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Genetic Vulnerability and Phenotypic Expression of Depression and Risk for Ischemic Heart Disease in the Vietnam Era Twin Study of Aging

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Abstract

Objective—To determine if depression contributes to incident heart disease after accounting for genetic, behavioral and medical factors associated with both conditions.

Methods—We used a prospective twin study with a 12 year follow-up. In 1992, lifetime diagnosis of depression was assessed in 1,159 male-male twins and merged with longitudinal health data from the Vietnam Era Twin Registry Study of Aging. Incident heart disease was defined as having myocardial infarction, heart surgery or angina at 12 year follow-up when twins were 55.4 years (s.d. 2.5 years) of age. Risks for heart disease were computed in a logistic regression model that included comparing twins at different levels of phenotypic expression of depression and varying levels of genetic vulnerability while adjusting for pertinent covariates.

Results—After adjusting for sociodemographics, co-occurring psychopathology, smoking, obesity, diabetes, hypertension and social isolation, twins at high genetic risk and exposed to depression remained at greater risk of developing ischemic heart disease (OR=2.55; 95% CI: 1.44-4.49) compared to those at low genetic risk and without phenotypic expression of depression. Odds ratios

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suggest twins at genetic liability but without phenotypic expression were at risk of IHD but the effect was not statistically significant.

Conclusions—A history of depression is a risk factor for incident heart disease after adjusting for numerous covariates. Twins with both high genetic and phenotypic expression of depression were at greatest risk of IHD. Trends suggest the genetic contribution to IHD that overlaps with depression may partly explain this association but studies in larger samples are warranted.

Keywords

depression; heart disease; twin; veteran

INTRODUCTION

Major depression is a well established risk factor for cardiovascular disease (1-5). Summaries of the prospective studies of initially healthy people suggest increased risk in heart disease attributable to depression is between 1.7 to 3.0 (6). Several reports have demonstrated that this risk remains even after adjusting for other well known cardiovascular risks including smoking, weight, and comorbid hypertension and diabetes (1,4,7-9). Skala and colleagues (9) recently reviewed mechanisms that have been posited to explain how depression affects cardiovascular health such as poor adherence to medical treatment and physiological changes associated with depression.

Although it has received less attention to date, increasing evidence also suggests common genetic vulnerability partly explains the association between ischemic heart disease (IHD) and depression. For example, it has been known for decades that coronary artery disease (CAD) runs in families (10-14). Twin studies have further established that this observed familial aggregation appears attributable to genetic, as compared to environmental, factors in twins (15-16). Similarly, a review and meta analysis of twin and family studies indicates that major depression is also more common among close relatives of individuals who have been depressed and at least moderately heritable (17).

Recent reports suggest mechanisms underlying the association between cardiovascular disease and depression, including heart rate variability and inflammatory processes share some common genetic variance with depression (18,19,20). Further, specific genes that may contribute to the association between depression and IHD have begun to be identified, including the serotonin transporter gene (21) and genes related to endothelial function, inflammation and platelet aggregation (22).

We have previously investigated whether common genetic vulnerability contributed to the covariance between depression and heart disease in a cohort of middle aged male twin members of the Vietnam Era Twin (VET) Registry. Using self report data collected when twins were relatively young (mean age= 41.9 years) we tested for common and specific genetic and environmental factors that might contribute to the lifetime co-occurrence of DSM-III-R depression and physician diagnosis of heart disease and or cardiovascular surgery. Results supported the hypothesis that the co-occurrence of depression and heart disease is partly explained by common genetic vulnerability (23). Recently, a study of Swedish twins showed depression increased risk of heart disease and vice versa. The authors concluded that a modest shared genetic liability for depression and heart disease in women was due to genetic effects and in men this association was due to environmental effects for older cohorts and genetic effects in younger subjects (23a). The latter finding was consistent with our first report on younger men from the Vietnam Era Twin (VET) Registry. However, both of these previous studies were not designed to adjust for the effect of a number of key cardiovascular risk factors such as hypertension, diabetes and smoking. As the VETR twin cohort aged, the number of

twins with non-fatal heart disease has increased and we are now able to build multivariate models that adjust for numerous covariates in a genetically informative design.

