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IMPACT OF CHRONIC DISEASE ON EMOTIONAL DISTRESS IN ADULT SURVIVORS OF CHILDHOOD CANCER: A REPORT FROM THE CHILDHOOD CANCER SURVIVOR STUDY

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Abstract

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Purpose—To examine associations among childhood cancer therapies, chronic health conditions and symptoms of emotional distress in adult survivors of childhood cancer.

Methods—Participants included 5,021 adult survivors of childhood cancer (mean[SD] age=32.0[7.6] years, time since diagnosis=23.2[4.5] years) who completed measures assessing symptoms of anxiety, depression, and posttraumatic stress (PTSS). Cardiac, pulmonary and endocrine conditions were graded using the Common Terminology Criteria for Adverse Events (CTCAE v.4.03; Grades 1-4). Structural equation modeling was used to examine hypothesized pathways between cancer treatment exposures, chronic health conditions, and symptoms of emotional distress. Multivariable models were used to estimate relative risks (RR) for associations between chronic health conditions and distress.

Results—Survivors with cardiovascular, endocrine or pulmonary conditions had significantly higher prevalence of emotional distress symptoms. In path analyses and multivariable models, significant effects were observed between endocrine ($\beta=0.12$, $P=0.002$; RR=1.3, 95% CI, 1.1-1.6) and pulmonary ($\beta=0.13$, $P<0.001$; RR=1.4, 95% CI, 1.1-1.7) conditions and depression, and between cardiac ($\beta=0.13$, $P=0.001$; RR=1.5, 95% CI, 1.2-1.8) and pulmonary ($\beta=0.15$, $P<0.001$; RR=1.6, 95% CI, 1.3-2.0) conditions and anxiety. All treatment-related chronic health conditions were associated with PTSS (cardiac: $\beta=0.09$, $P=0.004$; RR=1.3, 95% CI, 1.2-1.5; endocrine: $\beta=0.12$, $P<0.001$; RR=1.3, 95% CI, 1.2-1.5; pulmonary: $\beta=0.13$, $P<0.001$; RR=1.4, 95% CI, 1.2-1.6).

Conclusions—Chronic health conditions resulting from childhood cancer therapies contribute to emotional distress in adult survivors. Targeted mental health screening efforts in this at-risk population appear warranted. Therapeutic approaches should consider the complex interplay between chronic health conditions and symptoms of emotional distress.

Graphical Abstract

Precis: Survivors who have been exposed to cancer directed therapies in childhood are at increased risk for developing cardiac, endocrine and pulmonary chronic health conditions. These chronic health conditions contribute to emotional distress symptoms in adult survivors of childhood cancer.

Keywords

childhood cancer; survivorship; emotional distress; chronic health conditions; late effects

Introduction

Improvements in survival rates of childhood cancer over the last 50 years have resulted in a growing number of long-term survivors. Current estimates indicate that nearly 400,000 survivors are living in the United States.^{1, 2} Survivors who have been exposed to potentially toxic cancer-directed therapies in childhood are at increased risk for late health complications.^{3, 4} Results from the Childhood Cancer Survivor Study (CCSS) indicate that adult survivors of childhood cancer have a substantially greater cumulative incidence of a severe, disabling, life-threatening, or fatal health condition (53.6% vs. 19.8%) by 50 years of age compared with siblings.⁵ Clinically ascertained data from the St. Jude Lifetime Cohort

suggest the cumulative incidence of chronic health conditions (any severity) to be 95% by 45 years of age, with 56% of 10 year survivors of childhood cancer developing cardiac conditions (95% CI, 53.5%-59.2%), 65% pulmonary conditions (95% CI, 60.4%-69.8%), and 62% endocrine conditions (95% CI, 59.5%-64.6%).⁶

Subgroups of adult survivors are also at-risk for symptoms of emotional distress.⁷⁻⁹ In a longitudinal analysis, survivors who perceived their health status to worsen over time were at risk of increasing symptoms of depression and anxiety.⁷ Past studies also have reported that self-perceptions of health status and physical symptoms are associated with psychological distress symptoms in adolescent and young adult survivors,¹⁰⁻¹² however, to date, little information is available about the link between chemotherapy and radiotherapy exposure, subsequent chronic health conditions, and emotional distress symptoms in adult survivors of childhood cancer. In non-cancer populations, cardiac conditions including angina, myocardial infarction, and diabetes have been associated with anxiety.¹³ Diabetes and pulmonary disease have been associated with depression,¹⁴ with over 40% of individuals with chronic obstructive pulmonary disease reporting symptoms of depression.¹⁵⁻¹⁷ In this context, we sought to examine potential associations between chronic health conditions and emotional distress symptoms in adult survivors of childhood cancer while accounting for established associations between therapeutic exposures and chronic health morbidities.

