HOUSE OF LORDS

Science and Technology Select Committee

Corrected oral evidence: Ageing: Science, Technology and Healthy Living

Tuesday 5 November 2019

10.25 am

Watch the meeting

Members present: Lord Patel (The Chair); Lord Borwick; Lord Browne of Ladyton; Baroness Hilton of Eggardon; Lord Hollick; Lord Kakkar; Lord Mair; Baroness Manningham-Buller; Baroness Penn; Baroness Rock; Baroness Sheehan; Lord Winston; Baroness Young of Old Scone.

Evidence Session No. 7 Heard in Public Questions 51 - 57

Witnesses

Dr Marina Ezcurra, Lecturer in Molecular Biosciences, School of Biosciences, University of Kent; Professor Kay-Tee Khaw, Professor of Clinical Gerontology, University of Cambridge; Professor John Mathers, Professor of Human Nutrition, University of Newcastle.

USE OF THE TRANSCRIPT

This is a corrected transcript of evidence taken in public and webcast on www.parliamentlive.tv.

Examination of witnesses

Dr Marina Ezcurra, Professor Kay-Tee Khaw and Professor John Mathers.

Q51 **The Chair:** Good morning, ladies and gentlemen. Thank you for coming today to help us with our inquiry. We will be livestreamed, so if you have a private conversation it will be picked up. Please say who you are, from my left, and if you want to make an opening statement to get it on the record, please do so. Then we will start the evidence session.

Professor John Mathers: Good morning. I am from Newcastle University, where I am the professor of human nutrition and direct the Human Nutrition Research Centre. My main interest is in understanding how nutrition influences the ageing process and how we might reduce the risk of age-related disease.

Dr Marina Ezcurra: Good morning. I am a lecturer in the biology of ageing at the University of Kent. I study the fundamental processes driving ageing, in particular how the microbiome affects it.

Professor Kay-Tee Khaw: Good morning, I am a physician-epidemiologist at the University of Cambridge. My main interest is determinants of health in human populations, and my main research focus is long-term population studies.

Q52 **The Chair:** Thank you very much. Professor Mathers, you led me nicely to my first question. Your studies involve the influence of diet and nutrition on the ageing process and diseases and that there is a scientific basis to it. What is that scientific basis?

Professor John Mathers: I think most people agree that the basic biology of ageing involves damage to the big molecules that make up our cells, such as DNA, proteins and lipids. Over time, we accumulate that damage and then see what we recognise as ageing. What we have learned over the last 20 or 30 years of research is that nutrition influences both the acquisition of that damage—some things in food can be damaging and some protective—and the processes within our cells and tissues that enable us to process and repair that damage. Nutrition is fundamental to all the core processes involved in ageing.

The Chair: What do we mean by nutrition?

Professor John Mathers: We are talking about a whole range of biological molecules. Many of the vitamins and trace metals that we find in our diet, and the substances that are produced from diet such as individual proteins and so on, are important in the ageing process.

Actually, it is very difficult to put your finger on any one component of diet, and its totality is probably much more important than any single component. I guess the best example of that is the link with too much nutrition, whereby we store a lot of energy, add fat to our bodies and get heavier, because that in itself is a process that causes damage and accelerates ageing. Nutrition influences many different aspects of ageing.

The Chair: Do we understand the biological processes of disease or ageing that are at work when a person is obese?

Professor John Mathers: We understand some of them; some involve the changes that we see in the body systems of people carrying too much body fat. One of the best-studied areas is inflammation; people who are too heavy have a low level of systemic inflammation. Normally inflammation is a positive process, helping us to deal with cuts and bruises and such normal things in life, but when it continues day in, day out, year in, year out, that causes additional damage. It causes changes to all the big molecules and cells and contributes to the ageing process.

Dr Marina Ezcurra: Ageing and obesity have a big overlap in their biological mechanisms. A lot of the fundamental processes that drive ageing are also affected by obesity. There are studies in model organisms showing that many of the hallmarks of ageing that I am sure you have heard about over the last few weeks are activated by specific nutrients or obesity.

Professor Kay-Tee Khaw: I come from the completely opposite end in how I look at nutrition and ageing. Because I study populations, I look at the real evidence. The real evidence from human populations is that there are huge differences geographically and over time not only in life expectancy but in healthy life expectancy, between different countries and even in this country between the social classes.

Between the 10% most and least deprived residential areas, for example, there is something like a 10-year difference in healthy lifespan—a three-year to four-year difference in total life expectancy, but a 10-year difference in healthy lifespan. Costa Rica has the same amount of healthy lifespan as the United States. These big differences and time trends are not magic; they are telling us some big environmental differences between these different populations that, over time, have a profound impact on population health.

Our task as epidemiologists is to try to identify these environmental influences. There is damage, so you try to avoid damage such as pollution and infection, but you also try to improve resilience by building up bones and muscles, et cetera, and to maintain repair mechanisms to protect against the damage from ageing and environmental stimuli.

