>> Welcome to the podcast series of "Raising the Bar Sydney". Raising the Bar in 2019 saw 21 University of Sydney academics take their research out of the lecture theatre and into bars across Sydney all on one night. In this podcast you'll hear Luigi Fontana's talk, is living longer better? Enjoy the talk.

[Applause]

>> Hello. Good evening. So, it's pretty new for me because normally I'm used to present slides, you know, from, you know, scientific, you know, conferences, so it's a bit new setting. But, let's see, you know, if I'm able to tell you something interesting tonight. So, as you can hear I'm Italian from my pronunciation. I was born and raised in the Lake of Garda. It's close to the Lake Como. It's a beautiful area of Italy close to the Dolomites. And I did my medical training at University of Verona and my residency in internal medicine at University of Verona. Then I spent one year in London working on cardiovascular health. And then I started my PhD in metabolism and I spent most of my time in U.S. at Washington University in St. Louis. So, as soon as I started to work to – as a student then as a resident in medicine I realised that I didn't want to be the classical physician. So, I didn't want to spend my life, you know, to prescribe drugs to someone who was coming in, you know, with chest pain, or with blood in their faeces, or nodule in their breast, you know, I think, you know. Or maybe, you know, to put like, you know, for urinary incontinence, you know incontinence device. You know, I don't want to spend the rest of my life, you know, to put bandages, you know, to people who issues. And said, you know, is it possible, you know, biologically to live a longer life without getting sick? Is it biological possible? And so, I started to do some research, and if you go on Google and you put longevity, if you digit longevity, you're going to find calorie restriction. So, back then, you know, I started to research into what was known. And you know, there were a lot of data in animals showing that, you know, if you restrict calories by 20%, 30% in animals without malnutrition, with all the vitamins and minerals, this animal lives up to 50% longer. It's like for human being instead of living 80 years, we live 100, 130, 140 years. Pretty spectacular. You know, this is a very solid set of data. There are many labs around the world that have been, you know, proved that, you know, that's real, it works. Now, we have even data in known human primates that, you know, they live longer, they have less cardiovascular disease, less cancer, less, you know, degeneration, less sarcopenia, less frailty, less auditory loss, you know, with the 25% calorie restriction. And what is interesting is that again, you know, not only these animals they were living longer because I think nobody here is interested to live a long life and spend the last 30 years of his life, you know, with a stroke, you know, with a paralysis, or you know with demented, or you know, I don't think that's life. But unfortunately, that's what happens. What happens is that because of the huge advancement of medical, you know, technology now we're able to get a lot of people living much longer in a – with a kind of poor quality of life. And by the way, this is not sustainable, you know. Even in Australia, you know, there are predictions that the cost of healthcare in terms of GDP is going to double in the next 15 years. So, everywhere in the world

even U.S., you know, there's insurance-based healthcare, but there are a lot of people who are poor and they're on Medicare. We know that is not sustainable. So, the future is going to be prevention to health by the way. So, we have to change our way how we approach health. You know, this idea, you know, that you know people they accumulate damage because they have unhealthy lifestyle and you know, year after year they get, you know, more cellular damage, tissue damage, organ damage. And eventually they develop one disease and they live long enough they're going to develop two, three or four disease. Now we have elderly people they're taking 10, 15 medications every day, what a pain. And so, I said, you know, I want start understand, you know, if this data in animals are also applying to humans. Because, you know, of course you know we use flies, worms and yeast and mice because they're very easy to work with as a model to generate data. But, then you know, it doesn't mean that, you know, what we see in animals it applies to humans. So, I said, you know, I want to study, you know, what happens in humans if calorie restriction works in humans. So, I wrote an email to this professor, John Holloszy that he just died last year. He was my mentor, friend. And by the way he came – he was in Sydney here in 2000 and he won the gold medal at the Olympic Sydney Games as a recognition for his career, because of his, you know, discoveries in exercise physiology. He's basically one of the pioneer of exercise physiology. And exercise is a tool to improve, you know, metabolic health, reduce the risk of diabetes and many other important discoveries. And so, I wrote to him, I said, "You know look, you know, I'm interested in understanding, you know, if calorie restriction in humans causes the same adaptation that we see in animals that are living longer?" And he said, "You know, why don't come to U.S.?" And so, basically, you know, I left Italy and you know, I went to U.S. and I spent the last 17 years of my life there before I came here to Sydney. And I work basically on several studies on the effects of calorie restriction. We have been recruiting people that we're already doing calorie restriction without malnutrition they're rating 100% of the RDI for rich nutrients, so no vitamins or mineral deficiencies. And what we see that, you know that these people, yes, they're much healthier than the average Americans. It's not difficult by the way. But, you know, they're really super healthy. You know, they have very low cholesterol, high HDL cholesterol, the good cholesterol. Blood pressure is 110 over 60 even in people who are 70 years old, very low inflammations to reactive protein, very low glucose, very insulin sensitive. You know, we measure the – we check their carotid, they're very clean. The function of the heart is more elastic and efficient than – because there is less fibrosis. As we get older this – the inflammation is causing fibrosis of the tissues, special heart and blood vessels. And so, that you know, we find many of the typically adaptation that we see in animals that are living longer on calorie restriction are also occurring in humans. But, when we started to work on calo – when I started to work on calorie restriction 15 years ago there were some dogmas as always. One of the dogma was that the more calorie restriction the better, is not true. The other dogma was that the macronutrient composition of the diet, the quality of diet was not important, only calories were important, is not true. In the last

