The Contribution of Stress and Distress to Cardiovascular Health in Adult Survivors of Childhood Cancer

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ABSTRACT

Background: Childhood cancer survivors are at risk for cardiovascular morbidity and mortality that is not fully explained by cancer-directed therapies. We examined the contribution of emotional stress and distress to cardiac health in adult survivors of childhood cancer.

Methods: Participants included 3,267 adult survivors enrolled in the St. Jude Lifetime Cohort Study [median (range) 29.9 (18.1–64.5) years of age; 7.7 (0–24.8) years at diagnosis; 48.4% female]. Survivors completed comprehensive medical assessments and standardized measures of depression, anxiety, posttraumatic stress symptoms (PTSS), and perceived stress. Cardiovascular-related conditions included hypertension, diabetes, dyslipidemia, cardiomyopathy, dysrhythmia, myocardial infarction (severity graded 0–4), and metabolic syndrome (yes/no). Multivariable modified Poisson models examined associations between symptoms of stress/distress and cardiovascular outcomes. Longitudinal associations between stress/distress and new-onset cardiovascular outcomes, defined as a change from grade ≤1 at initial evaluation to grade ≥2 at follow-up (median 3.9 years) were examined in 1,748 participants.

Results: In multivariable cross-sectional models, stress/distress was associated with hypertension [risk ratio (RR) = 1.24; 95% confidence interval (CI), 1.07–1.43], dyslipidemia (RR = 1.29; 95% CI, 1.03–1.61), and metabolic syndrome (RR = 1.35; 95% CI, 1.17–1.54) independent of known cardiovascular risk factors. In longitudinal models, stress/distress was associated with new-onset dysrhythmia (RR = 2.87; 95% CI, 1.21–6.78), perceived stress with hypertension (RR = 1.42; 95% CI, 1.04–1.95), and PTSS and anxiety with dyslipidemia (RR = 1.72; 95% CI, 1.13–2.62; RR = 1.54; 95% CI, 1.01–2.35, respectively).

Conclusions: Stress/distress is independently associated with adverse cardiovascular outcomes among childhood cancer survivors.

Impact: Improving psychological health may serve as a potential intervention target for optimizing cardiac health among childhood cancer survivors.

Introduction

Adult survivors of childhood cancer are at increased risk for cardiovascular morbidity (1) and mortality (2) compared with their siblings and the general population (3). Exposure to cardiotoxic treatments at a young age is a significant risk factor for cardiovascular late effects (4, 5); however, individual variability in the prevalence and severity of adverse cardiac outcomes is not entirely explained by treatment exposures (6). Thus, examining risk factors beyond treatment exposures may identify targets for intervention to mitigate cardiac late effects among childhood cancer survivors.

Traditional cardiovascular risk factors, such as hypertension, diabetes, and dyslipidemia, are more prevalent among childhood cancer survivors and occur at younger ages compared with the general population (7) and siblings (8). A report from the Childhood Cancer Survivor Study (CCSS) found that diabetes, dyslipidemia, obesity, and hypertension were associated with cardiovascular outcomes independent of treatment exposures. Moreover, the combination of hypertension and treatment exposures potentiated risk of adverse cardiac outcomes, beyond anticipated additive expectations (8). While some portion of incidence of traditional cardiovascular risk factors, such as hypertension and diabetes, may be attributable to treatment exposures (9, 10), they comprise a small part of the overall fraction attributable to disease (7, 11). Cardiovascular risk factors in childhood cancer survivors may also be driven by modifiable lifestyle habits, such as smoking, drinking, and sedentary behavior. Among survivors in CCSS, the observed association between metabolic syndrome and unhealthy lifestyle behaviors was stronger than the association between metabolic syndrome and cranial radiation (12).

As recent studies have begun to examine the contributions of modifiable risk factors to cardiac late effects among childhood cancer survivors (8, 12), a possible risk factor that remains largely underexamined in the oncology literature is psychological health. Associations between stress, depression, anxiety, and cardiovascular disease are well established in the general population (13–16) and merit further study among survivors. While long-term follow-up studies of childhood cancer survivors suggest that the majority of adult survivors report normative levels of distress, there are subgroups of survivors at risk for significant psychological distress (17). To address this gap in

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the literature, we examined both cross-sectional and longitudinal associations between stress and emotional distress and cardiovascular health among long-term survivors of childhood cancer.

Materials and Methods

Study population

Participants included survivors enrolled in the St. Jude Lifetime Cohort (SJLIFE), an ongoing retrospective cohort study with prospective medical assessment (18). Survivors included in the analyses were treated at St. Jude Children's Research Hospital, age ≥18 years old at enrollment, ≥5 years from diagnosis, and had completed an on-campus medical assessment and behavioral health survey (n = 3,267). Survivors who did not complete their behavioral health survey within 6 months of their campus visit were excluded from the analyses (**Fig. 1**). Survivors who completed a baseline and follow-up visit were included in longitudinal analyses (n = 1,748). Community controls without a history of childhood cancer who were not first-degree relatives of St. Jude patients completed similar evaluations (n = 436) and served as a comparison group for psychological measures (Supplementary Table S1). The SJLIFE protocol was approved by the SJCRH institutional review board, and participants provided written informed consent.

