[MALE RESPONDENT]
[Other comments:]

Now if we could move on to the next talk, which will be given by Steffen Petersen, who's at the William Harvey Research Institute. Steffen has been a long-time member of the imaging working group and will tell us about outcomes from the heart data available. Steffen.

Thank you very much. It's a great pleasure to speak today and give an update on what the CMR Consortium has been doing over the last year, so I'm giving this presentation, really, on behalf of about a hundred collaborators around the world. This is as a disclosure, so this company, Circle Cardiovascular Imaging, is also part of this collaboration. They produce a software that allows the analysis and visualisation of cardiac MR scans. Here you can see, actually, CMR, this tool from Circle Cardiovascular Imaging in action, if you like. You've got two phases of the heart. When the heart's relaxed, in diastole, and when it's contracted and in systole. Is there actually a pointer somewhere? Ah, the pointer's here. You can see the systole, when the heart's contracted, and you can see that, basically. We are very grateful that the British Heart Foundation gave us a project grant over three years to analyse the first 5000 cardiac MR scans manually, which takes a lot of time, and I'll come back to that.

You need expertise to do this. It's not as simple as it may look at first glance, but this is really the basis of what I'm going to talk about and this is only part of what we want to analyse in the first 5000. What I've just shown you is basically the left ventricle and the right ventricle, and you can see estimates of how long it takes per subject to analyse these manually. What we are talking about today is basically the four points, left atrium, right atrium, left and right ventricle, and that has taken seven months, eight experts, full-time, to analyse those 5000 scans. Clearly, that is not really feasible to do that in the 100,000, or in the 25,000 that we have now imaged. The British Heart Foundation grant was really to lay the foundation to develop tools that allow us to do this, at scale, for 100,000 and Professor Rueckert will talk about that a little later, about our collaboration there. There are lots of more things that we have already analysed and are doing a lot of quality control that will be returned to UK Biobank, hopefully in the next few months, but what you can see is that the total duration of analysis per scan takes 140 minutes, which is essentially seven times as long as the duration of the image acquisition at UK Biobank. This is not doable in the 100,000.

The other point that I wanted to make is, again, these are people that work closely with us. The manual analysis really requires expertise, but even experts don't necessarily, 100 per cent, agree how to analyse these hearts. One of the major opportunities of UK Biobank is to contribute to standardisation. This paper here basically showed, quite nicely, that if you asked lot of people to draw contours, they do it slightly differently. Now, if you're in the middle of the heart, actually, people do agree that's quite straightforward, but when you're particularly at the base of the heart, people draw it differently. We used this consensus formation as a basis of our standard operating procedures and stuck to that as much as possible to come up, really, with a standard how the images should be analysed in UK Biobank. Then our first paper was scientifically maybe not that exciting, but I think clinically really useful, is to pick 800 of the 5000 subjects that had no cardiovascular

disease, no risk factors for cardiovascular disease, et cetera, were not on statins.

We had 800 left, then, in this cohort, and we used that to develop normal reference ranges for all of these clinical parameters we often use for left ventricle, such as ejection fraction, or left ventricular mass, or the atrium. What we've developed is a simple traffic light system. If you are male and you fall into the green category, then all is fine. If you fall in the red category, then you're outside the normal range and there's a borderline where you can look up, in age and gender specific tables, whether you're still in the normal range or slightly abnormal. This will be clinically useful. What we have seen on this data is that, actually, gender really influences cardiac structure and function, and also age does, to a lesser degree. What we were interested, similar to what Paul Matthews has shown earlier, is we were interested in modifiable risk factors that we know contribute to cardiovascular risk, how do they affect cardiac structure and function, because they are the ones that we can do something about. We can't do anything about our age, but we can do something about BMI, physical activity, blood pressure.