That is true nutrition. There are not that many environmental factors. There is what we have for nutrition, physical activity and environmental pollution, but those are the main factors. That is what I study. The challenge in human studies is to identify those factors to have more precision to get the evidence. That is where we work with the biological sciences to try to identify mechanisms. We see whether in practice these mechanisms are important in living human populations.

The Chair: Thank you very much—good teaching.

Baroness Young of Old Scone: We have two ends of the spectrum here: the big epidemiological whole-population stuff and the causal, detailed, cellular-level processes. Is there enough research on joining

those up yet?

Professor John Mathers: My view is that we have not yet connected that as well as we could. We have some excellent work going on in model systems, so we understand a lot of the basic biological processes quite well, but we are not doing well enough yet in translating that knowledge into work directly in people. That is due partly to challenges of working with the complexities of people, which are much greater than if we were working with a mouse or a worm. There is an opportunity to take the learning from both ends of the spectrum and bring them together in a much more focused way than we have done so far.

Dr Marina Ezcurra: We need more interaction between these different groups of researchers, more discussion and more trying to work together. As specialists, we tend to be quite isolated in our work, so treating ageing research as a whole, with more concerted effort, would be good.

Professor Kay-Tee Khaw: The United Kingdom is uniquely placed to bring this together. We are already doing it. The big constraint in human epidemiological studies has been the ability to study biology properly. When studying half a million people, as we have been, it is very expensive to measure biology, but new technical developments mean that it is now possible.

We are now able to characterise many of the biological mechanisms by measuring them in large populations, which we could not do before: metabolomics, proteomics, measuring diet and physical activity objectively. We are also able to get important long-term health endpoints—not just death, not just cancer, but functional health, cognitive function and ability to live independently—which is very difficult to do in other populations.

I think we are on the threshold of an amazing ability to link the epidemiological strengths in the United Kingdom and the biology perhaps through using microbiomes in the population as the common link and exploiting what we have already.

Q53 **Baroness Sheehan:** I would like to ask about recommended dietary advice for young people versus elderly people, and whether the same advice is applicable to all older people or whether it varies based on other factors, environmental or genetic?

Professor John Mathers: This is a complex question with many different aspects. I shall try to deal with each of them.

The first is what we know about nutritional needs across the life course. We know quite a lot about the nutritional needs of children, young people, young adults and middle-aged adults, but we know relatively little about the nutritional needs of very old people. It has been very poorly studied. Most of what we know is for people up to 70 or 75. Beyond that, we know relatively little.

Part of the problem is the complexity of the nutritional needs of older people, because that greater age is usually associated with a greater likelihood of people having multiple conditions—diseases of one kind or

another, combined with the use of a whole range of drugs. All those things influence nutritional needs. The kind of commonality that one can have in respect of the nutritional needs of babies and children one cannot have for older people; one needs to try to understand that in much more detail. We have not done that very well yet.

Baroness Sheehan: Do you think that personalised, individual nutritional advice is feasible? Are we there?

Professor John Mathers: Personalised nutrition up to now has been in vogue for much younger people, who are interested in it for all kinds of other reasons—maybe to look well or to help them with sports and so on. It has not been about keeping healthy in old age. A whole area of work is yet to be done.

Conceptually, the kind of work that has been done up to now lends itself to a more personalised approach. In principle, we can do it. The challenge then is rolling it out into public health and how we apply it within the public health system. There are some possible ways of doing it. Web-based systems are one way forward, but there is still a bit of work to do.

Dr Marina Ezcurra: There are strong indications that the nutritional needs of the elderly are different. For elderly people, for example, it is more difficult to build muscle. They need to consume more protein even to maintain muscle mass. That is just an indication that the needs at different ages are different and we need to understand them better.

Professor Kay-Tee Khaw: Personalised approaches work in clinical medicine, where one is targeting a small number of people, but if we are interested in population health, we have to target the whole population. Therefore, we have to look at dietary patterns in the entire population and not just at a tiny group of people who are at high risk, because that will have no influence whatever on population. We have to understand what in the whole population determines healthy ageing. That is my position.

Q54 **Lord Kakkar:** I turn to the microbiome and ageing and start with trying to understand the links between them.

The Chair: The panel might start by saying what you understand to be the microbiome.

Dr Marina Ezcurra: The microbiome is the community of microbes, which include bacteria, fungi and viruses that we have in different parts of our body. We have skin microbiome, oral microbiome, vaginal microbiome and the gut microbiome, which is the biggest one and which has been studied the most so far. I shall stick to what we know about the gut microbiome for today.

Over the past 10 years, because of new, more affordable sequencing techniques, many studies have been done in humans looking at the association between the composition of the microbiome and different health and deceased dates. These studies have shown an association

between the bacteria that you have in your gut and neurodegenerative diseases, cardiovascular disease, cancer, diabetes and other age-related diseases.

