A Twin Study of Depression Symptoms, Hypertension, and Heart Disease in Middle-Aged Men

JEFFREY F. SCHERRER, MA, HONG XIAN, PHD, KATHLEEN K. BUCHOLZ, PHD, SETH A. EISEN, MD, MSC, MICHAEL J. LYONS, PHD, JACK GOLDBERG, PHD, MING TSUANG, MD, PHD, DSC, AND WILLIAM R. TRUE, PHD, MPH

Objective: Epidemiological and clinical studies have established an association between major depression and cardiovascular disease. We utilized a twin design to test whether there are common genetic and environmental risk factors underlying depression symptoms, hypertension and heart disease. **Methods:** Association studies were conducted with 6,903 male-male twins from the Vietnam Era Twin Registry who responded to both a 1990 health questionnaire and a 1992 telephone administration of a structured psychiatric interview. Data from 2,731 complete twin pairs were used to fit genetic models which determined the extent to which lifetime depression symptoms, heart disease and hypertension shared genetic and/or environmental factors. **Results:** Heart disease was significantly associated with 1–4 symptoms and 5 or more symptoms of depression (odds ratio [OR] = 2.62; 95% confidence interval [CI]: 1.54–4.46 and OR = 4.02; 95% CI: 2.16–7.46). Hypertension was significantly associated with 1 to 4 symptoms and 5 or more symptoms of depression (OR = 1.29; 95% CI: 1.11–1.50 and OR = 1.49; 95% CI: 1.21–1.83). The genetic correlations were significant between depression symptoms and hypertension (r = .19), and between depression symptoms and heart disease (r = .42). Of the total variance in depression, 8% was common to hypertension and heart disease, 7% of the variance in hypertension was common with depression symptoms and heart disease, and 64% of the variance in heart disease was common with depression symptoms and hypertension. **Conclusions:** Men who reported cardiovascular disease were significantly more likely to have depression symptoms. The lifetime co-occurrence of these phenotypes is partly explained by common genetic risk factors. **Key words:** twins, men, depression, hypertension, heart disease.

MZ = monozygotic; **DZ** = dizygotic; **DIS** = Diagnostic Interview Schedule.

INTRODUCTION

Numerous studies have produced evidence that depression is both a causal factor and a consequence of heart disease, and an emerging literature suggests hypertension is a correlate of depression. Reports from clinical studies have found patients with coronary artery disease who have active depression, a past history of depression or depression following a heart attack, are at increased risk for further cardiac events and mortality (1–6).

Community studies have suggested a strong association between cardiovascular disease and depression (7). Even after controlling for potential confounding due to cigarette smoking and other cardiovascular risk factors, those with depression have a higher risk of dying from ischemic heart disease (8, 9). Longitudinal studies suggest baseline depression leads to increased risk of myocardial infarction (9, 10). Projects involving older men in the Normative Aging Study (11) and men and women in the National Health and Nutrition Examination Survey (12) found strong dose-response relationships between levels of depression and risk of heart disease in men.

The extant literature mostly supports the hypothesis that depression also contributes to hypertension. Prospective studies have found that symptoms of depression are an independent risk factor for incident hypertension in both men and women (13, 14). However, other prospective designs have observed this association only in women (15) or found associations limited to chronic depression (16), and others have not found increased risk associated with clinical measures of hypertension (17, 18).

Despite evidence that heart disease, hypertension, and depression co-occur, the causal mechanisms remain uncertain. Biological explanations include changes in adrenergic activity in depression leading to hypertension (14). Carney and colleagues (19) argue that decreased heart rate variability resulting from autonomic dysfunction may explain the increased mortality in depressed postmyocardial infarction patients. Because of the mix of study designs (clinical, community based, prospective, and cross sectional) and the variation in measures of depression and cardiovascular disease, it is difficult to conclude that heart disease causes, is concurrent or antecedent of depression. One hypothesis not tested is that heart disease, hypertension and depression share a common etiology. The co-occurrence of these disorders may be due to genetic, shared family environmental factors and nonshared environmental influences that underlie the risk for heart disease, hypertension, and depression.

Both depression (20, 21) and cardiovascular disease (22, 23) are heritable. To investigate whether the lifetime co-occurrence of symptoms of major depression, hypertension, and heart disease are due to the same or to separate genetic and/or environmental influences, we analyzed data from male-male twin members of the Vietnam Era Twin (VET) Registry. We analyzed data from both MZ and DZ twin pairs, which permits partitioning variance in risk due to genes, shared family environment, and nonshared environmental factors. DZ

School of Public Health (J.F.S., W.R.T.), St. Louis University Health Sciences Center; Research Service (J.F.S., H.X., S.A.E., W.R.T.), St. Louis Veterans Affairs Medical Center (VAMC); Medical Service (S.A.E.), St. Louis VAMC; Department of Internal Medicine, Division of General Medical Sciences (H.X., S.A.E.), and Department of Psychiatry (K.K.B.), Washington University School of Medicine, St. Louis, Missouri; Harvard Medical School, Harvard Institute of Psychiatric Epidemiology and Genetics (M.T.), and Department of Psychiatry, Massachusetts Mental Health Center, Boston (M.J.L., M.T.); Department of Psychology (M.J.L.), Boston University, Boston, Massachusetts; and Department of Veterans Affairs, Vietnam Era Twin Registry/Seattle Epidemiologic Research and Information Center and Department of Epidemiology (J.G.), University of Washington School of Public Health, Seattle, Washington

Address reprint requests to: J. F. Scherrer, MA, VAMC-St. Louis, Research Service 151-JC, 915 N. Grand Blvd., St. Louis, MO 63106. Email: scherrjf@SLU.EDU

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twins are needed because the genetic correlation between DZ twins is 0.50 on average as compared with MZ twins who share 100% of their genes.

