MEET THE SCIENTIST WEBINAR DECEMBER 2019

Changing the Way the World Thinks About Eating Disorders

Presented by: Cynthia Bulik, Ph.D.
Moderated by: Jeffrey Borenstein, M.D.

Jeff Borenstein: Good afternoon and welcome to the Brain & Behavior Research Foundation's Meet the Scientist Monthly Webinar Series. I'm Dr. Jeff Borenstein, President and CEO of the foundation and your host for today's webinar. Today, Dr. Cynthia Bulik will present Changing the Way the World Thinks About Eating Disorders.

Jeff Borenstein: The Brain & Behavior Research Foundation funds the most innovative ideas in neuroscience and psychiatry to better understand the causes and develop new ways to treat brain and behavior disorders. These disorders include addiction, ADHD, anxiety, autism, bipolar disorder, borderline personality disorder, depression, eating disorders, OCD, PTSD and schizophrenia. Since 1987, the foundation has awarded more than $408 million to fund more than 5,900 grants around the world. 100% of all donor contributions for research are invested in our grants to the scientists.

Jeff Borenstein: I'm delighted to introduce Dr. Cynthia Bulik. Dr. Bulik is Distinguished Professor of Eating Disorders in the Department of Psychiatry at the University of North Carolina at Chapel Hill School of Medicine, Professor of Nutrition at the Gillings School of Global Public Health, a founding director of the UNC Center of Excellence for Eating Disorders, and a 2017 distinguished investigator grantee. Today's webinar will begin with Dr. Bulik's presentation, this will be followed by a question and answer period. To submit your questions please use the questions tab on the control panel on your screen. Please feel free to submit your questions at any time following the presentation. I'll ask as many as possible in the time allotted. And now I'm pleased to introduce Dr. Bulik. Cindy, the floor is yours.

Cynthia Bulik: Thank you so much for the introduction and even more so, thank you so much for inviting me to give this presentation today on behalf of BBRF. The title of my talk is Changing the Way the World Thinks About Eating Disorders, and I'm going to minimize. There we go.

Cynthia Bulik: First disclosures. I've been a consultant for Shire and Idorsia, and I also am an author for Pearson. And this is my gratitude quilt, and amongst the many

funders who have supported the research that you're going to hear about today, including the Brain and Behavior Research Foundation. So I'll start off by saying everything you have ever learned about eating disorders is probably wrong. In fact, when I go back to my early career, I am sad to say that some of the things that I taught people about eating disorders were wrong. And the problem with that is that misinformation harms patients and families, it stunts the science and sends us down dark alleys. It hinders treatment.

Cynthia Bulik: And Gloria Steinem is one of my heroes, and what she said, and this is one of my favorite quotes from her is, "The first problem for all of us, men and women is not to learn but to unlearn." And I think one of the best examples that we have in science and medicine of the failure to unlearn has to do with the fraudulent science that linked autism to vaccines. And despite being retracted from the literature and being shown to be fraudulent, we still have people who believe that vaccines can cause autism. And now we're seeing countries around the world being devastated from that misinformation. So what are the real questions is how can we get people to unlearn myths? And in my case, myths about eating disorders.

Cynthia Bulik: So I'm going to start off by trying to just give you brand new information. So erase the things that you thought might be true about these illnesses. And let's start with a clean slate. So first off, I'm just going to go through the topography of the feeding and eating disorders as they stand today in DSM-5. So today we're going to talk mostly about anorexia nervosa, it affects about 0.9% to 1% of women and 0.3% of males. Marked by low weight and intense fear of weight gain an inability to recognize the seriousness of the low weight.

Cynthia Bulik: Bulimia nervosa affects about 1.5% of women and 0.5% of men in the United States. And it's marked by binge eating, which is eating an unusually large amount of food in a short period of time coupled with a sense of feeling out of control. And that's together with regular compensatory behaviors such as self-induced vomiting, laxative abuse, excessive exercise. And bulimia nervosa can strike at anybody weight.

Cynthia Bulik: The third and most common eating disorder is binge eating disorder, affecting around 3.5% of women and 2% of men. And that's marked similar to bulimia nervosa by binge eating but in the absence of those regular compensatory behaviors. And the binge eating does cause distress for the person experiencing it. And although people with binge eating disorder are often in the overweight or obese range, it can also happen at normal body weight. And then sort of the new kid on the block is ARFID or Avoidant and Restrictive Food Intake Disorder.

And we know much less about ARFID at this point since it is so new. And this is a feeding disturbance that includes both refusal to eat and fear of eating and children, but also adults can have nutritional deficiencies and weight loss or failure to gain weight. And unfortunately since the topic today is mostly about genetics, we know very little about the molecular genetics of Bulimia, binge eating disorder and ARFID. So we're really going to be spending most of our time today talking about anorexia nervosa.

