Speaker 1: Bonjour good morning. I'm not sure where to start after such an introduction. Okay. Thank you very much. It's an honor to be here. This is my fourth conference with chiropractors. You are an interesting bunch. You are a very, very interesting group. You're very friendly and I've actually have been a patient of yours also a very dear guy called Darren in Barcelona and somebody in Brussels called Dr Declan McMurphy. I think. So. I'm a testimony that it does help, but there's no better alternative to randomized control trials. You need to remember that. Okay. It's not showing on the screen here.

This. Okay. Thank you very much. Very, very dear Adrian for this introduction, which I hope even half of what you said is correct. I have reached to this way because of a student's question. In my culture, we say that the one who is embarrassed does not learn. We always learn by questioning. You know, a Jewish answer is a question, and we learn by questions, not by answers. And so a student asked me a question in Southampton in England. She said to me, "Uri, how does" with her cute accent. "How does the brain know that we have cancer?" And I answered, "I don't know", she meant before it's a tumor and when it's preliminary cells and that question led me to the nice voyage that I've been taking for 15 years on the vagal nerve in cancer and other diseases.

So we are being killed slowly but surely by these global burden of diseases worldwide. This is known to you. Ischaemic heart disease, COPD, cancer, et cetera and stroke. Even in developing countries, people die more from cancer than in other countries because of poor medical care. So we need to start thinking about cheaper and more efficient ways. And as Dr [inaudible] said, salutogenic ways that rather than fighting risk factors we should enhance resilience factors. A lot of these diseases have common behavioral risk factors. This is not new to you and this is just an example of world prevalence of cancer. So it's in developing developed countries, it's very high. But remember that in the developing countries, the mortality from cancer is high, the opposite is with COPD. And the question is can we actually find one resilience factor which predicts these diseases which is related to these behavioral risk factors, smoking, exercise, diet, physical activity, and which importantly biologically inhibits multiple contributing factors. So with all modesty, I would like to propose it. It is the vagal nerve.

We've presented similar models and other people have done it too. So we're building on upon this. So the vagal nerve, as you know better than me because you've studied anatomy and I'm a simple psychologist, the vagal nerve is a major part of the parasympathetic nerve. Most of the time the sympathetic and parasympathetic are opposing each other, but not all the time. And as you can see, of course the vagal nerve innovates multiple vital organs, the heart, the liver, the lung. We measure its activity and we'll see if this works. Yes it does. We measure activity by the intervals between the beats, normal beats. So this is your pulse, right? Number of peaks per minute. But the changes in between are under vagal control. The heart rate variability and heart rate variability is very profoundly correlated with the actual activity of the nerve of the vagus and it's causal. So if you give sympathetic drugs, HRV does not change. But if you give vagomimetic drugs, HIV changes.

Just to show you that it's a very subtle salutogenic or resourceful parameter. So students were put under stress, it's not difficult to do. And and they measured three systems, cardiac-diastolic blood pressure, hormonal cortisol and immune inflammation, but they split them into baseline high and low HRV at baseline. What they found was, so this is diastolic blood pressure, everybody, this is before stress, this is during the stress and an hour later. So an hour later is about recovery. Resilience is about responding. You need to respond to stress. If there's an alligator, an alligator coming in here, we need to respond to it, okay? But we need to know how to recover. Okay? I am living in a country, our South has been now bombarded for the last three days I was there. I went to help. When you get out of the place, you need to recover. You need to get out of that.

Then I'm coming to France with, the worst thing that can happen here is that the bottle of wine doesn't open on time. You have good problems in Europe. So what you find is that the people that recover fast from this in diastolic blood pressure from the stressor are people that had their baseline heart rate variability is elevated, so people that if you have a high vagal activity at baseline, you're going to recover. Your resilience is better. This is in diastolic blood pressure. This is in cortisol, a bit less clear and look at inflammation so these people never recover within the hour. These people do. So I view the vagal nerve as the Japanese pagoda. In several earthquakes in Japan they realize that when several buildings collapsed, the pagoda did not, and it's because the pagoda rotates around its central beam and enables the building to move, shift, but then go back to how it was. That's what the vagal nerve actually does to us. It enables us to respond in multiple systems and then go back to how we were before. That's why I see it as a resilience factor. And there's evidence for that.

