Aaron van Dorn (00:07):

Welcome to AJP Audio for November 2022. I'm Aaron van Dorn. This month on the podcast I spoke with Dr. Antonia Seligowski, a clinical psychologist at McLean Hospital and an assistant professor at Harvard Medical School. Dr. Seligowski and colleagues have a paper in the November issue of AJP looking at the potential shared genetic risk between post-traumatic stress disorder and cardiovascular disease. Afterwards, Dr. Ned Kalin, editor-in-chief of the American Journal of Psychiatry, discusses the rest of the November issue of AJP and what draws it together.

(00:33):

Dr. Seligowski, individuals with post-traumatic stress disorder or PTSD, are significantly more likely to be diagnosed with cardiovascular disease, such a stroke in myocardial infarction. Your study used a genome-wide association study or GWAS, using a large biobank sample to look at the shared genetic risk of PTSD and cardiovascular disease. What did you find?

Dr. Antonia Seligowski (00:50):

Well, we found that the genetic risk for PTSD was significantly correlated with the genetic risk for cardiovascular disease, suggesting that disorders once thought as orthogonal to one another may share genetic predisposition. This really highlights that psychiatric disease is not mutually exclusive from physical illness, that the brain and body are inherently linked. We also found support for a pathway leading from genetic risk for PTSD to hypertension and coronary artery disease. The pathway in the other direction with PTSD as the outcome was not nearly as strong.

(01:26):

This provides some support for the theory that stress related disorders like PTSD may lead to cardiovascular disease, but this really requires replication. There may also be some instances where adverse cardiac events lead to PTSD such as after someone has a heart attack. But overall, I think our findings suggest that PTSD and cardiovascular disease likely share genetic risk and PTSD likely increases risk for adverse cardiovascular events.

Aaron van Dorn (01:54):

Can you tell us more about how genome-wide association studies work and how you're able to use them to determine the links between seemingly very different conditions like PTSD, depression, and cardiovascular disease?

Dr. Antonia Seligowski (02:04):

Genome-wide association studies or GWAS, utilize the entire genome in finding areas of variation that are associated with the disease phenotype such as PTSD. These areas of variation are single nucleotide polymorphisms or SNPs. A GWAS approach does not look at a specific gene, which is a candidate gene approach, but rather it uses the whole genome and agnostically determines which SNPs are significantly associated with an illness.

(02:33):

You can look at how the genetic risk for one phenotype like PTSD or depression, is associated with risk for any other phenotype like cardiovascular disease. You can see if they are all associated with SNPs that are linked with immune function, for example, and that might provide a clue about the mechanism underlying their cooccurrence, meaning perhaps genetic variability in immune function predisposes an individual to both PTSD and cardiovascular disease.

Aaron van Dorn (03:00):

Your paper used a large data set from the Mass General Brigham Biobank. What can you tell us about sample?

Dr. Antonia Seligowski (03:05):

Our biobank contains data from patients throughout the Mass General Brigham healthcare system, so this includes Mass General Hospital, Brigham and Women's, Beth Israel, McLean Hospital, among others. All patients in the biobank have consented to having their healthcare data used for research, and some have provided additional data like blood samples specifically for research purposes. The biobank includes demographic data, diagnostic data, vital signs, et cetera, and the sample for our study included over 36,000 participants for whom we had these kinds of data.

(03:40):

We could see who had a diagnosis of PTSD, depression, hypertension, et cetera, from their medical record. And this allows us to look at a significantly larger sample than one might be able to obtain in a traditional research study. The big numbers help with statistical power, but of course it's different than having someone come in for a study visit and provide more detailed information about symptoms.

Aaron van Dorn (04:03):

What kind of limitations did your study face?

Dr. Antonia Seligowski (04:05):

I think one of the main strengths of this study is also its primary limitation. While the biobank provides this wonderfully large sample, the depth of the data is quite limited. For example, we don't know how providers determine that someone should receive a PTSD diagnosis. We have a gold standard interview in the field, which is called the Clinician Administered PTSD Scale, and for most people, that's not what's being used in clinical practice. It could be that they reported an assault and are having nightmares, so the provider puts a PTSD diagnosis in the chart. While that might be okay from a patient care perspective, it's not a rigorous symptom assessment like we would use in research.

