[MALE RESPONDENTS]
[Other comments:]

We've now got Nick Thomas, we could have obviously selected any number of areas to highlight here, but we're very grateful for Nick for being our example for the first session this morning. He's going to tell us about the insights that have been gained into Type 1 Diabetes from the use of UK Biobank data. Nick, welcome.

Thank you very much.

Pleasure.

[Aside discussion 0:00:33.2]

Good morning, thank you for having me to talk. My name's Nick Thomas, I'm a diabetes clinician and researcher from Exeter and I've been asked to talk about the work I did around late onset Type 1 Diabetes using the UK Biobank. The title from our paper is quite a mouthful and essentially it's using a novel genetic stratification methodology that we developed to differentiate Type 1 from Type 2 Diabetes, but even that's a bit complicated to quite get one's head around. I like to think about it as adult onset Type 1 Diabetes, trying to find the needle in the haystack and using the UK Biobank to do that. The background of our work is that Type 1 Diabetes is predominantly a disease of childhood and adolescence, well that's what Wikipedia will tell you, but we know that it can occur at any age. Here things start to get a little bit more tricky, how common is it over 30 years of age and what do these patients look like? The truth is we just don't know, or more accurately didn't know, because e epidemiological logical data in later life in Type 1 Diabetes is just very limited, and that's because almost all studies in Type 1 Diabetes are in children.

Why is that? It's because age is a key predictor of diabetes type, so in children almost all the diabetes is Type 1 Diabetes, so cases are easy to spot, standout and therefore easy to study, whereas an adult with a dramatic increase in the prevalence of Type 2 Diabetes, cases of Type 1 Diabetes are drowned out, much harder to find and much harder to study. Really we're up against it as researchers because there are no really well-defined clinical criteria for us to use, and clinicians classification and insulin prescribing is not systematic and occasionally, and a bit more than occasionally wrong. I like to think about this as a circle of difficulty, we've got a disease in late onset Type 1 Diabetes that's really difficult at an individual level to identify. If it's difficult at an individual level, it's difficult to do at a population level and therefore it's difficult to study, and if it's difficult to study it's difficult for us to find any more about it to make that diagnosis easier, so we're a bit stuck. That was until we found an alternative way using the UK Biobank and genetics to try and break the circle and make it a bit easier to study. The next part of my talk is about, and the journey of how we got to our findings, is around the Type 1 Diabetes genetic risk score.

Simply this is a way of capturing the polygenetic risk associated with Type 1 Diabetes and this is

through measuring 30 single nuclear type polymorphisms which increase your risk of Type 1 Diabetes. Now they don't all equally increase your risk, so we wait each allele depending on how much risk it confers. From that you get a score and every single one of us in this room has a Type 1 Diabetes risk score if we had our genetics measured. Of course we've done that in the UK Biobank, so we can work out a Type 1 Diabetes genetic risk score for all half a million participants. Then we can plot them on a histogram and when I do that that's the histogram I get, and then with the method we applied, the novel stratification method, what we simply did was put a line at the 50th centile right down the middle of that population. The next piece of information I need to get you is that Type 2 Diabetes doesn't share any of the 30 snips that are in the Type 1 Diabetes risk score, and what that means is that the type 1 genetic risk score has no bearing on your ability to get Type 1 Diabetes, Type 2 Diabetes, sorry. What that means is that in my population, on both sides of my 50th centile stratifying my population just by Type 1 Diabetes risk, there will be the same amount of Type 2 Diabetes.

To reiterate, the two one genetic risk score has no bearing on your ability to develop type two diabetes. My low score I have X number of cases and in my high score half I'll have X number of cases. However unsurprisingly, given that Type 1 Diabetes has, is associated with the Type 1 Diabetes risk score, almost all 95 per cent plus of cases will be in the higher score half. Now what I've got a situation is, I've got my Type 2 Diabetes in the low score half, the same amount of Type 2 Diabetes in the high school half, but this excess of cases here, which is restricted almost entirely to my higher score half. If I subtract the number of cases in my low score half away from my high score half, I get left with a number of cases of Type 1 Diabetes. This is exactly what we did in the UK Biobank and in blue we've got the lower half, remembering that this will be just Type 2 Diabetes, and in the higher half you've got the same number of cases of Type 2 Diabetes and the difference between them that you can see here and in green, that excess is contributed by cases of Type 1 Diabetes.

Then we looked at it in a bit more detail in decades of life and this is in the first three decades of life, from zero to 30, and what you can see here really reassuringly that sort of proves our methodology is that almost all the diabetes, as I explained in my opening slides, is Type 1 Diabetes. Then with increasing age we see this dramatic increase and prevalence of Type 2, again as anticipated, drowning out these cases of Type 1. The really exciting thing for us and the real interest was that actually when you add up the total number of cases either side of 30, 42 per cent of Type 1 Diabetes is occurring after 30 years of age, which was a real game changer. Then the next thing we ask was that's fantastic, but what do these people look like? Do they look like classical childhood Type 1 Diabetes? The answer is, yes, they do, they're slimmer than patients with Type 2 Diabetes, they're rapidly progressing to insulin, 90 per cent of them are on insulin within a year and they're much, much, much more likely to get DKA. Now this data has come from hospital records, linked data, and as Professor [?Subday 0:08:06.2] says it is quite messy but the joy of this is we stratified genetically, so it doesn't matter because we're just comparing groups.

It will be messy in both halves and what we can see here is when differentiating genetically there's a

disproportionate higher percentage with DKA in our type 1 group. Actually I haven't presented it here for time reasons, but this data looks exactly the same for those diagnosed under 30 that we've defined genetically, so they had the same BMI and the same amount of DKA as a discharge diagnosis. Yes, these patients we defined genetically, diagnosed with Type 1 Diabetes, over 30 do have what looks like Type 1 Diabetes. This was a whistle-stop tour of our research and I'll happily answer questions at the end, but essentially showing for the first time really that a large majority, a large proportion of Type 1 Diabetes occurs after 30 years of age. It's difficult to identify as we saw in the graph with this massive increase in the prevalence of Type 2 Diabetes, but these people really do look like Type 1 Diabetes and they have similar characteristics to those diagnosed under 30 years of age.

This work is only possible because of the large population dataset that we've now got available in UK Biobank and the link data that allows us to look at those hospital information. I'd like to thank you for listening to me on my whistle-stop tour, to thank all my colleagues in Exeter, and to particularly thank the UK Biobank for giving me this opportunity to talk and the resource that has allowed me to do my research. Thank you.

[END OF TRANSCRIPT]