



ALZHEIMER'S

THE SCIENCE OF PREVENTION

Episode 9: Move For A Better Brain



David Perlmutter, MD:

These days, with all of our conveniences and technology, it's really very easy to lead a sedentary lifestyle. And in fact, a great majority of us do just that. We go from our beds to our cars to our desks and our chairs to our sofa then back into our beds. However, this lifestyle is totally out of sync with that of our genes. As humans, we evolved to be active, curious creatures that interact with our environment through near constant movement. But our modern day, sedentary lifestyles are having a profound effect on our overall health and specifically the health of our brains.

David Perlmutter, MD:

I often remark that if a drug were to be developed that mimic the effects of exercise, it would absolutely be a blockbuster drug. Physicians would be prescribing it to the young, to the old, to the sick and to the healthy. And yet all of us have the ability to take advantage of exercise every single day.

David Perlmutter, MD:

Though we're still learning about the multiple mechanisms through which exercise benefits us, it remains one of the most powerful, the most impactful ways to maintain our health. Healthy levels of exercise are associated with everything from improved blood sugar and improved insulin sensitivity to better mood, better sleep and even a more robust microbiome. Despite this understanding, many of us still struggle to get adequate amounts of exercise.

In this episode, we're going to learn about how exercise impacts nearly every system in the human body and how it is one of the most powerful tools we have for actually preventing Alzheimer's disease. We will also learn simple ways to make it easy to incorporate this fundamental tool into your life. I'm Dr. David Perlmutter and this is Alzheimer's - The Science of Prevention.

David Perlmutter, MD:

In previous episodes of this series, we've learned that not only Alzheimer's on the rise, but in fact, it is a disease for which we have no meaningful treatment. More importantly, what we've revealed thus far is empowering information that shows us that our health destiny is not at the mercy of our genetics. And of course, this applies in the context of Alzheimer's disease as well.

David Perlmutter, MD:

We've already reviewed some of the important tools available to you to help reduce your risk for this disease, including dietary strategies, nurturing your microbiome, avoiding various toxins in the environment, optimizing sleep and avoiding and managing type 2 diabetes. And again, all of these tools focus on



reducing inflammation. As we explore the role of exercise, we will learn how it in fact may be one of the most powerful instruments we have for reducing inflammation in the human body.

David Perlmutter, MD:

Unfortunately, many of us do not prioritize exercise in our lives. This means we're missing out on the amazing benefits of this essential, brain supportive activity. Let's explore the importance of exercise, in terms of brain health.

Max Lugavere:

The problem is too many of us are just sedentary all day long. And we go from sitting in traffic to our jobs, working at our desk jobs for nine hours a day, driving the other 45 minutes back to our homes, sitting on the couch, watching our favorite streaming show on our favorite streaming platform

Kirk Erickson, PhD:

Exercise actually should not be a supplement for anything. Exercise should be a core component of your life and other things should actually be supplementing exercise. Exercise is so critical, it's so profound. It has such a promising effect, that it should be a normal part of our routine like eating and drinking. I really think that exercise should be considered to be one of the foundational elements of our existence.

Kirk Erickson, PhD:

People are becoming more and more inactive. We need to be promoting regular moderate levels of activity.

David Perlmutter, MD:

We all lead incredibly busy lives and manage countless commitments and unfortunately this means that in so many cases, exercise just isn't a priority. Let's learn about just how important exercise is and why it actually deserves to be a central piece of our daily lives.

David Perlmutter, MD:

Exercise has been shown to be associated with decreased risk for developing Alzheimer's disease. But how?

David Perlmutter, MD:

In this next section, we'll explore how exercise improves insulin sensitivity, helps reduce stress, improves sleep, and increases BDNF in the brain, increases blood flow and oxygen delivery to the brain as well, and even more.

David Perlmutter, MD:

So I want you to recognize that this is an incredible list of benefits and every single one of these is meaningful when it comes to Alzheimer's prevention. As we've been discussing, healthy insulin sensitivity is critical when it comes to Alzheimer's disease prevention. In episode 5, we learn that if you have

diabetes, your risk for Alzheimer's is more than doubled. And when you become insulin resistant, you are well on your way toward type two diabetes. However, there are ways to keep this from happening, and regular exercise is one of the important factors. Exercise is a powerful insulin sensitizer. This means it actually makes your cells hungry for glucose. And when this is combined with a healthy diet, this effect of exercise is amplified even further.