We first measured the magnitude of the association between hypertension and heart disease with different phenotypic definitions of depression among 6,903 VET Registry members. We then computed univariate, bivariate, and trivariate structural equation models to determine whether the phenotypes under study were due to genetic factors, and, if so, the degree to which these factors were disorder specific or shared common genetic and environmental etiologies. Because hypertension is a less extreme phenotype as compared with heart disease, we sought to determine whether different cardiovascular measures would result in comparable genetic relationships with depression symptoms and if the less severe condition of hypertension would have less common genetic factors with depression as compared with heart disease.

METHODS

Sample

The VET Registry consists of 7,375 male-male twin pairs born between 1939 and 1955 in which both siblings served on active military duty during the Vietnam era (1965–1975). The characteristics of the VET Registry and method of zygosity determination have been reported elsewhere (24–26). All twins were born into the same household. In a subset interviewed in 1995, we found that 99.5% of twins lived together until age 10 and 80.7 lived together until 18 years of age.

Data collection described below was conducted by trained interviewers from the Institute for Survey Research (ISR), (Temple University, Philadelphia, PA). The first data collection with Registry members was conducted in 1987 and consisted of a mailed survey of health. In 1990, ≈5,500 twin pairs from the VET Registry were invited to participate in a study conducted by the National Heart, Lung, and Blood Institute (NHLBI) (27). The 1990 mailed survey was designed to assess heart disease risk factors.

In 1992, approximately 5,000 twin pairs of the VET Registry were invited to participate in a computer assisted telephone (CATI) administration of the Diagnostic Interview Schedule, Version 3, Revised (DIS3R) (28), which allowed derivation of psychiatric diagnoses according to the Diagnostic and Statistical Manual of Mental Disorders, third edition, revised (DSM-III-R) criteria (29). Interviewers contacted twins and began interviewing after verbal informed consent was obtained, a method approved by the Institutional Review Boards at participating universities.

Twins were eligible for the logistic regression component of the present research if they met the following criteria: 1) they were identified from Department of Defense computer files (30), 2) twins and singletons completed the 1990 heart disease questions and the 1992 DIS depression questions, and 3) zygosity could be assigned. These criteria resulted in a sample of 6,903 MZ and DZ twins consisting of 2,813 complete pairs and 1,277 singletons. Only complete twin pairs were eligible for genetic modeling. Therefore, a slightly smaller sample of 2,731 pairs (ie, 1,561 MZ pairs and 1,170 DZ pairs) was utilized for genetic model fitting. The number of twin pairs was smaller for genetic analyses because both members of a pair had to have complete data from 1990 to 1992.

The mean age of the sample was 41.9 years in 1992 (SD ± 2.7, range 33 to 53 years). The majority (94.6%) of the twins were non-Hispanic white, 5.1% were African-American, and 0.3% were "other." The highest education completed as of 1987 was high school for 31.1% of the sample, and 40.2% attained a college degree or higher. In 1992, most (96.2%) were employed. Of these, 98.3% were employed full-time and 1.6% part-time. In 1992, 78% were married, 12.1% divorced, 2.2% separated, 0.4% widowed, and 7.3% had never been married.

Measures

Hypertension

Hypertension data were obtained from the 1990 NHLBI survey. Lifetime hypertension was derived from the response to the question: Have you ever been told by a doctor that you had hypertension or high blood pressure? Subjects who responded affirmatively were then asked at what age they first had high blood pressure.

Heart Disease

Heart disease measures were obtained from the 1990 NHLBI survey. Lifetime conditions were derived from responses to the questions: Has a doctor ever told you that you had angina pectoris? ...heart attack or myocardial infarction? ...coronary heart disease? We created a composite heart surgery (ie, balloon angioplasty and/or bypass surgery) variable derived from responses to the questions: have you ever had balloon angioplasty? ... coronary artery bypass surgery? The age of onset for each condition was queried as well as heart disease risk factors such as body mass index and cigarette smoking. Though other risk factors such as dietary habits are available from the NHLBI survey, it is beyond the scope of the current study to characterize all potential heart disease risk variables.

The prevalence of hypertension was large enough to permit genetic model fitting. To obtain sufficient power to fit a genetic model that included heart disease, we created a composite category defined as having a positive endorsement of one or more of the following: angina pectoris, myocardial infarction, coronary heart disease, or heart surgery (ie, balloon angioplasty and/or bypass surgery).

Major Depression

Depression data were collected via telephone administration of the DIS3R which allowed us to identify subjects with lifetime depression according to DSM-III-R criteria (29). Data from the DIS3R permitted creation of several depression variables that included a dichotomous lifetime diagnoses of major depression, a symptom count variable (ie, 0, 1–4 symptoms and 5 or more symptoms), DSM-III-R criteria for severity of depression and duration of depressive episode. Age onset of depressive episode was used to determine the proportion of subjects whose depression began before their cardiovascular disease.

For genetic model fitting of depression we utilized the three level depression symptom count variable. We selected this phenotype over the dichotomous full diagnosis of major depression for two reasons. First, there were too few subjects with both heart disease and full criteria major depression to resolve a best fitting bivariate genetic model. Second, logistic regression revealed that the association between these conditions became greater as the number of depression symptoms increased.

