different disease is. So, in the topic that we're discussing for the most part today, Alzheimer's disease, we know that the systems in brain which are most vulnerable to the earliest changes of Alzheimer's disease, as we've already discussed, occur in the midline of the temporal structures related to the hippocampus and the perirhinal cortex, it's just the really old parts of brain that are involved with memory, and including that structure that we talk about all the time, the hippocampus.

Other neurodegenerative diseases have

other populations that are vulnerable. In Parkinson's disease the population of neurons that are vulnerable occur in the motor systems that re in the brain stem, in the substantia nigra or in the basal ganglia, so those populations are preferentially affected in those illnesses. And another illness called frontotemporal degeneration, you can already guess because of the name, the frontal and the temporal regions are particularly vulnerable and progress over time. Lewy body disease is actually somewhere in between Parkinson's disease and Alzheimer's disease, and it affects mainly visual spatial processing and some aspects of attention and frontal function, and begins to develop very subtle signs of Parkinsonism. So the similarity between all these neurodegenerative illnesses is that each neuronal population begins with a preferred set of neurons that evolve over time to a dementia.

Alzheimer's disease is by far and away the most common for of neurodegenerative illness that occurs and because age is perhaps the greatest risk factor for Alzheimer's disease, it's almost become synonymous with dementia, even tough it's really just a subset within that larger category.

CS: Let's talk more about Alzheimer's disease because I think that's why most of us are here today.

MS: Alzheimer's disease is such a huge topic and it's taking an increasing amount of kind of news time and political time, and why would that be? And it's because this is an economic crisis. If the biggest risk factor for developing Alzheimer's disease is getting older, we know that the population is really aging. So at the moment there are approximately four million who have Alzheimer's disease, but in the next 25 to 30 years we're expecting that number to almost double. And so if there's going to be a huge increase in the number of people over the age of 80, because of all us aging baby boomers, then the predictability that a large number of those people will go onto develop Alzheimer's dementia is a reality that we have to face because it's going to be a real economic crisis.

Now, what is Alzheimer's disease? We've already sort of mentioned a couple of things about … we know the pathology of this illness very, very well. So in 1906 Alzheimer looked under the microscope and he recognized in a relatively young woman, she was in her 50s, certain pathological changes

that he could see under the microscope, which we still are focused on today, which are amyloid plaques and neurofibrillary tangles, and we spend all of our time sort of really dissecting the complicated roles that these two substances play. It's not simple what the relationship between the pathology and the illness is. As Dr. Biagioni already mentioned, there is often a discrepancy between how much pathology is present and how demented somebody is. Increasingly, we've come to recognize that the closest correlate between cognitive trouble and pathology is not so much with amyloid plaques, which is really what we spend a lot of time talking about, but it's much more closely correlated with how many tangles there are, and we touch upon that later.

But in any case, these illnesses, both on a public health as well as an economic perspective, are really taking an increasing amount of our focus because of just what a devastating impact it's going to have in terms of a social solution to it.

CS: The term that we often hear when we hear of Alzheimer's disease is mild cognitive impairment. If one has mild cognitive impairment, does that eventually lead to Alzheimer's

disease?

MS: Well, that's a really fundamental concept in sort of neurodegenerative illness. This notion that, you know, one doesn't wake up one day with dementia, it's a very slow, insidious process. And while now it seems somewhat obvious that there would be kind of a pre-stage before somebody was actually demented, that they might have milder trouble before they actually develop dementia, that was really a huge turning point in the field of study, being able to recognize a population somewhere in between normals and demented. So mild cognitive impairment has become a real concept changing sort of revolution in the ways of thinking about neurodegenerative illness.

As we mentioned earlier, the beginning changes of Alzheimer's disease begin in memory systems, and so the first cognitive difficulties that occur in Alzheimer's disease are related to memory. And so people who have the beginning changes of Alzheimer's disease often have what's called isolated memory impairment or isolated amnestic mild cognitive impairment. The analogies that I already presented earlier, that all neurodegenerative disease present with a beginning or prodrome

symptom applies, so if people are going to develop the beginnings of frontotemporal degeneration, they're going to have isolated trouble with frontal function. If people are going to go onto develop what's called a progressive aphasia, they're going to develop isolated language trouble. So being able to dissect with the neuropsychologist as well as he neurologist, what areas of cognition, as well as what aspects of neurologic examination are vulnerable really gives us a lot of insight into where we can guess the illness will progress.

The really important thing is, let's say somebody comes in and is given this diagnosis of the in-between stage of mild cognitive impairment, is it absolutely inevitable that they're going to go onto develop dementia? And even though we've been studying this so rigorously, the answer is still not clear cut. In general, and we've become much more sophisticated about being able to really delineate those individuals who seem to be most likely to go on to develop trouble, but in general, at the moment, the diagnosis still is a little bit equivocal in terms of what the likelihood of going on to develop dementia is. The numbers that I give related to people who have amnestic mild cognitive

impairment, what's the likelihood of their developing dementia over the next three to four years? In general we say two out of three people will go onto develop a dementia syndrome over a certain period of time, but approximately one third will either stabilize, or sometimes even get better, in which case we're thinking that the underlying cause of the memory problem was not, indeed, Alzheimer's disease but perhaps was looking similar to Alzheimer's disease. We know that memory problems can be caused by other things that can sometimes improve, and we haven't gone through that in a lot of detail. But there can be medical problems that can resolve over time. There are issues related to thyroid function or vitamin B12, which sometimes can, if tweaked, can improve memory. Sometimes the issue is, could depression be the issue that's looking like the beginnings of Alzheimer's disease, but actually being treated for the depression can improve the memory symptoms. So perhaps that can explain part of the heterogeneity in the individuals who have mild cognitive impairment and what goes on over time.

CS: So if we suspect that a loved one may exhibit one of the signs you just mentioned, or has some problems with

their memory, what would you say is the first step in seeking medical help?