David Perlmutter, MD:

Stress has been shown to increase inflammation in the brain. It also increases blood sugar, disrupts hormonal balance, alters your gut microbiome, and for these reasons, we want to reduce stress as much as possible. And thankfully, exercise is a great way to do this.

David Perlmutter, MD:

Exercise not only makes us more resilient to the effects of stress, it also increases the so-called feel good chemicals in our brains, making us more likely to continue exercising. It's therefore not surprising that exercise has been shown in multiple research studies to help improve depression. Exercise also plays a role in improving the quality of sleep. And as we'll learn in episode 10, sleep is critically important to brain health. For now, it's important to understand that sleep is the time during which our brains rejuvenate themselves and therefore quality sleep is essential. Exercise, when timed appropriately, improves sleep by increasing both sleep quality and sleep duration.

David Perlmutter, MD:

I mentioned BDNF. BDNF stands for Brain Derived Neurotrophic Factor and it's quite literally a growth hormone for the brain that plays a critical role in creating new neurons, a process called neurogenesis. BDNF is also able to protect existing neurons and encourages new connections between neurons. Trust me, you really want to increase your BDNF and exercise is one of the most effective ways to make this happen.

David Perlmutter, MD:

Exercise also improves blood flow to the brain and healthy blood flow in the brain is critical because blood delivers oxygen and essential nutrients, so important for brain health and vitality.

David Perlmutter, MD:

You mentioned exercise as being really important. Can you walk us through, mechanistically, why that might be?

Dale Bredesen, MD:

Absolutely. If you sat down and designed a molecule to help you, then exercise would fit that pretty nicely. On the one hand,

you actually improve your insulin sensitivity. You are improving your insulin sensitivity just by using your muscles. In addition to that however, you are also now improving or increasing your brain derived neurotrophic factor.

Dale Bredeesen, MD:

One of the best things you can do for yourself, with respect to Alzheimer's Disease, is to increase your BDNF and guess what? Exercise is one of the things that does that for you.

Dale Bredeesen, MD:

In addition, you reduce your stress levels. You improve your sleep. You improve your overall mood. There are just dramatic things that happen with routine exercise.

David Perlmutter, MD:

You've talked about exercise being very important for the body, for the heart, and now you're telling us that exercise is really important for the brain. Why is that the case?

Mark Hyman, MD:

Well, exercise is a lot of great things, right? It increases blood flow, which helps your body clean up the messes that it makes. It increases something called BDNF, which is a miracle grow for the brain. And it's this powerful compound that gets increased when you exercise. It also reduces inflammation and increases detoxification and increases your antioxidant enzymes. It helps your gut microbiome. It helps your sleep cycle and regulatory pathway, it helps your metabolism and reversing some resistance, all of which when they're dysregulated, lead to brain dysfunction or Alzheimer's.

Ayesha Sherzai, MD:

Exercise is actually the thing that grows the brain. When we exercise, there are a lot of hormones and chemicals created in our body. But one of the most important one that is created is called BDNF or brain-derived neurotrophic factor. It's like growth hormone for your brain. This BDNF goes and creates connections between brain cells.

Ayesha Sherzai, MD:

Your cells can have various little connections between them but 30,000 connections. These connections determine the speed of processing, your brain strength and resilience against disease. So when BDNF is circulating in your body, the brain actually makes these connections, and you can increase your BDNF significantly within hours of exercise. There have been studies that have measured these chemicals and these hormones in your circulation after one session of aerobic activity, and it's just sky high.



Ayesha Sherzai, MD:

So why is it important for us to have an exercise regimen in our life on a regular basis to prevent it? Because of BDNF.