Statistical Analyses

Logistic Regression Models

ORs were computed to evaluate the association of depression types with cardiovascular variables. We fit only unadjusted regression models because our primary purpose for testing for an association was to establish a basis for fitting genetic structural equation models. Genetic model fitting would not be meaningful if there was no association suggested by ORs. ORs were obtained from separate logistic regression models. Because twin pair data are not statistically independent observations, we used STATA (31) software to obtain the Huber-White robust variance estimator for appropriate 95% confidence intervals around the parameter estimate.

Genetic Model Fitting

Three sources of influences accounting for individual differences are additive genetic effects (denoted "A"), shared family environment (denoted "C"), and unique environmental effects (denoted "E"). Additive genetic influences are correlated 100% between members of a MZ twin pair and 50% among members of a DZ twin pair. Shared environmental influences are experiences that twins have in common such as exposure to the same parenting, diet, parental smoking or drinking and sociodemographic factors primar-

ily shared during youth. Shared environmental influences are assumed to contribute to similarities in both MZ and DZ twin siblings and are correlated 100% between members of a twin pair. Unique environmental influences are experiences that are not shared and contribute to differences within MZ and DZ twin pairs. Unique environmental influences are uncorrelated within twin pairs and include measurement error. The greater similarity for a phenotype among MZ twins as compared with DZ twins, as indicated by a higher MZ than DZ correlation coefficient, suggests genetic influences.

We fit both univariate and multivariate (ie, bivariate and trivariate) genetic models (32) to determine whether hypertension, the composite heart disease variable and depression symptoms are: 1) influenced by genes, shared environment and unique environment (A + C + E), 2) environmentally determined with some environmental elements resulting from experiences shared equally between both members of a twin pair (C + E), or 3) influenced by both genes and unique environment (A + E).

In the univariate models we tested for the influence of genes and environment separately for hypertension, heart disease and depression. In two separate bivariate models, we tested whether the genetic and environmental influences to hypertension and depression were correlated and whether the genetic and environmental influences to heart disease and depression were correlated. To determine how much of the variance in heart disease, hypertension, and depression was common and how much was specific to each phenotype, we fit a trivariate common pathway model to compare competing solutions. Competing solutions allowed for variation in the number of common and specific genetic and environmental pathways.

Genetic analyses began by computing twin pair contingency tables separately for hypertension, heart disease, and depression. Tetrachoric correlations (ie, correlation between binary variables) were calculated for dichotomous variables and polychoric correlations (ie, correlations between variables with three or more levels) were computed for ordinal level variables. Polychoric and tetrachoric correlations were computed separately according to zygosity. Correlations were computed under the assumption of a multifactorial threshold model in which multiple unmeasured genetic and environmental risk factors determine an underlying continuous liability for developing the illness. The liability threshold model assumes that there is a single normally distributed dimension of liability with abrupt thresholds. Above a given threshold the disorder is expressed and below the threshold, the individual does not develop the disorder. Further discussion of the liability threshold model can be found elsewhere (32).

Univariate genetic models were fit to contingency table data. Separate univariate models were computed for hypertension, heart disease and for depression symptoms. Univariate models estimated the proportion of variance attributable to additive genetic (A), shared environment (C), and unique environment (E) effects, including error. Submodels were fit which deleted either genetic (CE model), or shared environmental parameters (AE model). The goodness of fit of full (ACE) and submodels (AE or CE) was determined by likelihood ratio χ^2, with degrees of freedom for the χ^2 difference between the full and submodel computed as degrees of freedom of the submodel minus degrees of freedom of the full model.

For bivariate modeling, a 4 × 4 correlation matrix was calculated for MZ and DZ twin pairs' hypertension and depression. This resulted in two within-diagnosis cross-twin correlations, two within-twin cross-diagnoses correlations, and two cross-twin, cross-diagnoses correlations.

Bivariate analyses compared the fit of the full model (ACE) for nicotine dependence and alcohol dependence to that of reduced models which removed one or more genetic (A) or environmental (C, E) parameters. A χ^2 difference statistic determined the best fitting model. This procedure was repeated for the bivariate modeling of heart disease and depression.

For trivariate modeling, a 6 × 6 tetrachoric correlation matrix was calculated for MZ and DZ twin pairs' depression symptoms, hypertension and heart disease data. This resulted in three within-phenotype cross-twin correlations, three cross-phenotype, within-twin correlations, and six cross-phenotype, cross-twin correlations. The proportion of phenotypic variances due to additive genetic effects (denoted A), family or shared environmental effects (denoted C), and unique environmental effects (denoted E) for depression symptoms, hypertension and heart disease were estimated. A series of models were fit to the data to compare the fit of the full model, which includes all possible parameters to that of reduced models, which removed one or more genetic and/or environmental parameters. A χ^2 difference statistic determined the best fitting model. For all model fitting, a nonsignificant χ^2 indicates that the model fits the data. For univariate, bivariate, and trivariate model fitting, if two or more reduced models were observed to give an adequate fit for the data, the model with the lowest Akaike's Information Criterion (AIC) (33) was accepted as the best fitting model. The AIC is used to select the most parsimonious model. MX software (34) was used for the genetic modeling and PRELIS software (version 2) (35) was used to compute tetrachoric and polychoric correlations.

RESULTS

Among the 6,903 twins who responded to both the 1990 and 1992 data collection efforts, 18.3% had been told by a doctor that they had hypertension, 0.8% that they had angina, 0.8% that they had a myocardial infarction or heart attack, 0.6% that they had coronary heart disease and 0.5% had heart surgery. We found 1.8% of the sample met criteria for our composite heart disease phenotype. For depression, 9.1% of the sample met full DSM-III-R criteria, 42.4% had one to four symptoms and 12.5% had five or more symptoms of depression.

