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Depression and Obesity: Do Shared Genes Explain the Relationship?

Niloofar Afari[1,2], **Carolyn Noonan**[3], **Jack Goldberg**[4,5], **Peter Roy-Byrne**[6], **Ellen Schur**[3], **Golnaz Golnari**[1], and **Dedra Buchwald**[3]

[1]Department of Psychiatry, University of California, San Diego, La Jolla, CA

[2]Veterans Affairs San Diego Healthcare System & VA Center of Excellence for Stress and Mental Health, San Diego, CA

[3]Department of Medicine, University of Washington, Seattle, WA

[4]Department of Epidemiology, University of Washington, Seattle, WA

[5]Vietnam Era Twin Registry, Seattle, WA

[6]Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA

Abstract

Background—Studies have found a modest association between depression and obesity, especially in women. Given the substantial genetic contribution to both depression and obesity, we sought to determine whether shared genetic influences are responsible for the association between these 2 conditions.

Methods—Data were obtained from 712 monozygotic and 281 dizygotic female twin pairs who are members of the community-based University of Washington Twin Registry. The presence of depression was determined by self-report of doctor-diagnosed depression. Obesity was defined as body mass index of ≥ 30, based on self-reported height and weight. Generalized estimating regression models were used to assess the age-adjusted association between depression and obesity. Univariate and bivariate structural equation models estimated the components of variance attributable to genetic and environmental influences.

Results—We found a modest phenotypic association between depression and obesity (Odds Ratio = 1.6, 95% Confidence Interval = 1.2-2.1). Additive genetic effects contributed substantially to depression (57%) and obesity (81%). The best fitting bivariate model indicated that 12% of the genetic component of depression is shared with obesity.

Conclusions—The association between depression and obesity in women may be in part due to shared genetic risk for both conditions. Future studies should examine the genetic, environmental, social, and cultural mechanisms underlying the relationship between this association.

Keywords

Depression; Genetics; Heritability; Obesity; Twins

Correspondence should be sent to Niloofar Afari, University of California, San Diego, Department of Psychiatry, 9500 Gilman Drive, Mail Code 0738, La Jolla, CA 92093-0738, Telephone: (858) 534-2670, Fax: (858) 822-3777, nafari@ucsd.edu .

INTRODUCTION

Depression and obesity are prevalent, complex and costly public health concerns [1-3]. Approximately 10% of the U.S. population suffers from depression annually [4], and the prevalence of obesity is rising with up to 30% of the population obese and 5% extremely obese [5]. Both conditions are associated with negative health outcomes such as cardiovascular disease and diabetes [6-14].

Many studies have examined the association between depression and obesity, yet findings are inconsistent. While some studies have reported obese individuals have 5 times the risk of major depression than the non-obese [3,15-18], others have not reproduced these findings [19-22]. The relationship between depression and obesity also may be, to some extent, sex dependent [23]. For example, four studies have shown that middle-aged men appear to be less depressed than their normal weight counterparts [24-27]. However, in a recent large epidemiological study obese men were at increased risk for mood and anxiety disorders [28]. Conversely, obese and overweight women consistently are at great risk of experiencing depression across the lifespan [28-33]. These sex differences suggest that environmental factors influence the co-morbidity of depression and obesity. However, both depression [34] and obesity [35] have a strong genetic basis and shared genetic risk factors are possible. In that regard, the involvement of some of the same genes in the mechanisms underlying both conditions [36-43], highlights the potential for a shared genetic vulnerability to both depression and obesity.

Twin studies offer a unique opportunity to investigate shared disease etiology by evaluating the relative contributions of genetic and environmental factors to more than one condition. Despite the known substantial genetic contribution to both depression and obesity, no twin study has examined the potential for shared genetic influences for both conditions. Our goals were to: 1) determine if depression and obesity are associated in female twins from a community-based twin registry; 2) assess the genetic influence on each trait; and 3) estimate the magnitude of shared genetic influence that could explain the association between depression and obesity.