The present study uses previously collected data from members of the Vietnam Era Twin Registry and data from the prospective Vietnam Era Study of Aging (VETSA). The present investigation advances the depression-heart disease literature by simultaneously modeling genetic and measured environmental risk factors in order to test the following hypotheses: 1) depression increases the risk for incident IHD, 2) the increased risk for IHD attributable to phenotypic expression of depression remains significant in a co-twin design that includes adjustment for level of genetic vulnerability as well as anxiety disorders, substance use disorders, smoking, diabetes, hypertension, obesity, social isolation and sociodemographics.

METHODS

The present study was part of the Vietnam Era Twin Study of Aging (VETSA: 2002-2008); the VETSA has been described in detail elsewhere (24). VETSA twins are enrolled in the Vietnam Era Twin (VET) Registry which comprises a sample of male-male monozygotic (MZ) and dizygotic (DZ) twin pairs who served in the United States military during the Vietnam era (1965 to 1975), although the majority did not serve in combat or in Vietnam (25-26) were randomly selected from a pool of 3,322 VET Registry twin pairs who had participated in a telephone administration of the Diagnostic Interview Schedule Version 3, Revised (DIS3R) (27) in 1992.

VETSA inclusion criteria were that twins had to be between ages 51 and 59 at the time of recruitment and both members of a pair had to agree to participate (though they did not have to be tested at the same time). In VETSA, twins had to agree to travel either to Boston University or to the University of California, San Diego, for a day-long series of interviews and physical and cognitive assessments. In cases in which a twin could not travel ($n = 26$ individuals out of 1360 recruited, 1.9%) research assistants conducted assessments at a facility close to the twin's home. Overall, 1,360 twins were recruited to participate in the VETSA assessment protocol, and 1,237 completed the assessments. After excluding twins with heart disease onset prior to 1992, (of whom 2 cases had depression), 1,159 twins remained eligible for our analyses of incident heart disease. The 1,159 twins were comprised of 301 MZ pairs, 34 MZ singletons, 241 DZ pairs and 41 DZ singletons. Institutional Review Board approval was obtained at all sites, and all participants provided signed consent.

Diagnosis of depression

Data were collected from the 1992 administration of the DIS (27) which allowed derivation of psychiatric diagnoses, including depression, according to the Diagnostic and Statistical Manual of Mental Disorders, third edition, revised (DSM-III-R) criteria (28).

Incident IHD

Data to derive a diagnosis of IHD were obtained from a combination of self report surveys and medication utilization. Specifically, as part of the VETSA assessment, respondents were asked to complete a survey of health conditions including: 'Have you ever been told by a physician that you had any of the following conditions or illnesses...angina?...heart attack?', and whether they had ever had heart surgery for stent placement, angioplasty and coronary artery bypass (CABG). Positive responses were followed by asking the date onset of the diagnosis and/or surgery. Angina was also identified by a positive Rose questionnaire (29) or use of nitroglycerin. Incident IHD was defined as physician diagnosis of heart attack, self reported stent placement, angioplasty or CABG or angina since 1992. Last, a list of prescription medications was obtained from each respondent and twins who were using nitroglycerin were

considered to have angina. In summary, MI and cardiac procedures (i.e. stent, balloon angioplasty and CABG) were defined by self report alone, and angina was defined by a combination of either self report, use of nitroglycerin or Rose criteria. The summary IHD variable used in analyses was created by combining MI, cardiac procedures and angina. The extant literature suggests self reports that a physician diagnosed MI, IHD or angina are valid measures in population based samples (30-32), and we used a nearly identical heart disease variable in our previous study of common genetic vulnerability for depression and heart disease (23). Incident IHD was defined by the first diagnosis of any condition in the IHD variable after 1992.