Of the cardiovascular conditions examined, full criteria DSM-III-R major depression was most strongly associated with myocardial infarction (OR = 3.03; 95% CI: 1.55–5.94) (Table 1). Other types of heart disease significantly associated with major depression included coronary heart disease (OR = 2.44; 95% CI: 1.12–5.32) and our composite heart disease measure (OR = 2.12; 95% CI: 1.28–3.50). Though not significant, the point estimate suggests a modest association between major depression and hypertension (OR = 1.22).

For the symptom count variable, all types of cardiovascular disease were associated with 1 to 4 depression symptoms as compared with no depression and the magnitude of the association increased when subjects with no symptoms were compared with subjects with 5 or more symptoms of depression. The composite heart disease measure was significantly associated with the odds of having 1 to 4 symptoms of depression and 5 or more symptoms of depression (OR = 2.62; 95% CI: 1.54–4.46 and OR = 4.02; 95% CI: 2.16–7.46, respectively). OR did not increase as dramatically for hypertension which was significantly associated with 1 to 4 symptoms of depression (OR = 1.29; 95% CI: 1.11–1.50) and with five or more symptoms of depression (OR = 1.49; 95% CI: 1.21–1.83).

DSM-III-R depression severity was significantly associated with hypertension, myocardial infarction and the composite heart disease variable. Duration of depression was significantly associated with myocardial infarction, coronary heart disease and the composite heart disease variable.

Whereas a slightly greater proportion of subjects experienced major depression (52%) before hypertension, the majority (60–88%) had full criteria DSM-III-R depression before onset of each heart disease phenotype. The mean age (±SD) of onset for hypertension was 32.34 (7.29) years, for angina was 35.20 (6.37) years, for myocardial infarction was 35.86 (6.52) years, for coronary heart disease was 37.68 (4.86) years, for heart surgery was 39.26 (3.49) years and for the

composite heart disease variable was 35.25 (6.93) years. The mean age onset of full criteria DSM-III-R depression was 30.47 (8.20) years.

For MZ and DZ twin pairs, the tetrachoric correlations for hypertension (ie, the correlation between twin 1 and twin 2 for hypertension within zygosity) were 0.56 (±0.04) and 0.28 (±0.06), respectively. For MZ and DZ twin pairs, the tetrachoric correlations for heart disease were 0.64 (±0.10) and 0.31 (±0.17), respectively. For symptoms of depression, the polychoric correlation was 0.37 (±0.03) and 0.17 (±0.04) for MZ and DZ twin pairs, respectively. For each phenotype, the MZ twin pair correlations were approximately twice as large among MZ as compared with DZ twin pairs, suggesting a significant genetic influence.

Univariate model fitting results are presented in Table 2. For all phenotypes, the reduced AE model was superior to the reduced CE model and was not significantly worse fitting than the full model ($\Delta\chi^2_1 = 0.00$). Under the best-fitting models, genes accounted for 56.3% (95% CI: 48.8-63.2%) and the unique environment accounted for 43.7% (95% CI: 36.8-51.2%) of the variance in liability for hypertension; genes accounted for 64.6% (95% CI: 44.2-79.7%) and the unique environment accounted for 35.4% (95% CI: 20.3-55.8%) of the variance in liability for heart disease; genes accounted for 36.4% (95% CI: 31.1-41.5%) and the unique environment accounted for 63.6% (95% CI: 58.5-68.9%) of the variance in risk for depression symptoms.

The bivariate model fitting results are presented in Tables 3 and 4. The full model (model 1), which allowed for genetic, shared environmental, and unique environmental contributions to hypertension and depression symptoms and for correlations between the genetic and environmental influences, produced a good fit to the data ($\chi^2_5 = 9.08$, $p = .11$). However, the point estimate for the shared environmental correlation, r_C, was equal to 1.0 with a confidence interval of 0.0–1.0. This finding, along with univariate results which demonstrated the AE model best fit the data for hypertension and depression symptoms, suggested that the shared environmental contribution to both phenotypes could be removed. We fit the most parsimonious model (model 10) by allowing for additive genetic and unique environmental influences to hypertension and depression symptoms ($\chi^2_9 = 9.64$, $p = .38$, AIC = −8.36). The best fitting model fixed the unique environmental correlation to zero and allowed for a genetic correlation of 0.19 (95% CI: .11–.28). Reduction of the number of parameters produced significantly worse fits to the data. This is evident by the significant χ^2 value obtained after fixing the genetic correlation to zero ($p < .02$) (model 11) and then to one ($p < .001$) (model 12).

The same model fitting process was followed for data on heart disease and depression symptoms (Table 4). Again the full model (model 1) produced a good fit to the data but the shared environmental correlation included a confidence interval from 0 to 1. As with the best fitting bivariate model for

TABLE 1. Association Between Cardiovascular Conditions as a Function of Depression Phenotypes Among 6,903 Vietnam Era Twin Registry Members

