Journal of Affective Disorders 122 (2010) 247–252

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

Shared genetic factors in the co-occurrence of symptoms of depression and cardiovascular risk factors

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ARTICLE INFO

Article history:
Received 14 February 2009
Received in revised form 8 July 2009
Accepted 8 July 2009
Available online 11 August 2009

Keywords:
Depression
Cardiovascular disease
Lipids
Blood pressure
Glucose
Genetics

ABSTRACT

Background: We aim to investigate the extent to which shared genetic and shared environmental factors play a role in the co-occurrence of symptoms of depression and cardiovascular risk factors.
Methods: The analyses included 2383 individuals from a genetically isolated population in the Netherlands (mean age 48.7 years (standard deviation 15.1), percentage of women 56.9%). Symptoms of depression were assessed using the Center for Epidemiology Studies Depression Scale (CES-D) and the Depression subscale of the Hospital Anxiety and Depression Scale (HADS-D). Assessment of cardiovascular risk factors included systolic and diastolic blood pressure, plasma, glucose levels, high and low density lipoprotein (HDL, LDL) and total cholesterol levels.
Results: Overall, we found that HADS-D was significantly correlated to total cholesterol levels (correlation coefficient [ρ] = 0.05), and inversely associated to HDL ($\rho = -0.06$). Statistically significant genetic correlations (ρ_G) were found between CES-D scores and total plasma cholesterol ($\rho_G = 0.30$), LDL ($\rho_G = 0.31$) and total cholesterol/HDL ratios ($\rho_G = 0.25$). For HADS-D scores, a significant genetic correlation was found with total cholesterol/HDL ratios ($\rho_G = 0.27$). Environmental correlations (ρ_E) with an opposite direction were found between CES-D and both total cholesterol ($\rho_E = -0.16$) and LDL ($\rho_E = -0.15$).
Limitation: By adjusting for sibship, we are taking into account environmental effects, however we cannot exclude dominance variance.
Conclusions: Our study shows that there is evidence for shared genetic factors contributing to the co-occurrence of symptoms of depression and lipid levels. This finding suggests a joint genetic pathogenesis. Future research is encouraged to assess susceptibility genes for mood disorders to be studied for cardiovascular disorders and vice versa.

1. Introduction

Depression and cardiovascular disease (CVD) are two of the most common disorders in developed countries (Lopez and Murray, 1998). According to the World Health Organization estimates, 29% of all deaths globally are attributed to CVD each year, and depressive disorders are the most frequently occurring psychiatric disease with a life-time incidence of around 25% (Kessler et al., 2003). The prevalence of depression in patients with CVD is estimated at 20% to 35% (Rozanski et al., 1999; Lett et al., 2004). The causal mechanism behind this association is multidirectional, in that depression may lead to CVD, it may worsen CVD symptoms or it may result from CVD (Plante, 2005).

In recent years, there has been an increasing interest in the hypothesis that depression and CVD risk factors may share common genetic pathways. Both depression and CVD are partly determined by genetic predisposition. For both traits there is substantial evidence for a strong genetic component (Sullivan et al., 2000; Knuiman et al., 1996; Watanabe et al.,

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doi:10.1016/j.jad.2009.07.008

1999; Chien et al., 2003; Ober et al., 2001). The hypothesis of a joint genetic etiology is supported by genetic association studies that show association of the angiotensin I converting enzyme (*ACE*) gene, methylenetetrahydrofolate reductase (*MTHFR*) gene, tyrosine hydroxylase (*TH*) gene, dopamine receptor D4 (*DRD4*) gene, G-protein B3 subunit (*GNB3*) gene, and the serotonin transporter (*SLC6A4*) gene to depression and to CVD and its major risk factors such as hypertension and lipid levels (Bondy et al., 2002; Elovainio et al., 2005; Camus et al., 2004; Otte et al., 2007; Lopez-Leon et al., 2007).

Apart from these candidate gene studies, there has been limited research on the role of shared genetic pathways in the association between depression and CVD. Only one study has investigated the genetic correlation between depression and CVD risk factors (Scherrer et al., 2003). This study, among male twins from the Vietnam Era Twin Registry, showed a significant genetic correlation between symptoms of depression and hypertension and heart disease (Scherrer et al., 2003). The aim of our study was to investigate the extent to which shared genetic factors explain the association between depression and CVD risk factors in a large family-based study.

