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Cardiovascular Disease, Psychosocial Factors, and Genetics: The Case of Depression

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Abstract

Psychosocial factors are associated with cardiovascular disease, but little is known about the role of genetics in this relationship. Focusing on the well-studied phenotype of depression, current data show that there are *shared* genetic factors that may give rise to both depression and CVD, and these genetic risks appear to be modified by gender. This pleiotropic effect suggests that a single pathway, when perturbed, gives rise to the dual phenotypes of CVD and depression. The data also suggest that women contribute disproportionately to the depression-CVD comorbidity, and this unbalanced contribution is attributable, in part, to genetic factors. While the underlying biology behind this relationship is unclear, recent data support contributions from inflammatory or serotonergic pathways toward the comorbidity between CVD and depression. Even without knowledge of a specific mechanism, epidemiological observations offer new directions to explain the relationship between depression and CVD that have both research and clinical applications.

Keywords

Depression; Psychosocial Risk factors; Genetics; Cardiovascular Disease

Introduction

It is well established that psychosocial factors are associated with cardiovascular disease (CVD). Low socioeconomic status, lack of social support, stress at work and in family life, anxiety disorders and depression have all been shown to increase risk of developing CVD.[1,2] These factors are also associated with poor outcomes among patients with established CVD – for example, a higher mortality after myocardial infarction. It is also known that there is a substantial genetic component to the risk for CVD[3]. What is less known, however, is whether there is a genetic component influencing psychosocial factors, and whether this genetic component has an impact on CVD risk. At first blush, it might appear that psychosocial factors belong firmly in the domain of "environmental risk factors," and are

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mostly independent of genetic influences. Increasingly, however, evidence suggests that at least some psychosocial factors are influenced by genes, and that some of these genes may have implications for CVD risk. These data point to new ways of thinking about CVD disease mechanisms, which may provide critical novel information relevant to the pathophysiology and management of CVD.

Cardiovascular disease is a complex and multifactorial phenotype, but even with the crudest measures familial influences are apparent. For the extreme phenotype of death from coronary heart disease, heritability is estimated at 57% for males and 38% for females.[4] The younger a person dies from a cardiac event, the stronger the genetic influence is likely to be.[5] There are also substantial genetic influences on traditional cardiovascular risk factors, such as plasma lipid levels (50% heritable),[6] where genome wide association studies (GWAS) have identified over 95 genetic loci that contribute to the quantitative distribution of LDL cholesterol, HDL cholesterol, and/or triglyceride level.[6] Similarly, blood pressure is estimated to be between 31%-68% heritable,[7,8] and GWAS have identified > 20 loci that appear to influence either blood pressure or susceptibility to hypertension.[9] Despite these successes, results from GWAS have only identified risk variants with very small odds ratios, and their clinical relevance is unclear.[10] Given that psychosocial factors are associated with CVD risk, it is possible that the genetic risk for CVD is modified or shared by these psychosocial risk factors. As GWAS of CVD or CVD risk factors typically have not examined psychosocial factors, this hypothesis has not been tested[11].

Depression

Depression is one of the most well-studies psychosocial risk factors for CVD, and it too has a strong genetic component. For example, individuals with a first degree relative suffering from depression have a 2.8-fold higher risk for depression themselves, compared to someone in the general population.[12] Heritability, or the proportion of the variance due to genetic factors, is estimated to be 37%.[12] This has inspired GWAS to identify common genetic variants (with frequency >5%) that contribute to the risk for depression. A mega-analysis was recently conducted, where in the primary analysis data were contributed from nine different datasets, ultimately comprising 9,240 cases with major depression and 9,519 controls.[13] Genetic polymorphisms were analyzed for 1.2 million genome-wide sites, and of these 544 were selected for replication in an independent sample of 6,783 cases and 50,695 controls. In addition to the primary case-control analysis, secondary analyses included sex, age at onset, illness recurrence, and a specific subclass of depression where patients exhibit weight loss and insomnia. Despite this comprehensive effort, no polymorphism was significant after multiple-test correction in the discovery phase, in the replication phase or in any of the pre-planned secondary analyses.[13] These surprising results may be due to etiologic heterogeneity of the depression phenotype. If subtypes of depression could be identified to reduce heterogeneity, this might increase the power to detect genetic risk variants. Individuals with comorbid depression and CVD might represent one of these separate homogeneous subclasses. At the present time, however, GWAS approaches in this subset of individuals remain unexplored.

Depression itself is associated with CVD risk factors.[14] For example, depression is associated with becoming a smoker, an increased rate of daily smoking, and a lower probability of quitting smoking.[15-18] Depression is also associated with type 2 diabetes; three prospective studies have shown that individuals with depressive symptoms have an estimated 40% increase in risk for type 2 diabetes, even after adjusting for other risk factors.[19-21] Additionally, depression is associated with increased body mass index and obesity.[22,23] These data suggest an obvious hypothesis to explain the association between CVD and depression: that it is entirely accounted for by an increase in CVD risk factors.