That is association, not causation, which is where the field stands now: trying to understand whether and to what extent there is a causative link. Work in the lab using model organisms has shown that the gut microbiome can directly affect the ageing process. Experiments such as faecal transplants in mice, for example, or looking at germ-free animals—animals without any microbiome at all; sterile animals—have shown effects on the ageing process.

Lord Kakkar: What effects? Give us an example.

Dr Marina Ezcurra: In simple models like fish, we can directly affect lifespan through a faecal transplant from a young animal to an old animal. We can make that older animal live longer. There are similar studies in mice. We can affect the way an animal ages by manipulating microbial genes. By introducing, say, mutations into specific genes of the bacteria, we can affect how the host ages and improve the way it ages.

Lord Kakkar: What is the mechanistic basis by which the microbiome in general will affect the host's inflammatory response? What does it do?

Dr Marina Ezcurra: That is the big question. We know that gut microbes, for example, release molecules, metabolites, that can pass into the blood stream and affect different parts of the body and different tissues. We know that, as we age, the microbiome changes and becomes more pathological, which in turn affects the gut barrier, so we start to see leakage of bacterial molecules from the gut into the rest of the body. That in turn further promotes inflammation and possibly diseases.

Lord Kakkar: How does dietary intake modify the microbiome?

Dr Marina Ezcurra: Dramatically.

Lord Kakkar: Give us an example, if you would be so kind.

Dr Marina Ezcurra: There have been studies in humans showing that different human populations have a very different microbiome composition, and studies showing that if you change your diet as an individual, within three or four days you have changed some of the species in your gut. It seems as though diet has a very strong influence.

Of course, there are other environmental effects as well, because you are exposed to all the microbes around you, but diet has a very strong effect.[1]

[1] There is strong evidence that specific diets and nutrients affect the composition of the microbiome. E.g. the Mediterranean diet is associated with a larger microbial diversity and an increase in beneficial species. We are learning a lot about the links between nutrition, microbiome and health, but we know that the Mediterranean diet provides with dietary fibre from vegetables which are digested by gut microbes, producing molecules beneficial effects in the host. It is likely that the overall beneficial effects of the

The Chair: Give us an example of a diet.

Professor Kay-Tee Khaw: There are trials that show that increased oat beta glucans, which is high fibre, will change your gut flora. It provides a more conducive atmosphere for certain flora to persist, and a less conducive one for the more pathogenic flora. Things like cow lactobacillus do not survive, but if you have a diet that changes your gut environment, it facilitates your own endogenous beneficial bacteria to survive. There are randomised trials that show change in gut flora.

Lord Kakkar: How does that relate to an ageing microbiome over time? Is the principal influence on the microbiome environment and dietary, or does something else influence it physiologically over time as part of the ageing process? Is there a two-way relationship between host and microbiome?

Dr Marina Ezcurra: It is very much a two-way relationship, because as you age your gut function changes, and your immune system changes, these things will affect the environment which the microbes live in. So it will affect them. It is, as you say, very much a two-way response.

Lord Kakkar: How much do we understand about that in order to be able to provide public health advice? It might be simple enough to say—I want to come to this question—that individuals should have probiotics or prebiotics and should change their diet, but how do we understand how that advice should play with our understanding of the physiological change over time of the gut itself and the host?

Professor John Mathers: I guess one of the most dramatic examples of the influence of diet on the microbiome has been when people have swapped from a plant-based diet to an animal-based diet; the changes are very dramatic. The current thinking is that a more plant-based diet is healthier as we get older and would also be beneficial for the gut microbiome, largely because it provides the substrate for their growth; it provides the special carbohydrates which they use to grow.

The other part of the story that we should not forget is that many of the drugs that we take as we get older for all kinds of conditions influence the microbiome, although they are not antibiotics. Many of the commonly prescribed drugs have effects on the microbiome, so some of the things that are seen in observational studies and are related to ageing may relate more to the polypharmacy to which the person is exposed.

Lord Kakkar: One last question, if I may. If one were to intervene in the microbiome of somebody in their 20s and somebody in their 70s, would

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Mediterranean diet are mediated by the microbiome and thus that we can use diet to improve the microbiome.
On the other hand, meat rich diets result in increases of bacterial species promote cardiovascular disease, inflammation and inflammatory bowel disease. There are also studies suggesting that processed/industrial foods have a negative effect on the microbiome, and thereby affecting health.

you be able to predict a difference in response because of the broader physiology of ageing?

Professor John Mathers: My guess is that the current state of knowledge would not allow us to do that, because we have lots of associations but very little evidence of causality, so we still cannot make the kinds of predictions that we would really like to make. That is one of the challenges as we go forward.

Lord Mair: Lord Kakkar mentioned prebiotics and probiotics. Can you say a bit more about how much is known about how they can be used to manage the microbiome? How advanced is the science?

Professor John Mathers: Maybe I can start by saying a bit about the difference between the two classes of substances.

