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neuroticism, data, genetic, depression, model, correlation, phenotype, snips, genotype, causal inference, polygenic, parents, causation, testing, fact, methods, child, bmi, prediction, randomization

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as it is all my graduate school days and also maybe you may know his name because he's lost also observes a well known software. So I know his name, reserved software and also includes other baatein I also started major cities paper about the same stuff. So on how to have him today and the talk about researches in biobank data is so much

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in production. also like to thank Mark for inviting me to this fact I would also like to thank Mark even though he's not here for being my PhD examiner many years ago so today, I'm going to firstly give some general remarks about the impact of bioscience on biomedical research, and then going to describe two areas of research that my group has been working on in the last two or three years in that signature, deviant atomization session. So, some general remarks. genomic data is extremely powerful in biomedical research for some of these following reasons of genome is inherited from parents, and are constituted constitutes at conception and is relatively stable. Our genetic variation, pervasive and lifelong influences on health and disease. Even though our genomes are stable, there are still changes that we acquire throughout life and the somatic mutations contribute to diseases, especially tenses. Similarly, are not entirely static in the sense that gene expression is response to environmental changes through epigenetic modifications. Or developments in technology now has meant that we can genotype and sequence the entire genome, including cow inherited genome, somatic mutations and also epigenetic changes and the cost of sequencing has reduced so much that it can now be performed on large samples that's collected in outlines that described so well in this meeting. And so we have vast amount of information both Genomics and Health Research on very large samples of subjects and the goal of this of this SS research effort is firstly to identify causal factors while health outcomes and this is because only causal factors constitute potential points of intervention in order to prevent or alleviate negative outcomes that both the individual and population level A second goal is prediction. And so for prediction, we do not necessarily require causation and only Association. But nevertheless, if we can predict how our health outcome, then we can perform health and disease surveillance, and also identify high risk groups for targeted prevention or screening and early detection and intervention. And this is important because for many diseases, if detection and treatment can be can be done at an early stage of the illness, and the outcome can be much, much better. And lastly, the prediction of response to treatment. In other words to the patient stratification, and this will allow us to optimize treatment according to the patient's individual differences and pave the way for precision medicine. And that data is now changing how research is being done in research for over 30 years. So I know a little bit about the you know, how things work and how things are done now. So traditionally we tend to test specific hypothesis, every grant application, every paper, we need to state as specific hypotheses but with big data, you cannot interrogate all biological processes, and there is a risk when we do so many tests that we generate called false positives, but there is also the advantage, the benefits that we can sometimes find unexpected biological insights and I think there are many examples of this. And similarly, instead of, of testing specific causes and consequences now we can perform testing on all possible associations. And in fact, the one of the problem is that we can find so many associations that when we construct a network with high too many connections, so many connections, which are can be very confusing. But on the other hand, maybe reality is complicated, and that we are actually getting a more complete representation of reality. Of course, our challenge would be how to interpret this complexity. How do we pull out the most important features the points perhaps where interventions are most effective? 14 There's a lot of interest in how to interpret networks, how to find the top teams or teams that are influential. And another change is that instead of having always to test causality by intervention, we can deal with a statistically for example, using material randomization, that is a waste of into into produce false positive because these statistical methods require certain assumptions and some of these assumptions may not always hold. But on the other hand, if Ellison says that it's much cheaper to do this, testing biostatistics and we can do it on a much, much higher scope, sort of looking at many potential causes at the same time. predictions based on a few factors, we can make predictions based on many factors. Of course, there is a risk that our predictions may become more opaque, more difficult to understand, but the compensation may be that the prediction would be more accurate. So pick data also present sort of new analytical challenges and opportunities. And one interesting thing is that, that I realized that all big data so go for the perfect that there are always errors. And, and some of this is technical, may be a chip, which is not sort of manufactured properly. And some of this is human like maybe some from Mexico. But having these very large data set actually gives us a lot of opportunities for data chatting, or quality control. For example, sample mixamp may be picked up by sort of inconsistency between the reported Sex and the sex implied by the genotype. And another challenge is that with such a large number of features, some of them may be strongly correlated with each other. And this gave rise to two statistical issues such as co linearity, and, but the benefit though, is that now we can often impute what is missing in protection of IP protection is not routine. And they will ask multiple testing, of course, to produce false positives. But now, statisticians have the now the ability to look at the distribution of results. Instead of looking at one or two test results. We can look at the distribution of p values, the distribution or summary statistics, which are very informative and tells us whether there are systematic biases and allow us to perform multiple testing more,

