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The Molecular Evidence in Support of the Rising Cardiovascular Risk Incidence in Combat Disorder Stress Disorder Patients

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Abstract

Post-traumatic stress disorder (PTSD), a mental illness that can be brought on by severe trauma, is extremely debilitating.Negative somatic comorbidities accompany PTSD, despite its primary mental nature.In accordance with previous findings, we found a significant phenotypic correlation between PTSD severity scores and the various MetS components in this study's military veteran cohort of veterans with chronic PTSD presentation (n =). We used summary statistics data from large-scale genetic studies to conduct a genetic correlation analysis to determine whether the observed correlations between symptoms are the result of a shared genetic background. MetS is one illness that frequently occurs alongside PTSD. It is characterized by a collection of health risk/resilience factorsThere is a strong genetic correlation between obesity-related MetS components and PTSD (rg[SE] = 0.25, SE = 0.05, p = 6.4E-08).When genomic regions with greater local genetic correlation are prioritized, three significant loci are implicated.These findings generally suggest that the fact that PTSD and MetS share a significant amount of genetic material may partially explain why PTSD patients are more likely to develop MetS.

Keywords: PTSD (post-traumatic stress disorder); metabolic syndrome; MDD (major depressive disorder); genetic correlation; Obesity

Introduction

Post-traumatic stress disorder (PTSD) is a mental illness that can be caused by extremely traumatic events and is extremely debilitating. In addition to trauma exposure, the four additional criteria of symptom clusters that define and diagnose PTSD are re-experiencing, hyperarousal, negative changes in cognition and mood, and avoidance [1].In the United States, it is estimated to occur at a rate of 10–30% among military personnel and 6.8%–8% among the general public. Additionally, it has a higher prevalence rate among women and individuals who experienced challenging childhoods [2].

Despite the fact that PTSD is regarded as a mental disorder, it is characterized by somatic comorbidities that affect the entire body in addition to the brain.One of the conditions that frequently accompany PTSD is metabolic syndrome (MetS). MetS is a collection of abnormalities that are connected to metabolic dysfunction [3]. It includes hyperglycemia, which includes higher fasting blood glucose (FBG) and insulin resistance, elevated blood pressure, dyslipidemia, particularly lower HDL-C [high-density lipoprotein cholesterol], higher LDL-C [low-density lipoprotein cholesterol], and triglycerides. Observational studies based on epidemiological data demonstrated a clear link between PTSD and metabolic syndrome as a whole and its components separately [4].

In addition to the higher rate of co-occurrence with PTSD, the significant phenotypic and genetic association of MetS with other stress-related psychiatric disorders, such as major depressive disorder (MDD), is an intriguing fact [5]. MDD is a mood disorder that is similar to PTSD in many ways.There is a clear epidemiological co-occurrence as well as a significant genetic overlap between MDD and MetS, as evidenced by extensive research on several aspects of the connection. PTSD and MDD also share a lot of the same symptoms [6].The majority of studies aimed at gaining an understanding of the connection between PTSD and MetS focus solely on demonstrating that the two conditions co-occur in the population.Some Mendelian randomization studies also suggested that the direction of influence is from MDD to This frequently observed comorbidity's fundamental nature has yet to be clarified. However, it is unclear whether the genetic relationship between PTSD and MetS resembles that between MDD and MetS.Due to the disorders' high prevalence and negative effects, the answers to these questions have significant practical implications [7]. How does the severity of PTSD relate to the degree of metabolic dysregulation? How much of the observed correlation between PTSD phenotypes and MetS as a whole and its components is based on genetics? These include how to carefully select treatments from a group of comorbidities that target a specific illness to maximize benefits for an individual's overall health.For instance [8], if there are no causal influences between co-occurring disorders, treating one condition will not directly reduce risk for the other [9].

In recent years, genetic analyses of metabolic and psychiatric traits have utilized large sample sizes.In order to carry out a variety of investigations into the genetic component of disease mechanisms, the resulting summary statistics, which are frequently made available to the general public, may be able to account for a sizeable portion of the heritability of these intricate polygenic traits.The current study attempts to answer the aforementioned research questions by utilizing data from our own studies as well as large-scale publicly available GWAS (genome-wide association study) summary statistics data [10].

