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1 **Association between psychological distress and cardiovascular health amongst cancer survivors in**
 2 **the United States: findings from nationally representative data**

3 **Running title:** Mental health, cardiovascular health, and cancer

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 35 National Cancer Institute (P30 CA008748). Dr. Sharma has funding support from American Heart
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2 authors have no conflict of interest to report.

3 **Keywords:** cardio-oncology; cancer; psychology; mental health

4 Cancer is associated with increased long-term cardiovascular risks¹ and psychological distress.²
5 Whilst psychological distress has been linked to elevated cardiovascular risks,³ the strong correlation
6 between cancer and cardiovascular diseases may modify the cardiovascular effects of psychological
7 distress. It is thus unclear if these associations hold true for cancer survivors. Investigations in this area
8 are needed as the number of cancer survivors increases.⁴ We therefore investigated the relationship
9 between psychological distress and cardiovascular health amongst cancer survivors.

10 The methodology is detailed in the **Supplementary Methods**. This cross-sectional study used
11 data from the National Health Interview Survey (NHIS), which provides health data representative of
12 the non-institutionalized population of the United States. Harmonised data were obtained from the
13 Integrated Public Use Microdata Series.⁵ As all the data are deidentified and publicly available, this
14 study was exempt from ethics approval.

15 Subjects aged ≥ 18 years old sampled between 2013-2017 were included. Patients with missing
16 data for the outcome or any of the independent variables were excluded, as were those with non-
17 melanotic skin cancer as the only cancer diagnosis.⁶ Cancer survivorship was ascertained by responses
18 to the question, "Have you ever been told by a doctor or other health professional that you had cancer or
19 a malignancy of any kind?"

20 Measurement of the outcome, cardiovascular health, was based on the American Heart
21 Association's *Life's Essential Eight*.⁷ As the NHIS contains no dietary data, the cardiovascular health
22 score included seven one-point domains (hypertension, diabetes mellitus, dyslipidaemia, physical
23 inactivity, inappropriate sleep duration, smoking, and obesity); higher scores indicated poorer
24 cardiovascular health.⁸ Psychological distress was measured by the six-item Kessler scale (K6), a

1 validated screening tool with possible total scores of 0-24.⁹ Severe psychological distress (SPD) was
2 defined as $K6 \geq 13$.⁹ All data were self-reported as per the NHIS' nature.

3 Survey-specific statistics were used to generate nationally representative estimates. Multivariable
4 Poisson regression was used to investigate the relationship between SPD and the cardiovascular health
5 score, with risk ratios (RRs; representing the comparative risk of having worse cardiovascular health)
6 and 95% confidence intervals (CIs) as summary statistics. A restricted cubic spline was used to explore
7 the linearity of this relationship. Multivariable logistic regression was used to explore relationships
8 between SPD and each component of the cardiovascular health score amongst cancer survivors, with
9 odds ratios (ORs) and 95% CIs as summary statistics. Subgroup and exploratory analyses are detailed in
10 the **Supplementary Methods**. Two-sided $p < 0.05$ were considered statistically significant.

11 Of the 164,557 subjects in 2013-2017 NHIS, 138,001 (representing a weighted population of
12 203,223,831) were analysed after applying all exclusion criteria, of whom 13,485 (9.8%; representing a
13 weighted population of 17,648,471) were cancer survivors; 13,354 had data for the age of cancer
14 diagnosis, of whom 2.7% were diagnosed by 14 years old, 30.8% between 14-45, 41.8% between 46-64,
15 and 24.7% at ≥ 65 years old. The weighted mean cardiovascular health score was 2.8 ± 1.6 for cancer
16 survivors and 2.0 ± 1.4 for those without known cancer. Their respective weighted prevalence of SPD
17 were 3.8% [95% CI: 3.5%-4.3%] and 3.2% [3.0%-3.3%].