Depression Types	Hypertension (n = 1264)	Angina (n = 60)	Myocardial Infarction (n = 60)	Coronary Heart Disease (n = 39)	Heart Surgery[b] (bypass or angioplasty) (n = 36)	Composite Heart Disease[c] (n = 124)
Lifetime DSM-III-R major depressive episode	1.22 (.98–1.53)	1.82 (.85–3.90)	**3.03 (1.55–5.94)**	**2.44 (1.12–5.32)**	1.87 (.71–4.92)	**2.12 (1.28–3.50)**
Symptom categories						
0 vs. 1–4 depression sx	**1.29 (1.11–1.50)**	**2.51 (1.23–5.11)**	**2.57 (1.15–5.70)**	**2.98 (1.07–7.84)**	**5.07 (1.50–17.10)**	**2.62 (1.54–4.46)**
0 vs. 5 pls depression sx	**1.49 (1.21–1.83)**	**2.94 (1.24–6.97)**	**4.69 (1.91–11.47)**	**6.96 (2.37–20.47)**	**8.92 (2.45–32.53)**	**4.02 (2.16–7.46)**
Severity						
Mild	.99 (.65–1.53)	2.39 (.74–7.73)	0.96 (.13–7.11)	2.44 (.57–10.44)	1.31 (.18–9.75)	2.06 (.82–5.14)
Moderate	1.32 (.85–2.04)	1.02 (.14–7.48)	**3.70 (1.11–12.27)**	3.12 (.76–12.83)	3.35 (.78–14.38)	**2.63 (1.05–6.60)**
Severe	**1.50 (1.08–2.10)**	2.00 (.61–6.53)	**4.84 (2.05–11.44)**	2.05 (.50–8.34)	1.10 (.15–8.16)	**2.41 (1.12–5.22)**
Days depressed						
1–30 days	1.04 (.70–1.54)	2.09 (.64–6.82)	0.84 (.11–6.21)	2.14 (.52–8.71)	2.29 (.54–9.77)	1.44 (.52–3.95)
31–180 days	1.39 (.98–1.96)	1.34 (.32–5.60)	**4.88 (2.05–11.59)**	**4.12 (1.50–11.29)**	2.21 (.52–9.43)	**2.78 (1.34–5.73)**
180 days or more	1.24 (.86–1.80)	2.04 (.63–6.68)	**3.30 (1.15–9.44)**	1.04 (.14–7.78)	1.12 (.15–8.34)	2.11 (.90–4.94)
Proportion of subjects with major depression before cardiovascular condition for subjects with both depression and cardiovascular disease	52%	88%	**64%**	71%	60%	72%

[a] subjects in control group had none of the cardiovascular conditions in Table 1. All comparisons made with no heart disease control group (n = 5,559).
[b] heart surgery = balloon angioplasty or coronary artery bypass surgery.
[c] composite heart disease = angina + myocardial infarction + coronary heart disease + heart surgery.
significant odds ratios (OR) in bold text.
Sx, symptoms.

TABLE 2. Genetic Model-fitting Comparisons for full and Reduced Univariate Models of Additive Genetic Shared Environmental, and Unique Environmental Influences for Hypertension, Heart Disease, and Symptoms of Depression Among 2,731 VET Registry Twin Pairs

Phenotype	Model[a]	Goodness of Fit			
		df.	χ^2	p	AIC[d]
Hypertension	ACE	3	1.13	.77	−4.87
	AE	**4**	**1.13**	**.89**	**−6.87**
	CE	4	18.1	.001	.05
Heart disease[b]	ACE	3	.83	.84	−5.16
	AE	**4**	**.83**	**.93**	**−7.17**
	CE	4	4.52	.34	−3.48
Depression symptoms[c]	ACE	12	11.38	.5	−12.63
	AE	**13**	**11.38**	**.58**	**−14.63**
	CE	13	30.9	.003	4.9

[a] A = additive genetic effects; C = shared environmental effects; E = unique environmental effects.
[b] Composite heart disease = angina + myocardial infarction + coronary heart disease + heart surgery.
[c] 0, 1–4, and 5 plus DSM-III-R symptoms of depression.
[d] AIC = Akaike's information criterion.
Best-fitting model in bold text.

TABLE 3. Genetic model-fitting comparisons for full and reduced models of additive genetic, shared environmental, and unique environmental influences to hypertension and depression among 2,731 VET Registry twin pairs

Model	Bivariate Model						Phenotypic Correlations[a]			Goodness of Fit			Parsimony
	hypertension[b]			depression[c]			r_A	r_C	r_E	d.f.	χ^2	p	AIC[d]
1	A	C	E	A	C	E	0.13	1	0	5	9.08	.11	−0.92
2	A	C	E	A	C	E	‡	1	0.1	6	9.84	.13	−2.16
3	A	C	E	A	C	E	‡‡	1	0.1	6	25.23	<.001	13.23
4	A	C	E	A	C	E	0.17	‡	0	6	9.31	.16	−2.69
5	A	C	E	A	C	E	0.13	‡‡	0	6	9.08	.17	−2.92
6	A	C	E	A	C	E	0.17	1	‡	6	9.54	.15	−2.46
7	A	C	E	A	C	E	0.18	1	‡‡	6	146.39	<.001	134.39
8	A	C	E	A	§	E	0.17	NA	0	7	9.31	.23	−4.69
9	A	C	E	A	§	E	0.19	NA	‡	8	9.64	.29	−6.36
10	**A**	**§**	**E**	**A**	**§**	**E**	**0.19**	**NA**	**‡**	**9**	**9.64**	**.38**	**−8.36**
11	A	§	E	A	§	E	‡	NA	‡	10	27.78	.02	7.78
12	A	§	E	A	§	E	‡‡	NA	‡	10	166.13	<.001	146.13

[a] r_A = correlation between additive genetic contribution to heart disease and additive genetic contribution to depression symptoms, r_c = correlation between shared environmental contribution to heart disease and shared environmental contribution to depression symptoms, r_E = correlation between unique environmental contribution to heart disease and unique environmental contribution to depression symptoms.
[b] Hypertension = positive response to whether physician has told subject that they had high blood pressure.
[c] DSM-III-R major depression in a lifetime.
[d] AIC = Akaike's information criterion.
§ parameter fixed to 0, ‡correlation fixed to 0, ‡‡correlation fixed to 1.
NA = not applicable.
Best-fitting model in bold text

hypertension and depression, the most parsimonious model (model 10) for heart disease and depression allowed for additive genetic and unique environmental influences on both phenotypes ($\chi^2_9 = 4.51$, $p = .88$, AIC= −13.49). The best fitting model fixed the unique environmental correlation to zero and allowed for a genetic correlation of 0.42 (95% CI: 0.27–0.58). Attempts to further reduce the number of parameters produced significantly worse fits to the data. This is evident by the significant χ^2 value obtained after fixing the genetic correlation to zero ($p < .001$) and then to one ($p < .001$), models 11 and 12, respectively.