MATERIALS AND METHODS

Sample

The University of Washington Twin Registry is a community-based sample of twins derived from the drivers' license applications of the Washington State Department of Licensing. Detailed description of recruitment strategy, response rate, representativeness of the Registry twins is presented elsewhere [44]. In short, drivers' license numbers in Washington State are derived from a person's name and date of birth, thus, the Department of Licensing asks every new applicant if s/he is a twin to avoid issuing duplicate license and identification numbers to twins. The University of Washington Twin Registry receives lists of license applicants who are twins, and each member of the pair is invited to join the Registry and complete a health survey. The brief survey contains items on demographics, habits, doctor-diagnosed health conditions, symptoms, healthcare use, and various abridged, standardized measures of physical and mental health. While the Registry is an ongoing collection of participants, data presented here were obtained from 2002-2006. All Registry procedures and data collection involved in this study were approved by the University of Washington Institutional Review Board. Informed consent was obtained from all twins.

Self-report measures

Questions about childhood similarity that correctly classify zygosity with an accuracy of 95 – 98% compared with biological indicators were used to determine zygosity [45-48].

Sociodemographic factors included age, sex, race, education, and marital status. To determine lifetime depression, twins were given a list of conditions including depression and asked: "Has your doctor ever told you that you have any of the following conditions?" Body mass index (BMI) was calculated based on height and weight (weight/height^2), and obesity was defined as a BMI of ≥ 30 kg/m^2. All questions were asked concurrently.

Statistical analyses

Descriptive statistics for demographic and health characteristics were calculated using means and standard deviations for continuous variables and percents for categorical variables. To investigate the overall age-adjusted association of depression and obesity, we fit a generalized estimating regression model to account for the lack of independence of members of twin pairs. Further, the association between depression and obesity in monozygotic (MZ) and dizygotic (DZ) pairs was assessed by 3 types of polychoric correlations: phenotypic, twin, and cross-twin, cross-trait. Phenotypic correlations measure the association of depression and obesity within individuals, whereas twin correlations examine the within pair similarity for a trait. Cross-twin, cross-trait correlations assess the degree of association for 2 traits, for example, the relationship of depression in twin 1 and obesity in twin 2, as well as depression in twin 2 and obesity in twin 1.

Classical twin analyses compare phenotypic similarity in MZ twins and DZ twins; greater phenotypic similarity in MZ than DZ twins indicates a genetic component in the parameter of interest. We used univariate structural equation modeling to estimate the additive genetic (A), common environmental (C), and unique environmental (E) influences on depression and obesity individually [49]. Models were fitted assuming an additive genetic correlation of 1.0 for MZ and 0.5 for DZ twins, a shared environmental correlation of 1.0 for all twins, and a unique environmental correlation of 0.0 for all twins. Modeling began by estimating parameters for the full model (ACE), and then reduced models were constructed by removing specific parameters. The goodness-of-fit of each reduced model was compared with the full model using a likelihood ratio test. We present parameter estimates, 95% confidence intervals, and goodness-of-fit statistics for the full model (ACE), and models in which all variance was attributable to genetic and specific environmental factors (AE), and common and specific environmental factors (CE). Parameters were removed from the model if doing so did not result in a significant degradation of model fit ($p \leq 0.05$). Models were also evaluated using Akaike's Information Criterion [50], where a lower value indicates a superior fit. Finally, the proportions of variance due to additive genetics, common environment, and unique environment were estimated from the final best-fitting model.

Structural equation modeling can also be used to estimate the variability in 2 or more phenotypes due to shared vulnerabilities. We used bivariate structural equation modeling to estimate shared genetic and environmental vulnerabilities with a full Cholesky decomposition that specified a general multivariate covariance structure and allowed for both specific and shared influences on depression and obesity. We identified the final best-fitting, most parsimonious model by removing parameters that did not significantly degrade the fit of the model based on likelihood ratio tests and the Akaike Information Criteria [50] .We present goodness-of-fit statistics for the full and reduced bivariate models of depression and obesity, and trait-specific and shared variance components for the best-fitting model.