(04:46):

More importantly, this means we don't have symptom level data in the biobank because patients are not always given a standard set of surveys or interviews like this. That means we don't know anything about the severity of PTSD or depression symptoms, so we do lose some information there.

Aaron van Dorn (05:02):

Are there current clinical implications for your research?

Dr. Antonia Seligowski (05:04):

I think the primary clinical implication of this work is improved risk identification. For example, identifying individuals with shared PTSD and cardiovascular risk could allow clinicians to select PTSD interventions that are known to improve aspects of cardiovascular function. There's preliminary evidence that forms of cognitive behavioral therapy, which is the first line treatment for PTSD, might improve cardiovascular function, but this research is still in its early stages.

(05:34):

On the other hand, psychiatric and cardiovascular medications have well-documented effects on cardiovascular function, but few studies have tested the effects of these medications on subsequent cardiovascular risk in PTSD populations. A next step in this line of work is to determine if existing cognitive behavioral and pharmacological treatments actually reduce cardiovascular risk in PTSD and to determine if they're more effective for individuals with high genetic risk for both PTSD and cardiovascular disease.

Aaron van Dorn (06:05):

Your paper also looked at depression. How did you find that? Was that something you started out looking at or is that something that emerged?

Dr. Antonia Seligowski (06:11):

Depression is very highly comorbid with PTSD. Close to even 80% of individuals with PTSD will also meet criteria for major depressive disorder. And depression itself, like PTSD, carries a significant risk of cardiovascular disease. We think that these are probably inherently linked disorders. Given that especially that high comorbidity with PTSD and depression, we thought that we should look at depression as well in this population.

Aaron van Dorn (06:43):

Depression and PTSD also are highly comorbid for things like alcohol abuse, smoking, other risk factors like that. Are we looking at an epiphenomenon from kind of the links between cardiovascular disease because of the other things that PTSD, depression and other psychiatric conditions might lead people to?

Dr. Antonia Seligowski (07:00):

We didn't look at that in this study, but I do think that's really important to think about. Most likely it is some combination of predisposing genetic risk, and then you have the environmental risk, like the trauma in the case of PTSD, for example, and that leading itself to certain behaviors like smoking, like substance use, poor diet, less exercise, and those behaviors are going to increase cardiovascular risk themselves in addition to what we think PTSD itself is doing to the autonomic nervous system, for example, and disrupting our stress access. It's likely that all of these things are involved in linking an individual with PTSD to an increased risk of cardiovascular disease.

Aaron van Dorn (07:51):

What's next for your research?

Dr. Antonia Seligowski (07:52):

What I'm most excited about are the options we may already have to treat cardiovascular risk and PTSD. We still don't know how our existing gold standard treatments are doing when it comes to that, but both PTSD and cardiovascular risk can be treated behaviorally for many people with cognitive behavioral therapy and exercise. Combining these approaches and determining if they improve cardiovascular function among those with PTSD is something I'm hoping to do next. It would be really great to see how these shared genetic risk factors may be useful in predicting who will see the most benefit from these approaches as well as who might be better suited for medications, their combination, et cetera.

(08:35):

Once we have a better sense of how our existing treatments are affecting cardiovascular function, we can then optimize those approaches and develop ways to more directly target risk among those who are most vulnerable.

Aaron van Dorn (08:47):

Well, Dr. Seligowski, thank you for taking the time to speak with us today.

Dr. Antonia Seligowski (08:50):

Thank you so much for having me.

Aaron van Dorn (08:51):

Up next, Dr. Ned Kalin. Hi, Dr. Kalin, welcome back to AJP Audio.

Dr. Ned Kalin (08:55):

Thank you. It's a pleasure to be here.

Aaron van Dorn (08:57):

This month on the podcast, we're looking at issues of genetics and psychiatry. Earlier I spoke with Dr. Seligowski regarding PTSD, cardiovascular disease, and how they're related. What can you tell us about that article?

