2011

A test for common genetic and environmental vulnerability to depression and diabetes

Jeffrey F. Scherrer
Washington University School of Medicine in St. Louis

Hong Xian
Washington University School of Medicine in St. Louis

Patrick J. Lustman
Washington University School of Medicine in St. Louis

Carol E. Franz
Brown University

Jeanne McCaffery
Brown University

See next page for additional authors

Authors
Jeffrey F. Scherrer, Hong Xian, Patrick J. Lustman, Carol E. Franz, Jeanne McCaffery, Michael J. Lyons, Kristen C. Jacobsen, and William S. Kremen

www.AUSTRALIANACADEMICPRESS.com.au

ARTICLE AVAILABLE ONLINE
Twin Research and Human Genetics
Volume 14 ▮ Number 2 ▮ pp. 169–172

A Test for Common Genetic and Environmental Vulnerability to Depression and Diabetes

Jeffrey F. Scherrer,[1,2] Hong Xian,[1,3] Patrick J. Lustman,[1,2] Carol E. Franz,[4] Jeanne McCaffery,[5] Michael J. Lyons,[6] Kristen C. Jacobson[7] and William S. Kremen[4,8]

[1] *Research Service, St. Louis Veterans Affairs Medical Center VAMC, St. Louis, United States of America*
[2] *Department of Psychiatry, Washington University School of Medicine, United States of America*
[3] *Department of Internal Medicine, Washington University School of Medicine, United States of America*
[4] *Department of Psychiatry, University of California, United States of America*
[5] *Department of Psychiatry and Human Behavior, the Miriam Hospital and Warren Alpert School of Medicine at Brown University, United States of America*
[6] *Department of Psychology, Boston University, United States of America*
[7] *Department of Psychiatry, University of Chicago, United States of America*
[8] *Veterans Administration San Diego Healthcare System, La Jolla, United States of America*

Molecular genetic research has provided some evidence for the association between depression and metabolic disorders. We sought to determine if molecular findings are reflected in twin analyses testing if common genetic and environmental risk factors contribute to the co-occurrence of diabetes and depression. Data to derive depression and diabetes were collected from 1,237 male-male twins who participated in the 2005 Vietnam Era Twin Study of Aging (VETSA). The 1,237 twins were comprised of 347 MZ pairs, 3 MZ singletons, 267 DZ pairs and 6 unpaired twins. Depression was defined as a score below 46 on the Short Form-36 mental component summary score. Diabetes was defined by self report, use of anti-diabetic medications and insulin. Twin models were fit to estimate the correlation of genetic and environmental contributions to depression and diabetes. Consistent with other studies these data support the association between depression and diabetes (OR = 1.7; 95%CI: 1.1–2.7). Genetic vulnerability accounted for 50% (95%CI: 32%–65%) of the variance in risk for depression and 69% (95%CI: 52%–81%) of the variance in risk for diabetes. The genetic correlation between depression and diabetes was r = 0.19 (95%CI: 0–0.46) and the non-shared environmental correlation was r = 0.09 (95% CI: 0–0.45). Overall there is little evidence that common genetic and environmental factors account for the co-occurrence of depression and diabetes in middle aged men. Further research in female twins and larger cohorts is warranted.

■ **Keywords:** depression, diabetes, twins, behavior genetics, veterans

Background

Over the past 20 years evidence has accumulated to establish that major depression is a risk factor for developing type 2 diabetes (Anderson et al., 2001; Carnethon et al., 2003; Eaton et al., 1996; Golden et al., 2008; Knol et al., 2006; Palinkas et al., 2004). Meta-analyses have demonstrated that depression is twice as prevalent in individuals with type 2 diabetes compared to patients without diabetes (Anderson et al., 2001). Golden and colleagues (2008) demonstrated that depression predicts type 2 diabetes but found little evidence for the reverse. Recent meta-analyses concluded depression is a substantial risk factor for type 2 diabetes, but found only modest risk of depression following diabetes (Mezuk et al., 2008). The relationship between depression and diabetes may be due to poor health behaviors associated with depression, such as poor diet, smoking and lack of exercise (Strine et al., 2008). Depression may also contribute to diabetes via physiological abnormalities including dysfunctional neuroendocrine activity (Golden, 2007). Persons with diabetes

RECEIVED 31 August, 2010; ACCEPTED 08 December, 2010.