However, in statistical models that adjust for these risk factors, depression usually remains an independent risk factor for CVD,[24,25] suggesting a biological relationship between these two disease states that remains in part unexplained by an increase in traditional CVD risk factors.

Several models could explain the comorbidity between CVD and depression. Depression may precede CVD and accelerate CVD risk and progression, perhaps due, in part, to the association described above between depression and other CVD risk factors. Alternatively, CVD may come first, and its presence may cause biological or behavioral changes that ultimately promote depression. A third possibility is that there is a core biological pathway that, when disrupted, manifests with both CVD and depression phenotypes. If this third hypothesis were true, a genetic model, where inherited variation contributes to disruption of this core pathway resulting into the two phenotypes of CVD and depression, is highly plausible.

Twin Studies

One way to unravel the genetic contribution to a trait is with the use of a twin study. This is a standard study design comparing concordance rates for a given trait or phenotype between monozygotic (MZ) and dizygotic (DZ) twins. Conceptually, in a twin study it is assumed that whether a twin pair is MZ or DZ, their environmental exposures are approximately equivalent. This includes *in utero* exposures and beyond, continuing throughout life. Therefore, differences in concordance rates are assigned to genetic influences, since DZ twins share, on average, approximately 50% of their genetic material (the same proportion as non-twin siblings), but MZ twins are genetically identical. With a large sample size of twin pairs and sophisticated statistical procedures, it is possible to estimate the genetic and environmental components of single disorders or comorbid disorders.

A genetic pleiotropic effect (i.e., the finding that a single gene or set of genetic factors can influence the variance in multiple and diverse phenotypic traits) can be studied in twin studies using multivariate structural equation modeling, a technique that partitions variance due to genetic and environmental factors considering two or more phenotypes simultaneously. It can also be inferred using a co-twin design of MZ and DZ twins discordant for the risk factor of interest.[26] If a larger difference in the outcome is found within DZ pairs discordant for the risk factor than within MZ pairs (i.e., a significant interaction is present), this suggests that genetic factors play a role in the association. This concept is also known as “genetic confounding” and can be explained as follows. If any trait, or association between traits, is due to genes, then MZ twins cannot differ because they are genetically identical. This is analogous to other confounders in epidemiological studies, which can be eliminated from the analysis by matching for the confounding variable. DZ pairs, however, only share on average 50% of their genetic material. Thus, if the association between, for example, depression and CVD, is modulated by genes, it will be found within DZ twin pairs discordant for depression but not within MZ discordant pairs.

Twin studies have been employed to tease apart the genetic relationship between depression and CVD. One such twin study in 2003 used the Vietnam Era Twin Registry, ultimately including data from 2,731 twin pairs (5,462 individuals), comprising 1,561 MZ and 1,170 DZ twin pairs.[27] This study confirmed the depression-CVD relationship, finding that depression, measured with the Diagnostic Interview Schedule, was most strongly associated with self-reported history of myocardial infarction (MI), with a 3-fold increase in risk. Models were fit to explain genetic risk for depression and heart disease, and the best-fitting model to the data was one in which unique environmental factors, but also *common* genetic factors, explain depression and heart disease. This study, while informative, had several important limitations. It included a selected population of all-male, middle-aged veteran

twins, thus limiting generalizability to different populations. In addition, it was a cross-sectional study and CVD was self-reported.

Additional studies in this population have expanded the observation that co-occurrence of depression and CVD is partly explained by common genetic factors. Using positron emission tomography, one of these measured coronary flow reserve (CFR), the ratio of maximum flow during stress to flow at rest, in 289 twins from the Vietnam Era Twin Registry.[28] CFR is an index of coronary microvascular dysfunction, an abnormal vasomotor regulation of the small coronary arterioles which are the main determinants of coronary vascular resistance. Microvascular dysfunction is a marker of early coronary artery disease and has independent prognostic value.[29] It may be particularly useful in genetic studies because it is a quantitative trait which is etiologically less complex than clinical CVD endpoints. Among the DZ twin pairs discordant for major depression, the CFR was 14% lower in the twins with depression than in their brothers without depression. This association was not present in the MZ discordant pairs who are genetically matched.[28] These data suggest a shared genetic pathway between major depression and microvascular dysfunction. Such shared pathway points to common pathophysiologic processes between depression and early atherosclerosis. Thus, the relationship between depression and CVD appears to be at least in part heritable, and genetically predisposed individuals could be at risk for both depression and CVD.