Outcomes

Cardiovascular health

Cardiovascular conditions and cardiovascular risk factors were based on clinically ascertained medical assessments and classified using a modified Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 [mild (grade 1), moderate (grade 2), severe or disabling (grade 3), life-threatening (grade 4)], adapted for childhood cancer survivors (Supplementary Table S2; ref. 19). Medical records were obtained to validate any established cardiovascular condition or cardiovascular risk factor that was reported prior to a SJLIFE campus visit. Participants completed an echocardiogram, electrocardiogram, and physical health evaluation including a fasting laboratory panel. Cardiovascular conditions included: cardiac dysrhythmia (grades 2–4), cardiomyopathy (grades 2–4), and myocardial infarction (grades 3–4). Cardiovascular risk factors included: hypertension (grades 2–4), diabetes (grades 2–4), dyslipidemia (grades 2–4), and metabolic syndrome. Metabolic syndrome was classified on the basis of a composite measure of lab values and CTCAE criteria including elevated waist circumference, elevated triglycerides, reduced high-density lipoproteins, elevated blood pressure, and elevated fasting glucose. Participants who met at least 3 out of the 5 National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) criteria (Supplementary Table S3) were classified as having metabolic syndrome.

New-onset cardiovascular disease

For measures of cardiovascular health, new-onset conditions were defined as a change from grades ≤1 at the baseline visit to grade ≥2 at follow-up (with the exception of myocardial infarction, where new onset myocardial infarction was defined as a change from grades ≤2 at baseline to grade ≥3 at follow-up). New-onset metabolic syndrome was defined as a change from <3 criteria at baseline to ≥3 criteria at follow-up. CTCAE grading considers medication use for each condition (Supplementary Table S2). Thus, changes in medication management at baseline to follow-up are accounted for in our classifications of new-onset conditions.

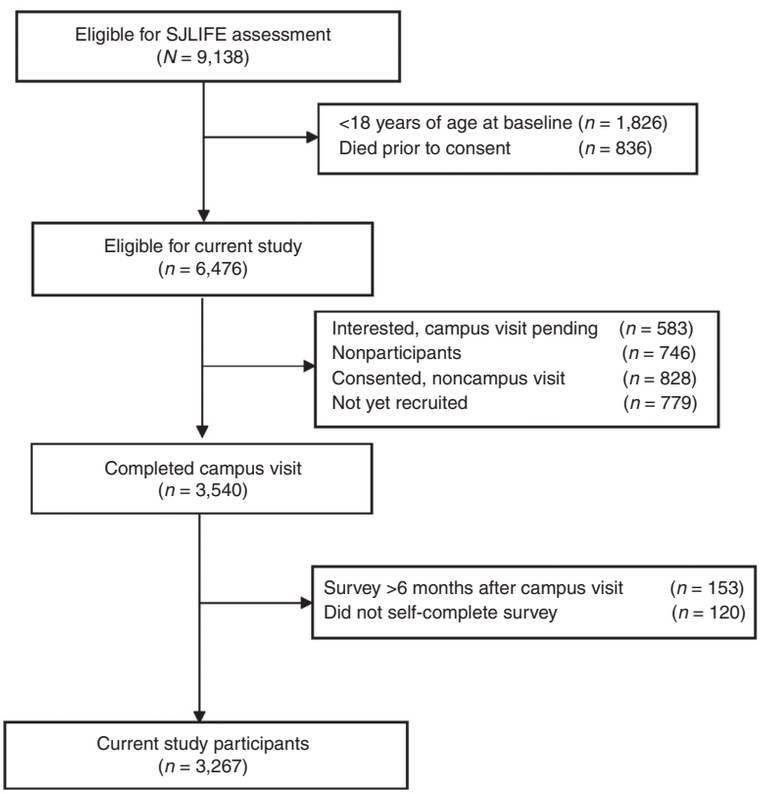

Figure 1.
Flow diagram of study participation.

