

It's really difficult to overstate the importance of mental illness, these are global public health, these are massive problems globally. Very recently for example the World Health Organisation announced depression is now the single cause of disability in the world, far outstripping what you might think of like heart disease and cancer and stroke, depression is the number one cause of disability in the world. So this is a hugely important problem currently, but it's also a problem that's going to get worse in the future and we need to understand it better and Biobank is one of the ways we can do that.

Just to recap it a little bit from what Cathie has said with a focus on mental health, there's lots of different ways that we can find out about your mental health, both in terms of how you reported things but also in terms of the linkage to health data, hospital data and then of course the thoughts and feelings questionnaire that I think 160,000 people so far have filled out which has been fantastic. We know about what medication you are taking, your family history of mental illness, we've got this really important personality scale which I'll show you more about in a second, which is about neuroticism, which is closely related and important for things like depression. Also I should say towards the last two years of UK Biobank recruitment there was an opportunity to get a little extra information in terms of depression and my area of interest which is bipolar disorder, so there were more specific questions about manic symptoms collected for about a third of participants recruited towards the end. All of this has been tremendously helpful and I hope to show you some of the interesting parts of it, three example areas of work. The first is this crucial area of overlap between mental and physical health, it's been underappreciated in the past I think and as I hope to show you this afternoon it's a massive area and really the division between mental and physical illness, so called, is very arbitrary and artificial and not real. It is an important avenue for research.

Likewise the genetic data has been really a step change moment for research into discovering genetic risk factors for things like depressive disorder, and later I'm going to be showing you some exciting examples of that. And then one area that I'm particularly interested in, which you might not have thought about in terms of mental illness is about our daily rhythms of sleeping and eating etc and how important they are for regulating mental health and increasing risk for mental illness as well. So I will show you a little bit of data there as well later.

I've got three quotes today, my first is from Plato, it's a very cultured place Glasgow obviously so, "The greatest mistake in the treatment of diseases is that there are physicians for the body and physicians for the soul, although the two cannot be separated." So obviously Plato was no slouch, he knew what it was about, having doctors that only look after your mental health and doctors that only look after your physical health is a very artificial separation. Clearly there is no difference between the mind and the body and I'll give you some examples of this. One example of course is depression, depression present with psychological symptoms, like feeling low, anxious, and not sleeping etc. but it's a whole body disorder. We know that it affects your risk of heart disease, your immune system, increases the likelihood of becoming obese. So increasingly we don't think of

depression as solely a psychological disorder but rather a disorder that affects pretty much every part of your body, it's hugely important.

Here is an early paper that we wrote using the Biobank data, really just a descriptive paper looking at how common for people with depression, people with bipolar disorder, and people who don't appear to have either how common or how much increased risk is there for things like high blood pressure, diabetes etc. and the key point here is, it isn't that these things are more common in these groups but because of the depth of the biobank data we were able to control for a lot of other factors, like where you live, your smoking and alcohol intake, and that depth of data is really important in trying to tease out the strength of some of these associations. So no big surprise actually that people with depression are at greater risk of high blood pressure, diabetes, heart disease and stroke. And then in my specialist are these risks are even greater for people with bipolar disorder and I think what that tells us is that it's partly about lifestyle and its partly about where you live and all that stuff but it's also an indication that there's a shared genetic vulnerability that cuts across your susceptibility of getting depressed, as well as your susceptibility of getting heart disease. And Biobank is going to be a fantastic tool for teasing that out.

Ok second quote, "Most of the time I don't have much fun, the rest of the time I don't have any fun at all". I was trying to find, who's the most neurotic person I can think of? so I went looking for picture of Woody Allen and lo and behold there was a quote from Woody Allen. So this is about neuroticism. This is a heritable personality trait, so it runs in families and in fact something like 40% of the risk of being highly neurotic is genetically determined, and that's important for discovering genes for neuroticism. It's all about how you respond to stress, some people are very resilient to stress, others tend to react to stress with high anxiety, low mood, so called negative affect. But the important thing about the personality trait of neuroticism is that it's associated quite strongly with depression, as well as with anxiety disorders. But also another range of mental health problems like PTSD, substance misuse, even schizophrenia. It's also; in general, overall, the broad definition of neuroticism is associated with dying slightly younger. Although there are subgroups of neuroticism possibly where you might live longer, but the broader picture is that it's not actually that good for your long term health. And of course if you scale that up a highly neurotic population is not good for the economy or public health, and we need to understand that a bit better.