Variation in the interval between heart beats, heart rate variability (HRV), can be measured noninvasively. Decreased HRV is associated with mortality after MI[30] and is also associated with depression.[31] HRV was directly measured in 288 twins from the Vietnam era Twin Registry.[32] Both current depressive symptoms and a history of major depression were significantly associated with lower HRV. There was a graded effect: power in each HRV frequency band was lowest in the highest depressive symptom category and gradually increased as depressive symptoms decreased. When analyses were stratified by zygosity, a significant within-pair association between depressive symptom score and HRV was found in the DZ but not in the MZ twins. These results, again, suggest a shared, genetically influenced biological pathway underlining the association between depression and lower HRV. In a subsequent study, structural equation modeling revealed that 80-90% of the covariance between HRV frequency bands and symptoms of depression was due to the same genetic factors.[33] These studies are significant because prior work focused on coronary artery disease or MI, which are complex events likely triggered by multifactorial causes. In contrast, HRV, as CFR, is a less complex phenotype, and can be quantitatively measured. It is also a function of the autonomic nervous system. By linking depression to HRV genes, new hypotheses about the underlying biology can be articulated. For example, dysregulation of the hypothalamic-pituitary-adrenal axis could influence both depressive symptoms and autonomic function. These two phenotypes could also be the expression of a more general neurobiological perturbation.

Additional work in this area has linked depression and inflammation through common genetic pathways. Inflammatory biomarkers such as C-reactive protein, interleukin-6 (IL-6) and myeloperoxidase are predictive of CVD.[34] The evidence linking inflammation to depression is also fairly extensive.[35] Recent twin studies have shown that common genetic factors influence both inflammation and depression.[36,37] For example, one study found that approximately 2/3 of the covariance between depressive symptoms and IL-6 is due to common genetic influences.[37] Another study found that genes involving the serotoninergic system (which is discussed in more detail below) appear to play a role. An analysis of 20 polymorphisms in the serotonin transporter gene SLC6A4 showed that 7 of these 20 polymorphisms were associated with depressive symptoms measured with the Beck Depression Inventory, and these same 7 polymorphisms showed an association with IL-6

levels.[38] Again, this is further evidence pointing to common genetic pathways involving neurohormonal, immune and inflammatory systems, that, when disrupted, may simultaneously increase the risk for both depression and CVD.

Sex Differences

The above studies focused on males, so questions about differential effects in men and women could not be addressed. Women are about twice as likely as men to develop depression; in addition, in women, depression tends to have an earlier onset and be more severe.[39] It is therefore possible that a different genetic substrate underlies depression in women and men. This issue was investigated by a twin study including a population of 15,284 twin pairs from the Swedish twin registry.[40] Of these, approximately 25% were MZ, and 53% of the population was female, with a mean age of 57 years. Depressive symptoms were assessed by telephone interview, and CVD status was obtained from nationwide hospital discharge and death registries. In addition to standard twin analyses, this study conducted time-dependent analyses, enabling investigators to assess the temporal relationship of the depression-CVD comorbidity. The relationship was discovered to be reciprocal, and modified strongly by gender. Onset of CVD predicted future depression risk, and onset of depression increased future CVD risk, supporting a model of common factors contributing to the risk for both disorders. However, for males shared genetic factors contributed to depression-CVD comorbidity in younger age groups only, replicating the 2003 twin study discussed above.[27] In older men, the depression-CVD comorbidity was mediated largely by environmental effects. In women, common genetic factors contributed to the depression-CVD comorbidity across all age groups.[40] This study established that genetic susceptibility to a psychosocial factor can be modified by gender.

The above study is particularly significant when integrated with what is known about sex differences for depression itself. Women are at greater risk for developing depression, with a 2-fold increase in major depressive disorder compared to men.[39] Women also have a more severe course of depression, with an earlier age at onset, greater severity of symptoms, and about twice as many depressive episodes as affected males.[12,39] Notably, genetic influences on depression are estimated to be stronger in females compared to males; a recent study predicted the heritability of depression to be 42% in women but only 29% in men.[41,42] From the studies discussed above, we can infer that depression is associated with CVD, and that depression and CVD are more likely to share root genetic factors in women. We also know that depression in women is both more severe and more heritable. From an epidemiological perspective, it then follows that women likely contribute a greater proportion of depression-related CVD, which is partly attributable to genetic factors.

An area where sex differences in depression may take place involves inflammatory genes. Leukotrienes are the most potent inflammatory mediators and their regulation is essential for normal brain function. A recent study found that a six-single nucleotide polymorphism haplotype in the leukotriene A4 hydrolase) gene showed a significant protective effect on depression in women, but not in men.[43] This same haplotype was protective towards coronary artery disease severity only in women, and 7% of the association between depression and coronary artery disease in women was explained by this haplotype.