Through this study, we want to learn more about the connection between PTSD and MetS and its components.We first test the phenotypic association between PTSD phenotypes (PTSD status and symptom severity scores) and multiple metabolic traits using data from the PTSD Systems Biology Consortium (SBC) cohort, a well-characterized group of US veterans of the Iraq and Afghanistan wars [11].Then, we estimate

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genetic correlations between metabolic traits and PTSD using data from large-scale GWAS summary statistics. We also used Mendelian randomization analysis to learn more about the presence and direction of causal influences between MetS and psychiatric disorders [12].We also found pleiotropic genetic regions that play a role in the shared genetics of MetS and PTSD **13**].

Correlations between PTSD and metabolic traits across the genome

SNP-array based heritability estimates were calculated using GWAS summary statistics to guarantee that recent large-scale studies on MetS-related traits with European-ancestry participants are sufficiently powered and that a sufficient proportion of the phenotype variance is explained.This was done to see if there was a genetic basis for these phenotypic associations.Estimates of SNP heritability greater than 5% are included in all summary statistics utilized for additional analysis. There is evidence that there is a genetic correlation between MetS and PTSD diagnosis (rg[SE] = 0.3305 [0.0564], p = 4.74E-09) using estimates from LD score regression (LDSC) [14].

The remaining MetS components, on the other hand, did not meet the Bonferroni multiple-testing corrected p-value significance threshold for our investigation of genetic correlation estimates (p 0.05/8 = 0.00625). Despite the strong phenotypic correlation, the current study did not find a genetic correlation that was statistically significant with sugar-related traits or PTSD. the specifics of the hypothesized genetic correlations that exist between PTSD and various metabolic characteristics.This could be because the GWAS summary statistics for these two traits are much less powerful than those for the other traits (about half the SNP heritability), which could be the reason why this is the case [15].

Discussion

Understanding the connection between PTSD and other mental health conditions like depression and anxiety, as well as physical conditions like metabolic syndrome, cardiovascular diseases, and type-2 diabetes, is essential for effectively mitigating their negative effects. One of the common comorbidities, MetS, was the subject of this study, which looked into the genetic overlap and phenotypic connection between PTSD and MetS.To begin, we demonstrated a correlation between the degree of metabolic dysfunction and the severity of PTSD symptoms.We found that estimates of genetic correlation closely reflected phenotypic associations, which is in line with Cheverud's hypothesis, even when they were estimated using completely different datasets.The phenotypic association between MetS and long-term PTSD presentation but not shorter duration PTSD supports the Mendelian randomization finding that psychiatric conditions play a causal role in increasing MetS onset but not necessarily the opposite. Effective PTSD/MDD treatment may slow down MetS-related risk factors, according to this causality.

A few of the study's clinical implications must be discussed. Recognizing that the link between MetS and PTSD is not only brought about by the rising prevalence of binary case–control comparison is essential.Additionally, a higher level of metabolic dysfunction is associated with scores for the severity of PTSD symptoms.Second, the epidemiological connection between PTSD and metabolic syndrome may have a genetic basis in common.It may be beneficial to incorporate this insight into future strategies for risk management and stratification. Thirdly, major depressive disorder and post-traumatic stress disorder share some metabolic features.Fourth, mental health conditions may contribute to metabolic dysfunction, but this is not always the case. Because metabolic-related diseases are among the most common causes of death in the general population, interventions that target psychiatric disorders may also help lower the risk of metabolic-related diseases. In point of fact, the high comorbidity with MetS and its components is thought to be largely responsible for the significantly higher (up to three times higher) mortality rate among PTSD patients.Before effective strategies for intervention can be developed, it is necessary to unravel the etiologic structure of these conditions that occur frequently. For instance, which illness should be treated first to benefit the most the other comorbidities and overall health condition will be determined by the order in which these pathological events occur.