Primary predictor variables

Stress and emotional distress were assessed via self-report. The Perceived Stress Scale (PSS-4; ref. 20) assessed survivors' perception of stress during the past month, a 4-item measure with higher scores indicating increased stress. The Perceived Stress Scale has been studied across patient and community samples and is recognized as a reliable and valid measure of psychological stress (21). Cronbach alpha coefficients for the short form have been acceptable, ranging from 0.60 to 0.82 across several studies (21). Because the PSS-4 scale does not include a recommended clinical cutoff, survivors scores were compared to SJLIFE community controls ($n = 436$). Scores ≥90th percentile of controls indicated elevated levels of perceived stress. Anxiety and depression were assessed via subscales of the Brief Symptom Inventory-18 (BSI-18; ref. 22). Using sex-specific normative data, survivors with a T-score ≥63 (90th percentile) on either subscale were classified with clinically significant anxiety and/or depression. The BSI-18 subscales have been validated among childhood cancer survivors. In survivors, Cronbach alpha coefficients for BSI-18 subscales ranged from 0.75 to 0.88 and a strong concordance between the subscales and their theoretical structure has also been reported (23). Posttraumatic stress symptoms (PTSS) were assessed using either the posttraumatic stress disorder (PTSD) Checklist civilian version (PCL-C; ref. 24) for surveys completed prior to 2015 or the PTSD Checklist for the DSM-5 (PCL-5; ref. 25) for surveys completed after 2015. The PCL-C is a 17-item measure with a recommended clinical cut-off score ≥44 to indicate PTSD (26, 27). The PCL-5 is a 20-item measure including updated questions and wording to reflect changes in the diagnosis of PTSD according to changes from the DSM-5, a clinical cut-off score ≥33 was used (25, 28). The PCL-C (29) and PCL-5 (25) have demonstrated good reliability and validity for identifying symptoms of posttraumatic stress. When assessing the reliability and validity of the PCL-C and PCL-5 among samples of college students, Cronbach alpha coefficients were 0.92 and 0.94, respectively. Furthermore, compared with alternate measures of trauma symptoms and psychological health scales, both scales demonstrated favorable patterns of convergent and discriminant validity (25, 29). Measures of stress and emotional distress were examined individually and combined as any stress/distress. The combined measure was defined dichotomously (yes/no). A score meeting the cutoff on any measure (e.g., perceived stress, anxiety, depression, PTSS) was indicative of a positive measure ("yes") of any stress/distress.

Covariates

Sociodemographic and lifestyle factors

Covariates were identified *a priori* based on known sociodemographic and lifestyle factors associated with cardiovascular health. The following sociodemographic factors were included: age at evaluation, sex, race/ethnicity, marital status (married or living as married vs. single, widowed, or divorced), and household income (≤$19,999; $20,000–59,999; ≥60,0000). Lifestyle factors included body mass index (BMI) and self-reported health habits. Physical activity was assessed by asking participants about weekly moderate and vigorous activities. The frequency of exercise sessions per week was multiplied by the reported duration of the session (inactive ≤150 minutes per week; ref. 30), one minute of vigorous activity was weighted as 1.67 moderate minutes. Current smokers included survivors who smoked ≥100 cigarettes in their lifetime and reported smoking within the last month. Survivors who reported smoking ≥100 cigarettes in their lifetime but did not smoke within the past month were classified as former smokers, and survivors who reported smoking <100 cigarettes in their lifetime were classified as nonsmokers. Alcohol use was classified according the guidelines established by the National Institute for Alcohol Abuse and Alcoholism (31). Heavy drinking was defined as binge drinking on 5 or more days in the past month. Risky drinking was defined as >3 drinks per day or >7 drinks per week for females or >4 drinks per day or >14 per week for males.

Treatment exposures

Treatment exposures known to be associated with adverse cardiovascular health among childhood cancer survivors were obtained via medical record abstraction and included age at diagnosis, cumulative anthracycline doses converted to doxorubicin equivalents in milligrams per body surface area in meters squared (mg/m^2; ref. 32), and chest-directed radiation doses. Anthracycline doses were classified as none, <250 mg/m^2, and ≥250 mg/m^2. Mean chest-directed radiation doses in gray (Gy) were estimated using previously established methods at MD Anderson Cancer Center (Houston, TX; ref. 33) and were categorically defined as none, <20 Gy, and ≥20 Gy.

Statistical analyses

Descriptive statistics characterized the study population. Two-sample t tests and χ^2 tests were used to compare these variables between participants with any stress and/or emotional distress (combined measure) at baseline and participants without stress and/or emotional distress at baseline. Stress and emotional distress measures at baseline were compared between participants and community controls using χ^2 tests. The prevalence of some cardiovascular outcomes exceeded 10%, therefore cross-sectional associations between measures of stress and/or distress and cardiovascular health were examined using modified Poisson regression models (34). Separate unadjusted and adjusted models were fitted for each stress and/or emotional distress measure and distinct cardiovascular outcomes (i.e., cardiac dysrhythmia, cardiomyopathy, myocardial infarction, hypertension, diabetes, dyslipidemia, and metabolic syndrome). Adjustments included all sociodemographic factors, lifestyle variables, and treatment exposures. Unadjusted and adjusted cross-sectional associations between psychological health and cardiovascular conditions were reported, given the potential for shared causal pathways (35, 36). Among participants who completed a baseline and follow-up visit, modified Poisson models adjusted for age at baseline, sex, and race/ethnicity, were used to evaluate the association between baseline measures of stress and/or distress and new onset cardiovascular health conditions.

Results

Participants

Stress, emotional distress, and cardiovascular health were evaluated among 3,267 adult survivors of childhood cancer. Among these, 1,748 (53.4%) completed a follow-up assessment (median time from baseline visit = 3.9 years) and were evaluated for new-onset cardiovascular health conditions (Supplementary Table S4). Survivors were on average [median (range)] 29.9 (18.1–64.5) years of age; 7.7 (0–24.8) years at diagnosis, 48.4% female, and 81.9% non-Hispanic white (**Table 1**). Almost one-third of survivors scored above the clinical cutoff on at least one measure of stress and/or distress as follows: perceived stress (19.5%), PTSS (11.0%), depression (14.9%), and anxiety (12.0%; **Table 2**). Differences in the proportion of stress and/or distress remained statistically significant between survivors and community controls even after adjustment for sociodemographic factors.