Probiotics are living organisms, so they are a microbiome themselves, which we ingest in foods—yoghurt is a typical example of something that can contain probiotics. Prebiotics, on the other hand, are the foodstuffs for the microbiome, and they are usually carbohydrates. So you are trying to influence the collection of organisms in two different ways, either by supplying commensals or competitors or by influencing the substrate.

The evidence for prebiotics' effect on longer-term health is stronger than for probiotics. That has certainly been the evidence that EFSA, the European Food Safety Agency, has seen when commercial companies have brought those kinds of products along and wanted to make a health claim.

The Chair: Are prebiotics and probiotics better ways of changing the microbiome than unpleasant ways such as faecal transplant, which you mentioned?

Professor John Mathers: In my personal view, the best way to do this is simply through normal foods. We do not need to rely on these special prebiotics and probiotics. Having a healthy overall diet and the kinds of things that Kay-Tee spoke about earlier would be a better approach and one that is more sustainable at the population level.

Dr Marina Ezcurra: I think we will learn a lot about how very specific microbial species—and the effect of both prebiotics and probiotics—affect our health. We know very little now, and we will learn a lot about them over the coming 10 years or so. Perhaps we will even start to be able to look at having specific microbial metabolites, which we know have beneficial effects on health, and take those directly.

Lord Kakkar: What evidence do we have of the stability of the microbiome over time? Is there a core element of the microbiome that is pretty stable as we age, or is it so sensitive to the environment and dietary intake that it is very difficult to talk about a fundamental microbiome?

Dr Marina Ezcurra: Overall, during adult life, it tends to stay very stable. Each individual will have a core microbiome; it is a bit different between different people. But if you take antibiotics or change your diet, you will alter it. As we age, in general there is a change in the sense that we decrease the diversity of our micro-organisms, and there tends to be a decrease in the beneficial microbes and an increase in the less beneficial ones.

Lord Kakkar: Are there large UK epidemiological studies that have characterised the microbiome at repeated intervals, and then follow the population for years?

Professor Kay-Tee Khaw: No, and one of the challenges is how you do it. One way in the past has been faecal samples, and there are population studies that are trying to collect them. You can imagine the challenges of doing that, but that would be one of the really attractive ways of doing this.

Another is trying to identify through new technology other ways of measuring the microbiome, apart from faecal samples.

Lord Kakkar: What are those technologies?

Professor Kay-Tee Khaw: Some people think that there are some blood markers that may be indicators, but we do not know yet. This is where metabolomics might help.

The Chair: I think you said that, as you age, the good microbiome decreases and the harmful microbiome increases. Is that a process of ageing.

Professor Kay-Tee Khaw: I think that is what you said.

Dr Marina Ezcurra: Is that a process of ageing? It happens as we age and, as we discussed before, it is probably—

The Chair: What is it about ageing that changes that microbiome?

Dr Marina Ezcurra: I do not think we know exactly, but we can speculate that it has to do with the function of our guts; the decline of our immune response or immunosenescence, that is the decline of the immune system, which will affect the microbes in our gut; and possibly other lifestyle factors such as how much you move, other aspects of health, diet of course.

The Chair: And that happens at different ages in different people?

Professor Kay-Tee Khaw: Overall, everybody ages, and we know that everybody ages. But the rate at which we age and the trajectory can be profoundly modified. In cross-sectional studies, in some communities the gut microbiome of people of different ages is vastly different. That just reflects the environment they are in. Part of the reason why people have the same microbiome is because they have the same lifestyle throughout

life, and we know from intervention studies that if they change their lifestyle they can change their microbiome profile.

Things are more fluid than we believe, but people have differences in lifestyle, and those are very stable over time. We know that families share very common features of the microbiome, and when they move house they leave traces of that behind. That implies environment.

The Chair: So apart from nutrition and food, what other factors influence the microbiome: tobacco, alcohol?

Professor John Mathers: Many of the substances that we ingest influence the microbiome. As I mentioned earlier, probably dominant in older people are the drugs we use. Many of those drugs, even if they are not antibiotics, have effects on the microbiome. We are only just beginning to understand that in detail, but large screening studies have now shown that many common drugs have influences.

The Chair: A detrimental effect?

Professor John Mathers: We do not yet know whether they are detrimental. We just know that they change the organisms that are present, or the metabolism of those organisms. They have a whole range of potential outcomes.

The other big effect related to getting older is the rate at which material passes along the gut—the transit of material through it. We see that in constipation, which gets more common as we get older. It has a profound effect on the bacteria, because it influences how they can grow in the gut. Something as simple as that has profound effects.

The Chair: I was going to say, "I hope not", but I will move on.

Q55 **Lord Browne of Ladyton:** Following that deeply interesting exchange about the microbiome, I hope the question I am about to ask will appear more complex than it might at first appear.