As shown in Table 5, a full trivariate genetic model (model 1) fit the data ($\chi^2_{15} = 23.85$, $p = .07$, AIC = −6.15). Model 2 which assumed no shared environmental influence common to depression symptoms, hypertension and heart disease gave a more parsimonious fit to the data as did a model (model 3) which removed both common and specific shared environmental influences (AIC = −12.13 and −16.60, respectively). Similarly, removal of all common unique environmental factors (model 6) produced a good and still more parsimonious fit to the data (AIC = −22.52). We arrived at the best fitting trivariate model by next removing the specific additive genetic

TABLE 4. Genetic model fitting comparisons for full and reduced models of additive genetic, shared environmental, and unique environmental influences to heart disease and depression among 2,731 VET Registry twin pairs

Model	Bivariate Model						Phenotypic Correlations[a]			Goodness of Fit			Parsimony
	heart disease[b]			depression[c]			r_A	r_C	r_E	d.f.	χ^2	p	AIC[d]
1	A	C	E	A	C	E	.35	1	.02	5	3.94	.56	−6.06
2	A	C	E	A	C	E	‡	1	.09	6	5.11	.53	−6.89
3	A	C	E	A	C	E	‡‡	1	.03	6	5.27	.51	−6.73
4	A	C	E	A	C	E	.46	‡	0	6	4.44	.62	−7.67
5	A	C	E	A	C	E	.37	‡‡	.02	6	3.94	.68	−8.06
6	A	C	E	A	C	E	.37	1	‡	6	3.98	.68	−8.02
7	A	C	E	A	C	E	.44	1	‡‡	6	23.2	.001	11.15
8	A	C	E	A	§	E	.42	NA	0	7	4.51	.72	−9.49
9	A	C	E	A	§	E	.42	NA	‡	8	4.51	.81	−11.49
10	**A**	**§**	**E**	**A**	**§**	**E**	**.42**	**NA**	**‡**	**9**	**4.51**	**0.88**	**−13.49**
11	A	§	E	A	§	E	‡	NA	‡	10	30.9	.001	10.88
12	A	§	E	A	§	E	‡‡	NA	‡	10	42.6	<.001	22.55

[a] r_A = correlation between genetic contribution to heart disease and genetic contribution to depression symptoms, r_c = correlation between shared environmental contribution to heart disease and shared environmental contribution to depression symptoms, r_E = correlation between unique environmental contribution to heart disease and unique environmental contribution to depression symptoms.
[b] composite heart disease = angina + myocardial infarction + coronary heart disease + heart surgery.
[c] DSM-III-R major depression in a lifetime.
[d] AIC = Akaike's information criterion.
§ parameter fixed to 0, ‡correlation fixed to 0, ‡‡correlation fixed to 1.
Best-fitting model in bold text.

TABLE 5. Results of Multivariate Model fitting of Depression symptoms, Hypertension, and Heart Disease Among 2,731 VET Registry Twin Pairs

Model	Common			Specific			Model Goodness of Fit			Parsimony
	DEP sx[a]	HBP[b]	HD[c]	DEP sx	HBP	HD	d.f.	χ^2	p	AIC
1	ACE	ACE	ACE	ACE	ACE	ACE	15	23.85	.07	−6.15
2	AE	AE	AE	ACE	ACE	ACE	18	23.87	.16	−12.13
3	AE	AE	AE	AE	AE	AE	21	25.4	.23	−16.6
4	AE	AE	AE	ACE	E	CE	21	45.27	.002	3.27
5	AE	AE	AE	AE	A	E	23	25.4	.33	−20.6
6	A	A	A	AE	AE	AE	24	25.48	.38	−22.52
7	**A**	**A**	**A**	**AE**	**AE**	**E**	**25**	**26.94**	**.36**	**−23.06**
8	A	A		AE	AE	AE	25	68.36	<.001	18.36
9	A		A	AE	AE	AE	25	56.16	<.001	6.16
10		A	A	AE	AE	AE	25	71.94	<.001	21.94
11		A	A	A	AE	AE	26	806.09	<.001	754.09
12				AE	AE	AE	27	82.9	<.001	28.29
13	A	A	A	E	E	E	27	224.6	<.001	170.6

DEP sx = Depression symptoms.
HBP = hypertension.
HD = heart disease.
[a] DSM-III-R major depression in a lifetime.
[b] Hypertension = positive response to whether physician has told subject that they had high blood pressure.
[c] composite heart disease = angina + myocardial infarction + coronary heart disease + heart surgery.
[d] AIC = Akaike's information criterion.
Best fitting model in bold text.

contribution to heart disease (model 7). Removing additive genetic common pathways (models 8–13) produced significantly poor fits to the data ($p < .001$). Under the best-fitting model 7 ($\chi^2_{25} = 26.94$, $p = .36$, AIC = −23.06), the lifetime co-occurrence of depression symptoms, hypertension and heart disease was best explained by common additive genetic pathways to all three phenotypes, specific additive genetic pathways to depression symptoms and hypertension and unique environmental pathways specific to each disorder.