10 years, you know, what we have been discovering that the quality of diet is as important as the amount of calories we're eating. We also discovered that, you know, probably, you know, the amount of restriction is not the same for everybody. And so, we have to develop new biomarkers to understand what is optimal, you know, that – you know, so you know we can really tailor what is the prescription. And with other people we discovered for example that, you know, what we eat is changing the bacteria even in our gut. You know, we have trillions of friends that are living in our intestine, on our skin, everywhere, but you know in our intestine. And these bacteria are processing the food we eat and they're creating metabolise that they get absorbed in the circulation and they have important effects. For example, we're discovering that, you know, some of these – if we eat a high-fibre diet, so you know, legumes and whole grains and vegetables and fruits, seeds, nuts. These fibres they get processed by the bacteria to produce short-chain fatty acids that have receptors on the epithelial cells of the gut and on the immune cells. We have a lot of immune cells, you know, in our gut because these are like soldiers that are protecting our body from the invasion of the bacteria in our gut. And what we have been discovering is that, you know, these short-chain fatty acids that are a byproduct of the digestion of fibre by the bacteria. They're inhibiting inflammation and they're promoting the growth of a subset of immune cells called 17 – TH17 T-cells that are very important for the prevention of autoimmune diseases and allergic diseases. So, there are more and more data suggesting that the big increase in asthma, type 1 diabetes, multiple sclerosis, Crohn's disease and other autoimmune diseases are in part due to the huge reduction that we have – we had in the last 15, 20 years in the consumption of high-fibre vegetable food. Because, you know, we eat a lot of refined carbohydrates, a lot of animal products. And basically, when I see patients in the clinic I say, you know – "Beans, what is beans?" You know, they don't know what anymore what is a legume, you know. People, you know, probably they eat legume once a year for New Year with the pork, you know. But you know, so that's the problem. You know, that you know, we have completely changed our diet and this has a huge impact. You know, we have solid [inaudible] and we're trying to become more sophisticated to understand, you know, how calories, the distribution of calories. You know, we – not only calories, but when we eat the calories is very important. You know, now there's all this fasting, you know, the intermittent fasting, or time-restricted feeding like the six, what is the 16/8 diet, you know. There are all these fat diet that are coming up, you know, that you know in some way they're wrong, you know. Because you know, the idea – I just finished a study in U.S. where basically we did, you know, five days of fasting and two days of – two days of fasting and five days of normal diet. The fasting was vegetables, non-starchy, raw or cooked vegetables. So, you have to count calories with tablespoon of olive oil and vinegar or lemon. And you know, the people were very happy, you know, because you know, they say, you know, "For five days I can eat whatever I want, you know, junk if I want. And two days basically I'm going to fast." In reality they lost 7% body weight similarly to other studies on calorie restriction, but for example, we don't see many of the

