



Great pleasure to be here, every time I hear about UK Biobank it's just inspiring it's fantastic and thanks to you guys for volunteering, it's just a tremendous resource and is really going to move health forward. I'm a psychiatrist so I'm interested in common psychiatric disorder and major depression and I haven't got a title slide, I'm allowed to be a bit weird I'm a psychiatrist. And the title is about three lines long and by the time I'd explained it that would have been the talk, so I'm just going to dive in right away and talk about what we do and what we don't know about depression and what we're hoping that by Biobank will help us to find out. I'm very interested in the brain and I'll come on to that in just a sec, I'm not going to take very much about the brain. First thing to say of course is that depression is unbelievably common, you read about this all the time in the newspapers about how common it is. About 20 percent to us develop a depressive illness at some time in your life, our lives, and by that we mean a period of being so depressed that you can't function normally and its interfering with sleeping and eating and so forth along the way. Of course there's a huge range of variation in that but it's one word here we speak about depression is as if it was one thing, we don't know much about what's going on in the brain, but I said I'm not going to speak a lot about that there is no chemical abnormality that we know about in the brain.

We do know that antidepressants like Prozac work by increasing serotonin in the brain you probably heard of serotonin and it's a neurotransmitter this made from tryptophan which you eat every day in your diet, and that's how they work, they definitely work on that and nearly all of them work in that way. So we're still on one thing, but depression is so common and so variable that it must involve lots of different mechanisms and that's why we're not seeing and understanding the mechanisms in the brain, because we're not dividing it up. I hope that by using UK Biobank we will be able to subgroup depression into different kinds and it will overlap with all sorts of other medical illnesses and find genes and find new treatments. We do know that there must be risk genes because it runs in families and you can figure out how heritable it is from twin studies, and the studies suggest that about 35 percent of the risk so

it's not that great 35% of the risk is due to genes. So they must be out there but we've been able to show as Tim said that we've been able to scan the genome in the last fifteen years. It's amazing how it moves on, just a thousand pounds per scan now, but we haven't found using those sorts of studies a single gene that's definitely involved, variation in that gene predicts risk of schizophrenia it's definitely going to be lots of little genes that are involved. It's similar to the position that we were in with schizophrenia about five years ago so it's less common the depression just got a little diversion into that, but it's 72 percent heritable and schizophrenia had nothing and now is fantastic in the last five years 100 genes for schizophrenia and I just want to speak about how that's come about whether we might be able to do something like that for depression.

So delighted that Tim explained about SNP's and things so I don't have too, it will save me some time. This is what a scan looks like so the SNPs arranged in terms of chromosomes along the bottom they're going from 12-22 and the X chromosome on the far right as you can see and each of those dots, well there's about a million of them, you need a million of them to mark bits of DNA throughout the genome and the reason there split up is simply asking the question for each one of those SNPs is a particular variety of that SNP more common in people with schizophrenia than in the controls. That's what that y axis is, you can see that in schizophrenia, all along the genome there are points where some versions of SNPs are more common in these samples than in the controls and we've got a hundred of those that is fantastic. The key point is that there are so many that each one of them has a very tiny risk is less than one percent of the risk so even with all those positive things we're only explaining like 30 percent of the genetic variation but it's a real advance and no one of them is going to be critical but if you look at the pattern then you can see that particular pathway seem to be, genes for particular processes seem to be effected. That helps us to identify what processes might be wrong schizophrenia, so that's schizophrenia, but we don't have that in depression Why is that? Partly because it's only 35% heretical and so you know to get a sample size sufficiently great will take an enormous number so the only reason we have this in schizophrenia is that we're looking at forty thousand cases and hundred and thirteen thousand controls and the way that's happened is because with a hundred versus a hundred all those collections have been pooled in a tremendous international collaboration to produce

those sorts of numbers and the numbers are going up and up and up all the time and now we got over 40,000 versus 100,000 now the genes begin to appear.

So to do that for something which is half as heritable I think isn't going to happen, it's not going to be the answer. These sorts of numbers though, going to be doing it in the Biobank because these are the sorts of numbers in the Biobank as you will see, we have this sort of number of cases of depression and that sort of number of control so the fantastic advantage of the Biobank is a you can do the whole genome wide thing in one go. You don't have to have three hundred and fifty different author's coming together donating their little connections of DNA, there's enough to detect effects, especially if you take environment into account and that's what we have to do. So the other things we know are that common sense factors in the environment are risk factors for depression. Bad things happen to you and these increase the risk of getting depression, the key ones are very bad things happening to you in childhood neglect or abuse. Recent bad things happening to and not having any social support so you're not resilient to things happening, and we have to include those I think to find interacting genes. So people vary enormously, you see people, I see people clinically who've had the most terrible abuse and it's understandable they got depressed and we know other people have terrible experiences and don't get depressed and those things are modified we think are modified by genes. So if you put the two together, the power of Biobank and this sort of environmental information then begin to find genes, we hope, and clues about pathways that may be involved. So we have to include those environmental factors I think to find interacting genes all those studies I showed you in schizophrenia there's no information at all apart from the diagnosis, we don't know if they had life stresses or that sort of thing. In the Biobank we've got all that, it's all there and I'm going to show you how it is. There may be all sorts of other environmental factors that we don't know about, you never thought about those unknown unknowns, which that confused American Defence Secretary spoke about. We think that diet may be very important so we are particularly interested in that and some medical disorders, like the ones you've heard about, obesity diabetes and cardiovascular disease just worth noting for example, that if you are depressed and you have a heart attack your mortality is very substantial increased. There is a big overlap between the two disorders but we don't understand the nature of that, it could be to do with particular pattern of genes so let me give you an example of a gene environment interaction.