Amy Berger, MS, CNS:

Exercise is very important for brain health. You might have even noticed, after you work out, you kind of feel a boost, you feel on your A game. I think there's a few reasons for this, specifically with regard to influencing Alzheimer's and reducing risk. There's two main things that I think exercise does in that regard. The first is, it improves insulin sensitivity. If chronically high insulin is a major driving risk factor in this illness and exercise helps improve insulin sensitivity, then that's a slam dunk right there. The other thing is, exercise increases the synthesis of something called BDNF. I'm going to quote a physician friend of mine, he said, "BDNF is like Miracle-Gro for your neurons." If you want to make new synaptic connections, have neural plasticity, BDNF is your friend, and exercise is one way to help increase that.

Max Lugavere:

It's pretty obvious to me, it's clear that when I walk into a gym, for example, I'm leaving the gym a different person than the person that walked in just because of the way exercise so deftly bolsters mental health. To me, it's clear that exercise makes my brain work better, and that's why it's perplexing that it has taken so long for the medical establishment to recognize the link between exercise and long term brain health. But to me, it's for lack of a better term, a no brainer that the two are connected.

Max Lugavere:

Exercise is incredibly important. It's one of the best ways of boosting a growth factor in the brain called BDNF. It's like the brain's miracle grower. It's been called that in books written for lay people, but also doctors and scientists refer to it as that as well. And the reason for that is that when you sprinkle BDNF on neurons in a petri dish, they sprout dendrites, which are the structures required for learning. It's this powerful fertilizer for brain cells. And one of the best ways to express it in the brain is through physical exercise.

Kirk Erickson, PhD:

What we've been able to demonstrate is that exercise influences cognition, it influences memory function through its direct impact on the size and function of these brain regions that support memory function. One of the ways that we know that exercise influences the brain is through its effects on Brain Derived Neurotrophic Factor.

Kirk Erickson, PhD:

BDNF is a really critical molecule in the brain that's involved in memory formation. It's linked to many different neurologic conditions, but interestingly exercise seems to positively impact this particular molecule. It increases the expression, it increases the amount of BDNF in the brain. We think that exercise might be influencing a number of different brain pathways, including memory formation and memory function through BDNF.

Dominic D'Agostino, PhD:

BDNF is brain-derived neurotrophic factor. They're essentially growth factors that are produced in the brain, in neurons or the neighboring astrocytes. BDNF, brain-derived neurotrophic factor, plays a key role in enhancing what we call synaptic activity or synaptic function. So the neurons of the brain or the cells of the brain communicate to one another through synapses. And the synapses are formed through a very dynamic process that requires BDNF. And we know that certain dietary protocols, and exercise in particular, can stimulate the amount of BDNF that the cells make and also the activation of BDNF receptors. And that can actually stimulate, by virtue of BDNF receptor activation, the formation of not only new neurons, but the strengthening of the connections between the neurons, which actually is a process called long term potentiation. And that is the underlying foundation of learning and memory.

David Perlmutter, MD:

Where does physical exercise play in?

Jeffrey Bland, PhD:

Well, I think exercise because the brain is an oxygen rich tissue and it has to get oxygen in order to stimulate its function. What do they say? It's something like 3-4% of body weight, but it consumes over 40% of blood oxygen. That's something like that. That's a very high percentage relative to its weight of the body of consumption, of glucose, blood sugar and oxygen. So when you're asking how do you deliver oxygen to tissues? It's very interesting that

Jeffrey Bland, PhD:

Every culture has some way of increasing oxygen delivery to tissues. So it could be yoga, it could be some form of tantric dancing. So exercise not only brings a more profusion of oxygen to the brain, but it also brings trophic factors that occur from exercise that stimulate cell renewal. But I wanna emphasize everything in balance, right?

Jeffrey Bland, PhD:

Because there are examples actually in the literature of excessive exercise, that lead to oxygen deprivation where you're into a continued ischemic situation where you're oxygen

deprived for long periods of time and like high altitude climbers have been worried about that. That causes neuronal injury. Again, everything in the proper balance, but exercise is a very, very important part of, a therapeutic delivery of probably the most important singular nutrient for the brain, which is oxygen.

Ayesha Sherzai, MD:

Also, when you exercise, what happens is your biggest pump, which are your legs, not your heart is your legs, pump a lot of blood back into circulation and into your brain. With better brain blood flow, the brain is able to get rid of all the toxic byproducts that it has accumulated over the day. So you have great hormones circulating around your brain, you have better blood flow that gets rid of all the garbage byproducts. And with the combination of these two, you've given your brain an excellent chance of resilience.