I actually don't have the figure here, but we did a similar study where we looked at brain immune communication and again these were Japanese students, which is even easier to stress and with a colleague, O'Hara, Hidecki O'Hara, they stress the students and we met, they looked at brain ACTH, brain, natural killer cell relation. And when we split the people into high and low HRV at baseline, it's fascinating. I'm sorry I don't have a slide here. In the people that have high vagal activity, you see correspondence between the brain and peripheral immune and peripheral hormonal levels. But in people with low HRV the brain and the body are almost like disconnected. It's like the brain is still on the weekend and the body's already on Monday. So again, the vagus also determines the synchronization between the brain and the periphery.

So global burden of disease. I'm going to take you through three paths please. On a Saturday morning. HRV predicts prognosis of all of these diseases, the onset and prognosis of these diseases. So first of all, you all know what is the metabolic syndrome is we were just challenging now our metabolic syndrome in breakfast. Some of us were not resisting. Some of us were resisting temptations, so the overweight, higher high lipids and high glucose are the main aspects of the metabolic syndrome. It is a risk factor on its own for multiple diseases, heart disease, cancer. HRV is inversely related to each of the components and to the full story. In fact this, you can't see it here, but this is HRV and this is the number of components of the metabolic syndrome. So the higher your HRV is, the fewer components you have of the metabolic syndrome. This has profound

public health meanings and I'm happy to work with and I'm honored to work with Dr [inaudible] who is a public health person and a chiropractor.

This is a sad slide in most departments worldwide. We do not measure in cardiology heart rate variability. Why? I don't know. Cause universities and hospitals are very childish I'm sorry to say, very childish. This is published in the number one leading journal in cardiology in Jack Jay, German American college of cardiology. As far as I remember, this is a meta analysis of 21 studies, not one, not two, 21 studies showing that the relative risk of dying after MI is four times higher if your HRV is low.

You know in epidemiology we jump when there's a relative risk of 1.9. We throw a party if it's 2.4. Here it's four! So I really think it's unethical not to measure people's heart rate variability in cardiology. It's an independent predictor of a longer survival. Our group has done a systematic review, actually also in 2018 and Enzo has done an a metanalysis in cancer. Heart rate variability independently predicts longer survival in cancer. I'm going to show you now why we think it does. It also predicts tumor marker levels, so higher people with higher HRV at diagnosis of cancer, their tumor marker levels will go higher slowly. They will rise much slower.

This is a study where we looked at pancreatic cancer. I think all of you know that this is one of the worst cancers. This is just from a ten second ECG, a ten second ECG. You can see that people with higher HRV live double of the time.

Okay. so this has taken a time, one near diagnosis and their survival of courses later look looking at later over a year, year and a half. Many of them died very fast within weeks or months. And it's an independent risk factor. So even after controlling for all of these confounders, heart rate variability still significantly predicts survival in pancreatic cancer.

In this study, I don't know if I have the slide here and no I don't. In this study we showed for the first time that the mechanism is by reducing inflammation and I'll come back to this. The vagus nerve reduces inflammation, which most physicians do not know. Most biologists do not know. Okay. There's a whole domain called in neuroimmunology which for childish reason is not taught in medicine and biology. The reason I do not understand, okay, there are several presidents here of schools around the world in Europe and in the United States and UK, UK, still in Europe, sort of like. We need to teach our graduates neuroimmunology. It's really the hardware between the brain and the body. It's not science, Hocus Pocus. It's real science. Okay. So in this study we actually showed that when you enter CRP, C-reactive protein into the equation, HRV does no longer predict because HRV predicts survival by lower CRP, by lower inflammation, because the vagus inhibits inflammation. I'll show you soon. HRV is also a predictor of COPD and its complications. So what is the biological path?