Cynthia Bulik: Anorexia has high mortality and poor outcome, and those of you who are as old as I am or older, remember perhaps the first case that many of us heard about, which was Karen Carpenter, the singer. So the most common age of onset for anorexia is adolescents, but it's so important to recognize that it can strike at any age. Anorexia also doesn't discriminate. It affects all genders, races, ethnicities, and people from different socioeconomic backgrounds. It has the highest mortality rate of any psychiatric disorder, only recently to have been surpassed by opioid related deaths in the United States.

Cynthia Bulik: The standardized mortality ratio has been estimated to be between six and 10 which means that someone with anorexia is six to 10 times more likely to die from the illness than their agent's ex-matched peers. It's the third most common chronic illness amongst adolescents. 20% of people with the illness develop a severe and chronic course and only 30% fully recover, which means there are a lot of people that partially recover and live with aspects of the disease for much of their life. And most importantly, we have no effective Medications for the treatment of anorexia nervosa, in part because we don't fully understand the underlying biology.

Cynthia Bulik: So features associated with anorexia nervosa are electrolyte imbalances, cardiac complications, osteoporosis, lanugo hair, you can see hair in this picture the thin downy hair that grows on different parts of the body, low blood pressure, low heart rate, people who develop anorexia nervosa while they're still growing often have growth retardation. And on the psychological side we see obsessionality, anxiety, depression, extraordinarily low self esteem, and cognitive impairment.

Cynthia Bulik: Suicide is the second most common cause of death in anorexia nervosa. One of my PhD students, Shuyang Yao at Karolinska Institute in Stockholm showed that the odds of death by suicide were elevated in anorexia over six but also elevated in bulimia nervosa and in any eating disorder. So other eating disorders and anorexia and bulimia. People always ask me, "Why did I get into this field?" And anorexia nervosa on so many levels is a perplexing and intriguing illness.

And I'm going to walk you through some of the idiosyncrasies of the illness that help explain why I'm so interested in it.

Cynthia Bulik: First off, most of us hate starvation. We find starving or hunger something that we run the opposite direction from. But people who are prone to anorexia nervosa actually find starvation to be reinforcing. People with anorexia also say that fats are reversive. They don't like the smell, they don't like the taste, they don't like the mouth feel. And that's where they contrary to what most people in the world experience. In fact, bacon is universally loved and especially if you throw some sugar in with it. That critical combination of fats and sugars are something that most people really enjoy.

Cynthia Bulik: Activity is more reinforcing and with food. In fact, we have some animal models called the activity based anorexia mouse where under certain conditions the mice will actually run themselves to death even in the presence of palatable foods. There's also a perplexing hypermetabolic period during renourishment when we nourish patients in the hospital, sometimes it's almost impossible to predict how many calories they're going to need in order to gain weight because their body's just burning the calories so fast and we don't completely understand what's going on in that situation.

Cynthia Bulik: And this next point we'll talk about more later, but their bodies tend to revert to a negative settling point even after therapeutic nourishment. Often after hospital discharge, they'll just lose weight again like a stone. And we don't completely understand why. So one of the ways that I think about this is that people with anorexia or people prone to anorexia have a paradoxical response to negative energy balance. And energy balance is basically that equation between how much energy or how many calories you consume versus how much energy you expend. And expended energy includes exercise, physical activity, rest, fidgeting, and in the case of eating disorders, purging as well. And in the case of anorexia nervosa being in negative energy balance is their preferred state. In fact, many people with anorexia nervosa say that starvation or a negative energy balance actually creates a sense of calm for them. So whereas most of us become sort of hungry and irritable and sort of seeking food when we're hungry, people with anorexia say they actually feel better when they are starved.

Cynthia Bulik: Now the other thing that's intriguing about anorexia is it defies global BMI trends. The rest of the world is increasing in size but these people are decreasing in size. And I'm going to just give a warning here is pictures of anorexia nervosa are upsetting to you. I'm going to just ask you to close your

eyes for a second and I'll let you know when you can open them again. But I think a lot of people don't understand what anorexia is because of all this misinformation and thinks that it's just what we see in the magazine. So I'm going to show that picture now of someone with anorexia nervosa. That is not what you see in magazines, that is what we see in the clinic.

Cynthia Bulik: And if you've closed your eyes, you can open them again. So the question is, what have we been missing? We are not good at treating anorexia nervosa when only 30% of people fully recover. So what I am really interested in and have been interested in for quite a while is understanding the genetic underpinnings of this illness. And the interesting thing about doing genetic research in anorexia nervosa is it doesn't just tell us about anorexia. Knowledge about eating disorders informs our understanding of many related phenotypes or traits. It tells us about those commonly co-morbid problems like depression and anxiety disorders, it tells us about physical activity, it can help us understand possibly obesity as well as metabolism and nutrition. So there's a wealth of information in studying eating disorders that goes beyond eating disorders themselves.