Descriptive analyses and polychoric correlations were computed using Stata 9.2 for Windows (Stata Corp LP, 2006). Structural equation models were fit using MxGui version 1.4.06 (Department of Psychiatry, Virginia Commonwealth University, 2003). A p-value of 0.05 was considered criteria for a significant degradation of model fit.

RESULTS

Descriptive characteristics

Table 1 presents the demographic and health characteristics of 712 MZ and 281 DZ female twin pairs that had complete data and were included in the analyses by depression status. The sample included 481 twins with self-reported doctor-diagnosed depression and 1,505 non-depressed twins. The depressed and non-depressed groups were similar in age, education, race, marital status, zygosity, and mean BMI. Overall, 19% of depressed twins and 12% of non-depressed twins were classified as obese. There was a positive age-adjusted association between depression and obesity (Odds Ratio = 1.6, 95% Confidence Interval = 1.2-2.1).

Polychoric correlations

Table 2 presents phenotypic, twin, and cross-twin, cross-trait polychoric correlations for depression and obesity by zygosity. Phenotypic correlations ranged from 0.14-0.20 in MZ twins and from 0.09-0.23 in DZ twins. Larger MZ than DZ twin correlations for depression (0.55 versus 0.36) and obesity (0.81 versus 0.51) indicated a genetic basis for each trait. The higher cross-twin, cross-trait correlations in MZ compared with DZ pairs suggested modest shared genetic influences on both traits.

Univariate structural equation modeling

Table 3 shows the results of the univariate structural equation models for depression and obesity. The best fitting model for depression included both additive genetic effects (57%) and unique environmental effects (43%). Similarly, the best fitting model for obesity included additive genetic effects (81%) and unique environmental exposures (19%).

Bivariate structural equation modeling

The best-fitting, most parsimonious bivariate model included only shared additive genetic influences for depression and obesity as presented in Table 4. Based on the best fitting model, we estimated that 12% of the genetic component of depression is shared with obesity. Figure 1 illustrates the full model with standardized pathway coefficients and the relative magnitude of the genetic, common and unique environmental effects on both traits.

DISCUSSION

To our knowledge, this is the first study to examine the shared genetic contribution to depression and obesity in a twin population. We found that a self-reported doctor diagnosis of depression was modestly associated with obesity, as well as significant genetic components to depression and obesity in female twins. Our analyses also suggested that the association between depression and obesity in women may be partially due to shared genetic risk factors for both conditions.

Our findings support previous research on the genetic basis of depression and obesity, separately. A meta analysis of twin studies found that the heritability of major depression is approximately 37% with minimal to no common environmental influences on the phenotype [51]. Similarly, a recent study with the largest twin sample to date estimated the heritability of major depression to be 38%, with heritability higher in women (42%) than in men (29%) [34]. Obesity also manifests a strong familial influence with the prevalence 2-8 times higher in families of obese individuals than in the population at large [52]. Heritability estimates for obesity range from 50% to 90% depending on the population [53], with higher estimates in twin studies (50%-80%) than in adoption studies (10%-30%) [52].

Both depression and obesity appear to be polygenic with multiple genes contributing to the development of each condition. Although results from linkage and association studies require replication, a recent meta-analysis of genetic studies on major depression identified 6 likely depression susceptibility genes [54]. Other studies have focused on genes involved in the serotonergic pathway in the brain [55], and polymorphisms in the promoter region of the 5-*hydroxylase-tryptamine transporter* (5-HTT) protein have been associated with personality traits that may predispose individuals to depression [56] or interact with environmental factors such as life stress to result in depression [57]. Likewise, studies on the genetics of obesity have revealed hundreds of associated genes [58-61], with variants of the fat mass and obesity associated gene (FTO) strongly associated with adiposity in multiple populations [62-65].