Table 1. Demographic, cancer treatment characteristics, cardiovascular risk factors, lifestyle behaviors, and cardiovascular disease in SJLIFE survivors with and without clinically significant stress/distress.

	Overall *n* (%)	Stress/distress absent *n* (%)	Stress/distress present[a] *n* (%)	*P*
Age at evaluation, years (M ± SD)	31.1 ± 8.4	30.7 ± 8.5	32.0 ± 8.0	<0.0001[b]
Age at evaluation, years (med, range)	29.9 (18.1–64.5)	29.4 (18.1–61.9)	31.1 (18.3–64.5)	<0.0001[b]
Sex				
Male	1,639 (51.6)	1,196 (52.8)	443 (48.7)	0.04
Female	1,537 (48.4)	1,071 (47.2)	466 (51.3)	
Race/ethnicity				
White, non-Hispanic	2,600 (81.9)	1,861 (82.1)	739 (81.3)	0.09
Black, non-Hispanic	449 (14.1)	307 (13.5)	142 (15.6)	
Other	127 (4.0)	99 (4.4)	28 (3.1)	
Marital status				
Single/widowed/divorced	1,670 (53.8)	1,169 (52.4)	501 (57.6)	0.01
Married	1,433 (46.2)	1,064 (47.6)	369 (42.4)	
Household income				
≤$19,999	527 (19.6)	294 (15.2)	233 (30.9)	<0.0001
$20,000–$59,999	1,146 (42.6)	814 (42.0)	332 (44.0)	
≥$60,000	1,017 (37.8)	828 (42.8)	189 (25.1)	
Diagnosis				
ALL	985 (31.0)	702 (31.0)	283 (31.1)	0.007
AML	109 (3.4)	77 (3.4)	32 (3.5)	
CNS tumor	372 (11.7)	283 (12.5)	89 (9.8)	
Non-Hodgkin lymphoma	229 (7.2)	155 (6.8)	74 (8.1)	
Hodgkin lymphoma	390 (12.3)	254 (11.2)	136 (15.0)	
Non-CNS solid tumors	540 (17.0)	388 (17.1)	152 (16.7)	
Soft tissue sarcoma	86 (2.7)	56 (2.5)	30 (3.3)	
Ewing/osteosarcoma	214 (6.7)	169 (7.5)	45 (5.0)	
Others	251 (7.9)	183 (8.1)	68 (7.5)	
Age at diagnosis, years (M ± SD)	8.5 ± 5.6	8.4 ± 5.6	8.8 ± 5.7	0.03[b]
Age at evaluation, years (med, range)	7.7 (0.0–24.8)	7.5 (0.0–24.8)	8.2 (0.0–23.5)	0.03[b]
Anthracyclines in doxorubicin equivalents (mg/m^2)				
None	1,348 (42.5)	976 (43.1)	372 (41.1)	0.08
>0–100	648 (20.4)	465 (20.5)	183 (20.2)	
>100–200	586 (18.5)	399 (17.6)	187 (20.6)	
>200–300	264 (8.3)	177 (7.8)	87 (9.6)	
>300–400	247 (7.8)	187 (8.3)	60 (6.6)	
>400	76 (2.4)	59 (2.6)	17 (1.9)	
Chest radiation				
None	2,301 (72.7)	1,670 (73.9)	631 (69.6)	0.05
<20 Gy	383 (12.1)	265 (11.7)	118 (13.0)	
≥20 Gy	482 (15.2)	325 (14.4)	157 (17.3)	
Cranial radiation				
None	1,505 (49.1)	1,116 (51.2)	389 (43.9)	0.001
<20 Gy	990 (32.3)	675 (31.0)	315 (35.6)	
≥20 Gy	571 (18.6)	389 (17.8)	182 (20.5)	
Lifestyle behaviors				
Smoking				
Ever	347 (11.1)	244 (10.9)	103 (11.5)	<0.0001
Current	695 (22.2)	369 (16.5)	326 (36.4)	
Never	2,092 (66.8)	1,626 (72.6)	466 (52.1)	
Physical inactivity (yes)	1,470 (47.2)	983 (44.1)	487 (55.0)	<0.0001
Risky or heavy drinking (yes)	1,159 (37.7)	797 (36.2)	362 (41.7)	0.005
Body mass index				
Underweight (<18.5)	111 (3.6)	75 (3.4)	36 (4.0)	<0.0001
Normal (18.5–24.9)	1,051 (33.7)	786 (35.2)	265 (29.8)	
Overweight (25.0–29.9)	891 (28.6)	665 (29.8)	226 (25.4)	
Obese (≥30.0)	1,067 (34.2)	704 (31.6)	363 (40.8)	
Cardiovascular risk factors				
Hypertension (yes)	697 (22.0)	441 (19.5)	256 (28.2)	<0.0001
Dyslipidemia (yes)	400 (12.7)	253 (11.3)	147 (16.4)	<0.0001
Diabetes (yes)	241 (7.6)	156 (6.9)	85 (9.4)	0.02
Metabolic syndrome (yes)	809 (25.8)	520 (23.2)	289 (32.2)	<0.0001