MS: Well, I think it goes without saying that if there seems to be kind of some health issue, that you should report to your internist, to just really get an overall sort of medical checkup. And we're going to touch on some of the many medical issues that can complicate and contribute to memory trouble, so that would be by far and away the first thing to do, to get your heart checked, get your metabolic profile checked, make sure your blood pressure is okay, and he or she can do different screens related to mood, and so just get an overall assessment. But it's very possible that the internist, after doing so, will go onto refer you for more detailed evaluation. He or she would have a couple of options in that regard as to who to send to a neurologist; to a psychiatrist, if it seemed as if perhaps mood was the underlying problem; to a geriatrician if the person was older and didn't have sort of a regular geriatric care specialist; or a neuropsychologist like Dr. Karantzoulis, who can try to parse out relative strengths and weaknesses related to different cognitive strengths.

CS: You touched upon mood and depression, so

if we could talk about that a little bit more in terms of depression linked to Alzheimer's.

MS: That is a really rich and complicated topic. I often say it's kind of a two-way street insofar as depression in and of itself, right, head in the clouds, being sad, can contribute to memory complaints. Is it because of impaired attention, impaired concentration? That can be debatable but that's certainly one part of the root. And, of course, we know that if one has memory problems and is worried about it and is stressed about it, can it, in and of itself, cause mood and anxiety issues? So it's a little bit of a cycle, and it's been very complicated trying to extract cause and effect and which came first and it's been a research tangle for people. And we still don't have absolute clear cut answers related to how significant, and exactly what is the mechanism of depression and memory problems. But we've learned a lot and so I don't want to sort of understate really how much we've learned. It's not random that mood and memory co-occur because they share an overlapping anatomy. The hippocampus, which we keep talking about over and over again is really very intrinsic to depression and depressive illness. In young people who are

depressed their hippocampus shrinks. We can see that on neuroimaging. And after they're treated with antidepressants their hippocampi plump back up again. Now, it turns out, and this is really quite clear, that the more episodes of significant depression that an individual has does put that person at increased risk of developing dementia late in life. It also seems to be the case that if one were to develop depression for the first time in midlife that that may be a risk factor for developing dementia late in life insofar as there is this overlapping notion between memory and mood and it's, again, exactly what the mechanism of that – different research studies have come up with slightly different conclusions in terms o which comes first. Is the depression really the harbinger of Alzheimer's disease or is depression just more common in people who develop neurodegenerative illness? But what we have recognized, once again referring back to the hippocampus and this overlapping anatomy, is that antidepressants, the main ones like SSRIs such as Prozac, the grandfather of the sort of class of medicines, that their mechanism of action is through something called neurogenesis, or at least that's one hypothesis. When I went to medical school, which wasn't that long ago, we were told

you were born with as many neurons as you are going to have and it was just a winnowing away process. And that was absolutely false. There are at least two regions in brain that are constantly regenerating new neurons, and one of them is our structure of interest, the hippocampus. And it turns out that SSRIs rev up the hippocampus. And so maybe that's part of its mechanism of action related to treating depression is by enhancing the neurogenesis, creation of new neurons in the hippocampus.

CS: One thing we often hear about is heart healthy equals brain healthy. Is that true.

MS: Yes. I can say that, you know, sort of emphatic thing I can say – I've been equivocating through a lot of our discussion – but that one is really kind of very clear cut and it plays out in lots of different ways. I'm going to just refer on thing back to Alzheimer's disease and that is the biggest risks related to developing Alzheimer's disease are related to age. I already mentioned getting older is the biggest risk, and also genetics. We know that there is one genetic marker, particularly related to something called Apo-E, which we believe is involved in cholesterol transport and maybe even involved in amyloid

transport, but we do know that having one particular type of this allele does increase risk of developing Alzheimer's disease late in life. Now, those are the two variables that we can do nothing about: age and genetics. But there's lots of other things that we can do that we have recognized really do play a significant role, and that's related to other overlapping medical illnesses that can occur, and vascular disease, heart disease, probably being top of the list, but there are other issues as well, and we can really exert a lot of influence over our management of those co-occurring medical issues.

I'm just going to make a couple of points about, you know, clearly the vascular disease of brain that is most obvious is stroke. We've all heard about people who have had sudden onset of loss of … weakness or numbness on one side, or sudden loss of language, and that's related to the acute onset of loss of circulation or hemorrhage in a particular part of the brain, leading to a very specific deficit. Now, we've come to recognize that having those kinds of events are in and of themselves big risks for developing dementia afterwards – not at the time, but subsequent to that. It's doubling the risk within five years. What

are the things that we can do to try to prevent large vessel stroke? Well, we know that the risk factors are very overlapping with the same ones that we've heard so much about related to heart health, which is control of blood pressure, cholesterol, managing diabetes, trying to keep your weight down. Now, we've tried to look at each of those variables – blood pressure, cholesterol, diabetes and obesity – related to what's their independent risk of going onto develop Alzheimer's disease. And they're all suggestive of increasing risk, but some are more suggestive than others. The one that seems to be clearest in terms of the research literature is that control of blood pressure in midlife seems to really have a beneficial effect related to the subsequent development of cognitive decline.

Now why would that be? The strong guess, or the strong suspicion is that there's another element related to vascular disease that we begin to see on imaging, on MRIs, which is called microvascular disease. So this is not large vessel strokes, the big carotids or the middle cerebral arteries that are named vessels that can have an injury or clots, but these are the tiny little branches off of branches off of branches that have no names and

that over time seem to harden. Hardening of the arteries, you know, is an old fashioned term but it's kind of experiencing a renaissance, and the more hardening of the arteries that's present in brain we have come to recognize the biggest association there is with cognitive trouble. One of the biggest revelations we've had looking at brains under the microscope as people age, is that it's relatively rare for people to have isolated dementia syndromes. It's unusual for an older person just to have plaques and tangles that looks exclusively like Alzheimer's disease. It's rare for the second most common form of dementia related to vascular, meaning vascular dementia, for there not to be any plaques and tangles. So, in fact, the majority of the time it looks like there's a mixed pathology between Alzheimer's disease and vascular disease, and we have really tried to garner our resources to try to get that message across because we really have a lot of control over managing blood pressure, cholesterol, diabetes and our weight, and we really encourage that. And exercise is, again, one of the main ways we have of doing so, so we appreciate the brain warm up.

CS: One of the items that you mentioned was diet

and we often get asked about vitamins and supplements and even earlier today someone had asked about coconut water and is that something that we can take or are there specific vitamins or supplements we can take that help us with our memory. So, what could you say about that.

