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Depression Among Adults with Neurofibromatosis Type 1: Prevalence and Impact on Quality of Life

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Abstract

Neurofibromatosis type 1 (NF1) carries a significant psychosocial burden for affected individuals. The objective of this study was to measure the prevalence of depressive symptoms among a large sample of adults with NF1 and to quantify the impact of depressive symptoms on QoL. This cross-sectional study used an Internet-based questionnaire to collect data from 498 adults who self-reported as having NF1. Using the Center for Epidemiologic Studies Depression scale, 55% of all participants (61% of females and 43% of males) scored above 16, indicating a high likelihood of clinical depression. In a multivariate regression model controlling for demographics and potential confounders, depressive symptoms accounted for 32% of the variance in QoL as measured by the Quality of Life Index. This study is the largest to date and found the highest prevalence of depression compared to prior studies. Our data provide more compelling evidence that individuals with NF1 are at increased risk for psychiatric morbidity and suggest that this population should be

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Ms. Cohen contributed to study concept and design, data analysis and interpretation, statistical analysis, manuscript writing and revision, and study coordination.

Dr. Levy contributed to study concept and design, and manuscript revision.

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Dr. Biesecker contributed to study concept and design, data analysis and interpretation, manuscript revision, and study supervision.

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routinely screened for depression. Because depression was found to be strongly associated with QoL and accounted for nearly one-third of the variance in QoL, it is likely that effectively treating depression may significantly enhance QoL for individuals with NF1.

Keywords

Neurofibromatosis; Depression; Quality of Life; Psychosocial burden

INTRODUCTION

Neurofibromatosis type 1 (NF1) is a genetic disorder that carries a significant psychosocial burden for affected individuals. Features of this neurocutaneous condition include multiple café-au-lait spots, skin-fold freckling, iris Lisch nodules, bony dysplasia, and neurofibromas, as well as predisposition to other benign and malignant tumors.[1,2] NF1 is inherited in an autosomal dominant manner with complete penetrance, childhood onset, and wide inter- and intra-familial phenotypic variability. NF1 is panethnic and affects approximately 1 in 3,000 people.[1]

Empirical evidence demonstrates a spectrum of psychosocial issues common in NF1. Aspects of NF1 that are especially challenging include the unpredictable nature of the disease, variability in severity of symptoms and medical complications, and vulnerability to stigmatization due to the highly visible and often cosmetically disfiguring features of the condition. Individuals with NF1 are at increased risk for experiencing social and emotional difficulties, including anxiety, depression, low self-esteem and/or body image, social withdrawal, difficulty forming interpersonal relationships, behavioral problems, and difficulties in school.[3–10]

Depression in particular appears to be common among individuals with NF1. Previous studies have found a significantly higher incidence of depression and psychiatric disorders among adults with NF1 compared to the general population. In a recent study of 248 adult patients with neurofibromatosis tumor suppressor syndrome (including 133 with NF1, the rest with NF2 or schwannomatosis), 37% of males and 46% of females scored at or above the cut-off of 16 on the Center for Epidemiologic Studies Depression (CESD) scale, which indicates a high likelihood of clinical depression.[11] In a previous study of 128 adult patients with NF1, one third (32.8%) had symptoms indicative of psychiatric morbidity, as assessed using the General Health Questionnaire (GHQ-12).[12] Similarly, a 12-year longitudinal study of 48 adults with NF1 found that 21% met DSM-IIIR diagnostic criteria for dysthymia and overall one-third of patients met criteria for at least one psychiatric disorder.[13] By comparison, an epidemiological survey of major depressive disorder in the general population found a lifetime prevalence of 16.2% and a 12-month prevalence of 6.6%.[14]

Several studies have documented reduced quality of life (QoL) among individuals with NF1. Three studies of adults with NF1 found that QoL was strikingly lower in all domains as compared to healthy norms, with the greatest impact in the emotional domains of QoL.[7,9,15] Children with NF1 were found to have similarly reduced QoL.[5,6,16–18] No studies have explicitly measured the impact of depression on QoL among adults with NF1 using

validated instruments. However, it seems likely that depressed individuals will have lower QoL.

The purpose of this study was to measure the prevalence of depressive symptoms among a large sample of adults with NF1 and to quantify the impact of depressive symptoms on QoL.