18 SPD was independently associated with worse cardiovascular health both in cancer survivors
19 (adjusted RR 1.24 [1.19-1.29], $p < 0.001$) and those without known cancer (adjusted RR 1.41 [1.39-1.44],
20 $p < 0.001$), but the former association was significantly weaker ($p_{\text{interaction}} = 0.001$; **Figure 1A**). The
21 relationship between psychological distress and cardiovascular health was grossly linear, regardless of
22 cancer history (**Figure 1A**). Amongst cancer survivors, SPD was independently associated with all
23 components of the cardiovascular health score except obesity (**Figure 1B**), with the strongest

1 association observed for inappropriate sleep duration (adjusted OR 3.70 [2.93-4.68], $p < 0.001$).
2 Exploratory analysis showed a strong relationship between SPD and known cardiovascular disease
3 amongst cancer survivors (odds ratio 2.95 [2.30-3.78], $p < 0.001$).

4 Subgroup analyses demonstrated that amongst cancer survivors, the association between SPD
5 and cardiovascular health was significantly stronger in those who were younger ($p_{\text{interaction}} < 0.05$; **Figure**
6 **2**) or female ($p_{\text{interaction}} = 0.014$), but did not differ significantly by family income ($p_{\text{interaction}} = 0.992$), race
7 ($p_{\text{interaction}} = 0.147$), or the presence of known cardiac conditions ($p_{\text{interaction}} = 0.187$). The association
8 remained significant in those with cancer of the breast (N=2445; adjusted RR 1.34 [1.21-1.49],
9 $p < 0.001$), prostate (N=1642; adjusted RR 1.23 [1.08-1.38], $p = 0.001$), colon/rectum (N=873; adjusted
10 RR 1.20 [1.06-1.35], $p = 0.004$), and skin (melanotic; N=1024; adjusted RR 1.46 [1.20-1.77], $p < 0.001$),
11 but not that of the lung (N=430; adjusted RR 1.08 [0.90-1.29], $p = 0.417$). Exploratory subgroup analyses
12 in participants without known cancer showed similar interactions for age groups, but not for sex
13 (**Supplementary Table 1**).

14 To the best of the authors' knowledge, this is the first study investigating the association between
15 psychological distress and cardiovascular health amongst cancer survivors. The significant association
16 between SPD and cardiovascular health was consistent with findings in other populations.³ The
17 association being weaker in cancer survivors was likely due to the adverse cardiovascular effects of
18 cancer and cancer therapies diminishing the relative influence of psychological distress. Importantly,
19 younger individuals were particularly vulnerable to this association, likely because ageing has more
20 dominant effects on cardiovascular health in older individuals. Female cancer survivors were also more
21 vulnerable to the captioned association, as observed elsewhere as well.³ The underlying mechanisms are
22 less clear, probably including social factors such as sexism,³ and biological factors such as lower vaso-

1 reactivity, greater stress-induced reduction in endothelial function in females, and female-specific
2 cardiovascular risk factors (e.g. hormone-related).¹⁰

3 Clinically, our findings highlighted the importance of a holistic and multidisciplinary approach
4 to the care of cancer survivors, specifically being attentive to their psychological well-being and
5 involving mental health professionals in a timely manner, and especially for younger or female patients.
6 Our findings also provided insights for policymakers about patients who may benefit the most from
7 quality improvement programs. Using data from a national survey, our findings were representative and
8 widely applicable. Nonetheless, the self-reported nature meant that recall bias and misclassification of
9 variables were possible, and residual/unobserved confounders could exist. Additionally, the cross-
10 sectional nature of the NHIS prevented establishment of causality. Reverse causality is also possible, as
11 poorer cardiovascular health may cause SPD.

12 In conclusion, SPD was associated with worse cardiovascular health amongst cancer survivors,
13 especially younger or female patients, although the association was weaker than that in non-cancer
14 subjects.

15
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22 Affairs, the National Institutes of Health, the World Heart Federation, and the Tahir and Jooma Family;

1 and honoraria from the American College of Cardiology (Associate Editor for Innovations). All other
2 authors have no conflict of interest to report.

3 **Data availability statement:**

4 All underlying data are publicly available from [https://www.cdc.gov/nchs/nhis/data-questionnaires-](https://www.cdc.gov/nchs/nhis/data-questionnaires-documentation.htm)
5 [documentation.htm](https://www.cdc.gov/nchs/nhis/data-questionnaires-documentation.htm) and <https://nhis.ipums.org/nhis/> .