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more effectively, for example, using things like the false discovery rate, and in terms of, of data sharing, of course, so a lot of effort for data sharing, but the sharing the water, so it's still problematic because of the issue of ensuring anonymity of subjects, but also just the logistics of the sort of finite capacity for data transfer means that storing a huge data set can take a lot of time. And this has sort of stimulated the development of statistical methods that do not require the raw data, but only require a summary statistics that actually capture most of the information that is now we only have can It is only necessary to share the summary statistics. And finally, are correlated observation because people are genetically related. So the data are correlated. And this is a nuisance for many statistical methods. Many methods sort of assume independent observations. But the benefits is that they can actually make use of these correlations to to estimate important quantities such as heritability, and call heritability between disorders, more subtle challenges and opportunities with very high level of polygenic setting of many contexts common diseases 1000s of or more of genetic risks. Low side means that the individual contribution must must be small. And this lowers the statistical power meaning that there will be many false negatives, which was challenging, that means that it is it is necessary to to polygenic risk scores and to do that as well as possible and then for Genesis, it also means that that we may have multiple instruments multiple variants for analysis, I said when dealing with an instrument and the very last number of genetic variants means that our data is of a very high dimension, even with the largest biobank the number of subjects is still less than the number of genetic variants. And if you try to model every variants, you assume you have the problem of co linearity and models that are not identified. But then so to their opportunities for the development and the application of dimension reduction methods of penalized regression to tie in favor simpler simpler models again, over the context models and approaches such as machine learning. And with a deep loss number of variables features that are investigated will have very large, highly connected networks. Because of this biological variables tend to be inter correlated. And this gives us the opportunity to apply causal modeling, not just within randomization, but other causal modeling methodologies. Such as directively, cyclic graphs. And, of course, finally, the availability of diverse omics data types, genome, transcriptome epigenome, and so on, give rise to opportunities for integrating multi omics which not only gives us more biological insights that also more accurate prediction, and pay stated are paving the way for jobs with physicians and personalized medicine. So next, I'm getting to move on to this area that we've been working on for the last few years genetic. So in psychiatry, I'm sure also the other fields of medicine. The courses of copies are often conceptualized as being either nature or nurture and this book by Robert Burton, and SME America, he was actually published 400 years ago. And already you know, this was recognized because in the past table of the book is a list of courses in terms of congenital which includes parents being parented to disease or and the best nature, but other factors, such as nurses, education, terrorists, and so on. These are upbringing environment, because these are external factors. So these this is a nurturer. And so, for many years, early part of the 20th century, there was a lot of debates of this nature nurture, you know, which is more important, and the, I think the most hated the most about it is IQ of nature nurture controversy, but it was subsequently well recognized that nature and nurture are not independent, in Santa. Nurture may be influenced by our nature, in the sense that what we experience, you know, the friends that we, we make, the hobbies that we adopt, in a way related to our own personality, which is genetic. So, in a way we modify or create our own environment. And this example of this is what we call genetic nurture, and to understand this we can think of first the, the mother's DNA, mother's genes, and of course, the mothers. The mothers Dean can influence as hard sanitize firstly through genetic transmission, because the

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nothing from the mothers did not hide the child. a foster child demo can affect the child's phenotype, but the mother's DNA can also affect the child's genotype through influencing the mother's behavior. The mothers indicate that the mother is part of the environment of the child, is it the mother brings up the child and affects the nurture of the of the child and so these two words can both grades. And what this means is that there is a conservative potential confounding between the genetic effect of a child's DNA and the the effect of the mother's type through the environment. And if we were to look at one without also taking into the hands of the other, then that means we can have a bias the estimates will be biased and some methodologies have been made to develop to address this, but all of these previous methodologies require the separation of the transmitted and the non transmitted early assignment parents. And I thought that this was unnecessary confrontation, because this partitioning of transmitted the non transmitter actually is computationally quite expensive and often cannot be done unambiguously to be just probabilistic. And so, we suggested that instead of of separation into transmitted and non transmitted value, we can simply model jointly the child genotype and the parents just in the usual way of how we normally console for confounding and we show that this works well. And using this we were able to show that the mother's tide has a small effect on the child's BMI or a small, whether tailored to the child's own genotype. And you can see that in addition to being small it is also increasing.