(Continued on the following page)

Table 1. Demographic, cancer treatment characteristics, cardiovascular risk factors, lifestyle behaviors, and cardiovascular disease in SJLIFE survivors with and without clinically significant stress/distress. (Cont'd)

	Overall *n* (%)	Stress/distress absent *n* (%)	Stress/distress present[a] *n* (%)	*P*
Cardiovascular disease				
Cardiac dysrhythmia (yes)	45 (1.4)	29 (1.3)	16 (1.8)	0.30
Cardiomyopathy (yes)	230 (7.2)	164 (7.2)	66 (7.3)	0.98
Myocardial infarction (yes)	112 (3.5)	78 (3.4)	34 (3.7)	0.68

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CNS, central nervous system; M, mean; Med, median.
[a]Responses in this column are defined as a clinically significant response on any included measure of stress and distress: perceived stress scale, PCL-5, BSI depression subscale, BSI anxiety subscale.
[b]*t* test.

Stress, emotional distress, and cardiac health

Unadjusted cross-sectional associations are summarized in Supplementary Table S5. In multivariable models adjusted for sociodemographic factors, lifestyle variables, and cardiotoxic treatment exposures, any stress and/or distress was associated with an increased prevalence of hypertension [risk ratio (RR) = 1.24; 95% CI, 1.07–1.43], dyslipidemia (RR = 1.29; 95% CI, 1.03–1.61), and metabolic syndrome (RR = 1.35; 95% CI, 1.17–1.54). Perceived stress was associated with diabetes (RR = 1.40; 95% CI, 1.00–1.96), and metabolic syndrome (RR = 1.31; 95% CI, 1.12–1.52). PTSS and anxiety were associated with hypertension (RR = 1.22, 95% CI, 1.00–1.50; RR = 1.28, 95% CI, 1.06–1.55, respectively). Depression and anxiety were associated with metabolic syndrome (RR = 1.25, 95% CI, 1.06–1.47; RR = 1.34, 95% CI, 1.12–1.59, respectively; **Fig. 2**; **Table 3**). Relative risks for all covariates are reported in Supplementary Table S6A–S6I for all models where measures of stress and/or distress were significantly associated with cardiovascular health outcomes.

Stress, emotional distress, and new-onset cardiovascular health

Among the 1,748 participants who returned for a follow-up visit with a median follow-up time of 3.9 years, new onset dysrhythmia, cardiomyopathy, and myocardial infarction increased by 1.6% ($n = 19$), 9.2% ($n = 140$), and 2.6% ($n = 28$), respectively. New onset cardiovascular health risk factors included hypertension (13.3%), diabetes (4.0%), dyslipidemia (8.9%), and metabolic syndrome (22.2%). In sex, race, and baseline age adjusted models, any stress and/or distress at baseline were statistically significantly associated with new onset cardiac dysrhythmia (RR = 2.87; 95% CI, 1.21–6.78). Perceived stress at baseline was associated with a 1.4-fold increased risk of new onset hypertension (RR = 1.42; 95% CI, 1.04–1.95). PTSS and anxiety at baseline were associated an increased relative risk of new onset dyslipidemia (RR = 1.72, 95% CI 1.13–2.62; RR = 1.54 95% CI 1.01–2.35, respectively), see **Table 4**.

Discussion

It is well established that long-term survivors of childhood cancer have an increased risk for cardiovascular morbidity and mortality. While cardiotoxic treatment exposures are the most salient risk factor, they do not fully account for risk, thus, consideration of other potentially modifiable risk factors associated with adverse cardiovascular health in survivors is important. In this large, prospectively followed and clinically assessed cohort of adult survivors of childhood cancer, we observed associations between measures of stress and emotional distress and cardiovascular health independent of known cardiotoxic cancer treatments and lifestyle factors. To our knowledge, this is the first study to examine the potential contribution of psychologic health to cardiovascular outcomes in survivors of childhood cancer. These findings are important because emotional distress and stress are risk factors that are highly amenable to intervention.

In unadjusted cross-sectional models, we observed that perceived stress was associated with all cardiovascular risk factors (diabetes, hypertension, dyslipidemia, and metabolic syndrome). As expected, after adjustment for cardiotoxic treatment exposures, lifestyle variables, and sociodemographic factors, associations between measures

Table 2. Prevalence of clinically significant stress and emotional distress in survivors and community controls.