MB: I can say that so far there is no vitamin that has proved a benefit for preventing Alzheimer's disease. This don't means (sic) that if you don't have a medical condition with a vitamin deficiency you shouldn't be treated, but that's another scenario. The scenario is whether you go to your doctor, you look for getting the diagnosis, you do have a vitamin deficiency, but that's a different scenario. The trials that have been done with vitamin B-12, vitamin D and vitamin E did not show that actually they prevent Alzheimer's disease.

Another topic very, very tied with vitamins are supplements, and this is a very tricky – for the industry, actually – because vitamins and supplements, they actually don't need to have FDA approval, Food and Drug Administration Approval, to be marketed. What does it mean? It means that they don't need to prove that they are efficient to be sold. And also it means that the

FDA does not look for evidence that they actually work. So what the FDA is allowed to do is to check that they are not harm for you, they check that you don't have adverse reaction to these supplements. And they are marketed, sometimes in a very tricky way, and it tells you that it's for that disease or for that disease, but by the FDA standards, a supplement is not meant to be developed for any disease. They are supplements or they are meant to be a supplementation of diet and that's what the FDA, if you want to go to the web page, also it's easy to find it there.

So regarding the research done in supplements, so far we are not allowed to recommend any of them in particular, even though there is very promising results with some of them, and others did not prove to be effective. One that is very common is ginkgo biloba. It actually went through a six-year trial where it didn't prove to prevent Alzheimer's disease or dementia in elderly. It did show some results with patients that already have Alzheimer's disease that it might be beneficial, but not to prevent the condition. And with other vitamins we didn't find anything unless you do have a condition to be treated. And with supplements, there are so many supplements on the market, a lot

of them are very promising. I could say that in my personal opinion, there are ones that are more related with omega-3 fat acids. They are actually very encouraging, what is being found in research. That means, actually, that somebody put in a pill what you have in the fish. So that's what a supplement does. It picks something that you have it in the environment and you put it on the pill. If you feel comfortable taking pills, it's good, but be aware that the best recommendation is discuss with your doctor whatever the supplements you are taking, so your doctor can know if any adverse reaction appears so he can report it. There is other supplements, the coconut and the other foods that are recommended, like apple and turmeric and, I don't know, there is a lot of new studies that are showing beneficial effects but you have to think about if it was proven in people actually, or is basic(?) research, and it's a different kind of a scenario, you say that it was actually proved in people, and we don't have that evidence to recommend any supplements so far, but we can say that it's promising, some foods, and some supplements may have evidence in the future, but so far we cannot recommend any of them.

CS: Moving onto talk about some of the treatments that are currently available. Dr. Shulman, what are the treatments that are here today?

MS: There are five FDA-approved medications for Alzheimer's disease. Four of the five are in the same category called cholinesterase inhibitors. None of the medications that have been approved for Alzheimer's disease reverse or prevent progression of the illness, and we know that to be the case. They have mild moderating effects on symptoms, that tend to be short lived, so we are frustrated at present with our current sort of therapeutic options. I'll go through them in detail. They're helpful and I strongly endorse them, but they have marginal benefits. We're, again, waiting for something more significant to prescribe, to intervene in a more substantive way. But the cholinesterase inhibitors are essentially medications that block the breakdown of acetylcholine, which we know is a chemical that exists particularly in memory systems, so we give the medication and it makes the chemical linger longer at the synapse. And it's kind of like a concrete – I always think it's an incredibly concrete hypotheses that, you know, let's give some medicine that will just (Inaudible) …

it's unusual to imagine that … it just seems so unsophisticated to like just give a medicine that will let the acetylcholine linger longer and will not really alter in any way. It's very much a band aid, right? Because it's just helping promote one particular area of brain function. Now, that chemical also exists in the rest of the body and so if you're enhancing acetylcholine in brain, you're also enhancing it in the gut, and that can be the main side effect associated with the medication is loose stools or diarrhea. It also is the chemical of the parasympathetic nervous system which has an effect on heart and so lowering of heart rate can sometimes be a side effect of medicine. We don't see that very often, but sometimes we do and so we always have to be cautious about prescribing a medicine to people who already have a low heart rate.

The four kinds of cholinesterase inhibitors that exist, their names are: Aricept, that's the brand name and the generic is donepezil; the other one is rivastigmine, the brand name is Exelon; the third is galantamine, and the brand name is Razadyne; and then the fourth is tacrine, which was actually the first one to come out, but it had a lot of significant liver toxicity so

it's no longer used. There's no particular benefit of one or the other of these medications. They're all approximately equivalent. There are some slight differences in the frequency of how often you have to take the medicine. Exelon, by pill, is given twice a day. Exelon can also be given by patch rather than pill and it seems to have a lower incidence of GI side effects.

The other medication that we prescribe routinely for more moderate levels of dementia is something called memantine, which is an NMDA receptor antagonist. That class of medicine tends to block glutamate, which is a chemical that we know is associated with excitability of neurons, so perhaps, as the theory goes, if we block glutamate it lowers excitotoxicity and keeps neurons protected, and so indeed it's called a neuroprotective agent. It's never been demonstrated to have benefits related to improved cognitive function, but in moderate to severe dementia it has been demonstrated to have benefits related to improved, just functional activities – being able to do their everyday activities a little easier.

CS: So all of these treatments really started at clinical trials before they were FDA approved. I think one thing I

want to mention here is at NYU we have a very active clinical trials program through the Alzheimer's Disease Center and there's more information about that as you leave today. But if one of you could touch upon some of the trials that are taking place and the benefits of these research studies.

MB: In general, a clinical trial is the most efficient tool that science has to build new treatments or diagnose methods or … it's the way we test drugs also, if they are safe, if they are effective. It's actually, you can have prevention trials to try to figure out what can prevent the disease. You have screening trials that are meant to diagnose or find out diseases or diagnosis trials to make the diagnosis more accurate, or treatment trials to deal with diseases. You can try new meds or devices or any other approaches to help these conditions. It's the only way medicine has to find, actually, new things that are actually for you. And there's no other way to do it without the patient, or the person, the participant, the subject, the way you want to call it. So actually, it's a very concerning thing for us, at least me that I do research, mostly in Alzheimer's and Parkinson's, that I am particularly trying to recruit all the time and try to make people get involved in

something and sometimes encouraging them to be more active.