So I've showed you the epidemiological path and now I'm going to show you the biological path. I was told to keep it simple. I don't know it much deeper than this. I'm a simple psychologist. A lot of these diseases begin by these three main mechanisms. There are other contributing factors of course in each of the diseases. But these three

emerge in many of the chronic diseases, oxidative stress, inflammation and sympathetic hyperactivity.

So oxidative stress is a situation where you have an atom that is starving for it, lost its external electron and it still is it from another one. If it happens to be from a lipid, then the lipid becomes oxidized. That's what starts the chain of reaction inside the arteries. It's one of the factors that starts atherosclerosis, oxidation of lipids. In cancer, these atoms will steal something from our DNA, and if it's not repaired, there's DNA damage. That's what starts the process of carcinogenesis. One of the processes.

This is just a graph showing that even in people with metastatic liver cancer, higher DNA damage predicts faster dying, so it's not only a predictor of the beginning of the disease, but it's predictive prognosis in cancer.

What about inflammation? We're used to thinking about the immune system is something that protects us. That's only partly true. You see, the immune system is like your uncle bringing you, I suppose most of you are Christians, so bringing you a Christmas present, which you don't like, and not only did they bring you Christmas present you didn't like but 10 of them. And that's really the inflammation. That inflammation is the immune system responding in the right way, in the wrong context.

So there are danger signals in this case, mutations of the DNA or other dangerous signals and the immune system, the innate immune system, macrophages, neutrophils are running to help, but the cancer is using it for its own benefit. So the immune system has two roles in cancer that some cells of the immune system attack the cancer. These are natural killer cells, cytotoxic T lymphocytes, CD8 but the other part, the more primitive part of the immune systems neutrophils and monocytes actually contribute to the cancer by inflammation. And just to show you the evidence, this is a study done in the South of Israel and Ben Gurion university. These are mice that were given a cancer. So 90% of them will have metastasis. If you knock out their ability to process inflammation, there's no metastasis. Okay?

By just knocking out inflammation. You don't need a T test for this. Okay. What about hyperactivity of the sympathetic response? So this is a group done, a German group with that they found a really outstanding finding. They found that cancer cells detach to regions that are rich in norepinephrine. They will migrate to regions, they will metastasize regions that are rich in a stress hormone. Again, if we don't take a neuroimmunological, not even talking about psycho-neuroimmuonlogical, God forbid, but a neuroimmunological perspective, we can't understand these things or even ask these questions. How many oncologists would even consider this? And the same group showed that you can reverse metastasis with the medication that I'm sure does not exist in France, UK or us called beta-blockers.

So there've been, it's not so simple. There's been some trials now running on this and not, not so successful, but obviously the sympathetic response is playing a role here.

So now the question is, can we find one thing that reduces oxidative stress, reduces inflammation, and reduces sympathetic activity. So again, with all modesty, I'm proposing, it's the vagal nerve. There are several studies showing that vagal activity is negatively related to oxidative stress. There's even experimental study with cardiac cells showing that if you activate the vagus, you reduce oxidative stress.

What about inflammation? I won't do this to you on Saturday morning, but we have several routes which are fascinating by which the vagus inhibits inflammation. This is a monocyte running around your body because of a infection or because of a cancer, God forbid, and it it speaks cytokine language. The vagus understands it because it has a receptor for interleukin one. Then it gets translated from French to English. Whoever has the brain, okay, Arabic to Hebrew or Hebrew to Arabic. Again, whoever has the brain and, joking, and you have an [inaudible] to acetylcholine. Acetylcholine triggers hypothalamic pituitary adrenal HPA axis to secrete cortisol, and cortisol is anti-inflammatory, so this triggers the whole anti-inflammatory. It's called the vagal anti-inflammatory reflex the other route is by the spleen. It's a bit more complicated and involve T-cells that are in the spleen that represent the vagus and secrete acetylcholine.