Variable	Measure	Survivor *N* (%)	Community control *N* (%)	*P*	*P*[a]
Perceived stress[b]	PSS-4	622 (19.5)	44 (10.2)	<0.0001	0.0007
PTSS[c]	PCL-C or PLC-5	353 (11.0)	24 (5.6)	0.0005	0.0225
Depression[d]	BSI-18 subscale	483 (14.9)	27 (6.2)	<0.0001	0.0030
Anxiety[d]	BSI-18 subscale	390 (12.0)	28 (6.5)	0.0006	0.0104
Any stress/distress[e]		909 (28.6)	71 (16.7)	<0.0001	0.0002

Abbreviations: BSI-18, Brief Symptom Inventory 18; PCL-C, PSTD Checklist Civilian Version; PCL-5, PTSD Checklist for the DSM-5; PSS-4, Perceived Stress Scale Short 4; PTSS, posttraumatic stress symptoms.
[a]*P* adjusted for age, sex, race/ethnicity, marital status, and household income.
[b]Clinical cutoff defined as a score >90th percentile of controls.
[c]Clinical cutoff for PCL-C >43, PCL-5 >32.
[d]Clinical cutoff defined as T-score ≥63 using sex-specific normative data.
[e]Any stress/distress was defined as scoring above the clinical cut-off on any measure and was dichotomized as a yes or no variable.

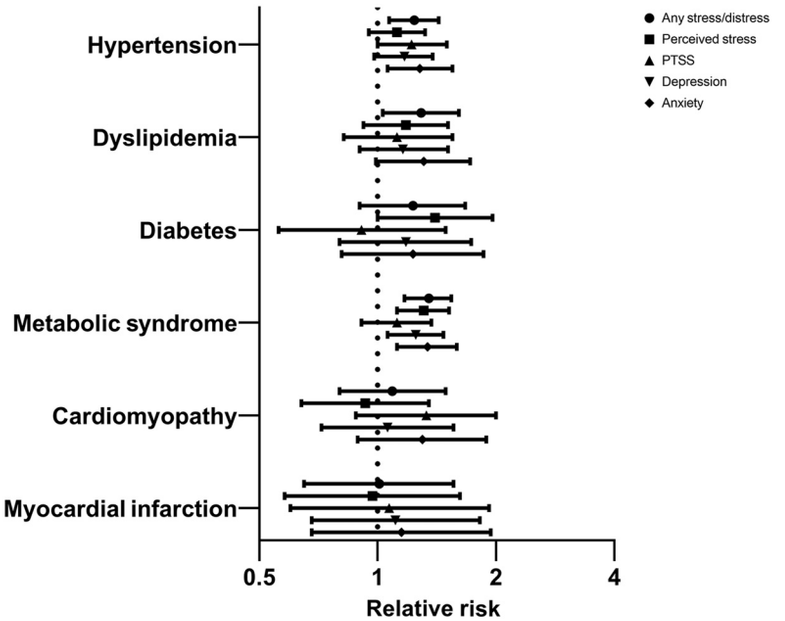

Figure 2.
Forest plot of adjusted cross-sectional associations between measures of stress and emotional distress and cardiovascular health. Models adjusted for age at evaluation, age at diagnosis, race, sex, household income, marital status, anthracyclines in doxorubicin equivalents, chest radiation, smoking, alcohol misuse, physical inactivity, and BMI (BMI not adjusted for in metabolic syndrome model). No adjusted model was computed for cardiac dysrhythmia due to small number of observed events.

of stress and/or distress and cardiovascular risk factors were attenuated. However, several associations remained statistically significant. Anxiety and post-traumatic stress symptoms were associated with a 20–30% increased prevalence of hypertension in adjusted models. Perceived stress, depression, anxiety, and any stress and/or distress were each associated with a 30% increased prevalence of metabolic syndrome. These findings are consistent with results from the general population that suggest associations between psychological health and cardiovascular disease often attenuate when accounting for lifestyle factors such as obesity, smoking, alcohol use, and physical inactivity (37, 38). However, for adult survivors of childhood cancer stress and distress are clearly associated with risk independent of lifestyle behaviors.

Although our cross-sectional results are unable to inform issues of temporality, we were able to examine longitudinal associations between baseline stress and/or distress and new-onset cardiovascular health outcomes among a subset of survivors who completed follow-up assessments approximately four years from baseline. Our measure of any stress and/or distress was associated with a nearly 3-fold increased risk of incident cardiac dysrhythmia. Post-traumatic stress symptoms and anxiety were associated with a 50%–70% increased risk of incident dyslipidemia. These findings align with several studies in the general population highlighting prospective associations between psychological health and cardiovascular morbidity and mortality. Systematic reviews and meta-analyses report that perceived stress and anxiety are associated with an approximately 1.27-fold increased risk of incident coronary heart disease (13, 15), depression is associated with a nearly 2-fold risk of incident coronary heart disease (13), and anxiety and depression are associated with an increased risk of cardiac death (13). In addition, trauma exposure and elevated posttraumatic stress symptoms are associated with an increased risk of cardiovascular events (myocardial infarction and stroke; ref. 39) and incident coronary heart disease (40). Our prospective findings support further consideration of measures of psychological health as casual risk factors associated with cardiac conditions and cardiovascular risks factors that greatly increase the odds of new-onset cardiovascular conditions.

Potential mechanisms underlying the associations between psychologic health and cardiovascular disease are complex. Moreover, these associations are likely multifactorial and involve bidirectional

Table 3. Adjusted[a] cross-sectional associations between measures of stress and/or distress and cardiovascular health[b].