ADDRESS FOR CORRESPONDENCE: Jeffrey F. Scherrer, PhD, St. Louis VAMC, Research Service (151-JC) 501 North Grand Blvd, St. Louis, MO 63103. E-mail: scherrej@psychiatry.wustl.edu

may develop depressed mood because of the health burden of diabetes and its complications (Talbot & Nouwen, 2000). An alternative explanation for the co-occurrence of these disorders is the presence of common genetic and environmental factors. Recently, Kloiber and colleagues (2010) reported that tryptophan hydroxylase 2 polymorphisms in a subgroup of depressed patients was associated with increased risk of metabolic disorders, and Chiba and colleagues (2000) found genetic polymorphisms of the tyrosine hydroxylase and insulin genes were associated with insulin resistance and depressive symptoms. Based on this evidence we tested whether twin structural equation models would support the hypothesis that the co-occurrence of depression and diabetes is due to common genetic and environmental factors.

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 (Kremen et al., 2006). 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 (Eisen et al., 1987; Henderson et al., 1990). VETSA twins 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) (Robins et al., 1989) 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 by traveling 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. The 1,237 twins were comprised of 347 MZ pairs, 3 MZ singletons, 267 DZ pairs and 6 unpaired twins. Institutional Review Board approval was obtained at all sites, and all participants provided signed informed consent.

Diagnosis of depression and diabetes: Depression was defined as a score of 45 or less on the SF-36 mental component summary score. The use of this threshold to identify depression has been previously reported (Tavella et al., 2010). Lifetime diagnosis of diabetes was defined by a respondent's report that a physician told them they had the condition or by use of anti-diabetic medications and insulin.

Analytic Approach

Logistic regression models. Odds ratios were computed to evaluate the association of depression and diabetes. We fit only unadjusted regression models to demonstrate an association between disorders which established a basis for fitting genetic structural equation models. Genetic model fitting would not be meaningful if there was no significant association between phenotypes. Odds ratios were obtained from logistic regression modeling. Analyses were computed using the SURVEYLOGISTIC procedure in SAS v.9.2 which adjusts for error variance of non-independent observations in the twin data.

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% between members of a DZ twin pair. Shared environmental influences are experiences that twins have in common such as exposure to the same parenting, shared friends and sociodemographic factors primarily 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 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 to DZ twins, as indicated by a higher MZ than DZ tetrachoric correlation coefficient, suggests genetic influences (see Table 1).

Twin modeling was performed by the assumption of a threshold model in which the unmeasured genetic and environmental risk factors determine an underlying continuous liability for developing depression or diabetes and determine the correlation between the liabilities for depression and diabetes respectively. The liability model assumes there is a single normally distributed dimension of depression and diabetes with abrupt thresholds.

We fit bivariate genetic models using Mx software to the raw data (Neale & Cardon, 2002; Neale et al., 2003) to determine if depression and diabetes are: (1) influenced by genes,

TABLE 1

Within-Trait and Cross-Trait Tetrachoric Correlations for Depression and Diabetes

	Within-trait tetrachoric correlation		Cross-trait tetrachoric correlations between depression and diabetes	
Zygosity	Depression	Diabetes	Within-twin	Cross-twin
MZ	0.49	0.69	0.14	0.11
DZ	0.33	0.39	0.14	0.09

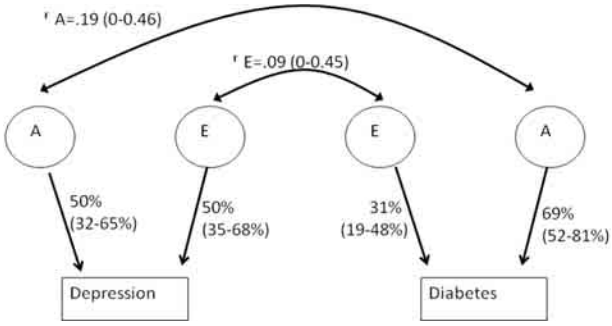

FIGURE 1

Variance component estimates and genetic and environmental correlations for the best fitting model of the lifetime co-occurrence of depression and diabetes.

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).

Bivariate analyses compared the fit of the full model (ACE) for depression and diabetes 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. We used raw data to fit the models. This procedure was repeated for the bivariate modeling of depression and diabetes. Under the best fitting bivariate model, we tested whether the genetic and environmental influences to depression and diabetes were correlated.