Dr. Ned Kalin (09:06):

This issue is a really interesting issue, Aaron. As you mentioned, it's really devoted to bringing together papers related to the genetics underlying the risk to develop various psychiatric illnesses. A particular focus of some of the papers is on the comorbidity between medical illnesses and psychiatric illnesses. The paper by Seligowski et el related to PTSD and cardiovascular disease is really quite interesting because it examines basically the extent to which the genetic mechanisms that are underlying PTSD are also underlying cardiovascular disease. It's been well established that there's a link between the two, but the genetics underlying the two has not been so clear.

(09:49):

What the investigators found basically was that there's a genetic correlation between PTSD with cardiovascular disease suggesting that the same genes that increase the risk for developing PTSD are at least in part, involved in the risk to develop hypertension. In this case, coronary artery disease. Similar types of correlations were found with depression to some extent.

(10:16):

And also the researchers then went on to do what's called a Mendelian randomization analysis or study, which allows you to basically control for the genetic effects and to look then for causality between PTSD and hypertension and coronary artery disease. And the evidence would suggest from their analysis that PTSD actually may be an illness that actually predisposes to and may mediate the development of coronary artery disease in some cases. So quite interesting,

Aaron van Dorn (10:49):

Continue with a theme of depression, we also have an article by Leone et al. all looking at the environmental and genetic contribution to endocrine metabolic disorders in depression.

Dr. Ned Kalin (10:57):

Yes, so this is another paper that addresses this issue of comorbidity between psychiatric disorders and medical disorders. And in this particular case, the investigators looked at depression and asked, "How do we understand the heritable and the nonheritable, usually environmental factors, that contribute to the likelihood of depression co-occurring or being comorbid with an endocrine or metabolic disorder. And what the investigators did in this case is they used a sample that allowed them to look at the relationship between siblings and relatives, and this is called a cosegregation method to look at heritability.

(11:39):

What they found was... This, I should say, it's an extremely large sample from the Swedish registry, so they looked at over 2 million individuals over an average of 27 years to look at how the relationship between the medical illnesses and depression played out. And what they found is that there's definitely an association between illnesses that are both autoimmune related and nonautoimmune related. Also, they found, for example, that the association between type 2 diabetes and depression was the strongest with an odds ratio of 3.48 for them to coexist.

(12:18):

Finally, when they looked at all this together and they did their analyses, they found that the genetic factors significantly contributed to these comorbid phenotypic correlations between the nonautoimmune conditions and depression. Whereas for the autoimmune conditions in depression, this was not the case. For example, the autoimmune conditions that were considered were things like hypothyroidism, hyperthyroidism, and type 1 diabetes, and these were not found to have the same parable factors contributing to both of the comorbidity. Whereas the nonautoimmune types of things like type 2 depression and obesity and polycystic ovarian syndrome the reason that they were comorbid was more likely to be related to parable factors.

(13:08):

So again, getting at the idea that we can begin to understand why a psychiatric illness is comorbid with a medical illness and to what extent is that level of comorbidity or co-occurrence related to factors that an individual inherits or to environmental factors, and in this case showing that for comorbid disorders that in this case are not related to autoimmune mechanisms, that the likelihood of the genetics inheritability underlying the comorbidity is much stronger than for illnesses that have these immune related mechanisms.

Aaron van Dorn (13:50):

Next, we have an article investigating statistical genetics tools looking at large dataset regarding mental disorders. What can you tell us about that?

Dr. Ned Kalin (13:57):

This is a really interesting paper, and I think it may have very important implications for the field. One of the things that's come out and that we're well aware of over the years of genetic study with GWAS studies and looking at single nucleotide variants and so on, is that there are multiple genes that contribute to the risk to develop a psychiatric illness, and there are multiple genes that also contribute to that may be protective. And so the general concept for most of how we think about the genetics of most illnesses is that they're polygenic in nature with many, many genes contributing relatively small amounts of the variance to the overall heritable contribution.