	Cardiomyopathy RR (95% CI)	Myocardial infarction RR (95% CI)	Hypertension RR (95% CI)	Diabetes RR (95% CI)	Dyslipidemia RR (95% CI)	Metabolic syndrome[c] RR (95% CI)
Perceived stress	0.93 (0.64–1.35)	0.97 (0.58–1.62)	1.12 (0.95–1.32)	**1.40 (1.00–1.96)**	1.18 (0.92–1.51)	**1.31 (1.12–1.52)**
PTSS	1.33 (0.88–2.00)	1.07 (0.60–1.92)	**1.22 (1.00–1.50)**	0.91 (0.56–1.49)	1.12 (0.82–1.55)	1.12 (0.91–1.37)
Depression	1.06 (0.72–1.56)	1.11 (0.68–1.82)	1.17 (0.98–1.38)	1.18 (0.80–1.73)	1.16 (0.90–1.51)	**1.25 (1.06–1.47)**
Anxiety	1.30 (0.89–1.89)	1.15 (0.68–1.94)	**1.28 (1.06–1.55)**	1.23 (0.81–1.86)	1.31 (0.99–1.72)	**1.34 (1.12–1.59)**
Any stress/distress	1.09 (0.80–1.49)	1.01 (0.65–1.56)	**1.24 (1.07–1.43)**	1.23 (0.90–1.67)	**1.29 (1.03–1.61)**	**1.35 (1.17–1.54)**

Note: Bold indicates $P \leq 0.05$.
[a]Models adjusted for age at evaluation, age at diagnosis, sex, race/ethnicity, marital status, household income, anthracyclines in doxorubicin equivalents, chest radiation, smoking history, alcohol misuse, physical inactivity, and body mass index.
[b]Multivariable model not calculated for cardiac dysrhythmia due to small number of observed events.
[c]Body mass index excluded as a covariate in the model for metabolic syndrome.

Table 4. Longitudinal[a] associations between measures of stress and/or distress and cardiovascular health.

	Cardiac dysrhythmia (N^b = 1,154)	Cardiomyopathy (N^b = 1,526)	Myocardial infarction (N^b = 1,096)	Hypertension (N^b = 1,295)	Diabetes (N^b = 1,464)	Dyslipidemia (N^b = 1,477)	Metabolic syndrome (N^b = 1,236)
New onset, *n (%)*[c]	19 (1.6)	140 (9.2)	28 (2.6)	172 (13.3)	59 (4.0)	131 (8.9)	275 (22.2)
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Perceived stress	1.44 (0.54–3.82)	1.16 (0.79–1.69)	0.52 (0.16–1.72)	**1.42 (1.04–1.95)**	1.01 (0.55–1.88)	1.08 (0.73–1.62)	1.19 (0.92–1.53)
PTSS	1.46 (0.45–4.68)	1.39 (0.88–2.20)	1.11 (0.34–3.62)	1.40 (0.93–2.09)	1.06 (0.50–2.26)	**1.72 (1.13–2.62)**	1.05 (0.75–1.46)
Depression	1.05 (0.32–3.45)	1.36 (0.92–2.01)	0.70 (0.22–2.27)	1.26 (0.88–1.80)	0.93 (0.45–1.93)	1.25 (0.83–1.89)	1.15 (0.87–1.52)
Anxiety	2.64 (0.98–7.11)	1.24 (0.80–1.94)	1.34 (0.47–3.76)	1.33 (0.91–1.96)	1.09 (0.53–2.24)	**1.54 (1.01–2.35)**	1.06 (0.77–1.45)
Any stress/distress	**2.87 (1.21–6.78)**	1.20 (0.85–1.68)	0.64 (0.24–1.68)	1.31 (0.98–1.75)	0.98 (0.57–1.71)	1.34 (0.96–1.88)	1.14 (0.91–1.43)

Note: Bold font indicates $P < 0.05$.
Abbreviation: RR, relative risk.
[a]Models adjusted for age at baseline evaluation, sex, and race/ethnicity.
[b]*N* = number of survivors who did not have the condition at baseline and returned for follow-up visit.
[c]*n* (%) = number and proportion of observed new-onset events.

relationships (41). However, the strength of previous prospective studies and our longitudinal findings suggest the potential for behavioral and/or biological causal pathways driven by stress and psychologic health disturbances (41, 42). Stress and emotional distress may influence cardiovascular health through behavioral mechanisms related to unhealthy lifestyles, such as smoking, physical inactivity, poor diet, sleep disturbance, and alcohol abuse. In a prospective cohort study of adults with coronary heart disease, depression was associated with a 31% increased rate of cardiovascular events, but this association was largely explained by physical inactivity (38). When examining the association between posttraumatic stress symptoms and heart rate variability, smoking, alcohol abuse, and sleep disturbances accounted for 94% of the shared variance between these two measures (37). There are also several underlying pathophysiologic associations that may be driven by psychological health. Stress exposure can cause disruptions in hormone and neurotransmitter production, in turn, influencing cardiovascular risk (42). Inflammation, a risk factor for developing atherosclerosis (42), is often increased among individuals with anxiety (43) and/or mood disorders (44), also serving as a potential mechanistic pathway. Autonomic dysfunction, resulting in activation of the sympathetic system and reduction in the parasympathetic system, can increase the risk for cardiovascular disease or sudden cardiac death (41, 42). In addition, in our study, each measure of stress and distress was associated with metabolic syndrome in cross-sectional examinations, suggesting that metabolic dysregulation may be a pathway between psychological and cardiovascular health (41). While the physiologic mechanisms of the consequences of metabolic syndrome remain poorly understood (45) a meta-analysis of prospective studies identified a greater than 2-fold increased risk of cardiovascular morbidity and mortality in individuals with metabolic syndrome (46). The interdependent and multifactorial aspects of metabolic syndrome increase the challenge of understanding the precise mechanistic pathways to adverse cardiovascular outcomes. However, the activation of the sympathetic nervous system, renin-angiotensin system, or increased adipocytokines and proinflammatory cytokines have been proposed as potential mechanisms (45). Elucidating associations between stress/emotional distress and cardiovascular outcomes in cancer survivors is important due to the emotional burden that can accompany a cancer diagnosis.