Methods

Participants

The CCSS is a multi-institutional retrospective cohort study with longitudinal follow-up of survivors of childhood cancer recruited from 26 institutions across North America. The institutional review board at each participating institution approved the CCSS protocol, and all participants provided informed consent. Participants in CCSS include those who (1) were diagnosed with childhood cancer before age 21 between January 1, 1970 and December 31, 1986; and (2) survived at least five years after diagnosis. The Baseline survey began in 1994, and subsequent follow-up surveys are conducted every 4-5 years. A detailed description of the cohort methodology and study design have been previously reported.^{18, 19} For the current analysis, eligibility required that participants self-completed all questionnaires and were at least 18 years of age at Follow-up 2. Survivors were excluded from the study if they reported a neurodevelopmental condition (i.e., mental retardation; $n=252$ [2.7%]). Because stroke is coded as a cardiac condition in the 4th version of the Common Terminology Criteria for Adverse Events (CTCAE v.4.03), participants reporting these events were excluded to ensure that cardiac morbidity consisted of cardiovascular events and not the neurologic consequences of those events ($n=160$ [1.7%]). Survivors with missing treatment ($n=263$ [2.8%]), chronic disease ($n=1,157$ [12.4%]) or emotional distress ($n=2,432$ [26.1%]) data also were non-evaluable. Of the eligible 8,873 survivors, 5,021 were included in the current analyses, with a participation proportion of 57% (see Figure 1). Compared with non-evaluable participants, participants in the current study were more likely to be female (53.9% *v.* 43.1%; Supplemental Table 1).

Treatment Exposures

Treatment data were obtained from medical records by trained abstractors. Treatment exposures previously associated with chronic health conditions were selected *a priori* for inclusion in path analysis models. To uphold the integrity of our statistical modeling, cumulative treatment doses were used when at least 20% of sample received a specific treatment, and were coded as absent or present otherwise. Therefore, cumulative doses of cranial radiation, thoracic radiation, anthracyclines and intravenous methotrexate (measured as cumulative dose in the first five years of treatment) were coded as continuous variables. Intrathecal chemotherapy was measured as number of methotrexate or cytarabine injections, and bleomycin and corticosteroids were coded as absent or present.

Chronic Health Conditions

Survivors self-reported chronic health conditions, including the date of onset of each condition, at Baseline and subsequent follow-up assessments (Follow-up 1, Follow-up 4). Only chronic health conditions with a date of onset prior to date of assessment of emotional distress symptoms (Follow-up 2) were included in the analysis. Any chronic health conditions reported at Follow-up 4 with a date of onset occurring after report of emotional distress symptoms at Follow-up 2 were not included in our analysis. Consequently, the reported date of onset of chronic health conditions preceded ascertainment of emotional distress symptoms. The severity of cardiac, endocrine and pulmonary conditions were graded for severity using the CTCAE version 4.03,²⁰ using the maximum grade per reported chronic condition for each organ system. Consistent with past CCSS reports,^{4,5} the following grading schema was employed: mild (grade 1), moderate (grade 2), severe or disabling (grade 3), or life-threatening (grade 4).

Distress Outcomes

Acute symptoms of depression and anxiety (e.g., within the past 7 days) were assessed using the Brief Symptom Inventory-18 (BSI-18).²¹ Using sex-specific normative data, elevated distress was defined as a T-score ≥ 63 (highest 10% of the normative population). Posttraumatic stress symptoms (PTSS) were assessed using the Posttraumatic Stress Diagnostic Scale (PDS); a 17-item measure of diagnostic symptoms criteria from the Diagnostic and Statistical Manual for Psychiatric Disorders, 4th Edition (DSM-IV).²² A positive endorsement of PTSS was defined as at least one re-experiencing symptom, at least three avoidance symptoms and at least two arousal symptoms.^{23, 24} All emotional distress outcomes were assessed at Follow-up 2.