As you would probably expect, we have been given evidence that suggests that we should take a whole-life approach to lifestyle as opposed to, as someone told us, the current focus on age alone as the target for interventions. The question is at what age people need to make changes to their diet for it to have an effect on their healthspan. We have also, I might say, had evidence from other people on lifestyle, including diet, which says that it is never too late to intervene. Could you tease that out a bit?

Professor Kay-Tee Khaw: It is never too early and never too late. The first thing to say about ageing is that a lot depends on the resilience that you have built up in your youth. Good nutrition in childhood is critical to making sure that children are well nourished and have big brain capacity and good muscles.

We have to start in early life. Then it is about maintenance throughout life, making sure that we can postpone deterioration by having a good

diet later in life to prevent deterioration and maintain repair. It is really important all through life, but the evidence suggests that it is also never too late to change, even at a very late age. Changing lifestyle can have a profound influence on future healthy lifespan.[2]

Lord Browne of Ladyton: Is it obvious that there are diminishing returns the later you intervene?

Professor John Mathers: The evidence we have is that there is a law of diminishing returns. The later you start, the less you can gain from it. Probably the best evidence of this comes from looking at muscle function; you can improve muscle function throughout the life course, but the later you leave trying to do something about it, the less gain you will manage to achieve. From a public health perspective, starting early would clearly have bigger advantages.

Lord Browne of Ladyton: Are there good examples, anywhere in the world, of engagement with younger people in the ambition of a healthy lifespan and at an earlier age having some effect on that?

Professor Kay-Tee Khaw: That is not what drives younger people to change, as we have learned from smoking, but there are other ways of encouraging them to have better nutrition—just not necessarily through old age, because that is not what drives their behaviour. This is where we need to understand what drives behaviour at younger ages. People are more motivated to change at older ages when they can see a real effect.

Lord Browne of Ladyton: From a parliamentarian's perspective on smoking—this one's, anyway—we got the improvement when we banned it in public places. It has been pretty consistent, in my experience, across a whole load of bad things we do not want people to do that we get a better result by making them illegal than by trying to get people to change their attitudes.

Dr Marina Ezcurra: That is a very good point. When you think of dietary interventions, one of the big challenges is how we get people to change their diets in an environment in which unhealthy foods are very inexpensive and accessible.[3]

Professor Kay-Tee Khaw: It is very controversial public policy, but we know that the ban on environmental smoking resulted in an immediate impact on admissions to hospital around the world in many of the places where it was employed. You could see immediate effects. While it is controversial, that is also true for things like the sugar tax and trying to discourage free and unnecessary sugars—some sugars are a necessary part of diet. That sort of approach might be relevant to younger children,

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[2] The importance of early interventions cannot be underestimated. We are much better off getting good habits for life as children than trying to change our lifestyle once we have reached middle-age, are suffering from health conditions and are stuck in bad habits. As a society we should strive for a healthy lifestyle throughout the life course.

[3] We are in urgent need for dramatic changes, enabling people to make healthy choices.

where childhood obesity and especially poor nutrition are problems. It is not just obesity; children are not getting proper nourishment.

Professor John Mathers: At that level, the sort of things that you can do structurally within the education system to make healthier foods available at good prices and to restrict the availability of the things you do not want people to eat are a good way forward and would certainly produce some benefits.

Lord Kakkar: I do not want to draw out the discussion about the microbiome, but I have one question. Do you think we might get to a position where the microbiome becomes a biomarker for ageing?

Professor Kay-Tee Khaw: There are dozens and dozens of biomarkers for ageing. Microbiomes are really important, because the two main sources of information are the lungs and the gut. But if you are really interested in improving health across the population, you have to look at the evidence linking diet, lifestyle or whatever and the health outcome of interest.

The biology in between the intermediate biomarkers is important, but that is not what people are interested in. They are not interested in their biomarkers; they are interested in whether they are healthy and able to work properly. That is the kind of evidence that we need: the outcomes and environmental factors that we can change that are of interest. That is the link.

Lord Kakkar: Exactly, but in terms of a research methodology to have some evidence at an early stage when interventions may be helpful, is there a biomarker approach or do we have to wait for these very large epidemiological studies?

Professor Kay-Tee Khaw: There is a biomarker approach. That has happened with things like cardiovascular disease, with cholesterol and blood pressure as intermediate markers. We can do it that way. That is great, but in the end we still need the long-term outcome evidence.

However, if we can mobilise the epidemiological population studies to measure all these intermediate factors so that we are much more confident about the biological pathways, that would be much better. That is what everyone is trying to do.[4]

Professor John Mathers: There is very unlikely to be a single biomarker of ageing, because it is such a complex process. We will probably need to have a panel of markers.

The Chair: So does the food that we eat, whether it be plant-based or animal-based, have its own microbiome?

Professor John Mathers: Absolutely. There is a whole science of understanding the microbiome of foods, but most of those organisms do

[4] It is not unlikely that in the future we can use the microbiome to predict diseases and markers of ill-health such as inflammation—but we are not there yet.

not persist once we have consumed them. They are killed in the stomach and do not have a long-term effect, but they are critical for the production of foods themselves.