Just to tell you something, once I spoke with a patient that did have Parkinson's disease and I wanted to try her, you know, to participate in our studies. And she said, "Okay, I'm 89 years old, I'm too old. Are you finding a cure for me?" So I was like, "Oh, probably not," and I said, "No, I'm not finding a cure for it, not right now with the trials I have running." And then I pick her list of medications and she was … you know, for Parkinson's there is a lot of medication but all of them are based in dopamine, this neurotransmitter that is getting low in the motor parts of the brain, and it's a very efficient treatment, so far the best treatment ever had, and it works for many, many years. And I saw that she had that. And so I asked her, do you know that for this particular drugs you are taking, this study that finds out that the dopamine works, was done here in New York, was in a city that – I wrote it down because it's (Inaudible) city in Brookhaven, Neuroscience Institute, and that was in 1967. So my patient was barely 40 years of age or surrounding that. And I said, so that, you know, we're New Yorkers that try that pill so you can have that treatment right now. So it's not a matter of how old you are. Sometimes you want to

just do something because somebody else did it for you. We all got medications. We all have blood pressure treatments, we all have hip replacement, everything that we have on our health that we need to be better, has been tried in other people, that actually they were … what the people says “I was a lab rat,” or “I was a mice,” or … but it’s not like that, but actually thanks to that we do have what we have right now, and you have what you have right now.

CS: Dr. Karantzoulis, I’d like to go back to you for a second and talk about head injury, because you’ve done a lot of research in that area, and we’ve also been reading a lot about …

MS: Can I just go through some of the clinical trials that we have here. Just to let you know, because we have many clinical trials underway here at NYU that are addressing really the most kind of fundamental aspects of looking at Alzheimer’s disease. We’ll do questions at the end.

Some of the research that we’re doing is looking at so-called targeted therapy, so we’ve been talking a lot this afternoon about those substances – amyloid and tau, which are so key to what we believe is the disease of Alzheimer’s

disease. And there are several approaches to managing amyloid at the moment. So we really know a lot about the mechanism of the toxic amyloid deposits in brain, and we have been giving people different blockers to the amyloid breakdown sort of products, hoping that that will lower the likelihood of amyloid deposition and we have several of those actively underway.

Another approach to amyloid that's been studied rigorously in many different approaches from different companies has been using an anti-amyloid vaccine which is using the body's immune system and using this agent which is an antibody to try to attack amyloid and have it cleared from brain. And so those are anti-amyloid vaccines, and we've been using those. Another topic is related to tau, and there have never even any treatment trials utilizing tau, but it looks like that's on the horizon, that we're going to start to be able to use substances that tend to try to stabilize the molecule tau so that it doesn't create these tangles, so that it doesn't collapse and create the tangles. We're going to try to give those medications. There have been numerous approaches to thinking about what role does inflammation play in the pathology of Alzheimer's disease? And so

there had been a number of trials that went on related to giving people nonsteroidals like Advil or Motrin, and those didn't seem to be of much benefit, but there's another approach to using a different agent, giving intravenous immunoglobulin that has really demonstrated some real reason to be cautiously optimistic that it really seems to modulate the course of Alzheimer's disease, and those studies are underway.

Then there's a new notion – we keep talking about this overlap between Alzheimer's disease and vascular disease, so sometimes people think that Alzheimer's disease is better described as type three diabetes, that it's really an illness related to trouble with metabolism. And so there have been many animal studies that are just recently been applied to human studies, which is using inhaled insulin to see whether that would affect the progression towards Alzheimer's disease. And then a new way of thinking about things is we have come to recognize that the vaccines that I mentioned earlier, it turns out that they work, meaning that they do clear the brain of amyloid to a great extent. The only problem is when those brains were looked at, at the end of life, the patients who had received the vaccines and

seemingly had gotten a positive result, meaning that their amyloid had cleared, they didn't get any better. So why would that be? We came up with this mechanism that seemed so right. And so now the theory is perhaps we're giving that vaccine too late. Maybe, by the time someone's developed full blown dementia, that there's too much brain injury. So now what we're doing for the first time are prevention studies. Remember, we were mentioning that the beginning changes begin 20 years before the onset of symptoms? Well, now we're trying to see if we can find those individuals who look like they're predisposed to developing Alzheimer's disease and we're thinking about giving them the vaccine, seeing if we can prevent Alzheimer's disease in *toto*. And we're looking at that in both people who are at risk, meaning that they're older people who have intact cognition but with other biomarkers that suggest that they may go on to develop Alzheimer's disease, or we're looking at it with people who have genetic forms of Alzheimer's disease and we know they're going to develop Alzheimer's disease, but maybe if we give them the vaccine it will really alter the course of their illness.

CS: Thank you. And once again, all that

information is on the table as you leave the auditorium. Dr. Karantzoulis, I just want to touch upon head injury and the correlation with Alzheimer's.

SK: We can do this together with Dr. Shulman, since both of us often get asked a lot about head injury and risk of Alzheimer's disease or future dementia. I think the main point to take home is just because you hit your head once, doesn't mean you're going to get Alzheimer's disease. A lot of people think that, you know, "I hit my head as a kid, I fell of a swing, I blacked out. Does that mean I'm at risk for Alzheimer's disease?" And there's really no evidence to suggest that a mild head injury means you're going to have Alzheimer's or dementia as you age. But some of the research that's come out of, I think what you said, Camy, earlier, from the sports literature, is that with repetitive head injury, so like if you think about football players who have hit their head multiple, multiple times in play, that there's some evidence to suggest that they are in fact at increased risk for dementia. It doesn't mean they're going to get the disease but that they are at some increased risk. We don't know how many times you have to hit your head, we don't know the force with which you have to hit

your head at to be at risk. But just because this is often in the media, that we do get asked that a lot.

Now, when you're talking about severe brain injury, that's a very different ballgame then when we're talking about a mild head injury like what many of us do sustain either in sport or from falling down. And severe head injury, for someone who has a traumatic brain injury, that is different, and there is research to show that with severe brain injury there is some link to future dementia, but it doesn't mean, again, that you're going to get dementia in the future. Is there anything you want to add, Dr. Shulman?