In both cases, higher vagal activity reduces inflammation. In fact, experimentally, you show it in people. You can reduce most cytokines and CRP, but active in your vagal nerve, either in the ear or here or electrically with the implanted thing and in animals you can give animals sepsis. The controls will die and if you stimulate the experimental group, their vagus, none of the animals or much fewer of the animals die. And of course the vagus reduces in sympathetic response because it's parasympathetic. So the vagal nerve, as I showed you, inhibits all of these three biological factors. We think today that there are more factors like hypoxia. Hypoxia is where there's lack of oxygen and some cancers actually favor and flourish under hypoxia. Of course, the vagus will reduce that because it is a [inaudible] Okay.

What about the behavioral path? Smoking, insufficient exercise, alcohol, diet. These are all risk factors for all of these global burden of diseases. You know this, I don't need to tell you that. This is a bit more complicated. The interplay between the vagal nerve and these health behaviors is bidirectional.

So when you smoke, the HRV goes down. When you exercise temporarily. Your HRV goes down, but in the longterm, your HIV goes up. And Mediterranean diet. For all of you who do not know, this is called hummus. Come to Israel and I'll give you lovely hummus. Every score increase in a score of a Mediterranean diet increases your heart rate variability. Aerobic exercise increases heart rate variability, but it's bidirectional. It's bidirectional because you choose to eat 10 waffles and butter or you choose to inhibit and do like what Adrian did and eat his healthy nuts and forest fruit next to me because he has a very strong executive function. I'm going to revenge too. He's a very smart person. He learned epidemiology, so he uses his executive functions. Adrian.

Now, executive functions are frontal activity. They are positively correlated with HRV. People who don't have healthy behavior, health behaviors have poor executive function, obese people, alcoholics, smokers, the executive functioning is working less well. These

regions. This is a meta analysis. This is a meta analysis of neuroimaging studies and HRV. You can see the correlation is very profound between frontal regions and HRV. There's a study done by Julian Tear, my colleague and friend from the United States.

And executive function those frontal regions is negatively related to these unhealthy behaviors. It inhibits us from eating these delicious things from smoking, et cetera. And indeed several experimental studies show that if you activate your vagus, you can modulate unhealthy behaviors. So doing HRV biofeedback, so you just take a simple machine or app that you can download and you do deep breathing, which enhances your HRV within eight seconds. Reduced food craving. We should do that before we eat lunch. I'm not saying we should not eat, but we should be careful what we eat. I need to reduce five kilos, four. Vagal nerve stimulation given to animals, made them lose weight, there are studies on all of these.

So this is my model, my simple model. So our, let's start in a mathematical way. We'll start from the end. These are the diseases we want to predict and try to prevent or treat. Obesity, metabolic syndrome, diabetic mellitus, ischaemic heart disease, CVA, stroke, cancer, and COPD. These are the major killers, chronic diseases, noncommunicable major killers, what predicts them? Behavior. We can predict them and we can try to prevent the biological path at the behavioral level. These are the risk factors, smoking, exercise, diet, et cetera.

They are bidirectionally related to vagal activity via the executive function. At the epidemiological level we predict these diseases inversely, so higher vagal activity predicts lower risk of these diseases or a better prognosis. And finally at the biological level, the vagus reduces these three factors which contributes to these diseases, otherwise, the vagus may slow down these horrible diseases because it slows down these contributing factors.

What about the positive side of the moon? This is a study done. Forgive me for all the vegetarians, and I'm also vegetarian, a study done in Japan in dogs where they were given an infarct. Controls have a 13% size of an infarct, so there, in fact, if this is the size of your heart more or less, the 13% of the ventricle was infarcted. If you stimulate the vagus immediately, immediately after the heart attack, you reduce the size of the heart attack by 80%.

If you wait an hour and a half, which is similar to a person coming to hospital getting help and by the time they get to the ambulance, okay, et cetera, et cetera, et cetera. 60% reduction in the size of the heart attack. Now these are dogs. I suppose that in humans it might be smaller, but still these are profound effects. Again, what are the public health implications of this? So I'm now in the process of trying to convince several cardiology departments in Israel, let's run a randomized trial in hospital immediately. If anybody here, please, if anybody in one of your countries can do this in the ambulance cause in Israel we're not allowed to. I know that the UK, it's allowed.