classical metabolic, positive metabolic adaptation of calorie restriction where we change the quality. For example, we don't see any improvement in insulin sensitivity, we don't see any improvement in insulin sensitive, we don't see any improvement in glucose, we don't see a reduction in inflammation that is typical of calorie restriction. Suggesting that what we eat in the non-fasting days is influencing the metabolic response to calorie restriction and is influencing that through probably the protein composition. There are more and more data, you know, the type of protein that we're eating is influencing, for example, insulin sensitivity independent of calorie intake. And the gut microbiome itself, you know, we have data, published data, you know, that you know what we have been eating for years is selecting the type of bacteria that are living in our gut. Just to give an example, you know. So, if you're a carnivore, so we did a study published in science, because you have a high meat intake you select bacteria that area specialised in cleaving proteins and chopping proteins. If you're an herbivore instead of, and you have a lot of vegetables, you select bacteria that are specialised in synthesising proteins. It makes sense. And so, what happens, you know, that you know, over generations some bacteria they completely disappear from our gut and that's one of the problem, you know. Basically, you know, what we're finding, you know, there are bacteria that, you know, they have disappeared, you know, because we have been eating for many years certain food. We have been selecting certain bacteria and we have killed, yeah, the bacteria because we didn't provide the right type of food that they like and they grow on this type of food. So again, you know what we're finding, you know, basically that nutrition is very important. But again, you know – what I don't like, you know, in science is that, you know, there are these fashions, you know. Now there is the keto, before there was the paleo and then there was the Atkin and then, you know, there was the 5:2 and who knows how many diets, you know. Every year or two there's a new diet and you know, people they like, you know, these very simple, you know, approach, you know, that it doesn't make any sense, you know. It's a bit more complicated. And for example, apart from diet and what we're trying to do is to understand how diet works by using these animal modes of longevity. So, what we have been finding there are animals that are living longer, much longer. And what we're finding that these animals are living longer they have mutations in these nutrient sensing pathways. And with this approach it is very scientific based, you know, we're starting to understand how we can manipulate these important pathways that are reducing the accumulation of damage, and therefore the risk of developing cancer, dementia, cardiovascular disease, autoimmune diseases. So, you know, that you know instead of working on one disease we're working on upstream in blocking the accumulation, and so we can prevent multiple disease. So, that's the beauty of this model.

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>> That you know, in medical school what we do, what we have been training to do is to diagnose disease that typically take 40 years to develop. You don't develop cancer, breast cancer in one year. It takes many, many years of abnormal

metabolic and hormonal factors that are increasing the risk of mutation. When you have enough mutations then the cells become malignant and then you need other mutation because the cell become a mastitis. So, it's accumulation of mutation and to do that you have to feed, you know, the cells, you know, with all these hormones that are allowing the cells to become more and more aggressive. The same is for cardiovascular disease. You only develop a myocardial infarction in one year, it takes many, many years of high cholesterol, high blood pressure, high glucose, smoking, you know, to develop a plaque that is unstable and is going to develop into a myocardial infarction. And so, what we do in medicine instead of what we teach to our medical students is to make diagnosis typically, you know, basically someone comes to my clinic and say, "You know look, you know, I have chest pain. I have blood in my faeces or I have a nodule." And so, what we do, what we train to do is, okay, okay. I do some blood test, I do some imaging and I make a diagnosis and then, you know, we're trained to treat this disease with drugs or surgeries or other procedures. So, basically there is almost no prevention, no knowledge about how important are these lifestyle factors in acting on several important pathways, so you know we can block or reduce or slow down the accumulation of damage and therefore prevent multiple chronic diseases. And what is beautiful in this animal longevity is that basically as I told you not only this animal live much longer, much healthier, 30% of the animal of calorie restriction they die when they're very old without any pathological issue. So, if you do an autopsy, you're not able to find the cause of death in these animals. That's fantastic. So, it means that biologically it's possible to live a long life without getting sick. And not only these animals they're 80 years old, the equivalent of 80 years old for human beings and physiological they look like 40 years old. And that's what I think, you know, we should aim for, you know, potentially to live a long life and when you're 70, 80 you still have the stamina, the energy, you know, the health of a 50 years old and so you can enjoy your kids, your grandkids. You know, you can have a new life and travel. But, if you're sick, you know, if you're demented or you're paralysed you take 15 medication, where are you going to go? Nowhere. You have to stay as close as possible to the hospital, so you know, when you have a disease, you know, when you have – not a disease. You have a new recurrence of something you're close to the hospital. So, basically you're a prisoner of yourself because you have done a lot of wrong stuff during your life that, you know, is making you, you know, frail and dependant to medical system. They're unsustainable by the way. So, what happens is that, you know, probably in the next years the wealthy people they're going to afford basically the very expensive healthcare and the rest of the people they're going to be waiting a long list, you know, to get a surgery or to get something because resources are not unlimited. So, apart from nutrition, you know, what we're finding is that exercise is very important. So you know, again you know, there is not one solution, exercise extremely important. There are different types of exercise, endurance exercise for example is very important to improve insulin sensitivity to increase – for example, this I discovered, you know my mentor John Holloszy did. You know, he was the first to discover, you know, when we exercise there is an increase in