Role for Serotonin

The serotonergic system is well known to influence mood[44]. Regulation of serotonin levels at the synapse is chiefly managed by a reuptake mechanism due to action of the serotonin transporter. In fact, many drugs for affective disorders are classified as selective serotonin reuptake inhibitors, targeting this very mechanism.[45] Genetic variation exists at the serotonin transporter on chromosome 17q11.2-q12, including a common well-characterized

polymorphism in the promoter region of this gene. It is an insertion/deletion polymorphism (or "indel"), where a 44-base pair segment is present (creating the "long" or L allele) or absent (creating the short or "S" allele). Functional data indicates the S allele reduces transcription.[46,47] The S allele has been associated with susceptibility to major depression, although this finding is not universal, suggesting compensatory mechanisms are at play.[46,48-50]

Most of the work on serotonergic function focuses on the brain. However, serotonin also plays a critical role in other systems, particularly the cardiovascular system, as it exerts influence in vascular smooth muscle and endothelial cells. Specifically, serotonin induces vascular smooth muscle proliferation, promotes platelet aggregation at sites of endothelial damage, and can stimulate vasodilation or vasoconstriction depending on cardiac conditions.[51] As in the brain, the serotonin transporter is also active in the periphery, working to clear serotonin from active sites of signaling. It is therefore entirely possible that the serotonergic system represents a biological link between depression and CVD comorbidity. Supporting this notion, several studies have shown associations between the well-studied L and S functional alleles of the serotonin transporter and CVD. For example, the S allele, previously associated with depression, has also been associated with subsequent cardiac events after an MI. This effect is not independent of depression, again suggesting a shared genetic pathway between depression and CVD.[52] In additional studies, the L allele was associated with coronary heart disease in a European population,[53] and in a Japanese population.[54] Note that while the S allele was most frequently associated with depression in research studies, results about associations of these alleles with CVD, while somewhat inconsistent, more frequently have shown the L allele as the "risk allele." These data hint at the complexity likely to underlie these biological systems, but they also offer a novel way forward for the dissection of the depression-CVD comorbidity.

Other Psychosocial Factors

We have focused on depression, but, as discussed above, many additional psychosocial risk factors have been associated with CVD. Studies trying to estimate the genetic contribution to other psychosocial risk factors have been few and overall inconsistent. For example, studies attempting to estimate the genetic contribution to hostility have mixed conclusions: some report suggestive evidence for a genetic influence on hostility[55] while other studies do not support a heritable component[56,57]. Part of this inconsistency may be due to measurement error – while studies attempt to use validated instruments, these are not the same across different investigations. It is also possible that measures of hostility are temporally influenced by experiences immediately prior to assessment. Depression, in contrast, has the benefit of a rigorous and consistently applied definition through the Diagnostic and Statistical Manual of Mental Disorders [39] or well-established depression scales[58]. It is possible that if hostility could be rigorously measured, genetic effects might be readily detected. It is also possible, but unlikely, that hostility is not influenced in a significant way by genetic factors. To add to the complexity of this field, various psychosocial risk factors, including depression, hostility, and social support, tend to correlate with one another, and this covariation can be explained in part by a shared genetic factor.[59]

Conclusion

The rich wealth of data from twin studies suggest a way forward for uncovering the genetics of both depression and CVD. As discussed above, GWAS of depression have not been fruitful despite strong evidence for genetic risk. Perhaps individuals who present with comorbid depression and CVD represent a distinct group with specific genetic liability. The

data suggest this comorbid phenotype should be studied independently. Discovering the genetic substrate for this comorbid phenotype should yield key data for the prevention of both depression and CVD. Depression is the domain of psychiatrists, while CVD is the domain of cardiovascular researchers; part of the difficulty in this area has been integrating these two fields.

We study independent risk factors and their relationship to CVD, such as smoking, diabetes, even depression, hoping it might lead to actionable ways to reduce CVD incidence and mortality. However, the genetic data suggest there may be an unobserved hierarchy, where many of these CVD risk factors are linked consequences of an upstream root cause[60]. If this were true, genetic studies may be the way forward to identify this sovereign entity. Clinical implications could be remarkable. Once identified, efforts aimed at correcting the root abnormality might attenuate multiple downstream risk factors simultaneously, ultimately serving to achieve our primary objective of reducing the public health burden of cardiovascular events and, at the same time, reducing the burden of depression and other psychosocial factors.

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Abbreviations

CFR	Coronary flow reserve
CVD	Cardiovascular disease
DZ	Dizygotic
GWAS	Genome-wide association studies
HRV	Heart Rate Variability
IL-6	Interleukin-6
MI	myocardial Infarction
MZ	Monozygotic

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