MATERIALS AND METHODS

Participants

The study population consisted of adult men and women at least 18 years of age who self-reported as having NF1 and were able to read and write in English. Participants were recruited through national NF1 organizations: Children's Tumor Foundation and Neurofibromatosis Inc. These organizations advertised the study through email listservs, newsletter mailings, and website postings. In addition, participants were recruited from NF1 clinical research protocols at the National Institutes of Health.

Procedure

The study used a cross-sectional design with quantitative methods to collect data using a one-time self-administered questionnaire. The majority of participants completed the survey online through a secured Internet site.

The study was approved by the Institutional Review Board at the National Human Genome Research Institute, National Institutes of Health (Protocol # 08-HG-N144).

Measures

Depression was measured using the Center for Epidemiologic Studies Depression scale (CESD).[19] This widely used and validated instrument consists of 20 items that assess how often the respondent has experienced various emotional and behavioral symptoms of depression in the past week. Each item was rated on a five-point scale anchored at "rarely or none of the time" (0) and "most or all of the time" (4). Although the original CESD was rated on a four-point scale, a five-point scale was used for the purposes of this study because most of the other measures in the survey instrument used five-point scales, and feedback from pilot testing indicated that keeping the scales consistent would reduce potential for confusion; this was not expected to affect validity of the scale. Items with positive valence were reverse-scored. No missing data were tolerated, and all items were summed to yield an overall score, which was then converted in relation to the original scale size by multiplying the overall score by 0.75. Scores can range from 0–60, with higher scores indicating the presence of more symptomatology. Although the CESD is not a clinical diagnostic tool, a cutoff of 16 or greater has been shown to reliably distinguish between clinically depressed and non-depressed persons.[20,21]

Quality of life was measured using the Ferrans and Powers Quality of Life Index (QLI), which consists of two 32-item sections encompassing four domains of QoL: Health & Functioning, Social & Economic, Psychological & Spiritual, and Family.[22,23] Respondents rated the degree to which they were satisfied with various aspects of life on six-point Likert scales anchored at "very dissatisfied" (1) and "very satisfied" (6). Corresponding importance

items were also rated on six-point Likert scales anchored at “very unimportant” (1) and “very important” (6). The instrument was scored by weighting the responses on the satisfaction items against the responses on the corresponding importance items, yielding scores for overall QoL and the four QoL domains. A maximum of 20% missing data was tolerated. Scores ranged from 0–30, with higher scores indicating higher QoL. Although the QLI has not been applied in an NF1 population, it has been employed in studies of populations with achondroplasia[24] and Marfan syndrome[25] as well as a wide range of non-genetic, chronic illness populations. The QLI has been shown to be reliable and valid. From a conglomeration of studies using the QLI, Cronbach’s alpha values for the QLI total scale ranged from 0.73 to 0.99 across 48 studies.[26]

The survey instrument also contained face-validity questions to gather information about demographics and potential confounders.

Statistical Analyses

Data were analyzed using SPSS 13.0 (Statistical Package for the Social Sciences). Each potential confounder was tested as a predictor of the outcome variable using a Pearson’s correlation coefficient, ANOVA or t-test. Any variables that resulted in a p-value ≤ 0.20 were considered as candidates for inclusion in all subsequent multivariate regression models. Multivariate regression modeling was used to test for the association of one covariate on the outcome measure while controlling for other covariates.

RESULTS

During the recruitment period from June to August 2008, a total of 498 individuals meeting eligibility criteria completed the survey in its entirety. The average age of participants was 38.9 ± 11.4 years and ranged from 18 to 69 years. Approximately three-quarters (73%) of participants were female. Demographic characteristics are listed in Table 1.

Depression was assessed using the Center for Epidemiologic Studies Depression scale (CESD), which demonstrated good reliability (Cronbach’s alpha = 0.94). Possible scores range from 0 (low levels of depressive symptoms) to 60 (high levels of depressive symptoms). The mean CESD score for the entire study population was 20.41 ± 13.04 (95% CI: 19.20, 21.63). Level of depressive symptoms was significantly higher among women than men ($p = 0.002$). The mean CESD score among women was 21.67 ± 13.14 (95% CI: 20.19, 23.14), and the mean CESD score among men was 17.23 ± 12.47 (95% CI: 14.98, 19.49). Sixty-one percent of women and 43% of men (55% of total study population) scored at or above the threshold score of 16, indicating that they had a significant level of depressive symptoms and therefore are at increased risk for clinical depression (Figure 1).