Approximately one-third of our sample met criteria for clinically significant stress and/or distress. Compared to community controls, survivors reported a higher prevalence of perceived stress, PTSS, anxiety, and depression, indicating an increased vulnerability among survivors. There are several efficacious treatments for anxiety and depressive symptoms; however, whether these interventions confer benefit to cardiac health in childhood cancer survivors has not yet been determined. In the general population, a stepped-care depression intervention in patients with acute coronary syndrome demonstrated a reduction in depressive symptoms and fewer major cardiac events compared to the usual treatment group (47). Sertraline interventions for depression have been associated with increased heart-rate variability (48) and a trend (albeit non-significant) in the reduction of severe adverse cardiovascular events (49). While such findings are promising, meta-analyses and systematic reviews also highlight mixed results of psychological interventions (50, 51). Future research is needed to determine if effective treatment of psychological symptoms may improve cardiac health in survivors of childhood cancer.

Study limitations

The findings from this study should be considered in the context of several limitations. Although our cross-sectional models included adjustment for lifestyle variables associated with cardiovascular disease, a strength of our analyses, we were unable to identify whether these variables were potential mediators as opposed to confounders because of the cross-sectional nature of the data. Our longitudinal models had a small number of cardiovascular events; thus, we were only able to adjust for age, sex, and race/ethnicity. Furthermore, the median follow-up time from baseline was approximately 4 years, which also may influence our findings as a longer interval of follow-up may allow for detection of a greater number of cardiovascular conditions. Given the small number of observed outcomes, we dichotomized our psychological health predictors and cardiovascular outcomes and did not examine potential dose–response relationships. Finally, we only had information on patient reported symptoms of psychological health and did not have information on actual mental health diagnoses.

Clinical perspectives

To our knowledge, this is the first study to examine the contribution of stress and emotional distress to cardiovascular health in long-term survivors of childhood cancer. We found several associations between measures of psychological health and cardiovascular conditions or cardiovascular risk factors in both cross-sectional and longitudinal analyses. These findings highlight the need to routinely assess and

provide interventions to optimize the psychological health of survivors. Although the integration of psychological care in survivorship continues to face many barriers (52), the efficacy of screening for psychological distress and the high acceptance among survivors has been reported (53). Furthermore, these findings may inform surveillance strategies, as survivors who experience clinically significant stress and/or distress may benefit from modified cardiovascular screening recommendations. However, additional research is needed to inform surveillance, as increased surveillance could impact the stress/distress that survivors experience. Increased short-term, but not long-term distress has been identified among patients with false-positive screenings for breast cancer and lung cancer, (54, 55); however, less is known about the impact of increased late effect surveillance on the psychological health of childhood cancer survivors. Furthermore, as individual differences exist in a survivor's preference for the amount and level of information they receive pertaining to their health surveillance (56), the integration of psychosocial follow-up as a standard of care in survivorship could also be utilized to address potential surveillance-related stressors based on individual needs. Future survivorship studies should examine whether psychological interventions can improve the cardiovascular health among adult survivors of childhood cancer, a vulnerable population at risk for early-onset cardiovascular morbidity and mortality.

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Authors' Contributions

M.M. Lubas: Conceptualization, methodology, writing–original draft, writing–review and editing. **M. Wang:** Formal analysis, writing–review and editing. **J.L. Jefferies:** Conceptualization, writing–review and editing. **K.K. Ness:** Conceptualization, methodology, writing–review and editing. **M.J. Ehrhardt:** Conceptualization, writing–review and editing. **K.R. Krull:** Conceptualization, funding acquisition, writing–review and editing. **D.A. Mulrooney:** Conceptualization, writing–review and editing. **D.K. Srivastava:** Conceptualization, formal analysis, supervision, writing–review and editing. **R.M. Howell:** Methodology, writing–review and editing. **L.L. Robison:** Conceptualization, funding acquisition, writing–review and editing. **M.M. Hudson:** Conceptualization, funding acquisition, writing–review and editing. **G.T. Armstrong:** Conceptualization, methodology, writing–review and editing. **T.M. Brinkman:** Conceptualization, methodology, writing–original draft, writing–review and editing.

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