As shown in Figure 1 under the best-fitting model, additive genetic influences common to all three disorders explained 7.7% (95% CI: 4.0–12.6%) of the variance in risk for depres-

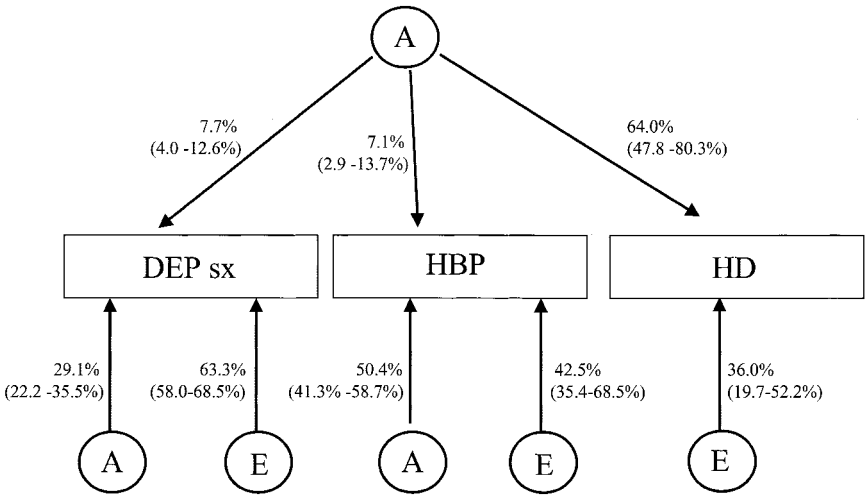

Fig. 1. A common pathway model for risk of lifetime depression symptoms (DEP sx), hypertension (HBP), and heart disease (HD) in 2,731 male-male twin pairs. The figure illustrates the genetic (A), shared environmental (C), and unique environmental (E) variance component estimates (95% confidence intervals) in common and specific to each phenotype. The "A" at the top of the figure indicates genetic influences common to all three phenotypes. The "A" and "E" at the bottom of the figure indicates genetic and unique environmental influences specific to each phenotype.

sion symptoms, 7.1% (95% CI: 2.9–13.7%) of the variance in risk for hypertension, and 64.0% (95% CI: 47.8–80.3%) of the variance in heart disease. The specific additive genetic pathways explained 29.1% (95% CI: 22.2–35.5%) of the variance in depression symptoms and 50.4% (41.3–58.7%) of the variance in hypertension. The unique environmental effects specific to each phenotype explained 63.3% (95% CI: 58.0–68.5%) of the variance in depression symptoms, 42.5% (35.4%-68.5%) of the variance in hypertension and 36.0% (19.7%-52.2%) of the variance in heart disease.

Given the small number of subjects with heart disease it was not practical to fit a trivariate model which adjusted for heart disease risk factors, such as race, smoking, and age. However, the results from logistic regression found that after controlling for ever smoking (ie, 100 or more cigarettes smoked in a lifetime), obesity, race, and age, 1 to 4 symptoms of depression as compared with no depression remained significantly associated with hypertension (OR 1.27; 95% CI: 1.09–1.49) and with heart disease (OR 2.49; 95% CI: 1.46–4.26). The association between five or more symptoms of depression vs. no depression also remained significantly associated with hypertension (OR = 1.52; 95% CI: 1.23–1.87) and heart disease (OR = 4.02; 95% CI: 2.15–7.56) after adjustment for smoking, obesity, race, and age. As the VET Registry cohort ages and new cases of heart disease develop, it should be possible to compute more complex genetic models that control for a number of heart disease risk factors.

COMMENT

In a nationally distributed, community cohort of male-male twin pairs with a mean age of 41.9 years, we found that full DSM-III-R criteria major depression was significantly associated with heart disease but not with hypertension. However, subjects with one to four symptoms of depression and five or more symptoms of depression were significantly more likely to report a history of heart disease and a history of hypertension as compared with subjects with no depression symptoms. This association became stronger as the number of lifetime depression symptoms increased. Genetic model fitting suggested that genes explained 56.3%, 64.6%, and 36.4% of the variance in risk for hypertension, heart disease, and depression symptoms, respectively. Unique environmental influences explained the remaining variance in risk for all three phenotypes.

The lifetime co-occurrence of hypertension and depression symptoms was best explained by a model that allowed for a small genetic correlation ($r = .19$) between both conditions, no correlation between unique environmental factors and no contribution from the shared environment. Likewise, the lifetime co-occurrence of heart disease and depression symptoms was best explained by a substantial genetic correlation ($r = .42$) between both conditions, no correlation between unique environmental factors and no contribution from the shared environment.

The model which best explained the risk for all three illnesses included common genetic contributions to depression, hypertension and heart disease and no specific genetic influence to heart disease. The remaining variance under the best fitting trivariate model was due to unique environmental influences. The genetic variance to depression symptoms was mostly disorder specific (29.1%) with the remainder (7.7%) common to hypertension and heart disease. The majority (50.4%) of genetic risk for hypertension was disorder specific, with only ≈7% of the risk for hypertension common with depression symptoms and heart disease. This finding is reflective of the small genetic correlation in the bivariate model of hypertension and depression. Remarkably, no genetic variance was specific to our heart disease phenotype which is supportive of our finding that the genetic correlation between depression and heart disease is substantial ($r = .42$). To ensure that the common variance to heart disease reflected more overlap

with depression than with hypertension, we computed bivariate analyses for hypertension and heart disease which found a genetic correlation of .32. With overlapping confidence intervals for the correlations, we conclude that heart disease shares at least as much genetic variance with depression as with hypertension. The evidence for a stronger genetic relationship between heart disease and depression as compared with the genetic correlation between hypertension and depression is consistent with the weaker and inconclusive evidence for an association between high blood pressure and major depression (13–18).