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On this graph, the middle line

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is represent the effect of the relationship between age and BMI for people who have italic score is average. Whereas those whose polygenic score is one standard deviation above the mean. And the lower is one standard deviation below. And I think that maybe that makes sense because what happens in fact of the maternal behavior is stimulated at birth as a child does not have time to go follow them up if they seem to have similar impact. And then subsequently, we'll also look at the issue of whether if we only model one parent is that enough? Indeed, if we only model one parent or the other parents has neglected, we still have a bias, then we need to model those effects both times and then subsequently we we, we propose that the solution one possible solution is imputation. So as a parent of both parents are missing, we found include Haitian devise Bayes theorem and the street we can simply consider all possible configurations of phenotype and then condition on the observed phenotypes to obtain the the conditional expectation of the earlier percent of the missing individual. And when we apply this, we develop this test of full siblings and half siblings and on educational attainment, we found that the mother's polygenic score for educational attainment actually hadn't set which was maybe slightly even better than the TAs own polytechnics for for educational attainment of its educational attainment. And this is using UK Biobank data. And we subsequently generalize that to all all nuclear families, so families such as parent or sibling has, and in this paper, we also looked at the issue of statistical power. In more detail, we found that the the loss of information is essentially the reduction in the variance in the in the intuitive genotype. So if you have no information you can only compute the mean so that no, no variation at all. And by doing this, we found that actually full sibling pairs are not very informative. That's a huge loss of information compared to the fully general type of sale. And Harun asked bring pairs and how sets are more information, the more informative to to, you know, pass on more and more valuable. And then, much. Most recently, we apply this methodology on on depression and neuroticism in the UK Biobank data. And this this firstly in 31st degree relatives in UK Biobank data, although you know until they are already provided, we for the week, we did it just to make sure I constructed the nuclear families and I wish to have the general facts of any missing parents. And then we calculated the polygenic scores using both the actual and unfiltered genotypes of depression neuroticism and other side effects and then we analyze offspring, depression and neuroticism using mixed linear mixed models and mixed model. random effects is necessary because when we have multiple offspring which are correlated, we simply have a double residual correlations. So this just gives us the number of different from the family configurations that we have. 10s of 1000s and our results are preliminary results. Positive that the offspring neuroticism score is associated with the potential of each earning score as well as the offspring. So this is significant paternal polygenic score is significant association between the federal Polytechnic School and the child cell. neuroticism means that there is some evidence of genetic nature of your offices. So, moving to the next area of material randomization so we saw you all know that correlation does not imply causation. And traditionally, the gold standard for causal inference is interventions that a randomized control trial, but nevertheless, epidemiologists have been trying to do causal inference that case control and homeless studies over the decades and of course, they've made a lot of efforts to try to overcome some of the the see the problems that can give rise to a false positive influence through matching or adjustment for potential confounders and the careful assets and so on. But it is easy to make a mistake because even though the association between smoking and lung cancer, it's now widely accepted to be causal, rather than suspicion. Otherwise, he thought that there was confounding from a genetic factor, which extend explain sign Association. President he'll, of course also recognize that the dangers of inferring causation from Association epidemiological studies and propose a bunch of criteria to assess the the likelihood of causality before these observed associations, but being sort of the statistical modeling of causation, I think what really started with civil rights, because even though causation even though correlation does not imply causation, but if you start out with a a hypothetical causal structure, that actually would imply the correlation pattern. So if you were to compare the implied correlation or pattern with the empirical correlation pattern from your actual data, you can you can tell whether that's also model is compatible with the optimism it is not that we can reject it. A very simple example is is this that the relationship between these three variables x and y could be like this lesson that's causing X and causing y or another possible pattern of causation could be that x is is caused by both y and Zed. And these have different predictions because under the first model, is that and why would they correlate this was under the second model is that and why would not? So so this means that these two models can be discriminated, if we were to have empirical data on the correlation between these these variable and similar right really formalize this methodology for causal inference of path analysis. And similar right together with his father Cellebrite actually was the first to come up with this idea of instrumental variable analysis, which is really the basis of automobilia randomization. And and the path diagram for, for instrumental variable analysis actually, this so

