



# Episode 176: Conditions of affluence and aging: fatty liver disease, macular degeneration

VOICEOVER

Welcome to Up Close, the research talk show from the University of Melbourne, Australia.

DYANI LEWIS

I'm Dyani Lewis. Thanks for joining us. As we get older, there are certain things that we have to accept will come part and parcel with experience and hopefully with a dash of wisdom. Wrinkles, perhaps an expanding waistline and loss of hearing or vision will remind us, at some point, that our bodies aren't as young as they once were. Joining us today on Up Close are two researchers who are examining conditions caused by bodily wear and tear, conditions that are the result of simple ageing and also of the lifestyles that we lead in the process. Both of our guests are trained medical doctors undertaking PhD research that will enhance understanding of their patients' illnesses. Later in the program we'll be talking to Dr Madeleine Adams about eyesight and a condition called age-related macular degeneration. But first we're joined by Dr Chris Leung. Chris's focus is on the liver and how many of us are perhaps unwittingly condemning our own livers to a fatty future and an early demise through what we eat. Welcome to Up Close Chris.

CHRIS LEUNG

Thank you.

DYANI LEWIS

Chris, to start with, could you describe for us your typical patient diagnosed with fatty liver disease? What sort of symptoms would they have that would lead them to go to the doctor in the first place?

CHRIS LEUNG

Most patients with fatty liver disease actually have no symptoms, so the majority are diagnosed almost incidentally either through blood tests or when they get an imaging investigation such as an ultrasound or CAT scan. So in fact most of the patients we see in our clinic are patients who are referred because of these reasons. That's why this disease, fatty liver disease, has been called our next silent epidemic, because you don't get any symptoms often as it progresses. So in fact the most recent studies show that it can affect up to half the population in Westernised countries and the problem with fatty liver disease is that it can then progress on to inflammation, which then can progress onto scarring of the liver. One of the major problems with scarring of the liver is that it can progress to liver cancer.

DYANI LEWIS

So you can't necessarily tell by looking at someone then whether they would have fatty liver disease?

CHRIS LEUNG

Certainly there are risk factors which predispose you to be more at risk of fatty liver disease and those are the features which you mentioned before, for example, being overweight or having diabetes or having high cholesterol. So certainly there are factors which make you more likely to have fatty liver disease. But

interestingly, our recent studies have shown that even those who don't have all of these risk factors but do live a sedentary lifestyle, can get fatty liver disease. So recent studies, for example, in Indonesia which looked just at the general population which is not overweight in general, 15 per cent of those have fatty liver disease.

DYANI LEWIS

So you've spoken about some of the risk factors of fatty liver disease and your work deals particularly with diet. Could you tell me about that?

CHRIS LEUNG

Yes, so when I see my patients in liver clinic who have been referred for fatty liver disease, the advice I can give them at the moment is to exercise and I tell them to exercise at least three times a week for an hour at a time and to have a good diet, meaning low fat, lots of fruits and vegetables, a balanced diet. But apart from that, there's not much else which I can advise them. There's currently no drug therapies for fatty liver disease and I felt that when I was speaking to my patients that my dietary advice wasn't particularly complete and as I read more and more and researched more into the area, I realised that there were these compounds in foods called advanced glycosylation end-products or AGEs for short. These compounds are formed when you heat the protein and lipids in foods at high temperatures and they react to sugars that you find in foods and it forms these compounds called AGEs. These compounds are actually responsible for a lot of the flavour components of food. So if you, for example, caramelize or brown foods, you get a high amount of AGEs. And it's all dependent on the duration and the degree of heat that you apply to foods. So for example, if you boil foods, you get a relatively low amount of AGEs because it's a relatively lower temperature, but if you bake or fry foods, you get a higher amount of AGEs because you apply a higher heat. Interestingly, when you barbeque foods you apply a very high amount of heat and it's also dry heat and that produces the most or the highest amounts of AGEs.

DYANI LEWIS

Do we know anything about the process by which AGEs cause fatty liver disease?

CHRIS LEUNG

So in my PhD we decided to explore this. We already knew from descriptive studies in humans that perhaps AGEs are responsible for the progression of various forms of liver disease. So we decided to set up an experiment in animals to see whether it affected the progression of fatty liver disease. So in my experiments I had basically three groups of rats. The first group of rats had normal livers, so they were fed a normal diet and their liver wasn't fatty at all. The second group of rats had fatty liver which I induced by altering their diet. The third group of rats had fatty liver and a diet which was high in AGEs.