Cynthia Bulik: If we look back at the twin studies of anorexia, bulimia and binge eating disorder that had been done in many Nordic countries as well as the United States and Australia, we know that these disorders are heritable. So the heritability of anorexia ranges from 0.48 to 0.74. Bulimia 0.55 to 0.62, and binge eating disorder about 0.39 to 0.45. So these illnesses from twin studies are moderately heritable, but as you can see, none of those heritability estimates are one. So that means of course that environment also plays a role. So to really understand these illnesses, we have to figure out a way to harness both information about genetics and information about the environment.

Cynthia Bulik: I'm actually going to bypass about a decade of research that we did when we looked at candidate gene studies, when we might've just plucked one gene out and see if it differed between people with the illness and healthy controls, because that was one of those dark alleys, we really didn't yield much from all of that work with the exception of the fact that it did get us a lot of samples that we could move forward into GWAS studies or Genome-Wide Association Studies, which is really the next big technology that came on board that allows us to look at the genetics of complex traits like anorexia, bulimia, and binge eating disorder.

Cynthia Bulik: So we'll start with just a little tutorial for those of you who don't know about Genome-Wide Association Studies. So the basics of GWAS are you take a large

sample of cases in our situation, individuals who have current or past anorexia nervosa and you can use people who are recovered because your genes don't change. They were there from birth and they carried on. So that helps us be able to amass large sample sizes in comparison to controls when possible finding people with no histories of eating disorders.

Cynthia Bulik: And what we do is we slather million markers across the genome and we compare all of your cases with all of your controls to see where differences lie. And here you can see we've got the C's are the same, that T's are the same, C's and C's but right here in the cases we see the C and in the controls we see the T. So what we're seeing is that in variant one, it's less common to have C's, for example, in your cases than in your controls. And we do this across the whole genome and stead of just plucking out one or two genes to focus on. And that really is a much more comprehensive way of identifying genetic differences between large samples of individuals with an illness and large samples of individuals without an illness.

Cynthia Bulik: And what comes out of that is something called a Manhattan plot. So this is really when you read a GWAS study, this is the main output that you get. And what you can see here is on the bottom you have the human chromosomes, on the side you have the significance level. And since we're doing a million comparisons, we have to be really, really strict to control for multiple comparisons because we don't want to have a lot of false positives. And the reason we don't is when we get a big hit, then we make decisions about where are we really going to put our resources to understand how that locus or those genes actually the illness. So we want to be sure that what we're looking at is really worth looking at.

Cynthia Bulik: And it's called a Manhattan plot because if you're lucky and you have significant results, it starts to look like the Manhattan skyline. So everything above this red line is a significant locus. In this case, this was actually a schizophrenia Manhattan plot. And this is the group that's doing all this work. So in 2013, I founded and have developed and now co-chair the eating disorders working group of the Psychiatric Genomics Consortium, we meet whenever we can. We have over 200 scientists and clinicians from around the world who are participating now and we're always interested in bringing more people on board and getting more samples to increase our sample size so that we can gain even more confidence in the results that we have from these Genome-Wide Association Studies.

Cynthia Bulik: So when we started this consortium in 2013 there were two groups that were doing Genome-Wide Association Studies and the first was the Price Foundation and Children's Hospital of Philadelphia Group, and we published a GWAS that had 1033 cases, 3,700 controls the PMIDs here, you can type those into PubMed, it'll take you right to the paper. But as you can see there were no hits above the red line in this particular GWAS. And at the time we didn't know it, but it's because the sample size was much too small to ever detect a significant hit for anorexia.

Cynthia Bulik: And then a second consortium that was funded by the Welcome Trust, GCAN the Genetic Consortium for Anorexia. We had almost 3,000 cases and 14,000 controls. And again we had no significant hits, although we were starting to see a little bit of action as some of these dots started finding their way up toward the red line. But the bottom line is this work cannot be done by isolated groups. The only way to do this kind of research is by collaboration and the Psychiatric Genomics Consortium provided the perfect platform to unite us to be able to advance this research further.

Cynthia Bulik: And so the first trace of the eating disorders working group united those two consortia into the PGC-ED and we published an American Journalist Psychiatry our first combined GWAS that was almost 3,500 people with anorexia, 11,000 people without anorexia. And as you can see, it's not exactly Manhattan, but we did have one skyscraper and that was on chromosome 12. And that locus had previously been associated with type two diabetes and autoimmune illnesses. And the first author of that paper was Larry Duncan, who is currently a faculty position out at Stanford. But what we learned from our colleagues who were doing this kind of work and other illnesses was we were still very underpowered. 3,500 people is not enough yet. And we had to do whatever we could to boost our sample size.

Cynthia Bulik: So the big question was how do we do that? Given the anorexia nervosa is fairly uncommon we don't have enough people coming into one or a few clinics in order to get the sample size that we need. So we had to get more cases. And thankfully we were given a grant by the Klarman Family Foundation that allowed us to collect samples in the United States, centered at the University of North Carolina, in Sweden at Karolinska Institutet, in Brisbane at the QIMR. And we had assistance from the University of Otago and great assistance from Aarhus University in Denmark where they can do this kind of work using PKU cards or blood spots from birth. Which is a very efficient way of genotyping individuals with and without illnesses.