Dominic D'Agostino, PhD:

Exercise improves overall blood flow. It's really the increase in blood flow that can facilitate many of the beneficial effects of exercise on the brain. So pretty much anything that's good for the heart is going to be good for the brain. So when we exercise, we're used to the idea that exercise improves cardiovascular health. Cardiovascular health is intimately tied to brain health. So I think that's a really important concept that... trying to make our brain healthy, we really have to focus on our heart.

Suzanne De La Monte, MD, MPH:

Exercise is good for the brain because there are a lot of studies showing that physical activity can in fact make the brain work better. In people who have strokes, for example, they're trying to use exercise, physical exercise to repair. So there's something about either the exercise itself that is good for circulation or it helps with the insulin responsiveness,

David Perlmutter, MD:

Another critically important role exercise plays in helping to prevent Alzheimer's disease is that exercise decreases inflammation. We've described how inflammation appears to be at the root of Alzheimer's disease. Thankfully, exercise seems to represent a weapon we can use to quell this inflammation at its very source. In fact, exercise combats inflammation through multiple pathways. One way in which exercise reduces inflammation is by calming down the immune system so that it doesn't make so many inflammatory proteins. It also appears to turn on our bodies' production of antioxidants, which protects our cells from damage by chemicals called free radicals.

Dominic D'Agostino, PhD:

So exercise can influence inflammation in a wide variety of ways. Acute exercise can actually increase inflammation in the form of free radicals, reactive oxygen species. And that's just a consequence of normal metabolic function, metabolism. And in some people, if the exercise is strenuous enough, they may experience delayed onset muscle soreness. That's a consequence of actually, increased inflammation. But it's the adaptive processes from the actual exercise stimulus that then creates the scenario of the body adapting to that inflammation and countering that inflammation through the production and activation of gene programs, which the exercise induces to suppress that inflammation, including molecules, complex molecules like the NLRP3 inflammasome, which is a big hub. And when exercise and ketones, which are increased by exercise, when they're elevated in the body, they can suppress that systemic inflammation by working on various anti-inflammatory pathways.

Kirk Erickson, PhD:

Inflammatory systems and pathways of inflammation are thought to be one of the leading pathways or mechanisms by which exercise positively influences the brain.

Kirk Erickson, PhD:

This is true, however, there's still a lot to learn. Inflammation is a key component. We know that inflammation is closely linked to brain, poor brain health, it's closely linked to Alzheimer's disease. We have a good sense that exercise seems to positively influence inflammation, that is decrease inflammation and decrease brain inflammation.

Kirk Erickson, PhD:

A lot of the key chemicals, a lot of the key molecular pathways affected by exercise are closely linked to pathways that control inflammatory systems. Exercise and inflammation in the brain are very tightly linked. We think that there's associations there that are mechanistic, that exercise is influencing the brain through its influence on inflammatory pathways, but we're still a ways from clearly describing and defining those associations.

David Perlmutter, MD:

We've now learned about some of the many wonderful benefits of exercise like improving insulin sensitivity, reducing stress levels, improving sleep, increasing BDNF, increasing blood flow and oxygen as well to the brain, as well as decreasing inflammation.

David Perlmutter, MD:

In addition to all these amazing gifts, there's still more that exercise can do to improve brain health.

Valter Longo, PhD:

The other possibility...are those that have to do with neurogenesis and the exercise promoting stem cell activation in certain areas of the brain, and so it is possible that these stem cells now are contributing to improved function, but we don't know. Certainly we know that people that exercise tend to do better at the cognitive level. It could also be circulation. Poor circulation in the nervous system can give effects that are similar to those caused by Alzheimer's, so exercise can also promote improved circulation in the nervous system and that alone could be responsible for some of these changes.

Valter Longo, PhD:

So, if you're getting more blood, and oxygen, and nourishment to the brain you're less likely to have dysfunction in the brain.

Lisa Mosconi, PhD:

There's always been some evidence that exercise is helpful to the brain. And there is increasing evidence that exercise is actually protective against Alzheimer's.