DYANI LEWIS

So what exactly are you feeding these rats?

CHRIS LEUNG

So the first group which were the control animals or the animals with a normal liver, they are fed a diet which is made up of the basic elements of food, not made from grass or meat per se, but in essence they were made from the building blocks for protein, sugars and fats. So the pellets themselves are made from basic elements, that way we knew exactly what the animals were eating. The second group, which was a group of rats which we induced fatty liver, we gave them a special diet which prevented the liver from getting rid of the fat that it normally accumulates; it's a special type of diet which gives you fat that only accumulates in the liver.

DYANI LEWIS

So how does that happen?

CHRIS LEUNG

So in the liver, there's an enzyme which is responsible for getting rid of fat from the liver and this enzyme needs a particular building block called methionine or choline.

DYANI LEWIS

Right, so they're amino acids?

CHRIS LEUNG

They're amino acids. So if you give these rats a diet which is devoid of methionine or choline, then their liver cannot export fat and becomes fatty. That way we were able to produce reliably in these rats fatty liver.

DYANI LEWIS

The third group?

CHRIS LEUNG

So the third group had the same diet as the animals who got fatty liver, devoid of methionine and choline, but we baked it as well, so we put it in a large oven, 160 degrees for one hour, just like the way you would bake a cake and made it very high in AGEs. So in just six weeks of this high AGE diet, we found that in the livers of these animals with fatty liver and the diet high in AGEs, that they had more inflammation in the livers and there was also trends towards more scarring in the liver.

DYANI LEWIS

So then it's something very specific to the AGE compounds themselves that's having this effect on the liver?

CHRIS LEUNG

Yes, that's right. So to explore this, we actually took the cells from the liver in rats which produce scar tissue and exposed them to these compounds called AGEs and in just 24 hours, after being exposed to these compounds, they started to produce more scar tissue and became more activated. So it does appear that these compounds both in the animal, but also in the cells which produce scar tissue in the liver, are responsible for the progression of fatty liver disease.

DYANI LEWIS

Do we know why they affect the liver in particular and not other organs in the body?

CHRIS LEUNG

In fact they do. We know that in diabetes not only can you get AGEs from your food, but AGEs are also formed in your body, so in diabetes where there's a lot of sugar hanging around in the body, these react and form AGEs in the body. So they can then lead onto complications in the kidney and that's where you get diabetic kidney disease, they're also involved when diabetes affects the nerves of various parts of your body. It also affects other organs as well, for example, the heart, also they eyes. So it's involved in a vast array of many of the complications of diabetes, which, as you know, affects a large proportion of not only Westernised countries, but other countries as well. AGEs are also formed as we age. They've also been implicated in Alzheimer's disease. And in fact there's now a drug in clinical trials that blocks AGEs which is being trialled in patients with Alzheimer's disease. So it's not just the liver, it's almost every organ that is

affected by diabetes or ageing.

DYANI LEWIS

How will all of this information change the way that you treat your patients in the future?

CHRIS LEUNG

Obviously we've only done it in animals, but we will have to repeat our studies in humans. So at the moment I don't tell my patients have a low AGE diet. And so an obvious next step is to confirm our animal studies in humans and to see whether a low AGE diet or a drug which blocks AGEs is beneficial in patients with fatty liver disease, or even other complications from diabetes as well.

DYANI LEWIS

Well thanks for telling us about your research Chris.

CHRIS LEUNG

Thank you very much.

DYANI LEWIS

Dr Chris Leung is conducting his doctoral research into fatty liver disease at the Austin Hospital in Melbourne. He's a PhD student at the Department of Medicine at the University of Melbourne. You're listening to Up Close, coming to you from the University of Melbourne, Australia. I'm Dyani Lewis. Our second guest on Up Close today is Dr Madeleine Adams whose research looks at the genetics of age-related macular degeneration. Madeleine is based at the University of Melbourne's Centre for Eye Research Australia and the Royal Victorian Eye & Ear Hospital here in Melbourne. She's joining us today via Skype from Byron Bay. Welcome to Up Close Madeleine.