Statistical Analyses

The prevalence of distress symptoms among survivors with and without chronic health conditions was compared using chi-square tests. Path analysis, a type of structural equation modeling, was used to examine the relations among treatment exposures, chronic conditions, and emotional distress outcomes. For each outcome, the analysis began with an *a priori* hypothesized path model (Supplemental Figure 1) with main effects and interaction terms selected based on existing evidence in the literature.^{9, 25-30} The model was expanded by adding clinically meaningful paths, one at a time, with a modification index of 3.6 or greater,

beginning with the largest index value. The path model was then reduced by removing paths, one at a time, if the absolute value of the standardized coefficient was <0.05 or the path lacked substantive meaning, beginning with the smallest coefficient. Further model reduction was conducted if the path had a P value exceeding 0.05 or was not substantively meaningful, beginning with the largest P value. This process was iterative until the following model-fitting criteria were met: the comparative fit index (CFI) and Tucker Lewis Index (TLI) exceeded 0.95, and the Root Mean Square Error of Approximation (RMSEA) fell below 0.05.³¹ To examine the magnitude of associations between chronic health conditions and emotional distress, log-binomial multivariable regression was used to estimate relative risk (RR) and 95% confidence intervals (CI). Exposures included in multivariable models were restricted to significant direct effects of treatment and chronic health conditions identified in our final path models. The path analysis was conducted using Mplus, and multivariable regression modeling was conducted using SAS version 9.3.

Results

Survivors were a mean [standard deviation] of 8.3 [5.9] years of age at diagnosis, 24.3 [7.8] years at baseline and 32 [7.6] years at time of Follow-up 2 (Table 1). Approximately two-thirds of the sample received some form of radiotherapy (65.0%) with almost one-third having received cranial radiation (29.0%), and 80% having received chemotherapy.

Prevalence of Chronic Health Conditions and Emotional Distress Symptoms

Twenty-five percent of survivors reported having at least one cardiac condition (any grade 1-4), 27% reported an endocrine condition and 17% reported a pulmonary condition (Supplemental Tables 2 and 3). The prevalence of elevated distress symptoms was higher among survivors with chronic health conditions compared to those without (see Table 2). For example, a greater proportion of survivors with endocrine conditions reported symptoms of depression (13.1% v. 9.8%; $P<0.001$), anxiety (8.0% v. 6.4%; $P<0.001$), and posttraumatic stress (20.9% v. 14.4%; $P<0.001$) compared to survivors without endocrine conditions. The prevalence of emotional distress symptoms by primary childhood cancer diagnosis is shown in Supplemental Table 4.

Pathways from Treatment Exposures to Emotional Distress

Depressive symptoms—Positive interaction effects for higher dose of CRT and shorter duration of time since diagnosis ($P<0.001$), higher dose of CRT and younger age at diagnosis ($P<0.001$), and higher dose of CRT and male sex ($P=0.027$) were associated with greater likelihood of endocrine conditions. A main effect of higher dose thoracic radiation also was associated with endocrine morbidity (P -value <0.001). Bleomycin exposure ($P=0.004$), higher dose of thoracic radiation ($P<0.001$), female sex ($P=0.001$), younger age at diagnosis ($P=0.004$), and shorter time since diagnosis ($P=0.001$) were associated with pulmonary conditions. The presence of endocrine ($P=0.001$) and cardiac ($P<0.001$) conditions also contributed to pulmonary disease. Significant direct determinants of depressive symptoms included male sex ($\beta=-0.08$, $P=0.007$) and grade 1 through 4 endocrine ($\beta=0.12$, $P=0.002$) and pulmonary ($\beta=0.13$, $P<0.001$) conditions (Figure 2; Table 3).

Anxiety symptoms—A higher dose of thoracic radiation, older age at diagnosis, longer time since diagnosis, and endocrine conditions had direct effects on cardiovascular disease (all P -values<0.001). Bleomycin exposure ($P=0.003$), younger age at diagnosis ($P=0.003$), shorter duration from diagnosis ($P=0.002$), female sex ($P=0.002$), endocrine ($P=0.001$) and cardiac conditions ($P<0.001$) had direct effects on pulmonary morbidity. While accounting for the associations between treatment exposures and chronic health conditions, cardiovascular ($\beta=0.13$, $P=0.001$) and pulmonary ($\beta=0.15$, $P<0.001$) conditions were the direct observed determinants of anxiety symptoms.