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interesting. Relation X and Y, Y is the outcome and x is the putative cause or risk factors, but in the presence of a confounder see the correlation between X and Y would result provide a unbiased estimate for the because the correlation also includes because the correlation induced by this confounding but civil rights and celebrate suggested that if, on the other hand, if we can find an instrumental variable, which is causal to x, but it is not related to either the confounder or to lie directly, then we can estimate the causal relationship from x to y by the ratio of the correlation between height and Why's the correlation between ima An example would be something like the relationship between smoking and lung cancer and using tobacco tobacco tax as an instrument because tobacco tax is very likely to influence smoking, but it's unlikely to affect lung cancer directly. So some of my colleagues and I decided to write a review on medical my DM analyzation and this will be published in the next week or so. Now, we've already got the draft from the Journal of psychological medicine. And this is a one figure from that and and this actually shows the assumptions of Medela minimization, the red dotted lines are relationships that are assumed to be pressed by accident. So if they are present, and that will cause a bias in the causal effect estimate. What is sometimes under appreciated is this reverse causation is that if, if the outcome y can influence X exposure, then that could that could bias the estimate of the causal and so so I think recently, there's been a lot of material and normalization that performed the the MMR in both directions, the first one, y x to y, and secondly, and separately from y to x. I think that's not too bad, but it's not. It's not entirely satisfactory because of this. This bias. And I think if that is indeed reciprocal causation, they should be analyzed together, join me in just a second. So, for this, we will introduce instruments for x as well. As instruments for y and recognize that there are some some tights or some berries which may affect the confounder and variants that we have to still take effects on. And he also pointed out the growth of MMR in psychiatry, a very rapid growth, as some more GWAS data are becoming available on morphine impact obviously, there's more opportunities to look at relationship between Michael also contributed to to see in a small way to this literature, is this paper looking at depression, risk of coronary artery disease and myocardial infarction? For the finding some evidence that depression may be increased risk of cardiovascular disease and this is another similar study despite looking at serum triglycerides and see whether that may have an effect on depression with some sort of tentative positive results. So our review also looked at the relationship between cannabis use and psychosis. So interestingly, there have been a number of studies looking at this relationship in both directions. And it's just the direction from schizophrenia to cannabis, which is more consistent. So in fact, all there were three analysis in this direction and they are all positive. So maybe having schizophrenia that people who have schizophrenia may have a tendency or self medication. I have observed in practicing psychiatry that many of my patients smoked. And so smoking is kind of common in defined economy and maybe this is possibly in the other direction, whether cannabis use can increase this is a premium the results are much more mixed about 5060 positive and in our review, we also start to catalogue the recently development this landmark and we were actually quite horrified and there are so many it made it may really prolong the writing process to have to have to have a study of these different recent methods. To be honest, even after reviewing I really don't know, I don't know what to recommend. And then I don't know probably no one knows what to recommend anymore. I think there needs to be a very sort of thorough and systematic comparison between these methods in order to help the researchers to decide you know what not to do, and as to say that our own group also contributed to this is this methodology of MRCI which stands for mixed model causal inference. So this is our underlying model that we assume that there are two y one and y two that may show reciprocal causal relationships. And we allow for residual correlation. And this can allow for sample overlap on another thing and then the snips are considered to fall into four categories, those that affect only one phenotype. And so these would be valid instruments, and snips that are not shown as snips that do not either and so those mousemat our method does not require these snips to be pre identified, but instead all snips all the CEUs summary statistics are entered into the program as well as the the LD data from a reference sample and models that have explicitly models. So the total p because of these production of these snips and matrix disequilibrium is taken into the account in the calculation of the standard errors in the various in the variance by using sort of robust sandwich estimator. And when we applied methodology to these very well spent phenotype, we were able to detect a few well established causal relationship, but not too many. So I'm quite pleased that we didn't sort of detect significant effects everywhere. So among these are a causal effect of type two diabetes on blood glucose. And the causal effect of LDL on top or on the contrary disease, and they sort of reciprocal effect between BMI and type two diabetes and this is quite interesting because because BMI is recognized as a risk. factor of two diabetes. But if you need any textbook, we also know that one of the symptoms of type two diabetes is weight loss, and in fact, we have a lot of discussion with the reviewers whether this is possible or how can we detect the reverse direction but I think it's just because not all snips that cause by VTS AX via BMI, so if they have a snip that cause diabetes, via some other pathways other than BMI that these snips would be associated with, with lower BMI. And can we have recently apply this method alongside other methods to look at the potential relationship between white blood counts and the suffering of different whites, types of white blood cells, the neutrophils, lymphocytes, basophils, eosinophils, and so on, what was the most significant was lymphocytes and there was some, so among the six methods that we we studied, four out of six, there is a significant result in the direction of of schizophrenia, causing attention. And again, in the other direction, we also have full auto sets of lymphocyte, causing increased risk of disappearing. And that is, in fact, a lot of literature already that suggests that viral infections especially early in age, may, may affect brain development and increases. So I just want to end with a sort of a caution in interpreting MRI results. And this actually came from my comment from a reviewer of review, who said that well,