Cynthia Bulik: And the way we did this was we sort of really put ourselves out there to do engaged science. And what I mean by that is we opened the gates to the Ivory Tower. We made clinicians, families, patients and advocates, partners in our science. We leveraged the powerful online presence of the eating disorders community. These people and their family members get so much information, positive information from the internet. And we really created the ANGI Community and ANGI's our goal and those stands for Anorexia Nervosa Genetics Initiative. We tried to close the us versus them gap, this is a picture of an old NIH study section lots of older gentleman in ties and one woman who was probably the secretary, and we just wanted to go so far beyond that scientific stereotype.

Cynthia Bulik: We got together with family members at family conferences. We explained our research to them and really drew them into the process, listening to what their concerns are, listening to the questions that they wanted us to ask. And also of course, soliciting their help in getting participants in our research. We did a coordinated multichannel outreach with social media, earned and traditional media, advocacy organizations, families and clinicians, and influential bloggers. There are, this is June Alexander, she's someone who recovered from anorexia nervosa as an adult and has a wide readership around the world giving people hope that you can recover from this illness at any age. And here she is demonstrating that she gave blood to ANGI and encouraging others to do the same.

Cynthia Bulik: And interestingly, the internet was the most effective strategy for our recruitment for eating [inaudible 00:24:06] anorexia nervosa. And that's because so many people spend time trying to get information about eating disorders from the web. And at first people were concerned if we're ascertaining so many cases via the internet, are they going to be less severe than the people that we're getting from treatment centers? And not surprisingly to me, but surprising to many people was that there were so many people who were distanced from providers who were not in treatment, who we accessed via the internet, who were as ill as people that we recruited from treatment centers.

Cynthia Bulik: In fact, if you look at the severe and extreme end of anorexia nervosa, 83% of the people we recruited from clinics and 63% of the people we recruited from the community qualified for severe or extreme anorexia nervosa. And that in and of itself for me is this big red light saying we have a problem. We are not bringing treatment to these people where they need it. So even though it was effective for recruitment, it was really frightening in terms of how poorly we are delivering services.

Cynthia Bulik: What we did through these strategies is we successfully recruited 13,000 anorexia nervosa cases and 9,000 controls in three years across these four sites with help from New Zealand. And this is the results of that work. So we took all of those cases that I showed you in that first PGC Freeze 1 where we had the one significant locus and we combined them with the new ANGI cases as well as cases from the UK, UK Biobank and some additional cases that we had from the Wellcome Trust study leading into a final sample size of 16,992 cases and 55,525 controls.

Cynthia Bulik: And the composition of the total sample, we had 33 datasets that came from 17 countries around the world. Now one of the things that's really important when you do this kind of work is you need to make sure that your controls are similar in terms of their ancestry as the cases because if you see differences between cases and controls, you want to make sure that it's due to the illness, not to the fact that your cases, for example, are from Finland and your controls are from Brazil. And we very much differ depend on where our ancestry is. That very much ties to geography and where we actually live.

Cynthia Bulik: So this is our Manhattan plot from the second freeze and as you can see, as we increased sample size, we increased the number of Genome-wide significant hits that were above that significance line that I showed you before. And how, Oh, let's go back. And Hunna Watson who was at UNC was the first author on that paper. And now we're going to dig into these hits a little bit because you might ask the question, okay, that's cool that you have eight hits, but what do we know about these low side? And as you can see here, the low side that we identified were associated with BMI, with some autoimmune illnesses, with IBD and chromes, and some obesity and metabolic traits, with Barrett's esophagus and some carcinomas from some drug response. And again, age menarchy obesity and body fat. So we're starting to see genes implicated in anorexia that have also been implicated in other autoimmune metabolic neuropsychiatric and sex hormones.

Cynthia Bulik: But that's not all that you can get out of the GWAS, in fact, we've only been looking at the top of these skyscrapers, the ones that go above the significance line, but there's also tons of information underneath that line. And that's where we're going to go next to delve into that a little bit more to see what we can glean from that. And to do that, we look at a technique called LD Score Regression, which was developed by someone who shares my name, this is one of my kids, Brendan Bulik Sullivan and this approach allows you to estimate genetic correlations from published summary statistics. So in the past, in order to figure out how things were genetically related, we would have to have the same measures on the same people. So it would have to have one big sample on

which we've measured both, for example, anorexia and depression. But LD Score Regression allows us to calculate genetic correlations between, let's say depression that's measured in one big study at the UK, and anorexia that was measured in our GWAS. So between different diseases, it's the genetic analog of comorbidity.

Cynthia Bulik: And I'm going to start with this slide, and then I'm going to break it down color by color. So this is basically all of the significant genetic correlations between anorexia nervosa and hundreds of different traits that we looked at. And the way you understand this is I have a red line down the middle and anything over on the right side represents a positive genetic correlation and anything on the left side represents a negative genetic correlation. So now we're going to go through piece by piece and this is going to show basically what the genetic correlations for anorexia nervosa looks like. So we're going to start with green. And as you can see here, there's nothing on the negative side, but there are quite a few, in fact, very strong positive genetic correlations with other psychiatric disorders and traits. And the strongest is with between anorexia nervosa and obsessive compulsive disorder, meaning that the same genetic factors are influencing both disorders.