If anybody wants to do this in the ambulance, please email me. I'm dying to do this already in numbers because the earlier we can intervene, you see this is immediately

after. This is an hour and a half later. The earlier we intervene it's important. This might be lifesaving and I'm going to show you that you can do it with chiropractic, also, think about it. Maybe we can imagine you add a chiropractic on the ambulance. That's going to be a funny study.

What would this do to your field? Okay, so one way to activate the vagus is by debriefing. You inhale from your nose, you hold and then you exhale from your mouth. You do one five, one, two, one five or one five one, two, one seven and every time you actually make it slower and slower, you keep up. I don't know what I just did. Sorry. You keep it the same pattern, but you make it slower and slower because the more you do it, your breathing is more relaxed.

This increases your heart rate variability within eight, ten seconds. We did a small, small, small study in France. A student of mine was, was desperate to get his Master's thesis fast, so I gave him this idea. We randomized people to do three times a day, these two, this for two minutes, just twice, three times a day, two minutes. They got an SMS message and the controls got an SMS saying, think about your stress, try to reduce it. Okay, just awareness and we measured perceived stress, physical symptoms in decision making and on two of the three we had significant reductions. These are the controls, no change. This is reduction in stress, perceived stress in the experimental group over a week and this is physical symptoms, no change in the controls, some but significant reductions in experiment.

This is very preliminary because it's only 50 people and a lot of these participants were family or friends of my students so I'm not sure how real these results are. We did not find any effect on decision making, although other studies show that vagal activity improves decision making also. A lot of you are treating pain. I'm going to try and show you that the vagal nerve is also responsible for our wellbeing.

This is a large study done on us soldiers coming back from Iraq. By the way, American colleagues, it's not Iraq, it's Iraq. I don't know why you always say that. Okay. Country has a name. It's called Iraq, like Iran and not Iran. Okay. Sorry. Just. Pain is negatively related to HRV. In fact, the vagus reduces pain. We're not going to become friends. This machine. Okay. This is a randomized trial where they took people with chronic headaches and they stimulated the vagus with the gamma core device that's here in the neck. These are the stimulation parameters and it was a double blind placebo controlled randomized trial. I don't remember how long it lasted. I think it was a few months.

You can see this is a percent of improvements, so 35% almost improved and the criteria was I think 50% reduction in headaches. This is a very tough criteria. This is not my study. It was by Silverstein and all and you can see compared to controls a very, very nice say effect.

I'm just going to show you a pilot study that we did. It's a very simple study. It's not a proper study, I'm ashamed to say because we didn't have proper collaboration from the doctors. This was done in Brussels. My former job in the school of medicine, the Free University of Brussels and we for a year and a half we recruited patients with metastatic

colon cancer. We wanted them to do vagal stimulation by biofeedback. So what do you do is you, you have a small device like that and you put your finger in, it derives your heart rate and from the heart rate it derives the HRV, the change in the intervals, and you do deep breathing and on the screen you get some kind of biofeedback. There are many, many of these devices. It's not something so special. And you train people within a few minutes to do it. So the reward is that you see your HRV going up and you also feel relaxed.

Our experimental group did this for three months, every day, 20 minutes. And there's a Pinocchio detector inside. Cause actually tells us if they did it or not. So this is just a graph showing that when you do five two five or five two seven, it goes up compared to baseline. And when you're telling people to relax in front of a calming movie doesn't do anything. It's like telling me to be tall.

So we had three patients only, after three months. Three patients. That's it. I thought, what am I going to do with these three patients? It's sad. I owe them a thank you. I owe them to see whether what they did helped and suddenly I had this idea, I don't know how and why. So one of our oncologist retroactively found a match for every one of them. They were perfectly matched. They all had colon cancer. They all had stage four metastatic colon cancer. They all got the same medical treatment. I repeat they all six of them got the same chemotherapy and then I more or less matched them on their baseline tumor marker CA okay. So they're very, very well matched. Three and three, it is not a good study. It's not randomized. It's retroactive case control, matched case control.