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if you believe that BMI, increases or decreases, diabetes list, how about amputation as a treatment, if you tell them of course that will decrease your weight that it will change about this list? And to me, it's nearly impossible because diabetes is a metabolic disorder. So why would cutting your arm off? So that makes me think that well, maybe, maybe it's not a BMI but something closely correlated with it, such as body fat in fact, there's a lot of evidence that body fat is, is is an endocrine organ. It secrete lots of hormones, and an excess of fat will serve some of the hormones in excess, and that causes all kinds of metabolic and it will make sense but the problem of course, is that BMI is highly correlated with with body fat, and so and so, it has to be very careful when we when we make this inference, we can only say that the data is consistent with a causal relationship, but it could be something closely correlated rather than the real causal factor. Okay, so I think in the interest of time, I will not repeat what I said thank you very much for your attention.

40:01

Thank you so much, Christians

40:12

Thank you very much for this very elegant talk. So, you talked in the first part about this kind of natural by nature, genetics also environment in its ensemble, it also offers example, you also pointed out that interpretations of the genotype but we also have the stance. For example, winds were one where you grew up with original arrows somewhere else, as well as studies, for example. It's a surrogate funnel. Certainly the mother baits are not original but they also create environment elsewhere. I'm just curious on your excellent,

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excellent point, is a more traditional quantitative genetic design twin studies, adoptions that were designed to address the relative importance of nature and nurture. And the Yeah, so for instance, if there were genetic notes, they should come up in the shared environment components and the shared environment components, the magnitude varies from several types of so for depression, it's actually quite large is a vignette is nonzero, but it's actually quite small, relatively genetic components versus the heritability 70%. Share the mind and maybe just the slightest sense, and then the unique alignment would be the rest. So I think, yeah, I think the more traditional quantitative genetic results might give you some boundaries, how big this thing I think.

42:44

I have a similar question about nature versus nurture, and I was wondering, socioeconomic factors and if there's a relationship, especially if parental generation goes from higher economic status, or lower or the reverse where maybe they start with a lower economic status that they're raised in a very high economic status.

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We haven't looked at that. Very well. Military is more narrow, it's how the parental influence the child's signified not via automatic transmission, but by by influencing the rental.

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effect it could be that that that that that phenotype of the parent and the fact that Hyles phenotype may be a different one. So, some say parental alcoholism may affect the child depression, for example. So the two, the two things may not always be the same. But I think in fact, I think that it would make sense for some brands to to parents may also contribute in a way that is not known as

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parents were quite quite extreme, but they kind of balance out maybe maybe the time they will not be affected someone.

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presses the first one is called the nurturer. Have you consider using the parents TRS is as a corollary to the phenotype of the child. So does that improve the TRS prediction?

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Yes, I think it's because I mean, if you want to predict the child's phenotype, and if the parent told you no tie sums, conveyed additional information, then it would include Express using both offspring genotype and parents will give you more accurate in fact, I mean, I mean, another related point is, is whether genetic nurture is a problem. If you are only interested in prediction, and it may not be as if you're if you're interested in prediction, but it doesn't matter what pathways association is caused by that there is still an association and association to the protection, but it's only for that causation. When you intend to continue. Because if they if they also pathway is through the mother phenotype, and then from the environment provided by the mother, then you don't probably intervening in terms of the biology of the child may not be may not be it may not be useful.

46:34

But I'm also make the training folklore challenging to collect because to collect everybody has to play their character. Well,

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yeah, yeah. You what we were able to do was to make use of the siblings in UK Biobank and kill the parents. Even that actually, that provided some degree of protection against despite. Of course, I think it depends on how much how many such tears if we only have very few hours to some extent, T sometimes the direct genetic transmission

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the second question is about this limitation. So you know, we also do sort of statistical fine mapping, but one challenge is how do you punch mark the accuracy of the prediction, right. So the ground school is not available there. So we do simulation, but you know, you can only call it some sense, because your simulation is based on very often based on the models that you propose, right? If I know the true model, I just Yes, or no, yes. Yeah, I

48:07

think we're it's very difficult when we have also influence I guess you could, you could have some I mean, if we have some examples of concessions that you regard as fully established, like like a thought, you know, like a what do you call it positive terms. Used fun. On positive controls, you give, give lots of very high power. Useful negative controls that you don't need don't make a lot of false positive, false positive. Again, negative control. Agree is not easy to come up with these positive and I think the simulation will still be valuable, as you said, simulations on simulations makes assumptions, but I think I think one would have to simulate under a range of conditions. That's why in fact, I was talking to George baby Smith, a few months ago, and I said something much the same thing and he was, he was saying that, in fact, they already planning to do a comprehensive evaluation of these different methodologies. And he also worried about what we said simulations will not be very helpful, because it depends on the assumption. So what he suggested that we do is

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sit down and consider or a wide range of scenarios. Hands this female type is utter genius and multiple distribution is skewed. I think is sufficiently sort of sufficiently concerned for him to the thing that is not not a one person.