2. Methods

2.1. Subjects

The present analyses were carried out using data from the Erasmus Rucphen Family (ERF) study. This family-based cohort study was designed to identify susceptibility genes for various complex disorders by studying quantitative traits. The ERF study is being conducted in a genetically isolated population located in the southwest of The Netherlands. The population is characterized by minimal immigration up until the last few decades. Genealogical information on this population was reconstructed using church and municipality records and is currently available in the form of a large database including over 63,000 individual records. In our analysis we included, 2383 individuals, who had complete phenotypic and genealogical information available.

Eligibility for participation in the study was determined by genealogical background, not by any phenotypes of interest. Twenty-two families were selected who had at least six children baptized in the community church between 1880 and 1900. All living descendants of these families aged 18 years and older, as well as their spouses, were invited to attend a series of clinical examinations. Data were collected between June 2002 and February 2005. A detailed characterization of this population has been presented elsewhere (Van Koolwijk et al., 2007; Lopez-Leon et al., 2009; Choy et al., 2009).

2.2. Procedures

All participants filled out questionnaires and underwent extensive medical examinations. These examinations were conducted by physicians of the academic centers according to a standardized research protocol. The questionnaires addressed symptoms of depression, among other variables. The medical exam included the assessment of medical history, medication use and blood pressure measurements. Fasting blood samples were drawn in order to measure lipid and glucose levels according to standardized procedures (Neeley, 1972; Van Gent et al., 1977). Data were collected between 2002 and 2005. The study was approved by the Medical Ethical Committee of the Erasmus University Medical Center Rotterdam and all participants gave informed consent.

2.3. Measurements

Symptoms of depression were assessed using the Centre for Epidemiology Studies Depression Scale (CES-D) (Radloff 1977), and the Depression subscale of the Hospital Anxiety Depression Scale (HADS-D) (Zigmond and Snaith, 1983). Both scales are validated and reliable self-report measures of symptoms of depression (Zigmond and Snaith, 1983; Radloff 1977). The CES-D consists of 20 items with total scores ranging from 0 to 60 and the HADS-D consists of 7 items with scores ranging from 0 to 21. Higher scores indicate more symptoms of depression.

CVD risk factors included blood pressure, glucose level and lipid levels. Blood pressure was measured twice on the right upper arm with the subject in a sitting position. Participants were asked to fast for at least 8 hours prior to blood withdrawal. Blood samples were then sent to the local laboratory for standard plama glucose and serum lipid measurements (total cholesterol, high and low density lipoprotein levels (HDL, LDL)) blood chemistry were analysed on a spectrophotometric chemistry analyser (Synchron LX20; Beckman, Fullerton, California, USA).

2.4. Statistical analysis

General characteristics were compared between men and women and tested using ANOVA for continuous variables and chi-squared test for dichotomous variables. Multiple linear regression models were fitted to assess the distributional assumption of normality. Systolic and diastolic blood pressure, plasma glucose levels, HDL, LDL and total cholesterol levels were natural log-transformed to ensure normally distributed residuals. The normality of residuals was tested using a one-sample Kolmogorov–Smirnov test. These analyses were performed using SPSS 11.0 for Windows.

Heritability estimates (h^2) were calculated as the ratio of the variance of the trait explained by additive polygenic effects to the total phenotypic variance of the trait. Bivariate analyses were performed to estimate the genetic and environmental correlations between the depression scores and CVD risk factors (Almasy et al., 1997; Williams et al., 1999). The genetic and environmental correlations can be calculated from the phenotypic correlations (ρ_P) by the following formula: $\rho_P = [\text{square root}]h_1^2[\text{square root}]h_2^2\rho_G + [\text{square root}](1-h_1^2)[\text{square root}](1-h_2^2)\rho_E$ (Falconer et al., 1996; Luynch and Walsh, 1998), where h_1^2 and h_2^2 are the heritability estimates of the traits, for which the phenotypic correlation is calculated, and ρ_G and ρ_E are the genetic and environmental correlations between these two traits. Significance of the phenotypic, additive genetic and environmental correlations was determined using a likelihood ratio test. To test whether a given correlation between two traits was significantly different from zero, the likelihood of a model in which this correlation was constrained to zero was compared with a model in which the same correlation was estimated. Twice the difference in ln-likelihoods of these

models yields a test statistic that is asymptotically distributed as a chi-squared statistic with degrees of freedom equal to the difference in number of parameters estimated in the two models.