Covariates

Psychiatric covariates were derived from the 1992 DIS survey and included: lifetime diagnoses of DSM-III-R posttraumatic stress disorder (PTSD), generalized anxiety and/or panic disorder, alcohol and drug dependence. Smoking, BMI, hypertension, diabetes, social isolation, race, age, education and marital status were obtained during the VETSA assessment. Lifetime regular smoking was defined as self report of having ever smoked 100 cigarettes or more. BMI was calculated by using in person height and weight measurement and was reported as a dichotomous variable in Table 1 (BMI >30), and modeled as a continuous variable in regression analyses. Hypertension and diabetes were included as predictor variables and defined by a respondent's report that a physician told them they had the condition. These conditions were also considered present if the respondent was taking antihypertensive or antidiabetic medications. Social isolation data was obtained by asking, 'How many people do you know who you can trust and confide in?' This social isolation was modeled as no confidants vs. any confidants reported at time of the VETSA assessment.

Analyses—Chi-square tests of association were computed to test the univariate associations between IHD and depression, sociodemographics, psychiatric diagnoses, BMI, hypertension, diabetes and social isolation. The SAS procedure SURVEYFREQ was used to compute chi-square tests in order to adjust for non-independence of twin data. Prior to adjusting for degree of genetic and environmental risk for IHD that overlaps with depression liability we computed a logistic regression model to test if depression was significantly associated with IHD. In this model depression was treated as a dichotomous variable.

We created a 4 level depression variable to represent genetic vulnerability for depression and environmental risk due to phenotypic expression of depression. Genetic risk is the common genetic variance in IHD that overlaps with risk for depression. In our design, environmental risk is the environment associated with the phenotypic expression of depression. Unlike the discordant twin pair design which uses information only from pairs in which the index twin has the disorder and the co-twin is unaffected, our 4 level twin design utilized all available data and adjusted for degree of genetic and environmental influence. Level 1 was comprised of all depressed twins regardless of zygosity and depression status of the co-twins. These twins have a high genetic risk for depression and have the psychological and physical consequences of phenotypic expression of depression. Levels 2-3 divide the non-depressed twins into those at high, medium and low genetic risk for depression. All twins in levels 2-3 have no phenotypic expression of depression. Specifically, twins in level 2 were non-depressed index twins who had monozygotic (MZ) co-twins with depression. Since MZ twin pairs share 100% of their genes, these twins had high genetic vulnerability for depression but were not exposed to the psychological and physical consequences of depression. Twins in level 3 were non-depressed index twins who had dizygotic (DZ) co-twins with depression. Since DZ twin pairs share, on average, 50% of their genes, these twins had medium genetic vulnerability for depression but were not exposed to the psychological and physical consequences of depression. Last, MZ and DZ twins in level 4 were concordant unaffected and had low genetic risk and were not exposed

to depression. Contrasts between groups allowed for testing the risk for incident heart disease associated with differing levels of genetic risk and for the direct effect of phenotypic expression of depression. Because our prior research suggests that genetic vulnerability to depression and heart disease is correlated in middle aged male VETTR twins (23), the present co-twin design permits the best natural test of the risk for IHD due to expression of depressed phenotype while controlling of confounding genetic factors in a model that simultaneously adjusts for other known risk factors including demographics, smoking, obesity, hypertension, diabetes and social isolation.

Logistic models to test the association between depression and IHD were built using the 4 level depression variable and including simultaneous adjustment for significant ($p < 0.05$) variables from the univariate analyses. All demographic variables including age, race, education and marital status were retained regardless of univariate results. Analyses were computed using the SURVEYLOGISTIC procedure in SAS v.9.0 which adjusts for error variance of non-independent observations.

RESULTS

The mean age of respondents with IHD was 55.6 (s.d. 2.4), and the mean age of respondents without IHD was 55.4 (s.d. 2.5). Among VETSA respondents in the present analysis, 11.1% had IHD, 5.9% had angina, 5.0% had MI and 5.1% had cardiac procedures. Among depressed twins, 15% had angina, 10% MI and 8.0% cardiac procedures as compared to non-depressed twins who had 5% angina, 4.6% MI and 4.9% cardiac procedures, respectively.