A reminder of the questions that you filled in, I'll just let you go through that, tot up your score again if you're interested, see put up your hand if you scored 12. On the face of it this questions don't tell us very much but together they are really, really helpful and its obviously tapping into anxiety and that kind of stuff. So one of the really exciting things that I was involved with a couple of years ago, was the opportunity based on the first release of the genetic data to try and find genetic variants that might increase an individual's risk of neuroticism. We were able to do this in a very large number of people from Biobank, as well as other people from other cohorts. And for the first time really discovered parts of the genome that were associated, there were gene variants that were associated with a slightly increased risk of being neurotic. Interestingly a lot of those areas we identified contained genes that had previously been associated with smaller studies of the biology of depression. So that was very, very important, that is now since been replicated and extended in about 350,000 people from UK Biobank, with even more areas of the genome identified. So this is an

evolving picture but really, really exciting for mental health. But perhaps even more exciting is the potential to discover genes for depression. So neuroticism is a trait related to depression, major depressive disorder. Discovering genes for depression has been difficult so far because of low sample numbers in the studies, but Biobank has now contributed to a very large global effort, from the Psychiatric Genomics Consortium to bring together samples and clinical descriptions to do properly powered studies to discover genetic risk variants for depression. With a lot of very recent success. So this is published as a pre-print, it's still not published generally but I think it's reasonable to tell you that when this group the Psychiatric Genomics Consortium looked at 130,000 cases and 330,000 controls, 44 areas of the genome harboured genes that are associated with increased risk of depression. So that's a bit of a game changer in terms of what we think causes depression. It sort of confirms depression as a legitimate brain disorder. But even more interestingly the genetic risk for depression overlaps substantially for other non-psychiatric conditions, like being obese, so some of the genes for depression are shared with the genes that make people put on weight, some of them overlap with genes that are associated with low educational attainment, and of course there is a genetic overlap with more severe mental illness like schizophrenia. This is really a huge study and a bit of a landmark in depression genetics. It is partly because of Biobank.

Ok final quote for founding father of the United States "Early to bed, early to rise, makes man, and women I presume, healthy, wealthy and wise." So Benjamin Franklin also no slouch, he knew what it was about. He was tapping into this idea of chronotype, that some of you may be aware of. So there is an opportunity for a small study here. Some of us are morning people, I'm a morning person, my wife's an evening person, it causes havoc at home, erm but morning people tend to prefer doing things early in the morning, night owls tend to do things more productively at night. Who would call themselves a night owl here? A proportion, so about 20% I would say, and morning people? Oh that's very interesting, so that's at least half of the group, lots of people are in the middle. So maybe we should have had this in the morning.

So chronotype is really important for lots of different health outcomes, and most of you will be relieved to know that early morning people tend to do better overall in terms of their long term health outcomes. Being an evening person isn't as good for you. So these are self reported and obviously subjective reports, so when you say you're an evening person, you may or may not be. So what's very important is getting an objective measure of morningness or eveningness, which we can get from the activity monitor that 100,000 of you did. There is a way to process the activity data to derive measures of rhythmicity of your rest/activity cycles, averaged over a week. And it's this rhythmicity which is much more interesting in terms of your health outcomes. As I said these are crucial for health and wellbeing and it's fantastic that Biobank have got this on a 100,000 people. It is not just your physical health it is obviously your mental health as well.

Just to give you some examples circadian disruptions, so called, or dysregulation of your sleep activity, your rest/sleep activity has been associated with a very wide range of problems. It is probably important for cancer risk, for obesity, for cognitive impairment and a big interest for me is a very strong association with mood disorders like depression and bipolar disorder. Just to give you a flavour of what is possible with some of this, we were able to construct for all of those 100,000

recordings measure of circadian rhythmicity. Such as relative amplitude and amplitude just refers to how robust the changes in your rest/activity cycle are over a week. And perhaps unsurprisingly but important because we were able to control lots of things is the reality that high amplitude, a nice robust wave of activity is better for your health in general, but it's having lower amplitude is associated with being more neurotic, lower self-reported happiness, lower health satisfaction, greater loneliness reporting, more smoking, more alcohol, more instability of your mood, increased risk of depression, increased risk of bipolar disorder. So this is going to be really helpful for us and one of the things we have done very recently that I'm not allowed to show you is that we've done a genetics study of relative amplitude and we found some really interesting results in terms of the overlap with bipolar disorder. This is going to be lots and lots of work in the future also highly relevant to mental health.

So that's me, I want to recap and say that hopefully I've convinced you that mental health and physical health disorders are not separate, they overlap substantially. This is a landmark study for discovering risk factors for depression, and when we know more about circadian rhythms that will be important from a public health perspective. Thank you for your attention.