Analyses were adjusted for age, sex, use of medication, degree of consanguinity and sibship effects. The degree of consanguinity, indicating the degree to which parents of each participant are related to each other through their ancestors, was estimated using the Fortran software Package for Pedigree Analysis (PEDIG) software (Boichard, 2002), based on the pedigree of the total population. PEDIG yields a coefficient for each participant, which was then entered as a covariate in the calculation of the heritability and genetic correlations. Sibship effects denote the exposure to early environmental factors that are shared by children of the same household. In this study, sibship effect estimates were phenotypic similarities induced in the progeny of the same mother. This effect is a combination of effects induced by shared early life environment and dominance genetic effects. Because of the small number of half sibs in our sample and the non-delineation of household effects in our data set, the effect due to sharing the same mother is almost indistinguishable from the sibship effect. The Sequential Oligogenic Linkage Analysis Routines (SOLAR) 2.1.2 software package (Southwest Foundation for Biomedical Research, San Antonio, Texas, USA www.sfbr.org) was used for the calculation of heritability estimates and for the genetic and environmental correlations. *p*-values lower than 0.05 (two-tailed) were considered statistically significant.

3. Results

The study included 2383 participants, 1355 women and 1028 men. Women reported more symptoms of depression and more frequently used antidepressive medication (Table 1). Men had worse cardiovascular profiles with significantly higher systolic and diastolic blood pressure, higher glucose levels, higher total cholesterol levels and lower HDL levels. Furthermore, men more frequently used antihypertensive medication and lipid modifying agents. Table 2 shows that there was a moderate correlation between the CES-D and HADS-D depression scores and between the cardiovascular risk factors. HADS-D was significantly associated to total cholesterol/HDL ratio levels ($\rho = 0.05$; $p = 0.05$) and inversely associated to HDL ($\rho = -0.06$; $p = 0.03$).

Heritability estimates were 0.24 (men 0.13, women 0.34) for CES-D and 0.22 (men 0.21 and women 0.37) ($p<0.001$) for HADS-D scores. Heritability estimates for CVD risk factors ranged from 0.18 ($p<0.001$) for systolic blood pressure to 0.46 ($p<0.001$) for HDL levels (Table 3). Table 4 presents the genetic and environmental correlations between symptoms of depression and CVD risk factors. Significant genetic correlations were found for CES-D scores for total cholesterol ($\rho_G = 0.30$; $p = 0.02$) and LDL levels ($\rho_G = 0.31$; $p = 0.02$) and for both CESD-D and HADS-D scores with total cholesterol/HDL ratios ($\rho_G = 0.25$; $p = 0.04$ and $\rho_G = 0.27$; $p = 0.02$) respectively. No evidence for a genetic correlation was found for glucose or blood pressure to either HADS-D or CES-D scores. Statistically significant environmental correlations in the opposite direction were found between CES-D scores and both total cholesterol ($\rho_E = -0.16$) and LDL levels ($\rho_E = -0.15$).

Table 1
General characteristics of the study population.

	Men ($n = 1028$)	Women ($n = 1355$)	*p*-value
Age, years	48.8 (14.7)	48.6 (15.3)	0.79
Symptoms of depression			
CES-D score	9.1 (8.6)	11.9 (10.2)	<0.001
HAD-D score	6.0 (4.1)	6.1 (4.5)	0.62
Cardiovascular risk factors			
Systolic blood pressure (mm Hg)	142.7 (17.6)	136.4 (21.0)	<0.001
Diastolic blood pressure (mm Hg)	81.6 (9.6)	78.7 (9.8)	<0.001
Glucose (mmol/l)	4.7 (1.1)	4.4 (0.8)	<0.001
Total cholesterol (mmol/l)	5.5 (1.1)	5.6 (1.1)	0.01
High density lipoprotein (mmol/l)	1.1 (0.3)	1.4 (0.4)	<0.001
Total cholesterol/HDL ratio	5.1 (1.5)	4.2 (1.2)	<0.001
Low density lipoprotein (mmol/l)	3.8 (1.0)	3.7 (1.0)	0.54
Medication use			
Antidepressants(%)	4.3	9.0	<0.001
Antihypertensives(%)	37.3	28.7	0.001
Insulin(%)	4.3	2.6	0.06
Lipid modifying agents(%)	26.2	16.3	<0.001

CES-D = Center for Epidemiologic Studies Depression Scale, HADS-D = Hospital Anxiety and Depression Scale. Values are means (standard deviations) for continuous variables and percentages for categorical variables. *p*-values were obtained using univariate analysis of variance for continuous variables and χ^2-statistics for categorical variables.

4. Discussion

We investigated genetic correlations between symptoms of depression and CVD risk factors and found significant genetic correlations of CES-D scores with total cholesterol, LDL and total cholesterol/HDL ratios and of HADS-D scores with total cholesterol/HDL ratios. Furthermore, we observed statistically significant negative environmental correlations of CES-D scores with total cholesterol and LDL.