Lisa Mosconi, PhD:

Clinical trials have shown that active elderly have a much lower risk of dementia later on in life than sedentary elderly. And we have shown with brain scans that you can see that in people's brains very clearly, also in people who are not actually over 60, but in people who are like in their 40s and those in their 30s and 40s.

Lisa Mosconi, PhD:

There's a very interesting new paper in PNAS showing that exercise is able to fend off genetic predisposition even in people with genetic mutations that cause Alzheimer's disease. So there's a very large study that was done in Colombia, in South America, which is one of the countries with the highest density and frequency of Alzheimer's genetic mutations, showing how in people who do carry this genetic mutations that were very physically active throughout their life, have a delayed onset of dementia compared to people from the same families carrying the same genetic mutations who do not exercise. So if exercise can delay the onset of Alzheimer's...there's strong reason to believe that it could be even more powerful for people who do not carry this genetic mutation.

Kirk Erickson, PhD:

As we get older, our brains are a bit like that silly putty that sits out too long. What happens when silly putty sits out too long? It starts to get hard. When you pick that silly putty up, that hard piece of silly putty, you hold it, you warm it up, you can start to shape it again. That's what exercise is capable of doing.



- Kirk Erickson, PhD: The brain is like that. The older adult brain is like that silly putty that sits out a little bit too long. It still retains its capacity for plasticity, it hasn't lost its capacity for plasticity. What it takes, what it requires is a little bit of holding, it takes a little bit of warmth, it takes a little bit of movement.
- Kirk Erickson, PhD: That's what's important about exercise, movement, and its movement that ends up taking advantage of that natural capacity for plasticity.
- David Perlmutter, MD: Exercise cannot be ignored. Take a moment and take inventory of your lifestyle. Is it sedentary? How often do you work out? Are your brain and body missing out on all the unique and wonderful health benefits we get from just exercising? I'm hopeful that you recognize how important this information is and realize how fundamental exercise is for your brain health today and in the future.
- David Perlmutter, MD: There are many practical steps, pun intended, you can take to ensure you're getting the right amount of exercise. Let's discuss some easy ways to add exercise to your life today.
- Sarah Gottfried, MD: Find a buddy. So here's what I did. My best friend Joe and I get together every single Sunday. So even when I'm traveling, I make it back by Saturday night, so that I can make my date with Joe. So here's what we do. If it's raining outside, we go to yoga class. If it's nice outside, we walk our dogs, we hike or we go running, or we do HIT training with running.
- Sarah Gottfried, MD: What I can tell you is that this is better than therapy. Because we're talking, we're connecting. We know that women especially, the most beneficial way for us to cope with stress, which by the way, raises your blood sugar, is to tend-and-befriend. To get together with someone you love and to talk about what's going on. To connect, to raise your oxytocin, the amount of love and bonding and also just to support each other. So it's this incredibly virtuous cycle to have a workout buddy. Bonus prize, if it's a woman.
- Kirk Erickson, PhD: One really important recommendation is take it slow. Don't think that you're going to run out of the gate and run a marathon right away. Take it slow, you don't want to injure yourself, and you want to make it fun. The second key component is to make it enjoyable, make it fun. One of the

things that we know about general human nature is that people don't like to do things that they don't enjoy.

Kirk Erickson, PhD:

Find some activity that you enjoy. If it's going for a walk, if it's going to the pool, if it's playing tennis, do something that you really enjoy doing. Another third component that's closely linked with the enjoyment is social support. Have some social support, if you know that your friend is going to meet you at the park every morning for a brisk walk, then that might be really helpful in making sure that you get out of bed and get to the park every morning.

Kirk Erickson, PhD:

Finding something that you enjoy, so even if you don't like that social support. Even if you might be the type of person where you prefer to exercise with headphones on where you ignore the rest of the world around you.

Kirk Erickson, PhD:

If that's what you enjoy, if that's the type of activity that really motivates you and helps you relax and you enjoy that, then stick to it, then really try to focus on that aspect of the enjoyment. That will help bring you back in and keep you going.

Kirk Erickson, PhD:

Exercise seems to be one of the most promising techniques and approaches for influencing the brain in a very positive way. Even small amounts of exercise are capable of taking advantage of brain plasticity and potentially preventing Alzheimer's disease.