This is the average CEA of the three that did biofeedback. This is the average CEA of the three controls at baseline. So they're very, very well matched. This is just a pilot, but the results are very promising. So this is the tumor marker levels in orange or I'm colorblind. I don't know what color this is. Every presentation it looks to me different. There's no change and this is red, I believe you can see in very nice reductions in CEA. It's almost even statistically significant with three and three, but this is a very not serious study, but it's shouting to be replicated and we're working on it right now.

We would like to do a similar study where we're giving it to breast cancer patients. Perioperatively. I don't know if you know that there's been little small revolution initiated by another Israeli by [inaudible] was showing that the mere surgery of cancer, the mere removal of tumors actually is the opportunity of very, very resilient cancer cells to survive because the surgery induces surgical stress hormones and inflammation and these cells love it and they resist the tumor removal and those are the cells that are probably going to make the relapse.

And he showed an animals and now he's working at it on people that if you perioperatively give animals ibuprofen and beta-blockers, there's no relapse after surgery. Again, if you don't have a neuroimmunilogical perspective, why would we even think about that? So as my dear friend and colleague, Adrian said, we need to broaden our perspective. But for a cardiologist to speak to a neuroscientist, it's almost like us and the people from Gaza making peace. Actually I think us in Gaza, it's easier for us to

speak than a cardiologist and a neuroscientist, certainly it's closer. So we are planning to do a study where we're, we would like to do a study where we're giving nerve vagal nerve stimulation around the operation because the vagus reduces inflammation and sympathetic activity. There's the two in one.

And with my dear friend, it won't be, ovarian. I made a mistake. I didn't, I actually was planning to just before this lecture I realized that all my slides were, something happened to it. So we just got a grant looking at the effects of chiropractic on cancer and why chiropractic? Because there are studies showing that if you stimulate C1 C2, you actually can increase HRV. This, there are now six studies already existing. So this study examined the effects of C1 C2 versus C6 C7 on people with chronic neck pain or healthy people, and they looked at the effects on heart rate variability. You can see that C1 C2 increases several parameters. This is purely vagal. This is vagal. This is mostly vagal. And it reduces blood pressure. Just stimulating here with your dedicated very good hands and fingers. I'm serious.

So Adrian and I, sorry this is the slide, Adrian and I not on diabetic mellitus, but on, on cancer are planning to do this on cancer and seeing whether chiropractic plus usual care. Sorry, this is a mistake. It should be cure. Yeah, sorry. Usual care versus usual care plus chiropractic. This is actually improved cancer outcomes and as Adrian said, we want to look at quality of life. We want to look at tumor markers. We're gonna look at inflammation and maybe other factors. And of course pain. We don't know if it's going to work. Okay. You need to do randomized trials. You cannot look at one person and say, yes, it works. Okay, you need to do randomized trials.

So in conclusion, we should consider first of all, routinely measuring HRV in the population to estimate the risk for global burden of diseases. I think we need to start measuring this in clinics, in your clinics, because it's going to be a good estimation of your patient's prognosis and it's correlated pain. It's correlated negatively with depression and anxiety. I did mention that, it's correlated positively with wellbeing. As I said, HIV is negatively related to inflammation, oxidative stress and sympathetic activity, and we should now be planning, which is what I'm planning, several randomized trials in the next years. Testing whether vagal stimulation by any method, does it actually help to treat or prevent heart attacks, cancer, stroke, COPD, et cetera. This is based on the domain of neuroimmunology that's the scientific but foundation and it's what I call neuromodulation of health and disease.

So please, if you want, this is not, this is my older email. Again, I didn't that you can write to me here if you want. And I just want to thank several of these people from around the world and this is a nice American expression. Thank you very much.