Results

17.7% of the twins met the SF-36 mental health component score indicating depression and 9.0% had diabetes by self report/medication. As compared to twins with no depression symptoms, diabetes was significantly associated with having depression (OR = 1.7; 95%CI:1.1–2.7).

The best-fitting twin model allowed for additive genetic and non-shared environmental contributions to depression and diabetes (Figure 1). The χ^2 obtained from subtracting the -2loglikelihood of the full model from the nested A E model was 0.50. This best fitting model did not allow for shared environmental variance. Under the best fitting model, genetic vulnerability accounted for 50% (95%CI: 32%–65%) of the variance in risk for depression and 69% (95%CI: 52%–81%) of the variance in risk for diabetes. The genetic correlation between depression and diabetes was r = 0.19 (95%CI: 0–0.46) and the non-shared environmental correlation was r = 0.09 (95% CI: 0–0.45). The small genetic correlation indicates that there was very little common genetic variance between diabetes and depression. Because the lower bound of the genetic correlation included zero, the point estimate was not statistically significant.

Discussion

To our knowledge this is the first report on whether there is evidence for common genetic and environmental contributions to depression and diabetes. As has been reported previously we found depression is associated with diabetes (Carnethon et al., 2003; Eaton et al., 1996; Palinkas et al., 2004; Anderson et al., 2001; Knol et al., 2006; Golden et al., 2008). Our data provide little evidence that the lifetime co-occurrence of depression and diabetes is explained by overlapping genetic contributions which is consistent with McCaffery's (2003) finding that co-occurrence of depression and metabolic factors are not explained by common genetic vulnerability in males.

Our data do not support the conclusion that the person who develops diabetes is at increased risk for depression because of genetic vulnerability and vice versa. This leaves only the physiological and behavioral consequences of diabetes as pathways to depression. Likewise physiological changes and poor health behaviors are pathways from depression to diabetes independent of common genetic and environmental factors.

Limitations

The number of undetected cases of diabetes may bias our results toward the null. Therefore the strength of association between depression and diabetes may be conservative. The cohort is an all male population and predominately white so results may not generalize to females and minority populations. 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 diabetes, depression or other correlated factors.

Conclusions

Further research is warranted in larger cohorts to establishing the genetic architecture to comorbid diabetes and depression to inform pursuit of research at the molecular genetic level.

Acknowledgments

National Institutes of Health/National Institute on Aging Grants U24 RR021382, R01 AG18386, RO1 AG18384, RO1 AG22381, RO1 AG 22982. J. F. Scherrer is supported by a VA HSR&D Career Development award. The United States Department of Veterans Affairs has provided financial support for the development and maintenance of the Vietnam Era Twin Registry (VETR). Numerous organizations have provided invaluable assistance in the conduct of this study, including: Department of Defense; National Personnel Records Center, National Archives and Records Administration; the Internal Revenue Service; National Opinion Research Center; National Research Council, National Academy of Sciences; the Institute for Survey Research, Temple University. Most importantly, the authors gratefully acknowledge the continued cooperation

and participation of the members of the VET Registry and their families. Without their contribution this research would not have been possible.

References

American Psychiatric Association. (1987). *Diagnostic and statistical manual of mental disorders* (3rd ed., rev.). Washington, DC, American Psychiatric Association.

Anderson, R. J., Freedland, K. E., Clouse, R. E., & Lustman, P. J. (2001). The prevalence of comorbid depression in adults with diabetes. A meta-analysis. *Diabetes Care, 24,* 1069–1078.

Carnethon, M. R., Kinder, L. S., Fair, J. M., Stafford, R. S., & Fortmann, S. P. (2003). Symptoms of depression as a risk factor for incident diabetes: Findings from the National Health and Nutrition Examination Epidemiologic Follow-up Study, 1971–1992. *American Journal of Epidemiology, 158,* 416–423.

Chiba, M., Suzuki, S., Hinokio, Y., Hirai, M., Satoh, Y., Tashiro, A., Utsumi, A., Awata, T., Hongo, M., & Toyota, T. (2000). Tyrosine hydroxylase genet microsatellite polymorphism associated with insulin resistance in depressive disorder. *Metabolism Clinical and Experimental, 49,* 1145–1149.