MADELEINE ADAMS

Hello.

DYANI LEWIS

Madeleine could you start by explaining for us what macular degeneration is?

MADELEINE ADAMS

Sure. Age-related macular degeneration, we tend to call AMD as it's a bit of a mouthful, refers to pathological changes in the central area of the retina at the back of the eye which may develop in those aged 50 years or greater. It's the most important cause of irreversible visual loss in elderly populations of the developed world. It has a prevalence of around 11 per cent of those greater than 80, but about two-thirds of people greater than 90 have it. As it affects older people, its prevalence is set to increase with the rising age of populations and it's estimated it's going to increase threefold by the year 2020. In Australia AMD is responsible for nearly half of legal blindness.

DYANI LEWIS

Your research relies on data from a large cohort study, the Melbourne Collaborative Cohort Study. Could you tell us about this study?

MADELEINE ADAMS

Sure. So the Melbourne Collaborative Cohort Study or the MCCS was set up in the early '90s to look at chronic disease, particularly cancer and it started off with around 40,000 people and on those people they collected extensive lifestyle data including diet, also blood samples so they could perform genetic studies.

It was piggy-backed by the Centre for Eye Research Australia and at this stage they've photographed as many people as possible, taking photographs of their retina, which are then graded for signs of age-related macular degeneration.

DYANI LEWIS

So what are some of those signs?

MADELEINE ADAMS

AMD is categorised into early and late. The hallmark of early AMD are drusen and these are yellowy-white deposits in the retina and they become visible when they're greater than 25 microns. So there's a spectrum of disease and we attempt to dichotomise the disease really into presence or absence when we examine them clinically. In late AMD, again there are two types, there's wet AMD as it's called, which is when you have abnormal vessels which grow and then bleed, or you can have dry AMD where you just have atrophic changes in the retina. But this also causes a complete loss of central vision. The late stage of AMD is what causes the visual loss. Most people with early AMD are unaware that they have anything wrong with the back of their eyes at all.

DYANI LEWIS

So in terms of the results out of this cohort study, what lifestyle factors have you found to play a role in AMD?

MADELEINE ADAMS

We have looked at obesity and we've also looked at alcohol and diet. So with obesity, previous studies had looked at BMI, but as AMD is a disease of the elderly and BMI is known to be an imperfect measure of fat in older people, we also looked at abdominal obesity measures such as waist-hip ratio and waist circumference. What we found was that in men and women, BMI wasn't associated with AMD, which was actually in conflict with previous studies which had found BMI to be a risk factor of AMD. But we did find a positive, that is a risk association with abdominal obesity and early and late AMD in men, but in women, the associations were actually inversed, that is, it appeared that having excess abdominal fat is actually protective for women, which obviously was a sort of a counter-intuitive finding. We think this is likely to be explained by survivorship effect which can attenuate or invert associations in elderly cohorts.

DYANI LEWIS

Could you explain what the survivorship bias is all about?

MADELEINE ADAMS

A simple way of looking at it is to think that if those that have extensive adverse exposures, such as smoking, obesity and excess alcohol use, if they live on into their 80s and 90s, it's likely that these people are protected in some way, perhaps genetically, from these exposures and then therefore when you perform associations of these in this group, you may get a distortion or even an inversion effect. This has also been referred to previously by different names; survival bias has been demonstrated in Alzheimer's disease where unless you take into account smoking related mortality, it can appear that smoking is protective of Alzheimer's. Also, reverse epidemiology is another word for it and it's been found, for instance, in the obesity paradox of heart failure, where it appears that obesity is protective of mortality in heart failure. So it's been demonstrated in other diseases, but we think that perhaps the effect of it is underestimated and that it may be producing spurious associations which perhaps smaller studies are unable to pick up on. We think if it can distort such a powerful risk factor, for instance, as obesity, then it's possible that genetic associations being reported by studies may also possibly be spurious. So we went on

to look at genetic associations as well.

DYANI LEWIS

So what did you find there?