Cynthia Bulik: Also, significantly positively correlated, major depressive disorder, schizophrenia, anxiety, depressive symptoms and neuroticism. So really we're seeing on a genetic level, sort of a reflection of what we commonly see in terms of comorbidity in anorexia nervosa with the exception of schizophrenia, we don't really see a lot of schizophrenia in our patients, although it does happen. And some of the work coming out of Karolinska shows that we also see elevated rates of schizophrenia and family members of people with anorexia nervosa. And then in the lighter green down on the bottom you see positive genetic correlations with years of education, college completion and attainment of a university or college degree.

Cynthia Bulik: Now this is really interesting because if I go back to the very beginning and talk about some of those myths associated with anorexia nervosa, people who have like sort of grown up in this field, blaming families would often say that these kids are high achievers because their families put so much emphasis on education and they pressure them. And that's not really the case at all. In fact, here, what these results suggest is that there are genetic sharing between anorexia nervosa and educational attainment. So on some level whatever the drive is to succeed or excel might be both correlated with the genetics of anorexia nervosa, but also driven by those genetic factors. So again, the genetics sort of help us rewrite some of the observations that we've had about this illness in the past.

Cynthia Bulik: And again, it mirrors clinical observations. And I think one of the things we see so often is obsessive compulsive disorder in people with anorexia nervosa and vice versa. People who have obsessive compulsive disorder who also display traits consistent with anorexia nervosa. So here, the genetics in some ways validates what we've been seeing clinically for decades, if not centuries. And now we're going to move on to physical activity, metabolic and glycemic traits. So here's another rewriting of the story. So one of the things we know about anorexia nervosa is these patients are often very physically active. Sometimes it's hard to get them to sit still, they'll spend a lot of time fidgeting and moving around, when we're trying to renourish them, they just feel compelled to go out and exercise. And frequently people will blame patients for doing this and saying they're undermining treatment or they're somehow standing in the way of themselves getting better.

Cynthia Bulik: But what this first bar on the top shows you is that there's actually a positive genetic correlation between anorexia nervosa and objectively measured physical activity, meaning some of that drive to move might actually be genetically driven. And then what you see here on the left, these are the first negative genetic correlations that are popping up. We see negative genetic correlations with fasting insulin with leptin, with type two diabetes, sort of unfavorable metabolic parameters. And the only positive genetic metabolic correlation we see is with HDL cholesterol, which is a more favorable metabolic parameter. So all of a sudden in anorexia nervosa, we're starting to see these genetic correlations with metabolic traits and we don't see these as strongly in other psychiatric disorders. So this was really the first piece that made us start thinking, "Oh, there might be a metabolic component to this illness as well."

Cynthia Bulik: And not only that, but in addition to metabolic, we also saw a whole host of negative genetic correlations with anthropometric traits, body fat percentage, fat mass, body mass index, and a whole bunch of different measures of body mass and obesity and physical measurements. Now this was very interesting to me because all of my previous career up until this point, people have often asked me, "Is anorexia the opposite of obesity?" And I always said no, I always said, "Anorexia poses a psychiatric illness. It's just on the surface that it looks like it might be the opposite of obesity." But what we're actually seeing here is that some of the same genetic factors that influence obesity and body weight are also influencing anorexia only in the opposite direction, these negative genetic correlations. And I'll unpack that a little bit more and the next few slides.

Cynthia Bulik: So again, going back to that first slide, all the genetic correlations, this is sort of like the pallet of significant genetic correlations with anorexia nervosa. Strongly

positively associated with other psychiatric disorders and physical activity as well as HDL cholesterol and then strongly negatively, genetically correlated with a whole array of metabolic and anthropometric or body measurement measures. And I think in some ways this is an intriguing snapshot and really the core of how we're hoping to change the way the world thinks about anorexia nervosa as being both the psychiatric and a metabolic illness.

Cynthia Bulik: And there's some more data that make us think about this. And this is what Zeynep Yilmaz did this along with our colleagues with the ALSPAC study. And basically what we looked at is we looked at 1,800 kids who were in the ALPAC dataset who, and we looked at their growth trajectories before they developed an eating disorder. But we knew they did because they were followed longitudinally and we compared them to kids who never developed an eating disorder.

Cynthia Bulik: And as you can see here, we'll start with the boys. The blue line is the growth curve for the children who never developed an eating disorder. And the orange line on the bottom is the growth curve for kids who later developed anorexia nervosa. And as you can see as early as age seven and really even earlier, the boys who later developed anorexia really fell off and stayed off their growth curve. And the same thing happened with the girls. Again, the blue are the people without eating disorders and here we have this orange where there's this dip down. So they're falling off the growth curve very early and then staying there as they later develop anorexia nervosa.

