Thanks very much. Haemochromotosis is a condition characterised by iron overload, with iron deposition in many of the major organs of the body. It's due to mutations which damage the control of iron absorption from the gut, resulting in a very slow accumulation of excess iron. It presents clinically with severe fatigue, chronic pain, arthritis - which often starts early and becomes widespread. Diabetes, liver disease which can progress to cirrhosis and liver cancer, and each year there are a number of early deaths from Age 40 and over. Ernest Hemmingway is one of the famous people who've had this condition, and several members of his family also had it. The wonderful thing about haemochromotosis is the treatment's incredibly easy. All they have to do is give blood; blood is very rich in iron and once the accumulation of iron has got rid of, they only need to donate blood four or five times a year to keep iron levels down. The blood can actually be used for transfusions for other people.

The problem however is many of these people are diagnosed very late, after irreversible damage has been done. The main mutation involved in European ancestry populations is the so-called C282Y mutation. It is the most common single-gene mutation in Europe. The annual frequency in UK Biobank is about 7.3 and incredibly close to other UK studies like L-SPEC and TwinsUK. In the European descent subsample, in Biobank there are 2890 homozygotes. The homozygotes are the ones that's the double mutation and the ones that are really high risk for the organ damage. This is very much a Northern and Western European disease so the carrier rates are much higher in North and West Europe. As you can see, the UK and Ireland are very much hotspots for this mutation.

The overall prevalence is about one in 156 people in the UK, 350,000 people probably, very close to the previous largest study of haemochromotosis in the UK, which was in 10,000 people in Wales. In January this year we published the baseline associations with this and a second minor mutation and some of the smaller effect variance in the BMJ. To cut a long story short, the male homozygotes were roughly - well, over four times more likely to have any sort of liver disease diagnosis. Over twice as likely to have osteoporosis or osteoarthritis. About 50 per cent more likely to have diabetes, and there were a few other associations as well. The associations are much weaker in women. The iron levels in women are lower, probably because of menstruation.

Thanks to the update of the hospital records in Biobank recently, we're now able to examine incident rates, hazard ratios for those major diseases separately. So taking out the people reporting these problems at baseline, and again we have very substantial excess risks of diabetes, osteoarthritis, liver disease and liver cancer in the male homozygotes compared to people without this mutation. The association with osteoarthritis has become significant in the women, and these associations are [?a bus 0:04:39.4] to all sorts of quality checks. The big question with this mutation, with the haemochromotosis mutation, is what the penetrance is. Previous estimates of penetrance are varied from as low as less than one per cent in community surveys, up to 50 per cent in family and hospital studies. Well, using the same kind of cumulative diagnosis graphs that you've seen, we now have about 25 per cent of the male homozygotes diagnosed, with haemochromotosis, about 12, 13 per cent of the women. That's extraordinarily similar to the data that came out a few years ago
from the EMERGE analysis of hospital medical system - seven medical system Biobanks across the US. Of course the American data suggest that the penetrance goes even higher at very advanced stages.

The big worry with Biobank of course is that it's not population representative, so we have compared the overall rates of any haemochromotosis diagnosis to an equivalent subgroup in the NHS Health Records for England, so this is whole population. There's no linkage between the individuals or anything; it's just the overall totals. We find that the baseline rates of diagnosis irrespective of genotype are very similar in women and the incident rates are very similar in women between the NHS records and Biobank. In men, there is an access of people with haemochromotosis, already diagnosed, taking part. But on reasonable assumptions, the difference it would make would only be three or four percentage points on that estimate. The incident data looks very similar to the full population-based [?HIS 0:06:54.1] records.

Another key issue with haemochromotosis is, people have argued that we shouldn't screen, look for this condition because there didn't seem to be excess mortality. That is true of the heterozygotes. They are virtually identical to people without this mutation, but the homozygotes do seem to have a sustained excess mortality - not huge; 1.22. Again this is robust to removing people who are diagnosed with haemochromotosis at baseline. This brings us to a point where we can really think about eradicating this excess clinical morbidity because we know that removing that excess through blood donation is effective if it is started early. Is it a big problem? Well, we did a separate analysis of the older sample in Biobank, 60-to-70-year-olds. In the men, 1.5 per cent of all the frail older people, older men, were C282Y homozygotes. 1.6 per cent of all the hip replacements across all ages in the men, in Biobank, had this double mutation, and 5.8 per cent of all the liver cancers were in this group.

We're really getting, thanks to Biobank, to understanding the natural history. We've got good clinical tests to find these people. We've got a good intervention if we could start early. We really need to start thinking about piloting early diagnosis and maybe even population screening, and adding iron and the HFE mutations to the routine health screenings. Biobank is helping us extend this extraordinarily, understanding the additional genetic variants that modify penetrance. The brain and liver MRI is imaging the excess iron in these people. The DEXA of the joints is showing us what the joint damage looks like. We've got more details on the liver enzyme results and even the humble full blood count is showing us - is validating claimed iron overload indicator that we could actually identify these people in clinical practice by this iron overload signature. Thanks again to the participants of Biobank and the team, the wonderful analysts who've worked on this, and the MRC for funding it. Thanks very much.

[END OF TRANSCRIPT]