MADELEINE ADAMS

So firstly we looked at a general called APOE or apolipoprotein E. This gene is most well known for its associations with Alzheimer's disease where one allele of APOE, the E4 allele, is a risk factor for Alzheimer's. Previous studies in AMD have shown counter-intuitively E4 to be protective of AMD. So in the cohort there was 22,000 people. In the genetic study, we just did a nested genetic case-control study, but it was still nearly 5000 people which is the largest AMD genetic study that we're aware of. So each case was individually matched for age and sex and then we examined associations with APOE between cases and controls. Essentially we didn't reproduce this E4 protective effect, well we did find an E4 protective effect, but only in current smokers, which we thought could indicate a survivorship effect. Where again, those people that had lived on to an older age and they carried on smoking and they also had this E4 allele which is a risk factor for Alzheimer's and also cardiovascular disease, that we thought perhaps in this group of people that what we were seeing was these risk factors acting as a proxy for protection, as a form of genetic protection, against these risk factors, both genetic and environmental.

DYANI LEWIS

So how can researchers go about designing their studies to avoid some of these survivorship biases?

MADELEINE ADAMS

I don't think that it's possible to overcome survivorship in elderly cohorts. That's not really what we're aiming to do. The reason why we think this is important is because other studies have done this and there are actually now genetic prediction models for AMD on the market, both direct to consumer and also physician administered and these claim to be able to predict people's risk of AMD purely by their genetic risk, that is they look for these well known genes which include complement factor H and also another gene, chromosome 10 and plug in the numbers and they give them a risk score in the next 20 years. We think these simplify both a complex disease and a complex life course. It's difficult to say what's going to happen to somebody after the age of 60 in terms of other diseases which may stop them from getting AMD either by killing them and making them too sick for us to realise that they have it. So what we want to do is look across all the genes associated with AMD and also see how they're modified by environmental exposures, then perhaps focus on those people with the excessive adverse exposures, looking for other genes which perhaps may not just protect people from AMD, but maybe these genes which protect people from adverse exposures more generally and these are sometimes referred to longevity genes.

DYANI LEWIS

So look for people who are doing everything wrong and find out who of those do the best?

MADELEINE ADAMS

Exactly, sort of a last man standing approach, in the sense that longevity studies often look at the super healthy centenarians, those over 100, who are doing everything right, but we feel that those that are doing everything wrong are more likely to be genetically enriched with these protective genes. We've also looked at complement factor H which is perhaps the most famous gene associated with AMD and we have looked at that in our study of 5000. We found that the genetic associations changed by age group. So the association was a risk association in older people, but in younger people it was the other way round, it looked like the same gene was then protective for the disease. It's this switch or reverse of associations which we find interesting, that something happens after the killing fields of midlife where people seem to

have a change in their susceptibility to adverse exposures.

DYANI LEWIS

Why did these other studies not pick these sort of trends up do you think?

MADELEINE ADAMS

Well like I said, this is the largest genetic study. At 5000 people, it's larger than most other cohort studies, never mind case control studies that have looked at AMD and additionally, because of the careful matching by age, we should have residual confounding by age, so each case is matched by one year of age to a control and also by country of birth to reduce population stratification and sex. We also have a reasonably wide age group to explore, so we have people aged less than 50 to people aged 86. Because it's a relatively large size, we can stratify and still have sufficient people in each stratum to make associations meaningful. When one wants to look at interactions, both gene-environment or gene-gene, one typically needs a much larger sample size, so in the range of four times greater than when one is looking for straight associations. So with this sample, we actually are powered to look at gene-gene- and gene-environment interactions and this is really the first genetic study which is able to do this.

DYANI LEWIS

Madeleine we'll leave it there. Thanks very much for joining us today on Up Close.

MADELEINE ADAMS

Thank you.

DYANI LEWIS

Dr Madeleine Adams is undertaking her doctoral studies at the University of Melbourne's Centre for Eye Research Australia, based at the Royal Victorian Eye & Ear Hospital. She was speaking with us via Skype from Byron Bay. Relevant links, a full transcript and more info on this episode can be found at our website at [upclose.unimelb.edu.au](http://upclose.unimelb.edu.au). Up Close is a production of the University of Melbourne, Australia. This episode was recorded on 15 December 2011. Our producers for this episode were Kelvin Param and Eric van Bemmelen, audio engineering by Gavin Nebauer. Up Close is created by Eric van Bemmelen and Kelvin Param. I'm Dyani Lewis, until next time, goodbye.

VOICEOVER

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