As shown in Table 1, among depressed twins, 22.6% had IHD and 10% of non-depressed had IHD ($p = 0.0002$). Lifetime DSM-III-R PTSD, GAD/panic disorder, alcohol abuse/dependence and illicit drug abuse/dependence were not significantly associated with twin IHD status. Lifetime regular smokers were more likely to have IHD as compared to non-smokers ($p < 0.0001$). Twins with BMI ≥ 30.0 were more likely to have IHD compared to twins with BMI < 30.0 ($p < 0.01$). Twins with hypertension and twins with diabetes were more likely to have IHD ($p < 0.0001$ and $p = 0.0014$, respectively). Twins who reported no social support were more likely to have IHD than twins with any social support ($p = 0.0024$). At the time of data collection, the mean age of participants was 55.4 years ± 2.5 (range 51-60). Age, race, education and marital status were not associated with IHD status.

The association between our 4 level depression variable and IHD is shown in Table 2. Depressed twins (LEVEL 1: high genetic, exposed to depression) as compared to non-depressed twins (LEVEL 4: low genetic, not exposed to depression) were more likely to have IHD (OR=2.71; 95% CI: 1.59-4.60). Unaffected MZ twins who were not depressed and had a co-twin with depression (LEVEL 2: high genetic, not exposed to depression) were not at significantly increased risk for IHD (OR=1.47; 95% CI: 0.60-3.56), and unaffected DZ twins with a depressed cotwin (LEVEL 3: medium genetic, not exposed to depression) were not at significantly increased risk for IHD (OR=1.55; 95% CI: 0.59-4.09) as compared to non-depressed twins (LEVEL 4: low genetic, not exposed to depression).

Prior to adjusting for genetic risk and phenotypic expression of depression, multivariate logistic regression (controlling for smoking, hypertension, diabetes, BMI, confidants and sociodemographics) results indicated that all MZ and DZ twins with depression as compared to all MZ and DZ twins without depression were at increased risk for IHD (OR=2.30; 95% CI: 1.30-4.07).

Results for our genetically informative logistic regression model are shown in Table 3. After accounting for genetic and environmental vulnerability and for significant covariates in multivariate logistic regression analyses, we found that twins with high genetic and high

environmental vulnerability remained at significantly greater risk for incident heart disease as compared to twins with no depression (OR=2.55; 95%CI:1.44-4.49). Even after adjusting for genetic and environmental vulnerability in our co-twin design, regular smoking (OR=2.33; 95%CI: 1.42-3.84), hypertension (OR=2.21; 95%CI: 1.40-3.48) and social isolation (OR=2.67; 95%CI:1.19-5.96) remained significantly associated with incident IHD.

DISCUSSION

The present study provides some of the best evidence that the combination of genetic vulnerability for and phenotypic expression of depression is a long term, independent risk factor for incident IHD. As compared with twins at low genetic and low environmental risk for depression (LEVEL 4), twins at high genetic and high environmental vulnerability (LEVEL 1) were more likely to have incident IHD even after adjusting for effects of smoking, hypertension, diabetes and social isolation (i.e. having any confidants). Point estimates of LEVEL 2 vs. LEVEL 4 and LEVEL 3 vs. LEVEL 4 (1.35 and 1.50, respectively) suggest there is some evidence that IHD might be partly due to common genetic vulnerability to heart disease and depression. However we lack sufficient power to conclude that the genetic contribution to IHD shared with depression is significant. However, such a finding would be consistent with our previous analyses of heart disease in a cross-sectional design (23). Using lifetime diagnoses of depression and lifetime heart disease in 1992 we found that significant genetic variance in common with depression and IHD accounted for the co-occurrence of these disorders. We did not detect a significant shared environmental or non-shared environmental correlation between disorders. Thus our earlier work combined with the present analyses support the hypothesis that high genetic risk alone, regardless of phenotypic expression, may increase risk for incident IHD. In the present analyses we found twins with both genetic vulnerability and phenotypic expression of depression had odds ratios for IHD that were almost twice those of twins with only genetic risk. However we did not have statistical power to reject the hypothesis of no genetic overlap between vulnerability for IHD and depression.