The association between depression and obesity could be due to several factors [1], including the influence of each trait on the other [66,67], shared environmental determinants, or shared genetic factors. We found a modest overlap in the genetic risk factors that increase liability to both depression and obesity. In contrast, a recent family-based study did not detect an association between symptoms of depression and measures of body composition (e.g., BMI) in a genetically isolated community in the southwest of The Netherlands [68]. Although more research is needed to reconcile these disparate results, our findings are consistent with association studies demonstrating that the glucocorticoid receptor gene, the corticotrophin releasing hormone receptor gene, the serotonin 2A and 2C receptor genes, and the dopamine receptor D4 gene are linked to both depression and obesity [36-43]. In addition, polymorphisms in the norepinephrine transporter gene have been associated with both depression and feeding behavior [69]. Finally, disturbances in the hypothalamic-pituitary-adrenal axis, immune functioning, and the serotonin/dopamine pathways in both conditions [70-72], raise the possibility that both depression and obesity are influenced by gene-by-environment interactions. Such interactions are encompassed within the significant additive genetic component noted in this study. Environmental and behavioral factors such as emotional eating and physical inactivity also may play a role in the influence of each trait on the other [23, 73-75]. Clearly, identifying modifiable environmental factors and examining the genetic, environmental, social, and cultural mechanisms underlying the relationship between depression and obesity can lead to more effective prevention and treatment strategies for both conditions.

This study has several limitations. First, because our variables were intended as screening items on a large survey, we were limited in our assessments of depression and obesity. The potentially higher level of error in these brief assessments would be expected to reduce genetic effects estimates. Therefore, our findings are likely a conservative estimate of the shared genetic contribution to depression and obesity. Second, the use of self-reported doctor diagnosed depression could have resulted in response bias or misclassification of depression. One study noted that self-report of a physician diagnosis of depression underestimated current depressive symptoms, though both self-reported physician diagnosis and depressive symptoms were independently associated with obesity [76], and therefore appear to be valid measures to assess the relation of depression and obesity. While the self-reported rates of doctor diagnoses depression in our sample were consistent with previously reported population-based rates of lifetime depression in women [77], nonetheless, our findings should be replicated with symptom- or diagnosis-based measures of depression. In addition, no measure of current depression was available, thus our findings are restricted to the association between lifetime depression and obesity. Second, BMI ascertained through self-reported height and weight may underestimate true BMI or be differentially reported by twins with and without depression. Although women tend to underreport their weight, subjective assessments of weight do not appear to be affected by depression or obesity [78]. Thus, potential misclassification due to self-report is unlikely to significantly affect the estimates of association and would not be expected to differ between MZ and DZ twin pairs. Finally, while the rates of obesity in this

sample are in line with those of White, well-educated women in Washington State [79], our results may not be generalizable to twin populations with different racial or educational backgrounds.

CONCLUSIONS

Our findings from a community-based sample of twins provide evidence for a modest shared genetic vulnerability to depression and obesity in women. Although future research should confirm these results using standardized clinical criteria to establish the diagnosis of depression and objective data to determine BMI, these results highlight the need for more systematic approaches to genetic association studies pertaining to depression and obesity. Such research may eventually yield new insights into the common pathophysiology and risk factors for these conditions. Additionally, examining the environmental, social, and cultural mechanisms in these 2 conditions jointly can identify targets for effective prevention and treatment strategies for individuals with comorbid depression and obesity.