MS: I'll just keep harping on prevention, so how can we prevent head injuries in an elderly population? And the main risks about that, as Stella mentioned, is falling, so to try to kind of keep a close eye, and sometimes we really encourage doing preventing physical therapy, meaning ask your internist or geriatrician to write a prescription for gait training falls prevention. And we really have demonstrated, it's been demonstrated that that is a very reasonable form of insurance to try to prevent falls. Other things – this is just common, right? We need to wear seatbelts,

because having head injuries in car accidents is a common thing; wearing helmets, going bicycle riding, that kind of thing, so to try to prevent the number of head injuries is a good strategy.

CS: I'd like to end with just one last question and that's to you, Dr. Biagioni, we've spoken a lot about the normal brain functioning and diseases of the brain. What can we do to help keep our brain healthy?

MB: We will share some of the NIH published summary about this matter, about preventing dementia or cognitive decline. It's stated that there is four things, majorly, that you could do, probably this is going to be (Inaudible) in a few years. The research on this is very broad. But so far we know that exercise, physical activity, mental activity, social engagement and vascular risk reduction are four pillars, very strong ones, to reduce your risk of having dementia or memory problems. Regarding what is increased mental activity, not necessarily has to be through these programs that Dr. Karantzoulis mentioned about working out your brain, it could be something more simple. I usually use the word hobbies, means whether you read books or you play card games or board games or learning to play a new instrument or play chess

or any other activity that may keep your brain active. Regarding the physical activity, there is not a particular physical activity that is encouraged. Any of them is helpful. The first thing you should know is that if you are going to start a physical activity plan, you have to know your limits. It's not bad to recommend to talk to your doctor firs to see what are you able to do, if you have another condition like heart disease or something, and try to do it with realistic goals. Don't try to go for it like crazy because sometimes you cannot keep up with that. Another recommendation about that is try to do something that you enjoy, so if you enjoy dancing you can get dance classes; if you enjoy the water, like when we are children, you can do swimming; if you enjoy the environment, you can do walking. If you don't enjoy anything of that, you just drop out from the subway one stop earlier and walk home, or if you live on the eighth floor of a building or the fifth floor, use the stairs, don't use the elevator every day. So, for example, that adds to your level activity very important if you add that, day by day, simple things, you can get a better physical help. And physical activity doesn't only prevent Alzheimer's, we do know that it's good for high risk, preventing … high blood pressure might get better, your

mood gets better, your confidence gets better, obesity could get better if you reduce your weight too. Bone loss also could get better with this. The benefits of physical activity are really very broad.

Regarding social engagement, what we encourage people is to build social networks, doesn't mean that you have to be in the computer having 1,000 friends on Facebook. It means that you actually have to interact with people. It doesn't mean that Facebook is bad, actually could be good but we don't know, but with people, like trying to do trips with people, try to visit family more often, try to go to picnics in Central Park or Park Slope, you know, get out of your house, be with a neighbor, go to someplace. Go to the museum. Museums have a broad range of activities that you can join. There is many things you can do and everything … we know that people that have a bigger social network live longer, and people that live alone die younger, so that's actually a fact.

The vascular risk we already mentioned. Many of the things, you know, the (Inaudible) is to have the best you can of your control of your risk factors, that means high blood

pressure, dyslipidemia, cholesterol levels; try to lower down the excessive weight; try to keep your diabetes on line. It doesn't mean that you have to be … having high sugar in the blood is bad, but also having low sugar in the blood is bad, so it would balance what is good. And smoking cigarettes, I'm sorry, it's not good whoever does that. Unfortunately, it has shown that it's bad for the heart and bad for the brain in many studies. And we do not have to take for granted diet. Diet is a great thing you can do. It actually impacts all these vascular risk factors. Now it is in the whole media about this Mediterranean diet or similar to Mediterranean diet from people that live in Crete or some other island from Greece or something like that, that actually have shown in several studies, very big studies, their benefits, and not only preventing cognitive decline but also heart disease, or any disease. The death rate is lower. So it's not only what it gets for the brain but also for other parts. Also, the results showed less incidence of depression and less incidence of diabetes with this diet. And just to give a brief, about the diet, that is on every media or you can get it online, on the computer, majorly, it's a diet that is very rich in fruits and non-starchy vegetables. It has a moderate to low

amount of dairy products like milk and cheese; replace fish the red meat actually, like use more fish, use less red meat. And you can use eggs, up to four eggs a week, and wine, red wine. This recommendation actually is for the people that actually drink wine, so it doesn't mean that you have to go there and buy wine and start drinking wine, and it doesn't mean that you can actually accumulate wine and drink it at the weekends. You have to drink less than … a glass or less with the food, it's like a low to moderate amount. And it's more recommended the red wine. We are still trying to see what is the case, it probably is the polyphenols, and if that is the case, it shares the same components like green tea. They do have the same. So far the Mediterranean diet is with that, and people add to that diet whole grain bread and cereals, that actually is not in the basics, but is very healthy, especially with aging, it helps a lot. And so far it's … don't underestimate the value of what you eat. That's very important.

And we didn't mention something related with sleep, but I think you could probably give a few recommendations.

MS: Sleep has just been a topic in the news recently and, obviously, we'll just maybe summarize with this. It's

just a huge topic and it's a truism that it's important to get good sleep and there are all sorts of things that we've come to recognize that developing sleep disorders can sometimes be a harbinger of neurodegenerative illness. It's present in Alzheimer's disease but it's even more prevalent in preceding Parkinson's disease or this other illness called Lewy body disease; obstructive sleep apnea we know is a really serious illness that's associated with heart disease and can really have cognitive effects. And so if there does seem to be marked changes in sleep, if people are having real violent episodes in sleep or they're falling out of bed or you're observing your partner have stretches of apnea, that absolutely warrants discussion with your doctor, and some sort of assessment, typically, with something called a sleep study. And sometimes that can be the start of a pathway of trying to understand what the relevant issues are.