The Chair: What happens with processed foods?

Professor John Mathers: It depends how they are processed. Processing involves an enormous range of technologies, but anything that involves heat processing will kill the majority of those organisms. Foods that are not processed by heat are likely to involve the consumer in direct access with the live organism. But, as I say, most of those are killed in the stomach and have no further impact.

Baroness Young of Old Scone: Does that mean that probiotics are actually a bit of a con?

Professor John Mathers: Probiotics are slightly different, because they have been selected to be acid-tolerant. The whole point about the stomach is that it is very acidic, with a low pH. Probiotics are selected to be resistant to that acid. That is their whole raison d'être.

Baroness Young of Old Scone: Is there an evidence base that they work?

Professor John Mathers: There is an evidence base that they survive passage through the stomach.

Baroness Young of Old Scone: That was not the question I asked.

Professor John Mathers: As you can see, I am rather sceptical about their long-term benefits for health. They certainly get through the stomach and into the rest of the gut, and do things while they are there. If you keep eating the product, you continue to have that benefit, but if you stop, it probably goes away.

The Chair: So why are prebiotics better?

Professor John Mathers: They are better, because they change the pattern of organisms by changing the substrate. In most cases, we then continue to have those organisms around, at least for some time after you stop consuming the prebiotic.

Q56 **Baroness Manningham-Buller:** My question naturally follows on from that. We have heard that, in mice models, calorific restrictions extend life. What evidence is there that this could work, or is working, in humans?

Professor Kay-Tee Khaw: I am afraid that I am going to be controversial in this.

Baroness Manningham-Buller: We like that. Keep going.

Professor Kay-Tee Khaw: The prevailing consensus has been that caloric restriction is good for ageing, but in the most long-term studies on

caloric intake, the monkey studies, which were followed for 20 years—one was the Wisconsin study and one was the National Institute on Aging study—one showed an increase in survival in caloric-restricted monkeys, but the other did not.

The experimental group had 30% caloric restriction. Researchers have looked at both studies to try to explain why there were such differences. The Wisconsin monkeys were given a diet that was very high in sugars but with less protein. The issue with a lot of the interpretation of these caloric-restriction studies is that it is not about the quantity of the calories but about the quality of the diet, so they are very hard to interpret.

As for evidence in humans, there has been a proof-of-concept short-term calorie study by the NIA, which had healthy middle-aged people on a 25% caloric-restricted diet. They showed some improved biomarkers but were able to reduce their calories only by 10% because they could not maintain the 25% reduction. They showed some improvement in biomarkers of ageing such as insulin, blood pressure and so on, including lower weight, but there was no hard health endpoint; they were intermediate markers.

With regard to the human evidence on caloric restriction, I do not know if you can imagine how hard it is to do these long-term human studies. The monkey studies were 20 years long and very hard to do. My interpretation of the monkey studies is that a lot of it was due to the differences in diet. In the Wisconsin study they restricted sugars when they had caloric restriction, whereas the NIA group was given a much more physiological monkey diet and showed no difference.

There were sex differences, too. A lot of the studies have not taken into account the differences in optimum nutrition and body-mass index between men and women. When it comes to the human studies, unfortunately we cannot do trials, so we have to rely on a lot of observational data, and there is not much observational data suggesting that restricting calories in free-living human populations has any impact on longevity. Their dietary pattern has a much bigger impact on life endpoints.

Baroness Manningham-Buller: So it is the combination of calories rather than the total—

Professor Kay-Tee Khaw: Yes. It is what the diet is rather than the quantity of calories.

The Chair: Are you saying that excess calories do not matter?

Professor Kay-Tee Khaw: It depends on what you mean by "excess calories". We are talking about a reasonable body weight and what the calories are. Most people who have excess calories in western society have them as free sugars—carbohydrates that are not nutrient-dense—whereas if you have a diet that is nutritionally balanced, that might be less relevant. We have some evidence of this from human intervention studies.

The Chair: Do the other two panellists agree, or are you going with the majority view that calorie restriction is healthy?

Professor John Mathers: Let me say a bit about caloric restriction from a global perspective. The theoretical biological modelling that has been done on this suggests that the benefits are great for short-lived organisms but get progressively less in longer-lived organisms. We are a long-lived organism so, at least on theoretical grounds, we would benefit less than, say, a mouse that lives for two years.

If there is a benefit, it is likely to be very marginal, and like Kay-Tee I think that is a distraction from the much bigger issue that too many people are overweight and obese, which has an adverse effect on the ageing process. It would be much better to focus on preventing people from becoming overweight and obese and dealing with that issue than trying to get lean people to try to be calorie-restricted, which I think is a nightmare.

Dr Marina Ezcurra: It is important to distinguish between caloric restriction and dietary restriction. This is exactly the point that Kay-Tee was making: exactly what nutrients you are ingesting, and in what proportions, might be more important than the overall calories.