Kirk Erickson, PhD:

With that being said, even just mobility, just movement can have a profound effect on risk for Alzheimer's disease. Get up, move, take the stairs, park a little bit further away from the entrance to the grocery store. Make yourself walk a little bit further. All of these little things can go a long way at increasing just the amount of activity that everyone is getting each day.

Kirk Erickson, PhD:

There's a lot of resources around many different neighborhoods, community centers, YMCAs, local gyms. Even if you don't have some of these activities, there's parks where often Tai Chi or yoga is being conducted in a group setting. You'll see people just taking walks around the park, which parks are very great places also for inducing more mindfulness types of activities.

Max Lugavere:

And in terms of a protocol, I think there's no debating that exercise is incredibly valuable when it comes to the brain. So try to get your 150 minutes a week of exercise, whatever that means for you. At the end of the day, the best form of exercise

is the form of exercise that you do and that you enjoy the most. So personally, what that means for me is that I really enjoy weightlifting, and I really love low and slow aerobic exercise, whether that means biking around the city or getting on a treadmill every now and then. I also love high intensity interval training. I do that in my gym very frequently.

Max Lugavere:

And an underappreciated form of exercise ... well, it's actually not exercise, but it falls under the category of physical activity that is very beneficial to the brain is non exercise activity. So everything from dancing to home maintenance to chasing your cat around the house or playing with your kids. Movement is so vital for life, and it's also incredibly important for the brain. So movement in whichever way that you like to do it. Stagnation is the enemy, and that applies to the periphery and your brain does as well.

David Perlmutter, MD:

We are really grateful to our guest speakers for sharing their incredible knowledge with us about exercise. We've learned that exercise and physical activity in general are absolutely essential for brain health. Here are some actionable steps you can take today so that you can reap the benefits of exercise:

- Increase physical activity in your life overall and here's how. If you can, consider walking or biking to work, taking the stairs instead of the elevator, or intentionally parking a little further away from the entrance of the grocery store.
- Incorporate community into your exercise routine. For example, make a plan to start an exercise program with a friend or family member, join a community center like the YMCA or a local gym, and look for group classes, check out online meetup groups to find group activities in your area.
- Find exercises that you enjoy and look forward to. Try experimenting with different forms of exercises until you find something that you really like.
- And take it slow when you're just starting out, then gradually increase your exercise intensity and duration over time.
- The goal should be at least 150 minutes of moderate exercise each week. But look, even if you don't get there, you're still doing your body and your brain a tremendous service.
- Find and protect a time for exercise as many days of the week as you can.

These simple but powerfully effective steps will absolutely help you make exercise a regular part of your lifestyle.



David Perlmutter, MD:

This could be as simple as calling a friend and making a plan to meet for a weekly walk. All of these seemingly little things actually add up and bring you closer to achieving better overall health while additionally setting up your brain for long-term success. There's no way around it. Exercise is fundamental. It's fundamentally important when it comes to Alzheimer's disease prevention.

Kirk Erickson, PhD:

If we could encapsulate the benefits of exercise into a pill form, it would be the most powerful pill that we have in existence, so it has a profound effect. What's really remarkable to me is that we can search for a powerful pill to try to prevent Alzheimer's disease, to reverse its effects, when a good pair of walking shoes and getting out, going for a brisk walk might be much more effective or as effective as any other treatment that we could come up with.

David Perlmutter, MD:

Exercise is available to all of us.

David Perlmutter, MD:

All you need is a pair of running shoes perhaps, or not. I can't stress enough. With all of this new information, we now understand that the effects of exercise on brain health are absolutely profound.

David Perlmutter, MD:

You have the power to drastically reduce your risk for Alzheimer's through exercise and you can start today. Remember, regular exercise is one of the most effective tools in our toolkit that can bring you one step closer to actually preventing Alzheimer's disease.

David Perlmutter, MD:

In our next episode, we will show you how good sleep maintains and actually improves the health of your brain. The research on sleep is nothing short of extraordinary

David Perlmutter, MD:

And I can't wait to show you how to harness this information to better your brain and strengthen your Alzheimer's prevention toolkit. I will see you in our next episode, The Power of Sleep, Nature's Brain Tonic.