Posttraumatic stress symptoms—Higher doses of thoracic radiation, older age at diagnosis, longer duration of time since diagnosis, and endocrine morbidity were directly associated with cardiac conditions (all P -values<0.001). Female sex and interactions of higher dose of CRT and younger age at diagnosis, higher dose of CRT and shorter duration of time since diagnosis were associated with endocrine conditions (all P -values<0.001). Bleomycin exposure ($P=0.001$), higher dose of thoracic radiation ($P<0.001$), female sex ($P<0.001$), younger age at diagnosis ($P=0.005$), and shorter duration of time since diagnosis ($P=0.002$) were associated with pulmonary conditions. Endocrine ($P=0.001$) and cardiac ($P<0.001$) conditions also contributed to pulmonary disease. Posttraumatic stress symptoms were directly influenced by all examined chronic health conditions (cardiovascular, $\beta=0.09$, $P=0.004$; endocrine, $\beta=0.12$, $P<0.001$; pulmonary, $\beta=0.13$, $P<0.001$).

Magnitude of Risk

In multivariable models restricted to significant direct exposures derived from our path analyses, endocrine and pulmonary conditions increased the risk of depressive symptoms by 30-40% (RR=1.3, 95% CI, 1.1-1.6; RR=1.4, 95% CI, 1.1-1.7, respectively; Table 4). Pulmonary conditions were associated with 60% increased risk of anxiety (RR=1.6, 95% CI, 1.3-2.0) and cardiac conditions with a 50% increased risk of anxiety (RR=1.5, 95% CI, 1.2-1.8). Similarly, cardiac (RR=1.3, 95% CI, 1.2-1.5), pulmonary (RR=1.4, 95% CI, 1.2-1.6), and endocrine conditions (RR=1.3, 95% CI, 1.2-1.5) were associated with a 30-40% increased risk of PTSS.

Discussion

While associations between primary childhood cancer diagnosis and treatment on risk for emotional distress have been well described, the impact of chronic health conditions, increasingly prevalent as survivors age through middle adulthood, has not, to our knowledge, been previously considered. The present analysis aimed to identify pathways from childhood cancer treatment and subsequent chronic health conditions to emotional distress in adulthood. Results demonstrated that survivors who develop cardiovascular, endocrine and/or pulmonary conditions resulting from cancer-directed therapies in childhood are at-risk for developing symptoms of depression, anxiety, and posttraumatic stress. These findings demonstrate the cumulative health effects of childhood cancer over the course of the lifespan, and underscore the importance of long-term follow-up and screening for physical and mental health morbidities.

Among survivors of pediatric malignancies, it is well-established that specific treatment exposures in childhood are associated with late health morbidities. Consistent with this literature, our results illustrate the cardiotoxic effects of chest-directed radiotherapy and anthracycline exposure^{32, 33} and the deleterious effects of cranial radiotherapy on pituitary and endocrine function.³⁴ Similarly, as expected, an interaction between higher CRT dose and younger age at diagnosis conferred greater risk for endocrine conditions.³⁴ While we observed a interaction between higher CRT dose and years since diagnosis, the risk of endocrine conditions decreased with time. For example, in our depression model, at 15 years post diagnosis, for every 10Gy increase in CRT the risk of endocrine conditions increased by 54%. However, by 35 years this risk was only 21%. This suggests that as follow-up time increased, the strength of the association between CRT and endocrine conditions decreased, though the association remained positive.