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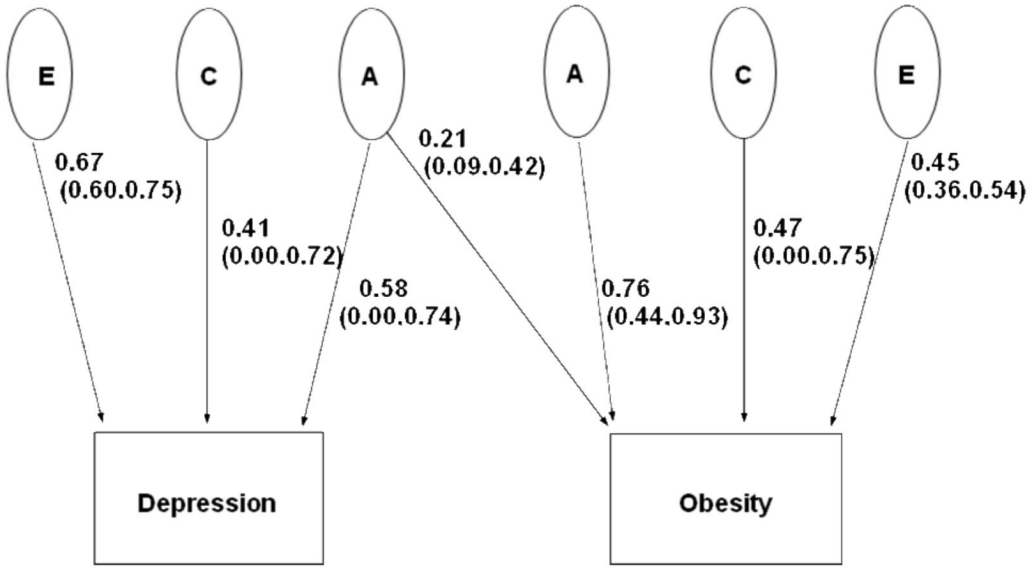

Figure 1.

Path diagram depicting additive genetic effects shared by depression and obesity plus additive genetic (A), common environmental (C), and unique environmental (E) effects unique to each trait. The parameter estimates and 95% confidence intervals are path coefficients, indicating the relative importance of the latent variables A, C, and E to depression and obesity.

Table 1

Demographic and health characteristics of depressed and non-depressed female twins

Characteristic	Depressed (*n = 481*)	Not depressed (*n = 1,505*)
Demographic		
Age, *mean years (SD)*	33.9 (14.1)	31.0 (14.7)
Education, *mean years (SD)*	13.7 (2.5)	13.7 (2.2)
White, %	89	85
Married or cohabitating, %	54	58
Zygosity, %		
Monozygotic	69	73
Dizygotic	31	27
Health		
Body mass index, *mean kg/m^2(SD)*	25.1 (5.7)	24.1 (4.8)
Body mass index, %		
< 18.5 (underweight)	6	4
18.5 – 24.99 (normal)	56	65
25.0 – 29.99 (overweight)	20	19
≥ 30.0 (obese)	19	12

Table 2

Polychoric correlations for depression and obesity in female twin pairs by zygosity

	Twin 1		Twin 2	
	Depression	**Obesity**	**Depression**	**Obesity**
Monozygotic				
Twin 1				
Depression	1.00			
Obesity	0.20 (0.04, 0.36)*	1.00		
Twin 2				
Depression	0.55 (0.44, 0.65)†	0.08 (−0.09, 0.25)‡	1.00	
Obesity	0.14 (−0.01, 0.30)‡	0.81 (0.73, 0.89)†	0.14 (−0.02, 0.30)*	1.00
Dizygotic				
Twin 1				
Depression	1.00			
Obesity	0.09 (−0.14, 0.31)*	1.00		
Twin 2				
Depression	0.36 (0.17, 0.54)†	0.02 (−0.20, 0.25)‡	1.00	
Obesity	0.06 (−0.17, 0.29)‡	0.51 (0.32, 0.69)†	0.23 (0.01, 0.45)*	1.00

*Phenotypic correlation between depression and obesity;

†Twin correlation;

‡Cross-twin, cross-trait correlation; Depression measure was self-report of a doctor diagnosis; Obesity measure was BMI ≥ 30.0 kg/m^2.

