Paul matthews JULY 2018 NW - PRESENTATION- 15 MINS
[MALE RESPONDENT]
[Other comments:]

Okay, well welcome back for the afternoon session. Before we start I just want to make an announcement, a lost and found announcement. I'm not going to mention the name but someone coming from Stratford has lost a Railcard, and I'll just give it briefly and then pass it on to Andrew at the end of this session, it's obviously an important document. Thanks very much for coming this afternoon, we're going to discuss the imaging enhancement over the next several talks. Let me just start with first saying what a privilege it has been for me to work with Rory and the many colleagues at Biobank over the last ten years in developing the imaging enhancement and various things around it. Most importantly let me give, and let us all give, the UK Biobank staff a tremendous round of applause for having hit the 25,000th subject this month. [Applause] They said it, in fact I said it couldn't be done ten years ago! Now, if we could go onto the first slide that I have, let's see if that works. No. Can you start my slides? Thanks. Well, I'm going to take you on a very quick romp through some of the early outcomes from the brain imaging component, which has been my particular interest within the broader group of the imaging working advisers that I chair.

As you know, the imaging enhancement is, involves studies of all the major organ systems in the body, brain, heart, body, bone and carotid using a variety of methods, you'll hear about them later. The ambitious plan is to complete imaging of 100,000 of the Biobank volunteers by 2023. It started only in 2014, it really came up to full speed in 2017 and already it's at 25,000 with three centres opened as of now and one more coming online. Most importantly it's really transformed the imaging world, because it's provided this extraordinary resource online for investigators worldwide. Now, I'm going to describe some of the outcomes, I'll present a number of plots like this, I think most or all of you are familiar with them. On the abscissa here we see a variety of the lifestyle, physical traits, cognitive traits and others that are collected within the Biobank resource. There are 11,000 of these along the abscissa and on the ordinate we're seeing negative logP of the significant scores for associations between any one of these factors, and some imaging quantitative measure that I'll describe.

Here, this is from a 2016 paper that Karla Miller offered on behalf on several people within the imaging working group, where she demonstrated rather beautifully that measures derive from the different imaging modalities in the brain protocol alone showed extraordinarily strong correlations, with a very wide range of phenotypic features across the Biobank population. The Bonferroni correction line is down here, it's obviously an extraordinary resource to our mind to understand. Within the Biobank resource there are also exceptionally still exceptional pieces of imaging data available, such as this, these measures of white matter structure that can be a huge range of measures using the most sensitive of current Multiband techniques, in this case using a method called [?Noddy 0:04:37.1] that provides a number of parameters, each different by physically each having a different kind of relationship to underline tissue microstructures. These show as a group, this is just looking at one class of them, even stronger associations than to the structural brain measures associated with size and shape of the global brain. In fact, they've been starting to be shown to be very sensitive to earliest stages of disease and prodromal disease in people.

I'll show you a couple of examples, this is from Hideaki Suzuki and colleagues in my group, showing changes in major tracts within the white matter of the brain, proceeding and without associated infarcts or other overt vascular damage exists not only in people who are hypertensive, but also in those that are prehypertensive. In fact, importantly what was discovered is that there was no clear cut-off as one looked at the relationship between blood pressure and injury to the microstructure in the brain. One can also in this sort of large dataset do kinds of propensity matching to look at the relative influence of different factors, and with the comprehensive nature of the data collected on a variety of organ systems and disease outcomes, begin to understand also what the relative contributions of modifiable lifestyle or disease factors are to brain outcomes in mid and later life.

Here, for example, just, I'll have you just focus on the pie chart in the first instance. The pie chart shows the magnitude of the age associated changes in brain grey matter and volume, but it's the shrinkage of the neurone part of the brain with age. The little pie that you see sliced out there is the relative component that, in midlife, that can be accounted for by modifiable risk factors. More than one tenth of our age-related changes as a population can be impacted by changes in improvements in lifestyle and other risk factors. Particularly important in this, looking again at the sizes of, not just of the slices in the pie, which is looking at the total, now we're looking at the total modifiable risk factor component. If you look at the slices of the pie for BMI or related to obesity, these, and as well as diabetes and systolic blood pressure, are amongst the highest. These then target us to identify what could be important in midlife to decrease and prevent late life degenerate, nerve degenerative diseases. It's not just about neurological diseases, those diseases that we know are associated with structural changes in the brain. In this rather elegant recent study from Ian Deary and Andrew McIntosh's MRC unit in Edinburgh, they interrogated the white matter microstructure in people who had reported major depressive disorder versus a well-matched healthy control group without neurological or psychiatric morbidities.