Diabetes, all-cause mortality, and adverse cardiovascular events are all significantly affected by MetS.It has been demonstrated that multiple MetS risk factors simultaneously raise the severity of the corresponding cardiovascular disease, and its components are also independently linked to cardiovascular diseases.For instance, compared to those without MetS, those with MetS face a fivefold increase in cardiovascular mortality risk and a threefold increase in the risk of stroke and coronary heart disease.As a consequence of this, gaining a deeper comprehension of the nature of the connection that exists between MetS and PTSD may provide insight into the mechanism by which PTSD patients have a mortality rate that is significantly higher than the average. This is because MetS and PTSD are linked.MetS and PTSD are connected, so this is the case.Metabolic dysfunction may play a role in the significant link between PTSD and cardiovascular disease, according to the current study.

MetS-related metabolic traits and the MetS diagnosis as a whole have previously been linked to PTSD phenotypes.PTSD has been linked to a higher body mass index (BMI), particularly central obesity, according to reports.Multiple studies and a meta-analysis show that PTSD patients have lower HDL-C levels but higher levels of LDL-C and triglycerides than healthy controls.Strong evidence suggests that these metabolic characteristics are strongly linked to major depression, a common comorbidity with PTSD.However, because these associations may not be consistent across gender and age groups, as some studies suggest, it is necessary to decipher subpopulation-specific patterns.In addition, PTSD patients exhibit hyperglycemia, or elevated insulin and fasting blood glucose.

This study included an estimate of the degree of genome-wide correlations.In the future, specific polymorphism, gene, pathway, and metabolite identification studies are required due to the common pathophysiology of metabolic dysfunction and PTSD.As a molecular phenotype in the cascade of biological processes closest to physiological and clinical endpoints, the abundance of many metabolites has been shown to be highly genetically influenced, making it suitable for our study's methods.Blood concentration levels of many small molecule biochemical (including metabolites) correlates of PTSD/MDD have high estimates of heritability, according to twin/family and SNP array studies.In some preclinical animal studies and observational human studies, numerous metabolite levels were found to be linked to PTSD and its psychiatric comorbidities.

When interpreting the study's findings, it is essential to consider its advantages and disadvantages.The majority of previous studies compared PTSD patients' and healthy controls' prevalence of MetS and metabolic characteristics associated with it.In this study, the phenotypic associations with PTSD were evaluated using two quantitative scores for the severity of PTSD symptoms.This method is capable of capturing the impact of disease severity in addition to a binary disease onset.Because

the estimates of genetic correlation are derived from the outcomes of extensive genetic analyses, the study has a lot going for it.The summary statistics data are used to calculate the SNP heritability, and only those with a sufficient minimum threshold are used, resulting in a more accurate estimation of genetic correlation.The summary statistics will therefore have a high power.

The primary limitations of the study are as follows:To avoid the effects of population stratification, only participants from genetic studies with European ancestry are gathered and analyzed to begin.As a result, it's possible that the conclusions drawn from this data summary won't apply to other ancestral groups.Second, metabolic characteristics and mental health issues have been linked genetically based on gender and age.In this study, we were unable to identify signals that were unique to a subpopulation using the data that was available.When interpreting the findings of the current study, it is important to take into account these and other potential uncontrollable confounding variables.Thirdly, a comprehensive reanalysis is required due to the exploratory nature of the Mendelian randomization results in subsequent studies with sufficient sample sizes.

Modern genetic analysis methods can be used to investigate heritable traits like PTSD, MetS, and its components by utilizing large-scale, publicly accessible GWAS summary statistics data.In this study, we carried out four distinct but related analyses.We first established a phenotypic link between MetS components and PTSD phenotypes on a well-defined group of military veterans with chronic PTSD presentations.Using publicly accessible GWAS summary statistics data, we then demonstrated significant genetic correlations between PTSD diagnosis and MetS as a whole and some of its components.Metabolic dysfunction may be one of the mechanisms that contributes to the high mortality rate of MDD and PTSD patients and is a harmful component of stress-induced psychiatric illnesses, according to our findings, which were obtained through the use of a bidirectional two-sample Mendelian randomization analysis.We also discovered genetic regions with a significant pleiotropic effect on MetS and PTSD through local genetic correlation analysis.

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