Our univariate models and the variance component estimates derived for each phenotype are consistent with prior research. In a larger sample of VET Registry twins, True and colleagues (36) found genes explained 52% of the variance in self reported high blood pressure ascertained in 1987. This estimate is nearly identical and well within the 95% confidence interval for the present results for the genetic contribution to self reported hypertension (56.3%; 95% CI: 48.8-63.2%) among a subsample of twins who participated in both 1990 and 1992 surveys. Our findings are also near the point estimates from other twin samples for measured systolic and diastolic blood pressures which range from 41% to 48% for systolic and from 41% to 51% for diastolic pressure (37). The heritability estimate of 61.7% for heart disease is consistent with the results of others who have found that heart disease and risk factors for heart disease are heritable (22, 23) and that the genetic impact is greatest in younger twins (ie, between 36 and 65 years of age) (38). It is logical that genes would have the greatest impact on young men's risk of heart disease and less so after a lifetime of engaging in cardiovascular risk behaviors. Although we did not find another study that reported the variance component estimates of self-reported heart disease, our analyses along with others, support a major role for genetic contributions to heart disease in middle-aged men. Consistent with analysis of VET Registry DSM-III-R full criteria major depression (20) and with other twin studies of major depression (21, 39, 40), we found that genes accounted for about one-third of the risk of developing depression when defined as a three level symptom count variable.

Common genetic vulnerability may influence the psychophysiology behind the association of hypertension, heart disease and symptoms of depression. Potential biological mechanisms for the co-occurrence of these diseases include increased aggregation of platelets and alterations in lipid metabolism among depressed persons and, recently, invariable heart rate (19, 41, 42). By reviewing psychobiological evidence, Sesso and colleagues (11) report depression is associated with increased sympathetic nervous system activity, higher cortisol levels, and increased blood pressure, which would subsequently increase the risk for heart disease. The genetic influence common with depression and cardiovascular disease may reflect an increased association between depression and heart disease risk factors such as smoking, but adjustment for these covariates in the logistic regression models indicated the relationship between depression and cardiovascular disease exists independently of behavioral risk factors. Further research in twin samples with sufficient prevalence of heart disease may be able to test if smoking and other health behaviors mediate the genetic correlation between depression and vascular disease.

Limitations should be considered when interpreting our study. First, the present results cannot be applied to women. Unfortunately, no nationally distributed female twin registry has been constructed for comparison with the VET Registry cohort. Because of minimum health standards required at enlistment into military service, Registry members may be healthier than the general population of similarly aged American males (26). Results may not generalize to nonveteran populations.

A second potential limitation is the narrow age range for VET Registry members. Our results may not be applicable to older men. The present findings are limited to rarer cases of heart disease that become clinically significant in middle-aged men; thus we have demonstrated the genetic overlap between cardiovascular disease and depression in a unique, relatively young cohort of men. It will be interesting to reexamine the relationship as the veterans' age and heart disease becomes more common and the power to fit causal models will exist. Our lack of statistical power to fit causal models limits the conclusions we can draw from the analyses; however, we believe these results set the stage for future studies in samples with increased heart disease.

The absence of data on mortality due to heart disease limits our ability to generalize these results to depression and heart disease deaths. It follows that nonresponse bias might also influence our results if more severely affected members were unable to participate due to illness or death associated with heart disease or symptoms of depression.

The composite heart disease phenotype might also be a limitation because we combined related cardiovascular conditions into one variable in order to obtain sufficient power for genetic model fitting. A twin cohort large enough to model angina and depression separately from heart attack and depression could confirm the rationale for our composite variable. At this time we are unable to make this comparison.

Finally, the hypertension and heart disease phenotypes were derived from twins who reported that a physician told them that they had the disorder. Because the sample is nationally distributed, it was not feasible to obtain medical examination on the entire cohort. However, others have found that self-reported heart disease has good validity. Olsson et al. (43) found 100% agreement between hospital record and self-reported myocardial infarction, and in the Nurses' Health Study (44) there was a 68% agreement between medical record and self-reported heart attack. In the absence of medical records for our study we argue that our ability to replicate self reported hypertension in two partially overlapping samples of veterans, the observation that the heart disease phenotype increased with severity of depression and the precision of our variance component estimates support the validity of our self report measures.

There are several strengths to our study. First, our assessment of depression was derived from a well validated and standardized structured interview from which we could derive symptoms of major depression. The DIS3R excludes symptoms of depression due to a physical illness or injury. Therefore depressive symptoms are not an artifact of having a cardiovascular condition. Second, standard survey methodology was used to obtain data for heart disease and hypertension. Third, data were collected without prior knowledge of respondents' physical or psychiatric status which reduced the risk of interviewer bias. Fourth, the large nationally distributed population allows US to generalize our results to middle-aged males in the United States. Fifth, the equal environments assumption has been tested for depression, alcoholism, and nicotine dependence in VET Registry twins (45). There is no evidence that potentially different rearing of identical as compared with fraternal twins influenced the twins' similarity for depression or for these heart disease risk factors.

We believe further research should examine the potential common inheritance of major depression and other cardiovascular risk factors such as high cholesterol, smoking, diet, and obesity to help focus the search for shared vulnerability genes. Discovery of risk factors, whether genetic or environmental, will help us understand the etiology, develop more refined definitions of disease, and lay the groundwork for future therapies that may target patients at high risk for the co-occurrence of depression and vascular disease.

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