Before interpreting the findings, some issues should be addressed. First, in our study symptoms of depression were assessed using two self-report questionnaires (CES-D and HADS-D). While the use of self-report questionnaires is widely accepted in epidemiological studies (Weissman et al., 1977), self-report scales do have their limitations. Items and answer scales differ between the two depression scales and these may lead to different inferences about the depression status of individuals. They may also explain the slight differences in the genetic and environmental correlations for the two scales that were observed in our analyses. Note that while the estimates of the genetic correlations differed in magnitude, the overall pattern of association was the same for the CES-D and the HADS-D scales.

A second issue is that we chose to use continuous variables instead of including dichotomous diagnoses because self-report questionnaires are easy to administer in large epidemiological studies and because analyzing scores as continuous variables increase the statistical power considerably (Almasy and Blangero, 2001). However, there are also disadvantages, for example when localizing genes, we cannot explicitly assume that these are specifically involved to a

Table 2
Phenotypic correlations between study variables.

	CES-D	HADS-D	SBP	DBP	Glucose	Cholesterol	HDL	Total cholesterol/HDL ratio
HADS-D	0.50***							
Systolic blood pressure (mm Hg)	−0.01	−0.01						
Diastolic blood pressure (mm Hg)	0.02	−0.01	0.60***					
Glucose (mmol/l)	−0.03	−0.01	0.23***	0.15***				
Total cholesterol (mmol/l)	0.02	0.01	0.17***	0.10***	0.05			
High density lipoprotein (mmol/l)	−0.02	−0.06**	0.04	−0.01	−0.11***	0.26***		
Total cholesterol/HDL ratio	0.03	0.05*	0.07*	0.09**	0.12***	0.40***	−0.73***	
Low density lipoprotein (mmol/l)	0.02	0.03	0.13***	0.10**	0.03	0.93***	−0.01	0.56***

CES-D = Center for Epidemiologic Studies Depression Scale, HADS-D = Hospital Anxiety and Depression Scale, SBP = systolic blood pressure, DBP = diastolic blood pressure. Adjusted for age, sex, consanguinity and medication (antidepressants, antihypertensives, insulin and lipid modifying agents) *$p<0.05$, **$p<0.01$, ***$p<0.001$.

Table 3
Heritability estimates of depression and cardiovascular risk factors.

	h^2 (se)
HADS-D	0.24 (0.04)
CES-D	0.22 (0.04)
Systolic blood pressure (mm Hg)	0.18 (0.05)
Diastolic blood pressure (mm Hg)	0.29 (0.04)
Glucose (mmol/l)	0.23 (0.05)
Total cholesterol (mmol/l)	0.26 (0.05)
High density lipoprotein (mmol/l)	0.46 (0.05)
Total cholesterol/HDL ratio	0.36 (0.05)
Low density lipoprotein (mmol/l)	0.28 (0.05)

All p-values<0.001, se = standard error. CES-D = Center for Epidemiologic Studies Depression Scale, HADS-D = Hospital Anxiety and Depression Scale, HDL = high density lipoprotein.

specific disorder but rather they may be predisposing to a more heterogeneous phenotype.

Thirdly, another limitation is that we did not take into account other disorders or medications that could be interacting, acting as effect modifiers or confounders. We only adjusted age, sex, medication, degree of consanguinity and sibship effects. We chose to adjust sex instead of stratifying in order to have more statistical power and as much information on the pedigree as possible. However, this approach assumes that the effects of other covariates are the same for men and women.

The only study to date that has assessed the genetic relationship between vascular risk factors and depression found an association between hypertension and symptoms of depression (Scherrer et al., 2003). Their study was conducted in middle-aged male–male twins from the Vietnam Era Twin Registry. We did not found any correlation between blood pressure and symptoms of depression. The different results could be due to the different scales used or perhaps to the age and sex differences between the two populations. Further research is needed to investigate the generalizability of our results.

Heritability estimates range widely between different study populations depending on the population investigated. For example previous studies have reported an heritability for depression that ranges from 0.17 to 0.78 (Sullivan et al., 2000). All the heritability estimates in our study were in line with previous studies, however ours lie compared to others on the lower side (Brenn, 1994; Mitchell et al., 1996; Abney et al., 2001; Snieder et al., 2003; Snieder et al., 1999). Until now, genetic studies have been performed in extended families selected on the basis of disease status or in affected sib-pairs, usually with comparatively small sizes, which inflate heritability estimates. Our population was not selected based on the presence of disease. In addition, our study was carried out in a large family-based samples which included second-degree and third-degree relatives, who do not usually share the same household, this may therefore generate more accurate heritability estimates.