But in terms of what, in the absence of having a sleep disorder, what can we do to try to maintain healthy sleep, you know, it's kind of simple, kind of intuitive things. I often say that just rituals, being very ritualistic about nighttime, like going to bed the same time every night, having several nighttime rituals

about either taking a bath at night or using warm milk, which within it, has its own sleeping pill in it. Warm milk has tryptophan that can be sleep inducing. If at all possible, we really think that sleep medications are not what we desire when we are really trying to think about maintaining cognition. We are trying to keep people sharper. Sleeping pills make people sleepy, often there's a hangover in the morning. So by and large we try to avoid sleeping pills.

Other kinds of things that you can do is make the bed exclusively for nighttime activities: either sleeping or having sex. There's no reading or watching TV or just all night long, that's what the bed is for. Other issues kind of related to just keeping sleep healthy is not having exercised in the evening, you know, exercise in the morning, try to avoid any caffeinated beverages at night. These are all things that I'm sure you all know, but it's just about being a little bit disciplined about nighttime rituals.

CS: Thank you. So this concludes this part of our program and we'd now like to open it up for questions from the audience. So if you could raise your hand and wait for the microphone to get over to you, and if you could try to keep your

question to just asking one question and also of a general nature, because we really can't offer any specific medical advice.

WOMAN: I have a question – actually, I have two short ones but they may be in keeping. One has to do with what are the effects of TIAs on brains? I was asking what the effect of TIAs are on possible dementia for the future. And then the other thing is I've just been aware of something called hospital-related dementia. I've seen it, and how is that a predictor?

MS: First let me touch upon TIAs, and again, I'm just going to give a definition of what that is. So a TIA is an acronym for transient ischemic attack. The definition of that means that typically there's an episode of neurologic trouble. So, the most common features of that would be loss of vision in an eye, weakness or numbness in an arm or leg, difficult speaking – but just for a very discreet period, so by far and away the most common length of a TIA is really short, it's about 20 minutes. But the definition allows it to go away within 24 hours and there's debate about how that should count. But for all intents and purposes, you know, a TIA is really brief, and it typically suggest that there's one blood vessel that has kind of a threatened

circulation that the ability for the blood vessel to continue to perfuse or to give good circulation to the region of brain it supplies, is transiently disrupted. And then, for various reasons, either a little clot has dissolved and has gone further on, or there's a change in blood pressure or some transient phenomenon, the circulation is restored and there's no loss of brain tissue.

Now, is there a risk of going onto develop dementia in the setting of TIAs? I don't think that's been studied particularly insofar as we know that if one is vulnerable to TIAs that they have this constellation of vascular risk. So whether they have plaque in their carotid arteries or plaque somewhere else in the cerebral blood vessels, that just alludes to some of the vascular risks that I mentioned earlier, so the answer is yes, that does confer increased risk only insofar as it suggests that the person has vascular disease. And then the second question was …

WOMAN: Hospital-related dementia and coming out of it.

MS: That's a little bit, I'm just going to say a little bit more equivocal and maybe Stella can talk about this as well. Now, if it doesn't meet my criteria for dementia, meaning that the

person was cognitively in tact when they came in, but in hospital developed something – we know it's not a dementia because it doesn't meet the criteria because they were okay when they came in. Dementia has to be longer than six months or a year. So transient things that occur relatively acutely or sub-acutely, we don't think of as dementia. There are other terms for that. It's called encephalopathy, which is just a transient change in circulation to brain and attention is typically the thing that's most vulnerable, and it's a setup in the hospital for people who are sick to develop an encephalopathy. I'm going to be a little bit of a stickler about what the right word is. That person can given lots of medications that are sedating or give them hallucinations, they're in a different place; they can be sick for whatever brought them into the hospital in the first place; they can have fever. And so that condition is more of an encephalopathy than a dementia per se.

Now, if somebody comes into the hospital already with some cognitive trouble, let's say it's mild cognitive impairment, if you put on top of that an encephalopathy, I'm sure it could cross the threshold to a dementia syndrome, but you have to have already had some cognitive impairment to start. So that

would be how I would dissect that term.

WOMAN: I wondered if there's any relationship between asthma, the loss of oxygen on a continuing basis, to the blood, and also tick-borne diseases, particularly Lyme and ehrlichiosis, because sometimes there is memory loss, and it can be repeated, so two areas?

MS: Related to asthma, I'll just say that we're a little bit ageist in that regard. We don't typically think of asthma as a risk factor for dementia, so to speak, because it typically affects younger populations and we're, you know, not quite so focused on asthma per se. Issues related to COPD – I'm just telling you, it's just … issues related to chronic obstructive pulmonary disease, things that tend to occur in older populations, we definitely do know are associated with cognitive trouble, especially with attention and concentration.

WOMAN: I'd just like to say about asthma, it seemed to me there are two types, one that's childhood and they often grow out of, but for mine and my family starts as an adult …

MS: No question, I'm just trying to share with you … The question is, does asthma for a risk factor for developing

Alzheimer's disease? And I said that we're a little biased that we typically think of asthma as occurring in younger populations, but absolutely, it's absolutely the case that older populations can also suffer from asthma. It just has not risen to the level of an overt risk factor that we know of, although we spend a lot of time talking about chronic hypoxia related to obstructive sleep apnea which certainly has sort of cognitive consequences associated with it and we do think that obstructive sleep apnea is definitely a risk factor for developing dementia down the line.

WOMAN: And the tick diseases?

MS: The tick diseases, again, I'm going to quibble about what the definitions are. So, Lyme disease typically could cause what's called an encephalitis or a chronic encephalopathy, which is just – I'm just playing a name game – it clearly can cause significant cognitive difficulties, but as far as we understand, we think that if somebody has Lyme disease and is treated for it, meaning there are several different prescribed oral antibiotics, and if it seems as if it's spread to the nervous system, and that can be documented by looking at whether Lyme disease is present in the spinal fluid, there's a particular prescribed duration of IV antibiotics

for that, we don't think it causes – once it's treated, we don't think it causes ongoing risk for dementia. We think it typically resolves. But there's terrible controversy and methodological issues related to that. And so that's kind of the conservative approach related to management of chronic Lyme encephalopathy.

WOMAN: You mentioned exercise and falling, two things that I'm very interested in. I do exercise because I have a dog and I walk like two miles a day, but I also have fallen from other things and I want to know, are there any specific exercises or any places that you can go to that have specific exercises for seniors to avoid this falling?