QoL was measured using the Quality of Life Index (QLI), which has a range of possible scores from 0 to 30. Bivariate analyses demonstrated that all of the subscales and the overall measure were significantly correlated with one another ($p<0.001$); therefore, the total QLI score was used in further analyses and hypothesis testing, in lieu of individual subscales. Total QLI demonstrated good reliability (Cronbach’s alpha = 0.93). The mean total QLI

score was 18.88 ± 4.62 (95% CI: 18.48, 19.29), with higher scores indicating better overall QoL. Figure 2 depicts the distribution of overall QLI scores and the normal curve.

Bivariate analysis demonstrated that level of depressive symptoms was significantly negatively associated with overall QoL (Pearson's correlation = −0.711, $p<0.001$). To estimate the amount of variance in QoL explained by depression, a regression model containing CESD score and demographics/potential confounding variables was created. CESD score was treated as a continuous variable, whereas the demographics and potential confounders were dichotomized. All variables that were found to be significantly associated with overall QoL at the $p<0.2$ level in the bivariate analyses (independent samples t-tests, data not shown) were entered into a regression model with QoL as the dependant variable. The variables included in the regression model were depressive symptoms (CESD score), partnered marital status, annual income greater than $30,000, college graduate education level, disabled employment status, learning disabilities, chronic pain, and positive family history. Having biological children, though not significant at $p<0.2$, was included because it may be conceptually relevant. Gender was also included in the model due to the significant association with depressive symptoms, even though gender was not significantly associated with QoL in bivariate analysis. The R-squared for the regression model that included all confounders and demographics was 0.598 (Table 2). When depressive symptoms was excluded, the model R-squared fell to 0.283, indicating that depression (level of depressive symptoms) accounted for approximately 32% of the variance in overall QoL (R-squared change = 0.315).

DISCUSSION

One of the most striking findings is the prevalence of depressive symptoms in this population of adults affected with NF1. Although the CESD is not a diagnostic tool, the cutoff score of 16 on the CESD has been shown to reliably distinguish between clinically depressed and non-depressed persons.[20,21] Over half of the individuals in this study population (55%) scored above this threshold, indicating that they had a significant level of depressive symptoms and therefore are at increased risk for clinical depression. The current study is the largest to date and found the highest prevalence of depression compared to prior studies, in which depression and other psychiatric disorders were reported in 21–46%.[11–13] Our data provide more compelling evidence that individuals with NF1 are at increased risk for psychiatric morbidity and suggest that this population should be screened for depression.

Depression (degree of depressive symptoms) was found to be strongly correlated with QoL, with an effect size of 32%, meaning that nearly one-third of the variation in overall QoL can be explain by level of depressive symptoms. Individuals with higher levels of depressive symptoms had significantly poorer QoL, a finding that also has direct clinical implications. Because depression was found to be associated with QoL, it is likely that recognizing and effectively treating depression may significantly enhance QoL for individuals with NF1.

Current guidelines for the management of NF1 patients focus primarily on the medical aspects of the condition with only brief mention of psychological problems.[2] Screening for depressive symptoms should be added to the list of standard management recommendations.

While it is unknown whether depressive symptoms are a manifestation of the disorder or a secondary reaction to living with the condition, the high prevalence suggests the former given the wide variability in manifestations and degree of potential stigmatization. Neurologists and other clinicians caring for NF1 patients should be trained to routinely evaluate patients for depression as a highly prevalent aspect of living with the condition.

The finding of a high prevalence of depressive symptoms in this population adds to existing evidence that individuals with NF1 may be at increased risk for depression and has profound clinical implications, especially given the adverse effect on QoL. It is important for healthcare providers to routinely screen for clinical depression among patients with NF1 and facilitate appropriate psychiatric treatment. While both genders should be screened for depression, it is even more important among women since they may have higher levels of depressive symptoms than men.