mitochondria. The mitochondria is organelles that are producing ATP, so that you know, you can – the muscle can contract and you can run or you can bike, whatever. And so, you know, if you do exercise constantly you have an increase in mitochondria, and so you're burning more calories. And the more efficient you're becoming, the less time you need to burn the same amount of calories. Meaning that, you know, at the beginning if you're 730, you start to exercise you don't see much benefit. But, as you build the number of mitochondria and the activity of mitochondria you become more efficient and then you start to see the benefits in terms of helping you to keep your body weight, you know, normal and to lose weight. And then there is, you know, the beneficial effect on insulin sensitivity include reducing glucose, increase in HDL cholesterol. There is a new paper that is beautiful. Basically, when we do exercise, for example, there is a protein is called cathepsin B that is produced by the muscle that goes to the brain to the hippocampus that is increasing BDNF. BDNF is the brain-derived neurotrophic factor, is a very important factor for memory and for the growth of synapsis. That's why exercise is very important for kids in schools, and not only for kids, even for people like any age, elderly people. Because by exercising you increase a molecule that is triggering, you know, the growth of synapsis and brain function and memory. It's also – BDNF is a powerful antidepressant molecule. So, basically by itself, you know, it's very important for mood. Then you know, there is other type of exercise, resistance exercise, very important for muscle mass and increase resting metabolic rate. There is flexibility, exercise. A lot of people as they get older they have, you know, posture issues and they have problem with a lot of neck pain. Think about it, you know. If you're getting more and more weak and you start to bend, what you have to do to walk is to lie back. Because otherwise, you know, you're going to – and after days and days of staying in this position, in this wrong position basically you have chronic neck pain and then you have problem on your back, and you have problem in your joints. So you know, there is a lot of problems with bad posture. And nothing is taught at schools or in hospital about postures and other stuff. So, then you know, there is cognitive training. There are more and more data suggesting that basically as we get older we have to keep learning new things because the brain is like a muscle, if we keep exercising, if we keep learning new stuff, you know, our brain is creating synapsis that are important for reducing cognitive decline. I mean, it's simple, but you know, for example, you know I've been living most of my life in Italy and U.S. and we drive, you know, on the left – on the right, but you know I'm on the left. When I came here, you know, at the beginning, you know, it was scary, you know. Because you know, when I was driving I couldn't – basically the street, you know it was, you know, how much space there is here and there, because my brain was used to that type of dimension. And now basically what I've discovered, you know, if I go to Italy I jump on the car and I'm fine, I come back to Australia I jump in the car I'm fine. So, basically I have developed new synapsis very quickly in a year that, you know, I can drive in both world, you know, without any problem. But, the first few months, you know, I had to be very careful you know when I was riding in Australia. Just to tell you how, you know, learning a new instrument,