I like this picture, we're a happy bunch of people called new mood disorders, it was a European consortium of 13 centres working on depression, some of us working on mice, mice get depressed apparently, rats and humans. So in Manchester and in Budapest we collected a pathetically sized sample of 1,300 people in Manchester, 1,300 in Budapest and recorded everything that we thought was relevant, all those life events and that sort of thing by questionnaire. We looked at particular genes in mice and the rat people said we think these are important for stress and one that we looked at, or a set of them actually this CREB- BDNF and TrkB pathway and it's a functional pathway, these genes make neurons grow and encourage neuron growth. We didn't see any difference, if you compare the different versions of these three genes in people with depression and controls there's nothing to find there's nothing there. When you plug in environment then you begin to see significant effects. If you look on the left-hand side here you can see along the bottom we subdivided the samples according to how much childhood adversity they had recorded and on the vertical axis you see their risk of depression as you can see in general the more they had experienced childhood adversity not surprising the more they reported depression, but that was influenced greatly by which version of BDNF they had. People with this version were less responsive if you like to childhood adversity in terms of getting depression whereas people with the risk allele show twice as much and it really amplifies the effect of adverse effect of childhood adversity. So that gene variation doesn't matter overall risk for your risk of depression, it does matter if you're in a particular circumstance of having had childhood adversity, and so using that sort of data, you can put it you know we put it together to make a sort of diagram of what we thought was going on and tested whether it's a significant or not. So we plugged in the various things have been measured that came out as significant, so there's a genetic effect, there's whether you had depression or not in your questionnaire measures, the thing about personality here rumination, whether you had life stress, childhood adversity and you can make the sort of map. So you see here childhood adversity acting through been modified by these genes to influence the risk of lifetime depression and that's what I think we need to do on a Biobank scale. That's what we're trying to do, do exactly that but do it across the whole genome and all the environmental things that we think might be relevant and plugging diet and other unknown unknowns that could be relevant and could fit into that equation. We're not going to end up with one map, but end up with several of them and the genes that we pull

out in that way will give us clues as to what's going on in depression and how we might prevent it and put it right.

So the practical aspects of it, what have we got in Biobank, so first of all we need to, this is the general stuff from 500,000 subjects, so you can see we know about their age and sex and medical conditions they've had, what medication they're taking, how active people are, whether they have had life events, got a record of that, self-rated. We are a bit lacking in early risk factors, you know the early psychosocial adversity but there's a new questionnaire going out which is going to address that. Lots of information about diet as you will see, we can use impedance to measure how much of that body fat you've got, we think that might be quite important and in 172,000 subjects, maybe some of you did the mental health questionnaire and that tells us about things like depressed mood. So we know that 90,000 of that 172,000 felt depressed for a whole week in their life which is getting on the level that I mentioned at the beginning, and you can see that this is a sort of thing you see on the touchscreen maybe you've been on how to look at the data, but you can pull this down for every question and it gives you all the basic information the mean and standard deviation and all that kind of thing and 90,000 felt depressed for a whole week in their life. So we have to decide how we're going to group this, there has been more detail here, so the mean length of a depressive episode is 16 weeks, that's quite a long time to feel depressed actually, a lot longer than two weeks and the mean number of depressive episodes was 6, 6 per person who felt depressed had it six times as a mean, so there's plenty of variation out there.

So in terms of being made to translate what we know from the Biobank questionnaire to make a diagnosis so we can categorize people into according to whether or not they had different levels of severity of depression, so you can see a quarter of that segment of 172,000 have depression of one form or another very in a more serious recurrent major depression severe 8,000, single episode seven thousand, recurrent major depression, moderate depression that's when you start treating with an antidepressant perhaps at 15,000 and the rest don't have it. So those are the sorts of numbers you saw in the schizophrenia consortium, all in one place with all sorts of other data to go along with it. So that's what we're, how we are going to group it up, that's what we're doing and we're looking at how to look at influences on that in the environment, from the environment.