A limitation of this study was that clinical data were not collected. The diagnosis of NF1 was not confirmed by medical record review, and depression/depressive symptoms were not clinically assessed. Because this study was cross-sectional, conclusions could only be drawn regarding associations between variables, but not about causal pathways or temporal relationships. Another limitation of this study is the recruitment methods. As the majority of participants were drawn from NF organizations and through the NIH clinical research protocols, this might have biased the findings in favor of individuals who actively seek out support groups and/or participation in research. It is possible that those individuals differ in important ways from individuals not involved in NF activities. On the other hand, the demographic data suggest that a wide range of the population was captured. One important exception is the lack of racial and ethnic diversity in the study sample (88% White); NF1 occurs with approximately equal frequency in all ethic populations, so the views of under-represented minorities may not have been adequately captured. Also, women were over-represented (73% female respondents), and NF1 is a disease that affects both genders equally.

Our findings are important not only in alerting providers to screen for depressive symptoms in patients with NF1 but can also inform clinical research. Studies can be designed to assess the efficacy of screening for depression including patients' acceptance of treatment interventions that may not only improve their mood state but also their quality of life. Data following up on our findings may eventually lead to improvement in well-being for persons affected with NF1.

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References

1. Radtke HB, Sebold CD, Allison C, Haidle JL, Schneider G. Neurofibromatosis Type 1 in Genetic Counseling Practice: Recommendations of the National Society of Genetic Counselors. J Genet Couns. 2007; 16:387–407. [PubMed: 17636453]

2. Ferner RE, Huson SM, Thomas N, et al. Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. J Med Genet. 2007; 44:81–88. [PubMed: 17105749]
3. Ablon J. The nature of stigma and medical conditions. Epilepsy Behav. 2002; 3:2–9. [PubMed: 12609300]
4. Benjamin CM, Colley A, Donnai D, Kingston H, Harris R, Kerzin-Storrar L. Neurofibromatosis type 1 (NF1): knowledge, experience, and reproductive decisions of affected patients and families. J Med Genet. 1993; 30:567–574. [PubMed: 8411029]
5. Graf A, Landolt MA, Mori AC, Boltshauser E. Quality of life and psychological adjustment in children and adolescents with neurofibromatosis type 1. J Pediatr. 2006; 149:348–353. [PubMed: 16939745]
6. Oostenbrink R, Spong K, de Goede-Bolder A, Landgraf JM, Raat H, Moll HA. Parental reports of health-related quality of life in young children with neurofibromatosis type 1: influence of condition specific determinants. J Pediatr. 2007; 151:182–186.e2. [PubMed: 17643775]
7. Page PZ, Page GP, Ecosse E, Korf BR, Leplege A, Wolkenstein P. Impact of neurofibromatosis 1 on Quality of Life: a cross-sectional study of 176 American cases. Am J Med Genet A. 2006; 140:1893–1898. [PubMed: 16906549]
8. Sebold CD, Lovell A, Hopkin R, Noll R, Schorry E. Perception of disease severity in adolescents diagnosed with neurofibromatosis type 1. J Adolesc Health. 2004; 35:297–302. [PubMed: 15450543]
9. Wolkenstein P, Zeller J, Revuz J, Ecosse E, Leplege A. Quality-of-life impairment in neurofibromatosis type 1: a cross-sectional study of 128 cases. Arch Dermatol. 2001; 137:1421–1425. [PubMed: 11708944]
10. Granström S, Langenbruch A, Augustin M, Mautner VF. Psychological burden in adult neurofibromatosis type 1 patients: impact of disease visibility on body image. Dermatology. 2012; 224:160–167. [PubMed: 22508340]
11. Wang DL, Smith KB, Esparza S, et al. Emotional functioning of patients with neurofibromatosis tumor suppressor syndrome. Genet Med. 2012; 14:977–982. [PubMed: 22878510]
12. Wolkenstein P, Zeller J, Revuz J, Ecosse E, Leplege A. Visibility of neurofibromatosis 1 and psychiatric morbidity. Arch Dermatol. 2003; 139:103–104. [PubMed: 12533184]
13. Zoller ME, Rembeck B. A psychiatric 12-year follow-up of adult patients with neurofibromatosis type 1. J Psychiatr Res. 1999; 33:63–68. [PubMed: 10094241]
14. Kessler RC, Berglund P, Demler O, et al. National Comorbidity Survey Replication. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA. 2003; 289:3095–3105. [PubMed: 12813115]
15. Kodra Y, Giustini S, Divona L, et al. Health-Related Quality of Life in Patients with Neurofibromatosis Type 1. A Survey of 129 Italian Patients. Dermatology. 2009; 218:215–220. [PubMed: 19088462]
16. Krab LC, Oostenbrink R, de Goede-Bolder A, Aarsen FK, Elgersma Y, Moll HA. Health-Related Quality Of Life in Children with Neurofibromatosis Type 1: Contribution of Demographic Factors, Disease-Related Factors, and Behavior. J Pediatr. 2009; 154:420–425.e1. [PubMed: 18950800]
17. Wolkenstein P, Rodriguez D, Ferkal S, et al. Impact of neurofibromatosis 1 upon quality of life in childhood: a cross-sectional study of 79 cases. Br J Dermatol. 2009; 160:844–848. [PubMed: 19067713]
18. Garwood MM, Bernacki JM, Fine KM, Hainsworth KR, Davies WH, Klein-Tasman BP. Physical, cognitive, and psychosocial predictors of functional disability and health-related quality of life in adolescents with neurofibromatosis-1. Pain Res Treat. 2012; 2012:975364. [PubMed: 23056937]
19. Radloff LS. The CES-D scale: A self report depression scale for research in the general population. Applied Psychological Measurement. 1977; 1:385–401.
20. Craig TJ, Van Natta PA. Current medication use and symptoms of depression in a general population. Am J Psychiatry. 1978; 135:1036–1039. [PubMed: 29500]
21. Myers JK, Weissman MM. Use of a self-report symptom scale to detect depression in a community sample. Am J Psychiatry. 1980; 137:1081–1084. [PubMed: 7425160]