Important new findings from this analysis include identification of several direct effects between late chronic health conditions and emotional distress among cancer survivors. A direct path was observed between pulmonary morbidity and depressive symptoms, with 40% increased risk for depressive symptoms among survivors with pulmonary conditions. This is similar to research in the general population documenting the association between emphysema and chronic bronchitis (the most common pulmonary conditions reported by survivors in the current study) and depressed mood.¹²⁻¹⁴ Similarly, the observed effect of endocrine dysfunction on depression is consistent with research in the general population linking thyroid dysfunction and growth hormone deficiencies to risk of depression.^{36,37}

Both cardiac and pulmonary conditions were associated with increased risk of anxiety symptoms (20% and 40% increased risk, respectively). Epidemiologic evidence in the general population supports an association between cardiac disease and anxiety, by way of health behaviors, increased hypertension, or the triggering of fatal coronary events.¹³ In addition, anxiety has been identified as a risk factor for exacerbations and hospitalizations in cohort studies of patients with chronic obstructive pulmonary disease.^{38, 39} Notably, pulmonary morbidity was the largest determinant of both anxiety and PTSS, which may reflect a shared underlying mechanism given that posttraumatic stress disorder is classified as an anxiety disorder in the DSM-IV.²²

While our results offer valuable new insights into potential sources of emotional distress symptoms in adult survivors of childhood cancer, they should be considered in the context of several limitations. First, chronic health conditions in the current report were assessed by self-report, which may be less sensitive than direct assessment and subsequently result in the misclassification of chronic health status.⁶ Second, we are unable to establish temporality between chronic health conditions and emotional distress. Although date of onset of survivors' reported chronic health conditions preceded the seven-day window of reported emotional distress symptoms, we do not have date of onset of emotional distress symptoms. In addition, survivors may inaccurately report the date of onset of their conditions, and, therefore, we cannot eliminate the possibility that emotional distress symptoms preceded and/or contributed to the development of chronic health conditions. Longitudinal studies may strengthen this evidence-base by establishing temporal ordering of chronic health conditions and emotional distress symptoms. Finally, observed effects between specific

health conditions and emotional distress outcomes may partially reflect shared symptoms. For example, survivors reporting endocrine dysfunction may be more likely to experience fatigue or low energy, which is also a symptom of depression. Reliance on self-report data for both exposures (chronic health conditions) and outcomes (distress symptoms) introduces the potential for bias from common method variance.

Our results suggest that chronic health conditions that develop decades after treatment for childhood cancer are associated with emotional distress symptoms in aging adult survivors. These findings provide support for routine psychological screening of adult survivors with chronic health conditions. Current long-term follow-up guidelines for childhood cancer survivors recommend screening based on specific therapeutic exposures.⁴⁰ Our results suggest that in adulthood, chronic health conditions may serve as a more proximal and reliable indicator of survivors in need of psychological screening than treatments received several decades earlier. Alternatively, survivors who received more intensive cancer-directed therapies may be at risk for both chronic health conditions and psychological distress. Ultimately, treatment for distress symptoms will likely involve evidence-based interventions such as cognitive-behavior therapy or pharmacotherapy regardless of etiology. However, screening an at-risk population may facilitate early identification of distress symptoms and timely intervention before symptoms become chronic and functionally impairing. Our findings also support a prophylactic approach to preventing emotional distress symptoms. Specifically, risk-based screening to identify chronic health conditions is important for this population⁴⁰ as treatment (including medication management) of physical health conditions may have the potential to offset emotional distress symptoms. However, it is also important to consider that the presence of distress symptoms may adversely affect self-management of chronic disease.⁴¹⁻⁴³ Finally, interventions such as physical exercise, with the ability to intervene at multiple levels (e.g. reducing both risk of chronic health conditions and of symptoms of emotional distress) are important to consider as direct and/or indirect methods to improve overall psychological functioning.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Selection of participants from the Childhood Cancer Survivor Study for the current analysis.

Figure 2. Final path models for emotional distress symptoms. Only direct paths are presented.

Table 1

Demographic and treatment characteristics of study participants (N=5,021)