so we got to organize these influences on depression the demographic and psychosocial stuff, diet and body composition, medical disorders and the genes. Maybe I don't know if this is the time to say it, but I got an email yesterday saying the genes are ready, there going to be downloaded from a hundred and fifty thousand people, that's a hundred fifty thousand scans with over a million markers and the 72 million amputations ready to be used. So that's just happens the rest is propriety work that we've been working towards. Organizing the demographic and psychosocial data, so we're going to record and put into our equations and models gender, ethnicity, socioeconomic status recent life events, self-reported functional impairment, that's a key aspect of diagnosis can you live your life normally with your symptoms, childhood trauma we will have in due course, measures of social support already there and measures of life satisfaction. So all of those would be individual items in our bigger equation trying to predict depression and this is the data about food about diet organizing that so that that takes a lot of organizing the huge amount of data on it was a 24 hour recall thing that is done online so what we have to eat and in the last 24 hours and your dietary habits. You can see the sorts of things cooked vegetable intake, salad blah blah blah... oily fish intake and so using this sort of information we can put people into categories that we can then put into our models, for example there's some evidence, not very strong, that Western diet is more of a risk than the Mediterranean diet having lots a cereals and having oily fish is protective against risk of depression, so we can slot that in and see if its modified by genes. See if it helps you cope with stress or it doesn't help you cope is also a possibility that we can be evaluated and so people have been doing work with the database already and extracting from those diaries actual nutrients, so alcohol, calcium intake, carotene, energy all those things are there. The ones we're interested in are carbohydrate intake, folate in blue, protein vitamins b12, vitamin D and you've heard of polyunsaturated fats PUFAs and that's the Mediterranean diet. So we're analyzing that using the data you can calculate from the diet history how much polyunsaturated fatty acids you have no time whether it's a lot of a little and so on and of course tryptophan which I mentioned at the beginning, it's an important factor because as a precursor of serotonin which seems to be a unifying I suppose aspect of depression.

So we certainly want to know about that and there's good evidence that variation in tryptophan in the blood influences risk in a small way and then there's a medical disorder that where we think there may be overlaps. To give you an idea of the complexity of working on this at the moment and again we just on the other slide when we calculated those things we put it back into the Biobank so other people can use those proof of data that we calculated to do that stuff with, so it's self-building in a way. So people said what medical disorders they had and there's a list of them, we've put the psychiatric ones at the top, depression in red and then there's 526 of those, quite a lot to put into an equation, we've got to simplify and boil it down. So we've recast them into disorder groups like cardiovascular disease, CNS disorders and at the bottom there according to the mechanism, inflammation for example would be at a mechanistic diagnosis of the many, many kinds of inflammatory disorders a huge amount of interest in inflammation and depression. So those boiled down variables I can show you a bit of data about that so this is a diagram from the Biobank and what Gabriella, who is really the driving force in the study, as you'll see in my title slide, did was to see the comorbidity between this disorder. So there's depression the number of people the circle, the number of people who said they had depression and size of these circles as the number of people who had obesity, hypertensive diseases, musculoskeletal diseases and so forth and the thickness of the line says how much they occur together. So we can see what the probability of that happening by chance and whether there is genuine overlap between risk of depression and these other medical disorders which might point to common genetic mechanisms, but it might be something like you know when you put on weight you get depressed about it. So it all has to be teased apart and that requires elaborate statistics.

So that's I think the final point I wanted to speak about in this is what's happening in Gabriella's department, she works half-time here and the rest of the time in the Budapest and they have very sophisticated Bayesian multilevel analyses of relevance to cope with all these predictive variables, just as a sort of cycle there's Bayes he was a Vicar in a small English Church 1701 he was born, 1750 something he published a very obscure letter to the Royal Society. He must have had friends to get someone to read his letter and it was an equation about chance and probability what's the chance that your belief is right if you get a new piece of evidence and that's all I can say. It's complicated I only half Google understand it. These are the sort of predictor variables here and the y in the middle is the risk of depression and you

can see that basically what Bayes does it instead of looking at all these things individually and whether predicts risk of depression it also looks at the interaction between them and so you can still see the causal pathways including the possibility that depression itself may influence some of these factors that we think are risk factors, so it's a two-way thing. I hope you understood some of that. So that's the approach and so to conclude our aim is to understand and identify subtypes of depression based on interaction between life experiences personality diet, medical disorders, and now genes. Wonderfully catalogued in 500,000 people in UK Biobank and this will help us to identify new genetic metabolic pathways to depression enabling us to get away from prozac and serotonin based on correcting something we know is, we will know is abnormal and there could be public health policy implications for prevention about how we live our lives, the kind of food we eat and so on. So I just want to say UK Biobank is uniquely powerful, sample size rich description genetics, organization and accessibility that enable us to understand, began to crack the complicated multifactorial disorder that is depression. This is my title slide you really want me to read that there's the collaborators, Gabriella Juhasz jointly with Gerome Brean who is at the MRC Unit at the Kings College, their good at doing the whole genome scans and Liverpool people know about nutrition so thank you very much indeed.