22. Ferrans CE, Powers MJ. Psychometric assessment of the Quality of Life Index. Res Nurs Health. 1992; 15:29–38. [PubMed: 1579648]

23. Cohen JS, Biesecker BB. Quality of life in rare genetic conditions: a systematic review of the literature. Am J Med Genet A. 2010; 152A:1136–1156. [PubMed: 20425818]

24. Gollust SE, Thompson RE, Gooding HC, Biesecker BB. Living with achondroplasia in an average-sized world: an assessment of quality of life. Am J Med Genet A. 2003; 120A:447–458. [PubMed: 12884421]

25. Peters KF, Kong F, Hanslo M, Biesecker BB. Living with Marfan syndrome III. Quality of life and reproductive planning. Clin Genet. 2002; 62:110–120. [PubMed: 12220448]

26. Ferrans, CE. [Accessed August 17, 2013] Quality of Life Index: Reliability and Validity. Available at: http://www.uic.edu/orgs/qli/reliability/reliabilityhome.htm

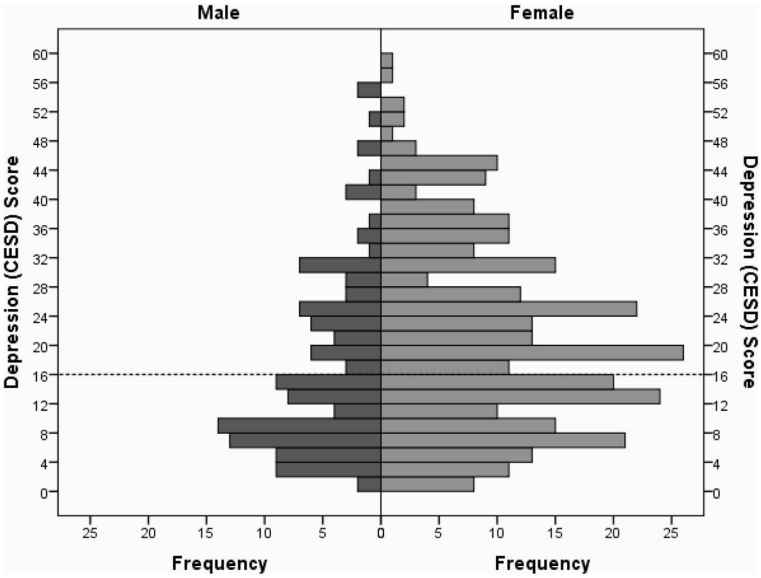

Figure 1. Depression Scores

Histograms depicting Center for Epidemiologic Studies Depression scale (CESD) scores for males and females. Possible CESD scores range from 0–60, with higher scores indicating the presence of more symptomatology. A cutoff of 16 or greater (indicated by dotted line) has been shown to reliably distinguish between clinically depressed and non-depressed persons.[20,21]