In adjusted analyses we found regular smoking and hypertension remained significantly associated with incident IHD. Two other established risk factors, diabetes and obesity were not significantly associated with incident IHD after multivariate modeling in this sample. This may be a function of high correlations between these and other predictor variables.

The effect of social isolation in the current study was consistent with previous evidence that the quality of social interactions predict incident IHD. Positive social support in men has been shown to be a protective effect for myocardial infarction (33).

Limitations

We do not have data on mortality due to heart disease which limited generalizing results to IHD deaths. In addition, non-response bias might influence our results if more severely affected members were unable to participate due to illness or death associated with IHD, depression or moderating or mediating variables. Unfortunately, no nationally distributed female twin registry in the United States, nor a registry that is racially diverse, has been constructed for comparison with the VET Registry cohort.

We recognize potential limitations exist in self reported measures of heart disease. It was not possible to validate past history of angina and myocardial infarction without complete medical records. However, others have found that self reported heart disease has good validity. Olsson et al. (34) found 100% agreement between hospital record and self reported myocardial infarction. Our point estimates and the robust association between depression and heart disease are consistent with the previous literature (6) including our own study of a larger cohort of younger VET twins utilizing a similar self reported heart disease phenotype (23).

Strengths—The present study is arguably the best controlled analysis demonstrating that phenotypic expression of depression is a risk for incident IHD because our cotwin design permitted simultaneously accounting for genetic confound and numerous cardiovascular risk factors. Because VETSA adds new information to VETR data that has been collected since 1987, we were able to rule out numerous previously obtained sociodemographic, psychiatric and physical illness risk factors as potential confounding variables. As previously summarized in the detailed description of VETSA (24), previous research demonstrates that the VET Registry twins are representative of all twins who served in the military during the Vietnam War and despite popular beliefs about Vietnam veteran socioeconomic status; veterans are not significantly different than their non-veteran peers. As compared to the 1992 Harvard Drug Study respondents, which was the source of VETSA subjects, VETSA respondents do not differ on age at induction, race, marital status in 1992, education at induction, Vietnam service or combat experience. The Armed Forces Qualification Test (AFQT) scores, a standardized assessment of cognitive abilities, were higher in respondents as compared to non-respondents. Thus baseline cognitive ability may be higher in respondents as compared to non-respondents. It is not clear how this may influence the association between depression and heart disease? Most relevant to the current study, VETSA respondents did not differ from non-respondents in regard to prevalence of nicotine dependence, drug dependence, alcohol dependence, PTSD and depression.

Conclusions

The present co-twin design is one of the best natural studies in psychiatric epidemiology and, to our knowledge, is the first applied to testing the effect of major depression on risk of incident IHD. After adjusting for smoking, hypertension, diabetes and social isolation, all risk factors that are correlated with depression and incident heart disease, twins at high genetic risk with phenotypic expression of depression were at significantly increased risk of IHD. In addition, trends in odds ratios suggest that twins with genetic vulnerability and without phenotypic expression of depression may be at risk for IHD, however sample size limitations preclude certainty in regards to this latter observation. Further research is warranted to tease out what known risk factors (e.g. smoking) for IHD share common genetic and environmental variance with major depression. In addition the present model would benefit from additional data on traditional IHD risk factors such as diet, exercise. Expanding models of latent environmental factors with measured environment in genetically informed designs will elucidate those factors that remain significant predictors even after controlling for genetic vulnerability. Public health efforts and clinicians may reduce risk of IHD by targeting those modifiable measured environmental components that contribute to heart disease above and beyond familial vulnerability.