Cynthia Bulik: And here is sort of unpacking how anorexia and obesity may be metabolic mirror images. If we look at this as the BMI spectrum with anorexia at the bottom, normal weight in the middle, and obesity on the end, we know that it's fairly easy to get someone who has obesity to lose weight. You can go on a diet, you can go on a medically supervised diet, that weight will come off, but nine times out of 10, that weight is going to be regained and more, and their body tends for one reason or another to go back to a high settling point. We hadn't really conceptualized it like this before, but you can take someone who has anorexia nervosa bring them into the hospital or do family based treatment and it's fairly easy to get them to gain weight, but likewise only in the opposite direction, their body seemed to pull them back down to a low settling point again.

Cynthia Bulik: We don't know what the mechanisms are that once you reach this higher low point makes your body want to go back there, but unpacking that and figuring out what it is, is going to be essential to understand how to develop lasting

cures for anorexia nervosa. So reconceptualizing anorexia nervosa as metabo-psychiatric, a couple of take home points. First, we see this early divergence from the BMI growth curves as we saw in the ALSPAC study. Second, they have a perplexing ability to reach and maintain a low BMI when the rest of the world is growing larger. Third, they frequently return to a negative settling point. Fourth, we see this negative genetic correlations with body mass index and other unfavorable metabolic parameters and positive genetic correlations with high density lipoprotein or favorable metabolic parameter. And they have this paradoxical reaction to negative energy balance whereby it feels better for them to be hungry and to be in a starvation state than when they are seated or fed.

Cynthia Bulik: So summarizing this genes clearly influenced risk for anorexia nervosa and genomic discovery is underway and accelerating. But genes don't act alone. If we go back to that early slide on twin studies, we know that the heritability wasn't one, so we need to figure out the role of environment as well. And so we'll spend some time talking about what we know about environment and eating disorders. Now, this first study done by Janne Larson, who's a PhD study of ours in Denmark. She did a fascinating study about childhood adversities and risk for eating disorders. And this was in almost 500,000 Danish women. And we've looked at childhood adversities between the ages of zero and five. And the way you read this radar plot is here we have the entire cohort and then we have it broken down by kids who developed anorexia, bulimia, EDNOS, eating disorders, not otherwise specified major depressive disorder, anxiety disorders and OCD.

Cynthia Bulik: And this dotted purple line going all the way around shows us what the average number of adversities were for the entire cohort. And anything above that above 0.5 means that there's increased risk and anything below it means there is decreased risk. So as you can see, obsessive people with obsessive compulsive disorder had higher childhood adversities than the norm. Anxiety disorders, higher childhood adversities than the norm. Major depressive disorder, higher adversities than the norm. Eating disorders not otherwise specified, more adversities than the norm bulimia as well. But curiously, the people who went on to develop anorexia nervosa actually had fewer childhood adversities banned the general population. So this was a little bit perplexing but also interesting. We don't have an explanation for it except for the fact that several of the studies that we're doing are suggesting that anorexia is somewhat different than the other psychiatric disorders, and even different than the other eating disorders.

Cynthia Bulik: And then the second environment study is from Lauren Breithaupt who looked at hospitalization for infections or treatment with anti-infectives and childhood. And she again looked at over 500,000 girls in Denmark who later developed anorexia, bulimia or eating disorders not otherwise specified. She followed them for over four million person years until a mean age of 16.2 years. And what you see here is hospitalizations for infections or treatment with anti-infective agents. Anorexia is green, bulimia is orange, and eating disorders not otherwise specified is blue. And what you can see is, especially from in that period between zero and three months after hospitalization or after treatment with anti-infectives, you see increased risk for eating disorders, especially in that particular time period, that three months.

Cynthia Bulik: Now, this is not unique to anorexia nervosa this has also been seen in other psychiatric disorders. But it is intriguing to ask what's happening in that three months post treatment that could be leading to increased risk. Is it associated with inflammation? Could it be associated with the intestinal microbiome? We know that treatment with antibiotics can't just wipe out, wipe out your intestinal microbiome. And does that somehow create a state that is right for the development of illnesses such as anorexia nervosa. This is an intriguing first step. We need to dig deeper into it to understand it, but it does show how environment can play a role in the development of eating disorders.

Cynthia Bulik: But the real trick is not just looking at genes and not just looking at environment, but bringing them together. And what we're able to do in both Sweden and Denmark is we're able to take all of the genotypic data that we get from these large Genome-Wide Association Studies and link them with the national registers. And in Sweden we have not only national registers that log every single inpatient and outpatient visit that you have and every diagnosis that you've received, but we also have eating disorders, quality registers that give you very in depth phenotyping about the course of illness, associated features, personality and it creates us a total picture, not just cross-sectionally but longitudinally of people who have the illness and have been detected by the healthcare system for treatment.