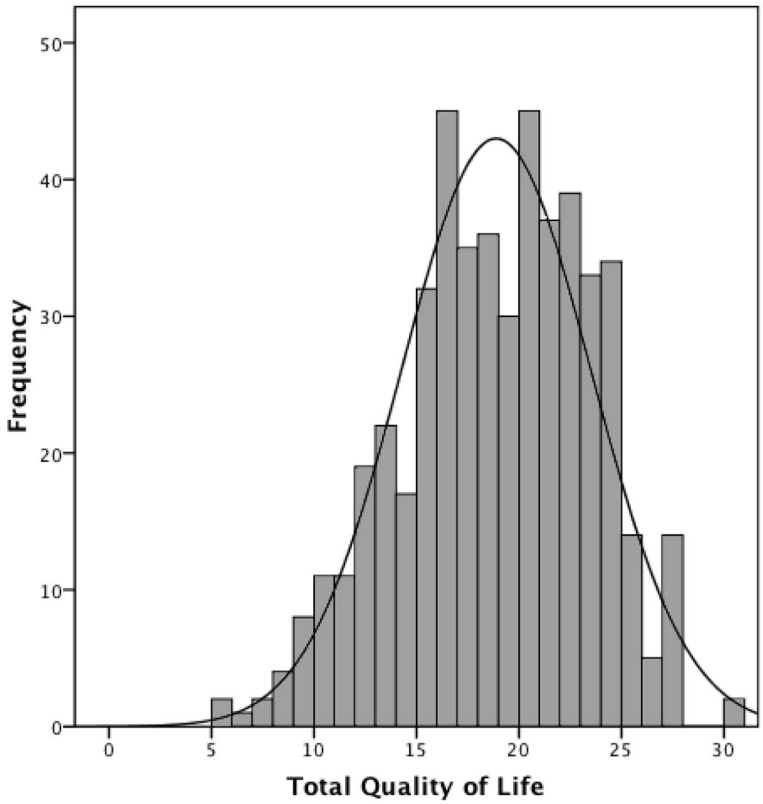

Figure 2. Quality of Life Scores

Histogram illustrating overall quality of life as measured by the Quality of Life Index, with scores ranging from 0–30 and higher scores indicating better quality of life.

Table 1

Demographic Characteristics of Study Sample

Demographic Characteristic		%
Race*	White	88.4
	Black/African American	5.7
	Asian	5.1
	American Indian/Alaska Native	2.7
	Native Hawaiian/Pacific Islander	1.1
Ethnicity	Not Hispanic or Latino	93.5
	Hispanic or Latino	6.5
Employment Status	Employed full-time	57.9
	Employed part-time	12.4
	Unemployed	14.7
	Retired	3.9
	Disabled for employment	11.9
Highest Level of Education	Less than high school	3.7
	High school/GED	20.6
	Some college	28.9
	Completed college	30.8
	Post-graduate	16.0
Marital Status	Single	36.1
	In a partnered relationship	10.6
	Married	41.9
	Divorced or separated	9.3
	Widowed	2.1
Annual Income	Less than $30,000	49.2
	$30,000 – 50,000	24.7
	$50,000 – 70,000	12.8
	Greater than $70,000	13.3

* Percentages do not equal 100%, as participants were allowed to choose more than one response.

Table 2

Regression of QoL on Confounders and Demographic Variables

MODEL (R^2 = 0.598)	Unstandardized β Coefficients	Std. Error	P-value
(Constant)	23.331	0.494	<0.001
Depressive symptoms	−0.223	0.012	<0.001
Partnered	0.593	0.332	0.075
Income over $30K	0.197	0.321	0.539
College graduate	0.437	0.312	0.162
Disabled/employment	−1.565	0.500	0.002
Learning disabilities	0.182	0.308	0.554
Chronic pain	−2.135	0.312	<0.001
Positive family history	−0.087	0.299	0.770
Biological children	0.258	0.336	0.443
Female	0.784	0.336	0.020