There is also the possible importance of when and how you eat, in which window of the day. Restricting, for example, the window of when you eat might have beneficial effects rather than the overall calories.

The issue is very complex. It is a very good question. It will be very interesting to see what the effects are. There are studies suggesting that reducing the diet has beneficial effects on some biomarkers.

Baroness Manningham-Buller: Could you elaborate on the point that you touched on about timing?

Dr Marina Ezcurra: I am sure you are aware of the intermittent-fasting diets that have been popular recently, where you do not restrict overall calories but you eat during specific times and do not eat during other times. This is quite new, but again there are studies suggesting that these patterns are also beneficial to health.

Baroness Manningham-Buller: But so far there is no substantial scientific evidence for that at this stage. That is what I think you are saying.

Dr Marina Ezcurra: No, there is not enough for public health recommendations yet.[5]

Baroness Sheehan: What is the level of increase in the lifespan of mice on calorie-restricted diets?

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[5] This is a very active research field and there is increasing evidence that there are substantial health benefits from dietary restriction, time-restricted eating and fast-mimicking diets. More studies will elucidate the detailed effects on humans.

Professor John Mathers: It depends very much on the strain of mouse that has been tested, but you can get extensions of lifespan of 20% or 30%. In some strains the figure is even higher, but it is very much strain-specific. There are a few strains of mice where caloric restriction has no benefit and has not increased the lifespan at all, but in general it increases the lifespan by 20% or so.

Professor Kay-Tee Khaw: The human epidemiological evidence, which is not trial evidence, suggests that the people who survive the best are those who are physically active and eat a lot. They are energy-balanced; they are not obese but are active and have commensurate energy intake. So it is about energy balance.

Q57 **Lord Borwick:** Are public health messages scientifically sound? Have they been working properly? Is, for example, the five-a-day message that is being pushed out of the Government an awful lot actually making a difference scientifically, and is it being taken up properly?

Professor John Mathers: People do not respond very well to being told things. Simply putting out information is largely a futile exercise. As we heard earlier about smoking, we got much bigger effects when we did something a bit more positive than just telling people not to smoke.

There are lessons to be learned there about how we engage with the community and society to find ways that are meaningful to them. We have been telling people for 15 or so years to eat five portions of fruit and veg a day, and the changes have been marginal. We need something a bit more sophisticated than just giving people information.

Lord Borwick: What sort of change would work, then?

Professor John Mathers: You need to engage the community with whatever you are trying to achieve. An example from another country is the North Karelia project in Finland. In the 1970s, people in that part of Finland had among the highest rates of heart disease anywhere on the globe. The community was concerned about it; men in their 40s and 50s were dropping dead from heart disease.

There was a whole-community exercise to understand why that was happening and to change behaviours in all kinds of ways. It was not top-down, with people being told to do something; it involved people at all levels of society, and it had really profound effects. The rates of heart disease in that part of Finland fell rapidly and are now among the best in Europe.

We need to engage people in a way that is meaningful to them, and some of the programmes that we have had up to now have not engaged the community.

Lord Borwick: So you are saying that it is possible to get a good message across, but we have just not managed to achieve it so far.

Professor John Mathers: Absolutely. People need to be able to see that it benefits them. As Professor Khaw said earlier, talking to children about ageing is probably not important.

Lord Borwick: Indeed.

Professor John Mathers: They have no interest. It is about engaging them in things that they are interested in—looking well, being good at sport, things like that—and using that as a way in to change their behaviours.

Lord Browne of Ladyton: How big was the population of North Karelia in the 1970s? What sort of scale was the project?

Professor John Mathers: The whole population in Finland is a fraction of that in the UK. There are more complexities with bigger populations, but it is still achievable.

Professor Kay-Tee Khaw: In North Karelia in Finland and in Switzerland and other countries, such as Portugal, where there was a big problem with blood pressure, there was a move to try to reduce salt intake. The main sources of salt intake at that time in many countries were bread and cheese. Work was done with manufacturers to try to reduce the salt in bread and cheese, but it was said that this was not possible because the bread and cheese would not keep and would not taste right.

However, the levels were reduced in the manufactured bread and cheese, which had a big impact on reducing salt intake in the population on average. This was accompanied by commensurate reductions in sodium intake in the population and in blood pressure levels, as well as a steep decline in the incidence of strokes. That has been shown in the UK as well, where there has been a halving a stroke rates in some of these communities. This was not quasi-experimental—it was not a randomised trial—but it was associated with changes in population intakes of sodium.

Baroness Young of Old Scone: We know that the supermarkets and the fizzy drink and processed food manufacturers kicked and screamed when the modest measures that the Government are currently taking on sugar were introduced. Do you believe that we should see more effective governmental requirements on the nutritional content of commonly eaten foods? The reduction in sugar has led to an increase in salt in many processed foods, so we will probably see an impact from that in the not-too-distant future.