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Acronyms

IHD ischemic heart disease

CAD	coronary artery disease
VET Registry	Vietnam Era Twin Registry
DSM-III-R	Diagnostic and Statistical Manual, 3 rd edition, revised
VETSA	Vietnam Era Twin Study of Aging
DIS-3R	Diagnostic Interview Schedule – Version 3, revised
MZ	monozygotic
DZ	dizygotic
MI	myocardial infarction

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Table 1

Prevalence (%) of incident ischemic heart disease (IHD)² across depression¹ and covariates among 128 male twins with ischemic heart disease (IHD)²

		IHD (n=128)	Rao-Scott Chi-square	p-value
Major depression:	NO	10.0	14.0	<0.001
	YES	22.6		
PTSD	NO	10.7	1.24	0.27
	YES	14.9		
GAD/Panic Disorder	NO	11.0	0.004	0.95
	YES	11.4		
Alcohol abuse/dependence	NO	9.2	2.79	0.09
	YES	12.5		
Drug abuse/dependence	NO	10.9	0.34	0.56
	YES	12.6		
Never regular smoker		6.1	14.90	<0.001
Ever regular smoker ³		13.4		
Body Mass Index:	<30.0	9.1	6.61	0.010
	≥30.0	14.3		
Hypertension	NO	6.3	18.13	<0.001
	YES	14.2		
Diabetes	NO	9.9	10.93	<0.01
	YES	20.7		
No confidants ⁴		27.8	10.15	<0.01
One or more confidants		10.3		
Caucasian race		10.9	0.16	0.69
Non-caucasian race		12.7		
Education:	0-12 years	12.8	1.57	0.21
	≥ 13 years	10.2		
Marital Status:				
Married vs.		10.6%	0.02	0.88
Divorced/Widow/Separated/ Never Married		11.0%		

¹ DSM-III-R depression on or before 1992,

² onset of heart surgery, angina or myocardial infarction after 1992;

³ smoked 100 or more cigarettes in lifetime,

⁴ social isolation: person has no one who they can trust or confide in.

Table 2

Association between familial vulnerability for depression¹ and risk of ischemic heart disease² in a cohort of 1,159 male twins

Twin-pair depression variables	Genetic risk	Environmental risk	Odds Ratio (95% Confidence Interval) for Ischemic Heart Disease
LEVEL 1: Depressed twins (n=93)	high	high	2.71 (1.59-4.60)
LEVEL 2: Index twin not depressed, MZ co-twin depressed (n=44)	high	low	1.47 (0.60-3.56)
LEVEL 3: Index twin not depressed, DZ co-twin depressed (n=35)	medium	low	1.55 (0.59-4.09)
LEVEL 4: Twins without depression (n=987)	low	low	1.00

¹ DSM-III-R depression on or before 1992,

² Onset of heart surgery, angina or myocardial infarction after 1992.

Table 3

Association between IHD and genetic vulnerability and phenotypic expression of depression¹, cardiovascular risk factors and social isolation² after adjusting for age, race, education and marital status

	Odds Ratio (95% Confidence Interval) for Ischemic Heart Disease
Depressed twins (high gene, high environment)	2.36 (1.32-4.20)
Index twin not depressed, MZ co-twin depressed (high gene, low environment)	1.35 (0.52-3.52)
Index twin not depressed, DZ co-twin depressed (medium gene, low environment)	1.50 (0.56-3.98)
Twins without depression (low gene, low environment)	1.0
Ever regular smoker ³	2.47 (1.48-4.12)
BMI (continuous)	1.00 (0.96-1.04)
Hypertension	2.27 (1.45-3.57)
Diabetes	1.84 (1.05-3.22)
No confidantes ⁴	2.63 (1.19-5.85)

¹ DSM-III-R depression on or before 1992,

² Onset of heart surgery, angina or myocardial infarction after 1992.

³ Smoked 100 or more cigarettes in lifetime

⁴ social isolation-person has no one who they can trust or confide in.