learning you know to do sculpture, new language, anything. Even if you're an elderly person is very important for developing and inhibiting the cognitive decline. Another important stuff, you know, we don't study in medicine is mindfulness. There are more and more studies, for example, there's a centre in Harvard Medical School just for mindfulness for treating anxiety, depression and may other conditions. So, one of the issues that you know I think, you know, we have in our Western society is that, you know, people they're constantly running, they're constantly thinking about – they're worried about the future, you know they have regrets about the past and they're not able to enjoy the present. They don't live in the present, they live or in the past or in the future. They're very stressed and they're basically missing an important chunk of their life. Because for example, if you're living in the present and we're enjoying what happens and we're accumulating all this information in our brain that we miss. You know if I'm sitting at a table with my son and I'm thinking about my problems and I'm not listening to him, basically I'm missing an important part of myself, of himself, I'm not tasting the food, I'm not, you know, exchanging emotions because I'm – my brain is somewhere else. And that's bad for several reasons apart from, you know, anxiety and other issues with, you know, a lot of these psychological psychiatric issues that are increasing in our society. And we don't have a clear understanding why there is this huge increase in anxiety, depression and many of the psych-related disease. But, I think you know apart from that there are more and more data suggesting that the people who are mindful they're more empowered and they're more creative. Because you know, if I'm here now and I'm – or if I'm walking somewhere and I'm really present and I listen and I absorb sounds, colours, something. This information that gets deposited in my brain and when I need something to create something is there. Instead of if I'm not attentive basically I'm missing an important part of my creative intelligence. So, emotional, creative intelligence, intuitive intelligence are a very important part that are in some way due to what we do in terms of exercise, nutrition, through these hormones like BDNF. But, is also a training about how we live life, how we perceive life. And if you're triennial to be present, to be more emotional connected is very important. With emotion connected there's another major problem is solitude. You know, we live in a society where more and more and more people as they get older they're living by themselves, they don't have connexion. And there are more and more study that it's very bad for depression, for suicide. You know, there is higher rate of suicide in elderly people who are living by themselves without the connexion of their son and daughters or nephews instead of, you know, in this society where there's a higher percentage of centenarians like in Okinawans, social connect is very important, you know. So, the grandparents they're taking of the nephews. And so, they're a part of this big net of society. And I think, you know, again in our Western society that's another part, you know, that we're missing. So, what I'm telling you is that, you know, there are a lot of pieces of the puzzle are very important. Of course, nutrition is extremely important. We have a lot of data showing, you know, nutrition and exercise they're very important in modulating these ageing pathways. But, there are other parts that are related to, you know,

our cognitive training, our mindfulness, our emotional intelligence. That you know we are – I think, you know, we're totally underappreciating. And I think it should become part of university, you know, educational system. I think, you know – and that's what we're trying to do at University of Sydney. And that's why I came here, you know, at Charles Perkins Centre with Steve Simpson and other colleagues here, with Margaret that is here in the audience, you know. Because I think, you know, we have an idea that you know, we can create a better world where, you know, we can avoid a lot of suffering. You know, there are a lot of disease that we see in our hospital they're totally preventable. The World Health Organisation claims that, you know, 80% of cardiovascular disease and type 2 diabetes are preventable and 40%, at least 40% of cancers are preventable. My data suggest it is much higher, probably 95% of cardiovascular disease and diabetes preventable type 2. And probably 70% of canc – common cancer are preventable. And so, you know, we create a huge amount of suffering, a lot of cost, a lot of, you know – that is unnecessary and in some way it's – you know, we spend a lot of time working. A lot of our time, you know, we spend working to pay for a very expensive healthcare where you know if people they knew how to be healthier they could spend time with their family, with their friends. You know, painting, playing an instrument, you know. And so, I think you know, we have to think about a better world where, you know, we do what we have been created to – as human beings, you know, to be creative, to be you know engaged with friends and culture activities and not spending and wasting our time, you know, to create a vicious circle of disease and expense, disease and expense. And think about also this problem with global warming. You know, 30% of global warming is due to intensive animal farming. And global warming is a major problem. And intensive animal farming is not only causing global warming, about 25% of particular matter of pollution is due to intensive animal farming. There is a huge consumption of pesticides, herbicides, you know. And I don't know if you have read, you know, that you know these intensive animal farming they use a huge amount of antibiotics and this is causing antibiotic resistance. The risk is basically 10, 15 years we may run – we may not have any more antibiotics to treat pneumonia. We're going to start to die of pneumonia, again unless we discover new antibiotics. So, what I'm saying, you know, there a lot of things we can do that are – we can do it now if people they start to think in a different way. They understand how much power we have now to change our life to be – to live a healthier, metabolic, emotional, cognitive life and enjoy our families, our friends and change the society.

[Applause]

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