We basically wanted to understand what contributes most to these phenotypes, so that we can measure using cardiac MR, and just as an example, left ventricular mass to volume ratio is basically how heavy is the heart, how thick is the heart compared to the size of the heart. Which is a remodelling of shape parameter, which we know the higher the value is, that is linked to outcome. What we can see here is that most of the association or the variation is explained by body mass index, and systolic and diastolic blood pressure. This is what we've found for most of these variables, that really it highlights the importance of body mass index and blood pressure on the heart health, as measured by cardiac MR. This was then the study that we published earlier this year, which got a lot of attention around the world, and I like going on to altmetrics. I'm a big altmetrics fan, because I've never had a paper with 788 after just a few days, and what you can see here is a map of where news articles were written, anybody that referred back to this, so I'm really proud that this paper hit the news so much.

I think this is because of the simple concept. We know that handgrip strength, as a measure of muscular fitness, is associated with outcome, and cardiovascular outcome, but the mechanism is not quite well understood. We thought, well, let's look in UK Biobank, whether we see changes in the heart already of those measures that we've done. This is a quite complex slide, but maybe we focus on this one here, which is, again, this left ventricular mass to volume index, which is a measure of remodelling. We know the higher that number it is linked to outcome, cardiovascular outcome. What you can see is the more muscular fitness you have, the more muscular strength you have, the lower your value, suggesting that maybe that could be part of the explanation why people who have got good handgrip strength do better than those that have weaker handgrip strength. Then I'm not going to go into too much detail, the week afterwards we published another article, again, with almost the same altmetrics index, again, published around the world, which touched on another really hot topic on hormone replacement therapy.

We know there's quite a lot of ambiguity whether hormone replacement therapy is protective or not for heart health and, again, we wondered whether we can see anything in the heart as an intermediary. We found

that there is no negative effect. If anything, there's a beneficial effect on what we see, in terms of cardiac structure and function. We then also know that COPD or altered lung function has an impact on cardiovascular outcomes, independent of cardiovascular risk factors. Obviously, smokers who have got impaired lung function, also have a higher risk of cardiovascular outcomes, but there seems to be an independent risk factor if you've got really altered lung function. What we were interested is, in the range of normal lung function, do we see an association with cardiac structure and function, and we again showed some associations there. I just want to highlight, again, the BHF funded our core labs. There were lots of people involved.

Actually, we have more faces now, with all the new phenotypes we're analysing, but what I wanted to say is that given this, and what we'll hear from Professor Rueckert later about automation of image analysis, because we can now automatically analyse these images, that allows us not only to analyse the heart when it's most relaxed and most contracted, two phases, we can do that in 50 phases, which would have taken 50 times as long to analyse. I'm sure you appreciate why we didn't do that manually. We can derive time to volume curves, which gives us a lot of information about diastole, how the heart relaxes, which we know is really important. There is something called radiomics, which I'm really excited about. It's something that's quite hard to understand, but you can break it down into measuring something about shape, size, edges, intensity, and texture, and you can see a lot of the things that we measure. We get over 500 variables talking about sharpness, irregularity, and oncology has used this technique and found that they can predict cancer outcomes quite well with radiomics.

These are things that the naked eye can't see, but we can measure on the images. Watch this space, this is really interesting, I think. This leaves me to conclude that UK Biobank provides unprecedented opportunities to investigate the determinants of health and disease. UK Biobank fosters collaborations to drive science. I think we contributed here to the standardisation of cardiac MR analysis and we think that there's already a clinical impact. With this normal reference range, we can differentiate health, look at the impact of risk factors, and protective factors on heart health, and we can classify or diagnose disease and look at severity of disease. The large-scale cardiac imaging sub-study presents challenges and in analysis you have a sense, I think, how much expertise you need, and how long it takes to do this, and at what cost. AI, which we'll hear about, can help clear some of these obstacles. UK Biobank will, no doubt, will get more powerful over time, by increasing the sample size for the imaging study, by having more and more outcome data available. Genetics, blood biomarkers, all the things we heard about and the multi-organ imaging.

With that I'd like to thank all these here, including, obviously, the UK Biobank participants, but everybody who has been involved in one way or another. Lots of people involved, so thank you for your attention.

[END OF TRANSCRIPT]