(14:41):

With that in mind, one of the things that's been found is that when we look across psychiatric illnesses, it's not uncommon to find what we call a genetic correlation, which means that they likely have shared genetic underpinnings to some extent that there's overlaps probably in the genes that are involved, for example, with depression and anxiety disorders. In this particular study, the investigators used very large databases where they had the genetic information and used a novel statistical procedure. I won't go into the details, but it allows for probably a more accurate estimate of the genes that are involved and also shared across disorders.

(15:25):

And the bottom line is what they found was is that there were considerably more genes that were overlapping across various disorders that they looked at, and these disorders included such illnesses as schizophrenia, bipolar disorder, ADHD, major depression. And so thinking about that, they really surmised that we have probably underestimated the number of genes that are shared across these disorders to create risk. What's also interesting is when they looked at studies that had individuals that didn't have the disorders but had traits of some of these disorders, they also found large numbers of shared genes across the traits that are associated.

(16:08):

This is suggesting that even though we knew that psychiatric illnesses are related to many genes that are contributing small amounts of variants to the overall heritability, this is suggesting that the numbers of genes that are shared across disorders is very high or much higher than we expected. And so how do we then think about why does someone develop schizophrenia versus depression versus bipolar disorder if there are lots of genes that are shared? And one of the points that is made in this paper is that they may be shared, but the way that they're acting may be in different direction. In one case, the gene may be upregulated and another case it may be downregulated, and this new analytic strategy allows one to detect genes that are both the same gene when it's upregulated and downregulated across different illnesses, which the other statistical technique did not allow for.

(17:02):

And then finally, the conclusion is is that many of the same genes may be involved across different illnesses, but the way these genes play out from the standpoint of their function and the way they relate to each other and the way they are functioning together may be very different across illnesses. It may not be so much that the genes are so different, but rather that the way the same genes are working together or working differently may be what may confer some of the specificity in relation to which type of illness an individual might develop.

(17:37):

All of these papers are fairly complicated from the standpoint of the genetics. But again, I just want to point out that we have a really good overview in this issue on polygenic risk scores, which I would encourage folks that are interested in understanding more about some of the details of how these analyses are taking place or what we mean by polygenic risk that they take a look at. And this is authored by Dr. Lewis and Dr. Vassos from Kings College in London.

Aaron van Dorn (18:03):

Speaking of polygenic risk scores, another article is looking at genotyping and polygenic risk scores to see if they could be associated with improvement after electroconvulsive therapy. What can you tell us about that?

Dr. Ned Kalin (18:13):

This is a way to think about how do we on the one hand, we can think about identifying genes that are involved with the risk to develop illness and thinking about how that relates to pathophysiology and to etiology and to risk, but we also can, and people are certainly doing this, think about looking at these polygenic risk scores in relation to treatment outcomes. And in this particular case, the researchers led by Dr. Sigström, asked the question, "To what extent do polygenic risk scores related to different illnesses predict outcomes for major depression when patients are treated with ECT?" And so they have a unique data set.

(18:54):

Also, this is from the Swedish National Registry for ECT. They had a sample size of around 2,300 individuals that had at least one course of ECT for major depression, and roughly 77% of these individuals suffered from unipolar depression. The remainder had other illnesses including bipolar disorder and schizoaffective disorder. What they found was really quite interesting. One thing that was a bit surprising was that individuals that had higher polygenic risk scores for depression tended to actually do worse with ECT than individuals that had lower poly risk scores for depression. And that's somewhat counterintuitive and not clear as to why that finding came out.

(19:42):

On the other hand, individuals that had high polygenic risk scores for bipolar disorder were more likely to have positive responses to ECT than individuals that had very low scores from the standpoint of their polygenic risk to develop bipolar disorder. When they looked at the polygenic risk score for schizophrenia, they found that that was not related at all to the ECT response. Again, beginning to think about how can we use genetic information to think about guiding treatment choice and making predictions about outcomes. And this is a nice early study using a pretty large sample that begins to get at that with some expected and also some unexpected findings that remain to be understood.

