

Then for the final talk before we come to questions, I'd like to turn to Nick Harvey from the University of Southampton, also a member of the imaging working group for Biobank. He'll tell us about UK Biobank arthritis data and some new and exciting collaborative programmes developing. Nick?

Well thank you very much. Well it's a great pleasure to tell you about the muscular skeletal aspects in UK Biobank, and I guess we've heard a lot about the cardiometabolic and brain aspects, so a slight change of direction. I thought over the next ten minutes I'll just introduce the burden of disease that results from chronic muscular skeletal conditions and say a little bit about our current approaches to risk assessment and how the gaps in that can be addressed through work in UK Biobank, and think a little bit about the DXA protocol and what it gives us, the image to our phenotypes and the works that's recently been funded by the Wellcome Trust to derive new phenotypes from the DXA scans. Just I thought I would set this in the context of the emerging issues of multimorbidity which is certainly very topical in our ageing population.

So, we know that muscular skeletal diseases, for example back pain, osteoporosis, osteoarthritis, place an immense burden of disability globally and so through the Global Burden of Disease initiative it's apparent that about three per cent of GNP equivalent is accounted by the disability, the years lived with disability consequent to these conditions. Osteoporosis, through fractures and osteoarthritis, through joint replacement, costs about £8 billion or £9 billion per year to the UK and are really very common. So, one in two women, one in five men over the age of 50 will have a fracture over their remaining lifetime and over the age of 65 probably about half of us will get some manifestation of osteoarthritis. So, these are conditions which are really very common and it's not just about those obvious events, but about the 20 per cent reduction in relative survival following fractures that means that these conditions have an impact far beyond the obvious immediate effects.

This burden of disease is set in the context of an ageing population in which increasing numbers of individuals have more than one common chronic non-communicable disease and this issue of multimorbidity addressed recently by NICE is an area that UK Biobank is uniquely well set up to explore. So, if you think about the way that we do primary prevention for osteoporotic fracture, we assess risk using the FRAX calculator, as you can see here online, gives us a ten-year probability of fracture feeding into our national guidelines accredited by NICE, but we know that that doesn't identify everybody who goes on to have a fracture. We know that there are ways in which we could make this better, we've done some of those already, to modify the FRAX score, but UK Biobank gives us a fantastic opportunity to explore ways of risk assessment as just an example, but linking the bone to other aspects, such as other body [?compartments 0:03:38.8], other diseases, other factors such as environmental and so forth, to generate novel markers of risk from the image-derived phenotypes. And to bring together measures from different organ systems from the imaging study, for example, together with the mechanistic data, the genetics, the biomarkers that have been

collected at baseline.

Just to say very quickly about the DXA protocol itself, this is based on the Lunar iDXA instrument you can see here which is a state of the art densitometer. We have a whole body scan that gives you body composition, as well as bone and also some regional breakdowns, so you can get android/gynoid ratios and so forth. A scan of the hips gives us bone indices and an image of that region. We get a DICOM image of the knees and then of the lumbar spine an image and bone indices and then a lateral view of the thoracic and lumbar spine that can be used for vertebral fracture assessment.

So, I think one of the added value things of UK Biobank, and this is coming back to Rory's point earlier about the imagination of the users, one of the groups of scientists who've been most interested in the DXA data have actually been the computer scientists, the engineers around the images that come out. So, of course we have the numerical data relating to bone and body composition which are immediately available, they don't require any post-processing, they go up on to Showcase, they're there for use, but we also have these rather beautiful high-resolution images generated by the DXA which can be used as you would any other radiograph, but also lend themselves to novel techniques. For example shape analysis, automated methods for detecting vertebral fractures and those images and their generation is the basis of the Wellcome Trust grant which we're very grateful, this is funded to the tune of £1.6 million by the Wellcome Trust through a collaborative award.

This is a study augment led by Professor John Tobias who's prof [sic] of rheumatology in Bristol and this brings together epidemiologists, clinicians and engineers, computer scientists and basic scientists across the centres you see there: Bristol, Southampton, Manchester, Aberdeen and Cardiff, to try to derive a way, ultimately derive better ways of stratifying the risk of muscular skeletal events. The idea is that we develop automated platforms, and indeed these are pretty much sorted now, to generate these images from - generates IDPs, so image-derived phenotypes, from these images in all 100,000 as they go through. The sorts of things we will derive is say an active shape model which gives you modes of variation in the proximal femur and we know that from smaller scale studies there's evidence that the shape of the femur is related to future risk of fracture and arthroplasty. We can look at signals for osteoarthritis, for example, in the knee and the spine, and identify vertebral fractures automatically and using these as exposures we can then link to incident outcomes such as fracture and arthroplasty, but we can also link to genotype and to the biomarkers to get an idea of the things that might determine these outcomes, and then look at further sort of causal type studies through Mendelian randomisation and link to laboratory investigations to further characterise potential targets for therapy. So, the outcome of this we hope will be that we can inform better approaches to risk stratification, but also be able to identify potential new mechanisms and potential targets for intervention in future studies and, importantly, this will generate a library of new image-derived phenotypes which are fed back into the UK Biobank resource and are therefore there for future researchers to use in coming years.

So, I've asked this question: what's different about UK Biobank? Well I think we've heard really throughout the day what's different about UK Biobank and in terms of DXA it's very much the combination of

the numerical data and the images, and the images have added a huge new dimension to what's possible here, but of course UK Biobank is unique in its size and depth and breadth of phenotypic information. In the context of the things I'm interested in, muscular skeletal research, it gives us this unique opportunity as we go forward to investigate muscular skeletal relationships in the context of other organ systems and other morbidities. Just to illustrate that, this just summarises a few of the studies that are ongoing at the moment that I know about and there'll be many others that aren't on here, but as we move from the baseline data of the genes, and the myriad of data collected at baseline through the imaging enhancement that will eventually be of 100,000 and then to the instant outcomes through linkage, there are fantastic opportunities here and a wide range of things one can look at. For example, food environment in relation to muscular skeletal disease, we've got biochemistry, genetics, body composition, linkage to brain, a study that we're just starting funded by BHF relating bone to heart with Stefan Petersen leading, together with of course the Wellcome Trust-funded work.

So, to summarise, UK Biobank gives us this unique opportunity through its breadth, depth, vast numbers, to really address our questions of choice, not just in the context of a single organ system, as we would have been able to do previously, but in the context of pretty much everything you can think of wanting to look at and phenotypes in exquisite detail and with state-of-the-art methods. This is really highly relevant in our ageing society with increasing burden of multimorbidity and it gives us the opportunity to bring together the observational epidemiology, the understanding of mechanism to inform novel interventions and that's not just therapeutic interventions, but ways of better assessing risk and of identifying those who need treatment. I hope that the end result of all of this over years to come will be that we refine our ways of assessing risk and treating to reduce the burden of these chronic conditions. So, I'll just finish by thanking very much indeed the whole UK Biobank team and colleagues on imaging group and the various other committees, of course the funders and then finally the UK Biobank participants, without whom none of this would be possible. Thank you [applause].

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