	Mean (SD)	Median (IQR)
Age at diagnosis (years)	8.3 (5.9)	7.0 (3-13)
Age at baseline (years)	24.3 (7.8)	24.0 (18-30)
Age at Follow-up 2 (years)	32.0 (7.6)	32 (26-37)
Time since diagnosis (years)	23.2 (4.5)	23 (19-27)
n (%)		
Sex (female)	2,707 (53.9)	
Race (White)	4,629 (92.5)	
Primary diagnosis		
Leukemia	1,697 (33.8)	
CNS Tumor	499 (9.9)	
Hodgkin Lymphoma	720 (14.3)	
Non-Hodgkin Lymphoma	377 (7.5)	
Wilms Tumor	473 (9.4)	
Neuroblastoma	316 (6.3)	
Soft Tissue Sarcoma	470 (9.4)	
Bone Cancer	469 (9.3)	
Surgery		
Central nervous system	550 (11.0)	
Respiratory system	417 (8.3)	
Cardiovascular system	50 (1.0)	
Other surgery	2,750 (54.8)	
None	1,208 (24.1)	
Radiotherapy		
Cranial	1,451 (29.0)	2,400 cGy (1,800-3,500)
Thoracic	1,035 (20.7)	3,100 cGy (2,000-4,000)
Abdominal	963 (19.2)	
Pelvic	713 (14.2)	
Other Radiotherapy	421 (8.4)	
None	1,750 (34.9)	
Chemotherapy		
IT Methotrexate or Cytarabine (any)	1,851 (36.9)	
1 injection	1,274 (25.4)	
2 injections	525 (10.5)	
3+ injections	52 (1.0)	
Corticosteroids (y/n)	2,425 (48.3)	
IV Methotrexate	940 (18.7)	3,580 mg/m ² (360-7,929)
Bleomycin (y/n)	260 (5.4)	
Anthracyclines	1,777 (36.7)	293.6 mg/m ² (176-388)

Abbreviations: SD = standard deviation; IQR = interquartile range; CNS = central nervous system; cGy = centigray IT = intrathecal; IV = intravenous.

Median (IQR) reported for treatment exposures if 20% of the cohort was exposed and if continuous dose was available from medical record abstraction. Median (IQR) only reported for survivors who received the exposure.

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Table 2

Prevalence of emotional distress symptoms by chronic health conditions

	Cardiac			Endocrine			Pulmonary		
	Present	Absent		Present	Absent		Present	Absent	
	% (95% CI)	% (95% CI)	<i>P</i>	% (95% CI)	% (95% CI)	<i>P</i>	% (95% CI)	% (95% CI)	
Depression	12.4 (10.6-14.3)	10.2 (9.2-11.1)	0.025	13.1 (11.3-14.9)	9.8 (8.9-10.8)	0.001	14.0 (11.7-16.3)	10.0 (9.1-10.9)	
Anxiety	9.2 (7.6-10.8)	6.1 (5.3-6.8)	<0.001	8.0 (6.5-9.4)	6.4 (5.6-7.2)	0.053	10.2 (8.2-12.2)	6.1 (5.4-6.9)	
PTSS	21.1 (18.8-23.3)	14.5 (13.4-15.6)	<0.001	20.9 (18.7-23.0)	14.4 (13.2-15.5)	<0.001	22.4 (19.6-25.1)	14.8 (13.7-15.9)	

Abbreviations: CI = confidence interval; PTSS = posttraumatic stress symptoms.

Table 3
Path analysis beta estimates for direct determinants of emotional distress symptoms

	Depression		Anxiety		Posttraumatic Stress	
	Beta	P	Beta	P	Beta	P
Sex (female)	-0.08	0.007	--	--	--	--
Time since diagnosis (years)	--	--	-0.05	0.12	--	--
Cardiac conditions	--	--	0.13	0.001	0.09	0.004
Endocrine conditions	0.12	0.002	--	--	0.12	<0.001
Pulmonary conditions	0.13	<0.001	0.15	<0.001	0.13	<0.001

Dashed line indicates variable was not selected for optimal path model. Abbreviations: CRT = cranial radiation therapy.

Table 4

Risk estimates for direct effects of chronic health conditions on emotional distress outcomes

	Depression	Anxiety	Posttraumatic Stress
	RR (95% CI)	RR (95% CI)	RR (95% CI)
Cardiac conditions	--	1.48 (1.19-1.84)	1.32 (1.15-1.51)
Endocrine conditions	1.34 (1.13-1.59)	--	1.33 (1.16-1.52)
Pulmonary conditions	1.38 (1.14-1.66)	1.58 (1.25-1.99)	1.40 (1.21-1.62)

Abbreviations: RR = relative risk; CI = confidence interval.

Depression model adjusted for sex.

Anxiety model adjusted for time since diagnosis.

Dashed line indicates variable was not entered into model.