Aaron van Dorn (20:27):

Finally, we have a paper looking at copy number variants and early onset psychosis and autism spectrum disorder.

Dr. Ned Kalin (20:32):

I was just mentioning the idea that polygenic risk is related to genetic alterations that contribute very small amounts to the overall heritability. The idea being that there are numerous genes, hundreds of genes or thousands of genes that may be involved in mediating risk in general. Having said that, we also have examples which are less common, where there are bigger genetic alterations, structural genetic alterations, that may confer risk that are not polygenic in nature. And one good example of that that we've talked about in the past, I think, is the 22q11.2 deletion, which falls into the copy number variant deletion category, which confers a very strong risk for the development of psychosis and schizophrenia like symptoms or syndromes.

(21:25):

What this particular paper did was to look at copy number variants, and these are, as I mentioned, our larger structural genetic alterations that are characterized by duplications or deletions of genetic sequences. They're fairly common in the human genome, but there are a number of them that can have quite deleterious effects. One of which I just gave you an example for 22q11.2 deletion syndrome. And what these investigators did was they were very interested in early onset psychosis in children and wanted to ask the question, "To what extent are there copy number variants that can be identified that

may account for early onset psychosis?" And also provide some leads about biological systems or mechanisms that might be involved in early onset psychosis.

(22:14):

And what they basically were basing their logic on was data that is well known from individuals that have autism where it's well known that number of copy number variants have been identified that directly contributed via their mutations to the development of autism. And so in this particular study, they not only looked at children or individuals that had early life onset psychosis, but they also looked at individuals with autism to compare these two neurodevelopmental types of syndromes. One of the reasons they're so interested in early onset psychosis is because it's not totally uncommon, but it is a forerunner frequently of schizophrenia or other types of psychopathology.

(22:56):

And what they found was they basically looked at 47 copy number variants that were known to be associated with psychiatric disorders. And they asked the question, to what extent were these prevalent in individuals with early onset psychosis and also an autism spectrum disorder? And they found that there is really a considerable number of identifiable copy number variants that fall into this category of being associated with neuropsychiatric disorders in individuals with early onset psychosis. And one of them that actually came out was this 22q11.2 deletion, which would be predicted given what we know about it in relation to its role in the likelihood of developing psychotic symptoms or schizophrenia like symptoms.

(23:46):

And they also then went on to show that not only are there a large number of these copy number of variants, but they came up with a metric called the copy number variant risk score, which is sort of akin to the polygenic risk score, which is basically taking into account all of the CNVs or copy number of various, within an individual's genome. And what they found was is that they found significantly higher copy number of variant risk scores than individuals with early onset psychosis and autism spectrum disorder when compared to controls.

(24:19):

The long and the short of this is that like autism, there is a fairly high density of copy number of variants in some individuals with early onset psychosis, and the authors suggest that individuals with early onset psychosis actually ought to undergo genetic testing to identify these copy number of variants. Right now that would not be particularly helpful from the standpoint of treatment, but it would be very helpful for the standpoint of us understanding more about the etiology of the disorder of that individual as well as from the standpoint of us developing a database that could later be used for understanding much more at a population level about mechanisms underlying early onset psychosis.

(25:03):

Taken together, these papers are all along the same lines from the standpoint of genetic risk and are beginning to provide interesting insights into the risk. While it's very early from the standpoint of thinking about using these types of methods clinically, this is, I think, the forerunner of what we can expect many years down the road when we think about using genetic information in relation to being more precise about our treatment approaches and personalized treatment approaches.

Aaron van Dorn (25:32):

Dr. Kalin, thank you once again for leading us through this issue.

Dr. Ned Kalin (25:35):

You're very welcome. Take care.

Aaron van Dorn (25:37):

That's all for this month's AJP Audio, but check out the other podcasts offered by APA. This month on the AJP Residents Journal podcast, the Residents Journal media editors get together to discuss the September issue of the journal with the focus on minority mental health and diversity. That and the other APA podcasts are available at psychiatryonline.org/podcasts or wherever you get your podcasts.

Outra (25:56):

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