Table 3

Univariate structural equation models of depression and obesity in female twin pairs

	Estimates of variance components† (95% Confidence Intervals)			Test of model fit			
Model*	**Additive genetic (A)**	**Common environment (C)**	**Unique environment (E)**	**χ^2**	**df**	***P* value**	**AIC‡**
Depression							
ACE	0.42 (0.00, 0.65)	0.14 (0.00, 0.51)	0.44 (0.35, 0.55)	–	–	–	–
AE	**0.57 (0.46, 0.66)**	**–**	**0.43 (0.34, 0.54)**	**0.49**	**1**	**0.48**	**−1.51**
CE	–	0.50 (0.40, 0.58)	0.50 (0.42, 0.60)	3.92	1	0.05	1.92
Obesity							
ACE	0.59 (0.20 – 0.87)	0.21 (0.00, 0.56)	0.20 (0.13, 0.30)	–	–	–	–
AE	**0.81 (0.72, 0.88)**	**–**	**0.19 (0.12, 0.28)**	**1.08**	**1**	**0.30**	**−0.92**
CE	–	0.71 (0.62, 0.78)	0.29 (0.22, 0.38)	9.57	1	0.002	7.57

**ACE* refers to a model that includes additive genetics (A), common environment (C), and unique environment (E), *AE* only includes additive genetics and unique environment, and *CE* only includes common and unique environment;

†Proportion of variance caused by additive genetics, shared environment, and unique environment according to each model;

‡Akaike's information criterion (AIC) is a global measure of goodness of fit; the best-fitting and most parsimonious models are shown in bold.

Table 4

Bivariate structural equation models of depression and obesity in female twin pairs

Shared component	Estimates of variance components (95% Confidence Intervals)			Test of model fit			
	Additive genetic (A)	Common environment (C)	Unique environment (E)	χ^2	df	*P* value	AIC*
ACE				–	–	–	–
Depression	0.38 (0.03, 0.64)	0.16 (0.05, 0.48)	0.45 (0.35, 0.56)				
Obesity	0.59 (0.20, 0.84)	0.21 (0.00, 0.56)	0.20 (0.13, 0.29)				
CE				0.75	1	0.39	−1.25
Depression	0.36 (0.00, 0.61)	0.18 (0.08, 0.54)	0.46 (0.36, 0.57)				
Obesity	0.57 (0.19, 0.84)	0.23 (0.00, 0.58)	0.20 (0.14, 0.30)				
AE				0.01	1	0.92	−1.99
Depression	0.38 (0.01, 0.64)	0.17 (0.00, 0.52)	0.45 (0.35, 0.56)				
Obesity	0.58 (0.20, 0.69)	0.22 (0.00, 0.56)	0.20 (0.13, 0.29)				
AC				1.16	1	0.28	−0.84
Depression	0.38 (0.01, 0.64)	0.16 (0.00, 0.51)	0.45 (0.35 (0.56)				
Obesity	0.57 (0.20, 0.86)	0.21 (0.00, 0.56)	0.20 (0.13, 0.29)				
A				**1.32**	**2**	**0.52**	**−2.68**
Depression	**0.38 (0.02, 0.64)**	**0.17 (0.00, 0.51)**	**0.45 (0.36, 0.56)**				
Obesity	**0.58 (0.20, 0.87)**	**0.22 (0.00, 0.57)**	**0.20 (0.13, 0.29)**				
C				3.24	2	0.20	−0.76
Depression	0.37 (0.00, 0.60)	0.17 (0.07, 0.53)	0.45 (0.36, 0.57)				
Obesity	0.58 (0.20, 0.82)	0.22 (0.02, 0.57)	0.20 (0.16, 0.30)				
E				5.73	2	0.06	1.27
Depression	0.36 (0.00, 0.63)	0.17 (0.00, 0.53)	0.46 (0.36, 0.58)				
Obesity	0.56 (0.18, 0.85)	0.22 (0.00, 0.42)	0.21 (0.15, 0.31)				
None				12.89	3	0.01	6.89
Depression	0.38 (0.00, 0.64)	0.16 (0.00, 0.53)	0.45 (0.36, 0.57)				
Obesity	0.59 (0.20, 0.86)	0.21 (0.00, 0.56)	0.20 (0.13, 0.30)				

*Akaike's information criterion (AIC) is a global measure of goodness of fit; the best-fitting and most parsimonious model is shown in bold.