Eaton, W. W., Armenian, H., Gallo, J., Pratt, L., & Ford, D. E. (1996). Depression and risk for onset of type II diabetes: A prospective population-based study. *Diabetes Care, 19,* 1097–1102.

Eisen, S., True, W., Goldberg, J., Henderson, W., & Robinette, C. D. (1987). The Vietnam Era Twin (VET) Registry: Method of construction. *Acta Geneticae Medicae et Gemellologiae, 36,* 61–66.

Golden, S. H. (2007). A review of the evidence for a neuroendocrine link between stress, depression and diabetes mellitus. *Current Diabetes Review, 3,* 252–259.

Golden, S. H., Lazo, M., Carnethon, M., Bertoni, A. G., Schreiner, P. J., Diez Roux, A. V., Lee, H. B., & Lyketsos, C. (2008). Examining a bidirectional association between depressive symptoms and diabetes. *Journal of the American Medical Association, 299,* 2751–2759.

Henderson, W. G., Eisen, S., Goldberg, J., True, W. R., Barnes, J. E., & Vitek, M. E. (1990). The Vietnam Era Twin Registry: A resource for medical research. *Public Health Reports, 105,* 368–373.

Knol, M. J., Twisk, J. W. R., Beekman, A. T. F., Heine, R. J., Snoek, F. J., & Pouwer, F. (2006). Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. *Diabetologia, 49,* 837–845.

Kloiber, S., Kohli, M. A., Brueckl, T., Ripke, S., Ising, M., Uhr, M., Menke, A., Unschuld, P. G., Horstman, S., Salyakina, D., Muller-Myhsok, B., Binder, E. B., Holsboer, F., & Lucae, S. (2010) Variations in tryptophan hydroxylase 2 linked to decreased serotonergic activity are associated with elevated risk for metabolic syndrome in depression. *Molecular Psychiatry, 15,* 736–747.

Kremen, W. S., Thompson-Brenner, H., Leung, Y. M. J., Grant, M. D., Franz, C. E., Eisen, S. A., Jacobson, K. C., Boake, C., & Lyons, M. J. (2006). Genes, environment, and time: The Vietnam Era Twin Study of Aging (VETSA). *Twin Research and Human Genetics, 9,* 1009–1022.

McCaffery, J. M., Niaura, R., Todaro, J. F., Swan, G. E., & Carmelli, D. (2003). Depressive symptoms and metabolic risk in adult male twins enrolled in the National Heart, Lung, and Blood Institute Twin Study. *Psychosomatic Medicine, 65,* 490–497.

Mezuk, B., Eaton, W. W., Albrecht, S., & Golden, S. H. (2008). Depression and type 2 diabetes over the lifespan. A meta-analysis. *Diabetes Care, 31,* 2383–2390.

Neale, M. C., & Cardon, L. R. (1992). *Methodology for genetic studies of twins and families.* Dordrecht, The Netherlands: Kluwer.

Neale, M. C., Boker, S. M., Xie, G., & Maes, H. H. (2003). *Mx: Statistical Modeling* (6th edition). Richmond, VA. Department of Psychiatry: Virginia Commonwealth University.

Robins, L.N., Helzer, J.E., Cottler, L., & Goldring, E. (1989). NIMH Diagnostic Interview Schedule. Version III — Revised (DIS-III-R). St. Louis, MO: Washington University School of Medicine, Department of Psychiatry.

Scherrer, J. F., Xian, H., Bucholz, K. K., Eisen, S. A., Lyons, M. J., Goldberg, J., Tsuang, M., & True, W. R. (2003). A twin study of depression symptoms, hypertension, and heart disease in middle-aged men. *Psychosomatic Medicine, 65,* 548–557.

Strine, T. W., Mokdad, A. H., Dube, S. R., Balluz, L. S., Gonzalez, O., Berry, J. T., Manderscheid, R., & Kroenke, K. (2008). The association of depression and anxiety with obesity and unhealthy behaviors among community-dwelling US adults. *General Hospital Psychiatry, 30,* 127–137.

Talbot, F., & Nouwen, A. (2000). A review of the relationship between depression and diabetes in adults. Is there a link? *Diabetes Care, 23,* 1556–1562.

Tavella, R., Air, T., Tucker, G., Adams, R., Beltrame, J. F., & Schrader, G. (2010). Using the Short Form-36 mental summary score as an indicator of depressive symptoms in patients with coronary heart disease. *Quality of Life Research, 19,* 1105–1113.