Professor John Mathers: We need to engage industry in making these changes, because it is responsible for producing the food and selling it to us in all kinds of different ways. We need to engage with it and get it on board with the changes. The sugar tax, if I can call it that, is a beginning, but only a beginning. We need to do more and do it in a more pervasive way. Many sectors of the food industry are receptive to that, because they are in this for the long run. They want to supply food that is

beneficial to society; it is not just a quick buck. We need to do that in a way that works for industry and for society. The sugar tax is just a beginning.

Baroness Sheehan: I have a further question to the previous question on caloric restriction, and it relates to proteins and the type of nutrients that you restrict. Proteins can come in many different forms—animal proteins, plant proteins—so has any work been done to see which sort of protein restriction or increase is beneficial?

Dr Marina Ezcurra: Work on specific amino acids, for example, suggests that certain amino acids are more detrimental than others. Work on methionine, for example, suggests that meat proteins are more detrimental. As far as I am aware, this is mostly work done on laboratory animals.

Professor John Mathers: That is right. There have been very few attempts to try to translate that kind of work into humans. Many of these manoeuvres—changing individual amino acids—produce a challenge to the homeostasis of the cell, which responds in positive ways to that challenge. It is that positive response to the challenge that then translates into better health. Many of these things will be seen to have a common biological basis.

Baroness Sheehan: It is not a contradiction, but there is evidence that decreasing protein intake is beneficial, while, in older people, increasing protein intake is beneficial. Can you say where the evidence for that second part comes from?

Professor John Mathers: You are absolutely right. Most of the epidemiology for younger people is that very high protein intakes are associated with poor long-term health outcomes. Very old people, particularly frail older people, have particular problems maintaining their lean tissue—essentially, the muscle in the body. That is largely because they have very small appetites; they eat very little food and are not consuming enough protein.

The evidence that we have, although it is incomplete, is that in that situation there needs to have a higher proportion of protein in the diet to ensure that there are enough amino acids to synthesise the proteins to maintain body tissue.

Baroness Sheehan: So you have not done those experiments, apart from on mice.

Professor John Mathers: Those experiments have been done on a small scale. Lots of small-scale studies on older people show that, if you give the extra amino acids, particularly leucine, in combination with exercise, you can increase lean-tissue growth. That is well-established in small scale. The challenge is to translate that into the population.

Dr Marina Ezcurra: It is possible that, say, a high-protein diet has both beneficial effects and some detrimental effects. For example, it could

have detrimental effects by activating signalling pathways such as mTOR, which you might have heard of, but it could also be required for building muscles.

The Chair: We have had a lot of discussion about the microbiome and its importance. Briefly, what is the current stage of research on microbiomes and healthy lives?

Dr Marina Ezcurra: It is a field at its very beginning; it is very early on. I think that much more work will now be done to understand the effects on health of the biological mechanisms and interactions between bacteria, microbes and their hosts. At the moment, we mostly know about the association. Some studies have been done in mice and other laboratory models, which have started to suggest the molecular effects.

The Chair: I am more interested in the state of research on microbiomes, rather than any specific studies. Where is the UK in the research on microbiomes related to health?

Dr Marina Ezcurra: There is much more in the US. The UK is a bit behind when it comes to microbiome research. There are groups doing research here and there, but it is not a major theme.

Baroness Sheehan: Is industry filling the vacuum there?

Dr Marina Ezcurra: There is huge interest from the food industry and within pharma but I wouldn't say they are filling the vacuum, also within industry the research efforts are relatively small. There is a need to expand this research, both within academia and industry.

The Chair: Presumably the industry interest is in producing products that it might sell, but there might not be scientific evidence to do so.

Dr Marina Ezcurra: There is definitely work within industry to try to understand the underlying mechanisms, but with the overall goal to sell profitable products.

Baroness Young of Old Scone: Do you think that the money which the Government are putting into the healthy ageing challenge, which is primarily technology-based, would be better spent on understanding these basic processes and the links with epidemiology?

Dr Marina Ezcurra: Better spent than on what?

Baroness Young of Old Scone: Whatever they are spending it on at the moment, which we have not yet heard.

Dr Marina Ezcurra: When it comes to the links between diet, microbiome effects on human health and the interactions with human genes, that would hugely benefit our understanding of how we can use diet to improve health.[6]

[6] The microbiome most likely links many aspects of health, such as diet, ageing and

Professor John Mathers: The opportunities here for business are considerable, but at the moment there has been too great a fix on technology and too little consideration of the social aspects of ageing. That is where there is a real opportunity for growing smart businesses that deal with the social aspects of ageing, rather than thinking that we are going to come up with a gadget or a tool that will solve the problem.

The Chair: Thank you very much indeed. It has been a most interesting session and we are grateful to you for coming today.

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disease—understanding the exact mechanisms underlying these links could have major impact on healthy ageing and help us to age better.