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defenses that have to sit down together and imagine all kinds of scenarios

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using like longitudinal data without for example, the exposure happened before the night so then you have an information

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that could possibly also help.

51:04

Question from zoom on Debian randomization has so many papers you said to the extent of many people producing a lot of these papers. What do you think that can be done to stop the bar vapor?

51:31

Yeah, I don't necessarily agree. I think it is a problem. But I think, I think to say that we should stop doing Mr. It may not be the right answer. It's a bit like in the early days of UAVs, and people would say, you know, why are you testing all these snips when there's no evidence? You can make a hypothesis. Instead of saying, you know, I've stopped doing association studies, we should do them all, and make the necessary statistical adjustment. So So maybe, something like that. might be helpful, some kind of a situation on a more global level and says, Well, how many things if we were to do Mundaneum randomization on all possible pairs of phenotypes that we have GWAS data on? How many is that? And then there's some kind of I don't know what you call it, some terawatt. All pairwise adjustment or something like that. P value will have to be 10 to minus five but of course, it does come in Dr. Multiple testing is not just a number of hairs of phenotype, but there's also a number of methods. There's these different methods of Steve method results that are so never very consistent with something you believe so, we have picked on very pragmatic counting. Okay, performed six methods and see which relationships are supported by by the most number of methods. It's not satisfactory at this present moment, because it'd be the best thing we can just do one. Two or three today, at least half a dozen.

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Okay, thank you so much. Charles. If you want you can speak

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here's a question.

54:00

Very interesting talk. I was wondering if you've done anything about like potential backdoor paths, snips,

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whatever the federal type may

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know, like, whether there's some associate because I from from the model, it looks like there was an assumption that all of the snips are independent of each other here, so Oh, no, you do have connected. Yes.

54:27

So the LD is not exactly model is just that the LD is included in the in the in the variance estimate. So the start that this is likely to face but there's a tool called a profile likelihood when you pretend you pretended the attendance and you calculate the likelihood in a normal way, but then when you come to calculate the standard errors and so on. take that into account and all these other errors. Why? Thank you.

55:20

Thank you for your very interesting progress. I will have one question regarding the study you have written to the score for parenting depression only two to the childhood neuroticism. I was wondering, for such study because actually, by definition, depression is one kind of phenotype of neuroticism. So, so this kind of study how we control for that, know that we are starting out this disease but not like what should we take into control for this kind of analysis.

56:03

Yes, neuroticism is a personality trait is highly predictive of depression. Because it is a it's part of the what's called the iSeq Personality Questionnaire. neuroticism. introversion psychoticism as a personality trait is supposed to be relatively stable. But it's actually not true that it's not actually completely unchanging because when someone is depressed

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most of the neuroticism slightly higher than that depression is it is it is kind of episodic episodes, but for us, you know when we say it's going abroad depression is a lifetime as long as you ever had depression before. So moving on because we do that kind of becomes less of a trade and less office estate anymore. But the thought for us, these are, these are traits of depression and erotism that are that are strongly correlated but not not identified. So yeah, I'm not sure what the answer is.

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Do think that if we use genetic therapy, without position, improve or not related to topics,

58:04

you mean? You mean whether if we ignore that geometric measure, what is the customer?

58:14

Maybe in individual settings might be involved in association sizes and if we use the information, we can direct that in the Mandela randomization studies, what we usually use is exercises based on

58:39

Oh yes. Yes. Yes, well what is the dramatic effects are biased by by failure to take

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Yes, I It's interesting. I haven't thought about that before, but it's a tool, similar sites that you are trying to make causal inference on, say if one of them is subjected to genetic match or not the other one, and I think yeah, that could give rise to a bias because the validity of that also estimate depends on both correlations to be unbiased. With this ratio of the instrument, outcome, instrument exposure, that way, the denominator is is underestimated and that makes the ratio the ratio of unbiased estimate

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is a no other questions. I like to close today's workshop. Thank you. So much for everyone's happy speakers today.