The major finding in our study was that there is evidence for shared genetic factors contributing to the co-occurrence of symptoms of depression and lipid levels. Previous studies show a strong support for the hypothesis that abnormal lipid

Table 4
Genetic and environmental correlation between symptoms of depression and cardiovascular risk factors.

	CES-D		HADS-D	
	ρ_G	ρ_E	ρ_G	ρ_E
Systolic blood pressure (mm Hg)	−0.15 (0.16)	−0.03 (0.05)	0.11 (0.18)	−0.07 (0.04)
Diastolic blood pressure (mm Hg)	0.008 (0.12)	−0.04 (0.04)	0.15 (0.13)	−0.08 (0.04)
Glucose (mmol/l)	0.12 (0.14)	−0.05 (0.05)	0.24 (0.17)	−0.03 (0.04)
Cholesterol (mmol/l)	0.30 (0.13)*	−0.16 (0.05)***	0.21 (0.15)	−0.07 (0.05)
High density lipoprotein (mmol/l)	−0.10 (0.11)	−0.03 (0.05)	−0.20 (0.11)	−0.003 (0.05)
Total cholesterol/HDL ratio	0.25 (0.12)*	−0.06 (0.05)	0.27 (0.12)*	−0.02 (0.05)
Low density lipoprotein (mmol/l)	0.31 (0.13)*	−0.15 (0.05)***	0.20 (0.14)	−0.05 (0.05)

CES-D = Center for Epidemiologic Studies Depression Scale, HADS-D = Hospital Anxiety and Depression Scale, HDL = high density lipoprotein. ρ_G = genetic correlation, ρ_E = environmental correlation.
Values between brackets are standard errors. Analyses are adjusted for age, sex, use of medication (antidepressants, antihypertensives, insulin and lipid modifying agents), degree of consanguinity and sibship effects. *$p<0.05$, ***$p<0.001$.

and related fatty acid metabolism contributes to depression (Horrobin and Bennett, 1999). The enzymes, and other proteins that regulate the phospholipid metabolism, are for a large part genetically determined and clearly of interest in relation to depression and symptoms of depression. A review listed more than 100 candidate genes encoding for proteins involved in the metabolism of phospholipids and fatty acids which are localized in regions previously associated to psychiatric disorders (Bennett and Horrobin, 2000). To date the apolipoprotein E gene has been associated to depression (Lopez-Leon et al., 2007), and the prostaglandin and lipoprotein lipase genes have been related to bipolar disorder (Bennett and Horrobin, 2000). To what extent other lipids are involved remains to be determined.

Of note is that the environmental correlations between the CES-D scores and CVD risk factors showed an inverse relation. While shared genetic factors contribute to the co-occurrence of symptoms of depression and higher plasma total cholesterol and higher plasma LDL levels, shared environmental factors contributed to the co-occurrence of depression and lower plasma total cholesterol, and lower plasma LDL levels. When comparing the genetic and environmental correlations, genetic correlations were higher resulting in an overall positive correlation when ignoring the genetic or environmental origin of the correlation. The significant inverse environmental correlation may be related to the fact that (extremely) low cholesterol levels have been related to a higher prevalence of symptoms of depression and suicide (Horrobin and Bennett, 1999). Although there may be biological explanations for this inverse relationship, alternatively one may hypothesize that the low lipid levels result from the dietary habits or medication that are a consequence of symptoms of depression.

In conclusion, we found evidence for a shared genetic origin of the co-occurrence of symptoms of depression and blood lipid levels as well as for a shared environmental factor explaining the opposite direction. These findings are compatible with the view of a shared genetic origin of symptoms of depression and blood lipid levels, or, alternatively of symptoms of depression and brain lipid levels. The identification of these overlapping etiological pathways encourage future research to asses genes previously studied for mood disorders to be studied for cardiovascular disorders and vice versa.

Role of funding source

Funding for this study was provided by the Centre for Medical Systems Biology (CMSB) in the framework of the Netherlands Genomics Initiative (NGI) and the Dutch Brain Foundation (Hersenstichting Nederland). They had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Conflict of interest

All other authors declare that they have no conflicts of interest.

Acknowledgements

We thank the patients and relatives from the ERF study, the local healthcare centers, and the municipality for making this study possible. This study was supported by the Centre for Medical Systems Biology (CMSB) in the framework of the Netherlands Genomics Initiative(NGI) and the Dutch Brain Foundation (Hersenstichting Nederland).

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