MS: I'm going to say that I'm sure that there are senior centers, the different Y's, et cetera, that have exercise programs for senior populations. I know that to be the case. But I'm going to just give one little tidbit that I share with my patients a lot, and that is that you don't have to go to a gym, or it doesn't necessarily have to be an exercise class, because it turns out that walking is probably the best, at least the one that we have the most research to support, the best related to helping keep us cognitively fit. And I just quote this study, they looked at sedentary people

between the ages of 60 and 80 and they put them on an exercise regimen of stretching or walking, 40 minutes three times a week. And before they put them on the exercise plan, they did images of their brains and volumes of their hippocampi. And then they did this for three months and then they re-imaged them at six months and at a year. I can't remember whether they were for three months or six months, but in any case, they imaged them at six months and a year. And the people that were on the aerobic exercise, the walking 40 minutes three times a week, their hippocampi actually grew, as opposed to the ones that were on the stretching regimen – and I'm not telling you not to stretch – but it just doesn't have quite the same benefits. The stretching group, their hippocampi shrunk a little bit, but in keeping with what we estimate is the natural change of shrinkage associated with aging. So that just seems to be a very resonant piece of data. Just walking 40 minutes three times a week will serve you well, and anything else you do on top of that is extra, but that would be a good minimum.

MB: And I would like just to add to that, that if you are interested in doing something else you might consider yoga,

t'ai chi or dance because it's more likely kind of activities that will probably empower your balance, all three of them. Each, the three of them, now choose the one you will enjoy the most.

WOMAN: Neuropathy, is that a degenerative disease? And if so, does that put one in more danger for dementia or Alzheimer's?

MS: Neuropathy affects the peripheral nervous system and it doesn't fall into the degenerative category even though it can be progressive. But it doesn't fall into one of the neurodegenerative diseases, and it doesn't confer increased risk.

MB: I want to add something to that. Just in case, if you do have diabetes – there is not very strong evidence, but some evidence shows that if you do have diabetes or prediabetes, and you have a neuropathy, you are more likely to have a cognitive decline. But it's a very … not something that is that strong, but some research has been done and it's of course related with diabetes and neuropathy and cognitive impairment.

MS: And again, the link being vascular disease. That's the overlap.

WOMAN: The doctor in the center, you mentioned one

computer game that the research has shown to be beneficial but I didn't catch the name of it.

SK: It's from the Posit Science program, P-O-S-I-T, Posit Science, they're California based, and I think they offer more than one program. The one that was investigated was the Brain Fitness Program. And again, just to repeat that they did it five days a week for eight weeks, one hour per day. So to show some benefit, it looks like that's the sort of optimal amount.

MAN: Is there much evidence to suggest that the use of Aricept in combination with Namenda, as opposed to Aricept alone or Namenda alone, can improve or slow down the progression of dementia in a person with mild dementia?

MS: Again, there's no evidence to support prevention, right? We already mentioned that. So these are used for symptomatic management. Now, the studies that were done with Namenda were always in conjunction with Aricept, so it's a benefit in the setting of moderate dementia in combination. Just this past year *The New England Journal of Medicine* published a paper saying that there didn't seem to be any sustainable benefit related to being on both medications, and so there is some

equivocation about truly, how advantageous is it to be on both medicines. But the previous studies did seem to sort of suggest it in a rigorous way, so it's constantly being reevaluated, and of course it's a cost issue if it's not repeatedly demonstrated to be of benefit, to be on more than one medication, that the recommendations need to be altered.

WOMAN: Have there been any studies about any correlation between when children have juvenile diabetes and repeated low blood sugar episodes over a span of years, and later in life the early onset of Alzheimer's?

MS: I actually know this subject pretty well. No, there is not. There is no association with increased risk in juvenile diabetics who have had recurring hypoglycemic reactions.

WOMAN: Hi, these are fairly quick questions. One is with respect to brain plasticity. As you mentioned, it's a lot more positive these days. And then the re-networking. So what would be the limitations of that neuroplasticity with respect to degenerative … the degenerative expressions of Alzheimer's? And two, you mentioned one of your drugs helps to ameliorate some of the symptoms of Alzheimer's, and it works on glutamate.

It's interesting because it's on memory loss, but glutamate also shows up as one of that symptoms of that are – is it Guillain-Barré? And also autism has a connection with glutamate. Is there a toxin in the environment that can trigger some of these factors as well? That's the two questions.

SK: I'm going to say that … it's a complicated set of issues that you present. I'm going to try to … from my perspective on it is that there are only so many brain chemicals and so to link really disparate problems, just having the common link of being one of these brain chemicals, is probably not a rigorous thing to do. Glutamate is an excitotoxic neurochemical that exists in the brain and one could plausibly make a theory about some insult related to excessive stimulation. It clearly plays a role in epilepsy that's constantly being sort of discussed in that way. But I'm going to not say that there's a link between all neuropsychiatric illnesses in glutamate.

WOMAN: And the brain plasticity limitation question?

SK: Could you repeat that? I don't think that I got that.

WOMAN: Before it was, as the doctor to your right had

mentioned …

SK: Dr. Shulman.

WOMAN: When she was in medical school, that you were born with a certain number of neurons and they die off and that was it. But now they are talking about regenerative …

SK: Neurogenesis only occurs in a very discreet part of brain. And so the notion of plasticity is not exactly applicable to this notion of very discreet regions that are regenerating neurons. Obviously, we can hypothesize perhaps, but I don't think we're there yet.

WOMAN: So the re-networking is limited.

SK: I'll say yes, but humbly.

WOMAN: You talked about brain activities, puzzles, et cetera. I've heard that doing two things at once is counterproductive, like doing crossword puzzles and watching television, and so on. Is there any truth to that?

SK: Sure. I would say that if you're going to do a cognitive task like a puzzle, that you focus all of your attention that, so to minimize any other surrounding distractions. And frankly, as we do age one of the areas that we do see a change is in

multitasking. And so I would recommend that you avoid doing that. Really focus on the task at hand, finish that, and then move onto the next one.

WOMAN: Sleep apnea – is obstructive sleep apnea the same as sleep apnea, or is that synonymous? And could you explain how sleep apnea could cause dementia? And if you use that CPAP machine, are there any exceptions?