What they found is that in a number of tracts within the white matter each colour represents a specific anatomical tract connecting different parts of the brain, in different parts of the brain in these subjects, they found changes in microstructure, more abnormal microstructure that correlated with the presence of a history or current, major depressive disorder. This psychiatric disease which hitherto in smaller populations has really defied identifying structural correlates with this large dataset, is starting to yield some important new clues. Now, one of the most interesting of these recent studies that have been done comes from the groups of Jonathan Marchini and Steve Smith in Oxford, it's now on bioRxiv if you want to go and read about it further. They did a large scale genetic association analysis with a variety of the quantitative brain phenotypes. When they looked at the T2* hyperintensity phenotype, T2* just refers to one of the types of structural imaging data available. This one happens to be highly sensitive to the presence of tissue iron, they found that there was a strong correlation between T2 hyperintensities in specific regions of the brain outlined here in these beautiful colours, particularly in the deep grey areas, and snips within the genome.

Here you can see a typical Manhattan plot in which this is by chromosome, this is the association and

here you see highlighted with a total burden of T2 hyperintensities, four major hits, one of which here is, encodes the hemochromatosis protein, a particularly interesting candidate to associate with brain disease in midlife. Again, a very recent report, completely independent of Biobank, has demonstrated that the same snip in the hemochromatosis gene is responsible for changes in functional, functional changes in cholesterol synthesis. Here you see the measure of cholesterol synthesis in a cell model of the, with the gene mutation and you see it's much reduced from the control, this is due to changes in the HMG-CoA reductase levels. Here you see a Western Blot Data, a control and cells carrying the protein and here in a mouse carrying the same gene mutation, one sees accelerated brain atrophy, here's volume. In this case one is looking for expansion of the volume in the ventricles, the fluid-filled spaces in the brain which is indicative of atrophy of the rest of the brain, and you can see it clearly in the gene carrier relative to the [?wild 0:11:52.6] type

What this tells us is that this gene identified in this population that is really without symptoms of dementia, long before the disease comes, is another, a new kind of risk factor for late-life neurodegenerative disease that can be identified with this kind of large population analysis. Then finally I want to close, I've talked a little bit about some clues to understanding the mechanisms of disease, some clues to understanding risk of future disease, I want to speak more directly to prognosis over - Daniel Reukert is going to tell us about AI learning methods, artificial intelligence, in a few minutes. There's been an explosion of these recently, this is some, a piece of work that was published by James Cole about a year and a half ago. James was a postdoc at Imperial and what he did is he sort of stitched together a number of very paltry datasets of 1000 or 2000 brain images, but he came to a really important conclusion, and I say paltry only with tongue and cheek. What he found is if one looks at the relationship between brain structural measures developed using an AI method, sort of brain age and chronological age, where there were deviations from brain age either higher or lower than the predicted mean from the population cohort, there were consequences for future health.

Looking at the five-year mortality for people who had a brain age that was higher than their chronological age, their brains looked older than their chronological age suggested, as I often feel, they showed far substantially reduced five year, substantially poor five-year outcomes than those who did not. With the Biobank data this is new analysis using a different alga rhythm by [?Aaron Bourne Cogninson 0:13:58.5] at Imperial, with a more powerful 3D convolutional network, demonstrating that one can really refine these estimates of population means for changes with time in order to improve these estimates in populations like Biobank much more powerfully. This really starts to point the way, to the way in which one can use these tools to help doctors and patients better understand risks of medium-term disease risk.

Finally, I just want to close by, there's so many people to thank, first I want to start with Steve Smith, Karla Miller and Fidel Alfaro Almagro who have played such an important role in getting the image derived phenotypes out to the research population from the brain imaging programme. I want to emphasise that like the rest of the imaging working party, which has been huge with, if one includes all of the advisers that are included, there are many, many more people in the academic community who have been trying to help Biobank over the last several years, make this into an important resource and of course, I want to thank the

funders. Thank you.

[Applause]

[END OF TRANSCRIPT]