Cynthia Bulik: And in Denmark we also have the National Patient Registers and in parts of Denmark we also have clinical records that we can link to. And what this gives us is an unprecedented opportunity to model how genes and environment both act and co-act in influencing risk for eating disorders. And that work is currently underway, and hopefully I'll be invited back to tell you more about that once those data are ready for prime time.

Cynthia Bulik: And the take home message here is that environment is important, but it's more complex than simplistic models. And going back to some of the earlier socio-cultural theories before we had this genetic information where we were talking about people wanting to look like models or just focusing on thin, ideal internalization we could never explain why, given that we're all exposed, exposed to the thin cultural ideal, why everyone doesn't develop anorexia nervosa. But by having both the genetic and the environment information, we're able to start looking at why some people are more vulnerable to those environmental messages and those environmental insults than others are. And that really is where we need to go in unpacking risk more.

Cynthia Bulik: And in many ways then the genomic data make the study of environmental factors more tractable because we're able to understand why people are differentially vulnerable to adverse events including teasing and bullying or having coaches who make you lose weight in order to do your sport, any of those things that we've been looking at on the environmental side for years to understand why some people just might find them being the trigger step to take them down the slippery slope to anorexia nervosa.

Cynthia Bulik: Some critical points to consider. First, anorexia nervosa, maybe best conceptualized as a metabo-psychiatric disorder. When you think about anorexia nervosa, remember that purple and green palette of genetic correlations and how not only is this a psychiatric illness, but it clearly also has metabolic underpinnings. Second, greater attention to metabolic factors may improve the outcome. Our treatments up till now of course, we renourish people, but we very much focus on the psychiatric piece. Perhaps focusing more on the metabolic piece will lead to better outcomes than 30% full recovery.

Cynthia Bulik: Our results may explain why adequate refeeding is essential to preventing relapse. So many people who have this illness will come into the hospital, be renourished, reach a target weight, and then weight relapse again only to be in this revolving door scenario where they come back in for more treatment, gain the weight, lose the weight again.

Cynthia Bulik: It's highly relevant to family based treatment as well as inpatient therapeutic renourishment. If we are not adequately refeeding people, we're doing them and their families a disservice. Setting low target weights and discharging patients prior to the re-equilibration of metabolism is a recipe for high risk of relapse. And this is something, a battle that we fight with insurance companies all the time, in some countries we're allowed to keep people in the hospital until they reach a target weight and stabilize their, in the States often patients are

punted out of therapy or inpatient treatment way too frequently and too early before their bodies and their metabolisms have had an opportunity to reset at a higher weight. And that is just very dangerous for relapse.

Cynthia Bulik: And this is something that we talk about therapeutically all the time and that is the individuals with histories of anorexia should avoid negative energy balance at all costs. People always ask, "Is it possible to recover from this illness?" And yes, it is possible to recover from this illness at any age, but it still remains part of your health legacy. And if you are biologically prone to like that state of negative energy balance that can still represent a risk state for you. We've seen far too many times where people who have been seemingly completely recovered for a decade or more might undergo a turbulent time or some situation that leads them to negative energy balance and somehow that just flips the switch and can lead to a relapse. So we strongly encourage people to always be mindful that negative energy balance is really a potential trap for relapse for them.

Cynthia Bulik: We have a massive task ahead. As I said in the very beginning all we have is genetic information on anorexia nervosa. We have studies underway for the other eating disorders and I only mentioned three of them. A fourth one that we have to think about that's getting a lot of attention, although not enough attention lately, is what's currently called atypical anorexia nervosa. And those are people who are living in larger bodies but who were functionally in a starvation state from being on chronic diets. And they are not included in our GWAS study, and we don't even know what the actual prevalence of that eating disorder is. So we basically need to repeat what we've done for anorexia nervosa for the rest of these eating disorders. And that will also answer the question, the extent to which these eating disorders are genetically associated with each other. Do we know that bulimia nervosa and anorexia nervosa are actually driven by the same underlying genetic factors? Those are questions yet to be answered.

Cynthia Bulik: So a couple of studies that are underway that are going to answer some of those questions. The first one is the Binge Eating Genetics Initiative and that study is taking place both in Sweden and in the United States. In Sweden, we are recruiting 4,000 individuals with bulimia or binge eating disorder. We have over 900 completed. And the Begin Study is cool because it's not only collecting saliva for DNA, we're also collecting fecal samples for microbiota. So we're going to be looking at the way genes and the microbiota, intestinal microbiota interact and the impact of host genomics on the microbiota and vice versa. And of course we'll also be linking to those registers and quality registers to get the deep phenotyping about eating disorders. In the States, with funding both from

BBRF and NIMH, we're in the middle of a study where we're collecting 1,000 individuals with bulimia or binge eating disorder and we're having them log their behavior and their food on an Apple Watch using the Recovery Record app.