MS: Again, obstructive sleep apnea is associated with an increased risk of dementia, it doesn't cause it, just to be kind of precise. Now, sleep apnea just means cessation of breathing that can occur in a couple of different clinical circumstances, including in infants. So obstructive sleep apnea is the one that we're most familiar with and have been in the news, and that's typically related to literally laxity of the muscles in the back of the throat that obstruct the air passage, and there are a couple of very obvious risks associated with that including girth, kind of being obese, having significant abdominal girth is a big risk factor for that. But sometimes, literally, neck size can be a risk. There are lots of different things. Now, it's been recognized to be closely associated with cardiac disease and increased risk for

heart attack, obstructive sleep apnea. And that is by far and away the area of emphasis that we place on obstructive sleep apnea is its cardiac risk. Now, without question there are cognitive complaints associated with people who have obstructive sleep apnea and it's not hard to imagine why that would be – they're having disrupted, frequent wakenings and they're tired in the morning, and if you're tired you're not terribly focused or acute related to your attention. There have been other, more recent studies that seem to think that memory itself requires sound sleep in non-REM stages and in REM stages. Crucial aspects to memory consolidation occur in sleep. So for this confluence of different reasons, obstructive sleep apnea is a risk for cognitive trouble, but it's really being sorted out exactly what the risk is associated with Alzheimer's disease itself, because it has all these overlapping issues related to vascular disease, the risk associated with obesity and heart disease.

CS: We have a few more minutes left for a couple more questions. If you could please limit your question to just asking one so that everyone has a chance to ask a question in a limited time.

WOMAN: How might mental and physical trauma affect the brain? How is this diagnosed and what kind of remedy would be offered?

MS: Can you repeat the question? I don't think we heard exactly.

WOMAN: How might a traumatic experience affect the brain?

SK: When you first started, you said something about mental. Are you talking about a …?

WOMAN: Mental and physical, so it's really a two-part question.

SK:S Okay, so to address … when you first asked the question you said, "How many …?" and I don't think there's any real number that we can give you in terms of that. I think (Inaudible / Overlap) … oh, how might? I thought I heard you say how many. Well, it does put you … we know that stress affects the brain, especially the hippocampus, and over time the more stress that you're adding to the brain certainly is going to take a toll on someone's cognition. It doesn't necessarily mean that you're going to get a dementia, but it does make a person more vulnerable, and

Dr. Shulman did talk about depression and its relation to Alzheimer's disease and that sort of fits in because that is a psychological trauma that is affecting the brain. And so we do know that mood, improving your mood does help to improve your cognition. So whatever it may be, either via therapy, via exercise, do something to improve your mood. Even keeping busy a lot of people say helps to improve their mood. So whatever you can do to reduce your stress, especially emotionally, is really going to help your brain. But of course, also from a physical perspective, like I mentioned earlier, we don't want you hitting your brain. We don't want you falling down and knocking your head, because that isn't good for anyone, let alone a person who is aged.

CS: We have time for one more question.

WOMAN: My question is, you said that supplements are not FDA approved and they're good for additions to your diet but not for much else. And you said sleeping pills are not recommended especially if you want to stay sharp. So my question is, where does melatonin fit into any of this? Is there any new evidence of anything?

MB: Yes. Melatonin is a supplement and it's been

used for insomnia problems, maybe more related with jet lag, when you do trips on airplanes or you work in some shifts that changes through the week, so you can restore that. And actually, from the clinical aspect, the best that I can tell that it works is for patients that have a disorder that's called REM sleep behavioral disorder, where these people try to act out their dreams, so they are sleeping, totally sleeping, but they are acting out what they are doing during sleep. Sometimes they hit their bed partner, sometimes they try to strangle the bed partner, and sometimes they lie that they have the disorder to strangle the bed partner – no, that's a joke. But in this scenario we can say that the efficacy of the medication is, is near 60, 70 percent, as good as clonazepam, that is the other treatment for the same condition. So for my field, that is Parkinson's, at least it's very helpful and I don't actually know for other aspects, but yes, it's a supplement. There is some research that supports to use it in these specific situations.

CS: If you have any further questions we have forms outside where you could fill out your question, your name and phone number and one of our panelists or someone from the Center on Brain Aging will give you a call back. But as we end

now, I'd like to just ask the panelists for one bit of advice that we can all take home with us to help us lead healthier lives, hear-healthy, brain-healthy lives. Dr. Shulman?

MS: I'm just going to repeat what I said earlier. Walking rigorously 40 minutes three times a week is the best thing you can do in terms of just maintaining kind of physical fitness, cognitive health.

SK: I'll reiterate what the fitness trainer said, use it or lose it. I'm a very big advocate of keep your brain engaged. Do whatever you want at home, read a book, see a movie, talk to someone about current events. Just keep your brain engaged.

MB: And I wills ay, like a little bit longer, but try to figure out what it is that you need to change first, make an assessment – are you eating good? Are you exercising good? Are you going out often enough? Are you having a social, good environment? So try to assess what it is that you want to change, then start with little things. You don't need to change all at once. When these things, you don't see a reward immediately, you get tired, and if you say, "Okay, I will probably reduce my risk of Alzheimer's in ten years or 20," you are not that kind of excited

about doing changes, about not going to McDonald's or walking 45 minutes three times a week at once. But if you do an assessment, say, for example, that you go three times a week to McDonald's and you walk once a week, so try to do it like, okay, if you go three times a week, go just once, on Friday dinner, only if I walk three times a week 45 minutes. So go there, enjoy your nasty fries and your burger, but enjoy knowing that you did an effort and you're actually eating less fat, trans fat food, than before, and you earn it. That's your right. And probably two or three weeks later than that, you will change that for turkey burger and you will change three weeks later the potatoes with a salad and you will be eating fish and salad in a two month period, and then you will be sitting there seeing other people eating and you will have the right to say, "Oh, my God, these people eat so bad." And you earned that right. But if you don't exercise and you go there and you eat it anyway, try to think about today, remember me saying you should not do that, but if you actually do it, shame on you. But I wish you can do it next week. I trust that you can do it. Okay.

CS: Thank you everyone for joining us today. Thank you for sharing your afternoon with us and if you do have

any questions, please feel free to ask us.

(END OF TAPE)