Cynthia Bulik: And the really cool thing about this study is our eventual goal is a therapeutic one, and that is to be able to predict ahead of time by amassing this massive amount of data over 30 days in each participant to use those data, to predict when an individual is at risk for engaging in a binge or purge episode. Because now when we do therapy, you basically log your behaviors during the day and then you talk about them at the end of the week with your therapist but that's too late to change your behavior. We want to be able to do it in real time. We want an Apple Watch or some wearable to be able to signal you and say, "Hey, according to your data, it looks like you're about to enter a high risk epic for a binge. You might want to use one of your alternative strategies to try to avoid that unhealthy behavior." So more on that to come, but I think including wearables and cognitive behavioral therapy is the next major advance that we're going to see in improving treatment for these illnesses.

Cynthia Bulik: And then the next big endeavor the last one for anorexia was ANGI, the next one is EDGI or the Eating Disorders Genetic Initiative, NIMH is funding the United States, Australia, New Zealand and Denmark, we're launching in early 2020. The UK has independent funding where they're also going to be collecting samples, we're going to be looking at anorexia, bulimia and binge eating disorder. And we have other countries around the world who are also joining us and we're trying to get our instruments translated into as many languages as possible because we want to reach 100,000 cases. So that we can study the genetics of bulimia, binge eating disorder and anorexia nervosa. So keep your eyes open, you're going to be hearing a lot more about EDGI, and we're looking forward to launching in the beginning of 2020.

Cynthia Bulik: And it takes a village, I'm the only speaker, but all of these people have been involved and more in collecting these data and doing this research in the analysis and interpreting them. And these are my two teams. I spent half my time at UNC and half my time in Sweden at Karolinska and deep gratitude to all the people who participate and helped us in this research.

Cynthia Bulik: And a couple of take home points and we'll stop on this slide. Please follow us on Twitter, I'd like to tweet about eating disorders and genetics and the PGC genetics group. We'll keep you informed about genetics of many psychiatric disorders. I have some resources here the National Center of Excellence for

Eating Disorders, the Academy for Eating Disorders and the National Eating Disorders Association, all of which have rich information for patients and families and clinicians and researchers. And then just some take home points, and I would say genes play a role but do not act alone. Anorexia is best described as a metabo-psychiatric illness. Greater attention to metabolic factors may improve anorexia outcome, an ongoing work will help us understand how genes and environment influence the other eating disorders as well.

Cynthia Bulik: And that's all I have for you today. Thank you so much for attending.

Jeff Borenstein: Thank you so much. This has been Cindy, an outstanding presentation. I appreciate how you were able to take so much information and present it in a user friendly way for a lay audience and for a scientific audience. But obviously the focus is a lay audience. We've received a number of questions, you answered a lot of them in the course of your presentation, but I have one question I want to ask you. Often people who are experiencing anorexia really don't have insight into their condition and it's hard to get them to go to treatment, to go for an evaluation, what do you recommend to family members who are in such a situation often a desperate situation when they want to help their loved one?

Cynthia Bulik: I think that is probably the single most important question that you could pull out of the numerous questions that you got. And I'm going to give you a resource for that and I wish I had put it up here. There is an organization called Feast. And if you just Google F-E-A-S-T eating disorders it is a family organization that is comprised with parents from around the world who have been in exactly this situation. They have a forum, they have chats, they have meetings on an annual basis and these parents have all been there. They have been in that situation where they know their child needs help. But the child is just unable to recognize how serious the illness is.

Cynthia Bulik: And I have found no better help than the help that you get from other parents who have been there. So there's no simple answer, but the longer answer is to get support, to get help from others who have been there and to try the things that they suggest and that worked for them. It's a very hard situation to be in, but you're right, it is part of the illness that inability to recognize the serious of the illness is a core component, which is unlike other disorders where if you have a phobia, you want to get rid of it or if you're really depressed, you want to feel better. So that's an extra challenge that families of people with eating disorders have to deal with.

Jeff Borenstein: Well, that's a very useful piece of advice and I think the two things that I get from that is number one, seek guidance from others, especially people who've been there. Obviously seek professional guidance and don't give up.

Cynthia Bulik: Yes.

Jeff Borenstein: Don't give up. Keep trying. Don't give up.

Cynthia Bulik: Absolutely.

Jeff Borenstein: I just want to again say thank you for the work you're doing, the work you're willing to continue to do on this very important issue. And I will definitely check you up on your promise to come back when invited to get more information on the gene and environment interactions. So thank you for all that you're doing.

Cynthia Bulik: Thank you for having me.

Jeff Borenstein: The webinar has been recorded if you've missed any portion of this, so we'd like to share it with family or friends, please visit the events and webinar page on our website. I hope you'll join us again next month when Dr. Gregory Light Professor in Residence in the Department of Psychiatry and Deputy Vice Chair of Psychiatry Education and Training at the University of California, San Diego, will present, **Using Tools Of Neuroscience To Make Personalized Care A Reality In Schizophrenia**. This webinar will take place on **Tuesday, January 14th at 2:00 PM** Eastern Time.

Jeff Borenstein: I want to say thank you to everybody for joining us, we appreciate your support and I want to wish everybody and their family a happy and healthy holiday and New Year.

Jeff Borenstein: Take care everyone.

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