6
7 **Authorship:** JSKC and DIS contributed to the conception of the work. JSKC and ECD contributed to
8 the data curation of the work. JSKC contributed to the methodology, formal analysis, and visualization
9 of the work. JSKC drafted the manuscript. GS, SSV, TL, and GT supervised the work. TL and GT
10 acquired funding for the work. All critically revised the manuscript, gave final approval, and agree to be
11 accountable for all aspects of the work ensuring integrity and accuracy.

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14
15 **Figure legend**

16 **Figure 1.** (A) Restricted cubic spline showing the relationship between the six-item Kessler score and
17 cardiovascular health, stratified by whether the subjects had known cancer. Risk ratio and 95%
18 confidence intervals are shown, with risk ratio > 1 representing an association with more cardiovascular
19 risk factors (i.e. worse cardiovascular health). (B) Forest plot showing the associations between severe
20 psychological distress and individual components of the cardiovascular health score amongst cancer
21 survivors. Adjusted odds ratios and 95% confidence intervals (CIs) are shown.

- 1 **Figure 2.** Forest plot showing the results of pre-specified subgroup analyses amongst cancer survivors.
- 2 Adjusted risk ratios and 95% confidence intervals (CIs) are shown.

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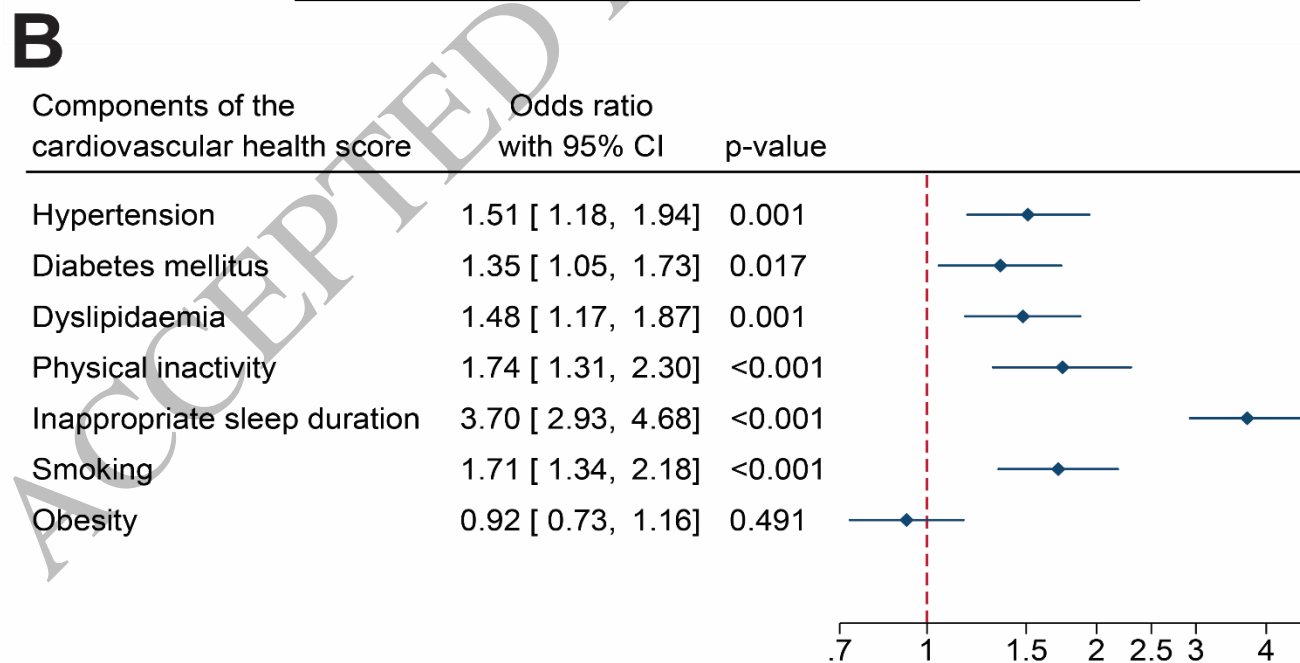
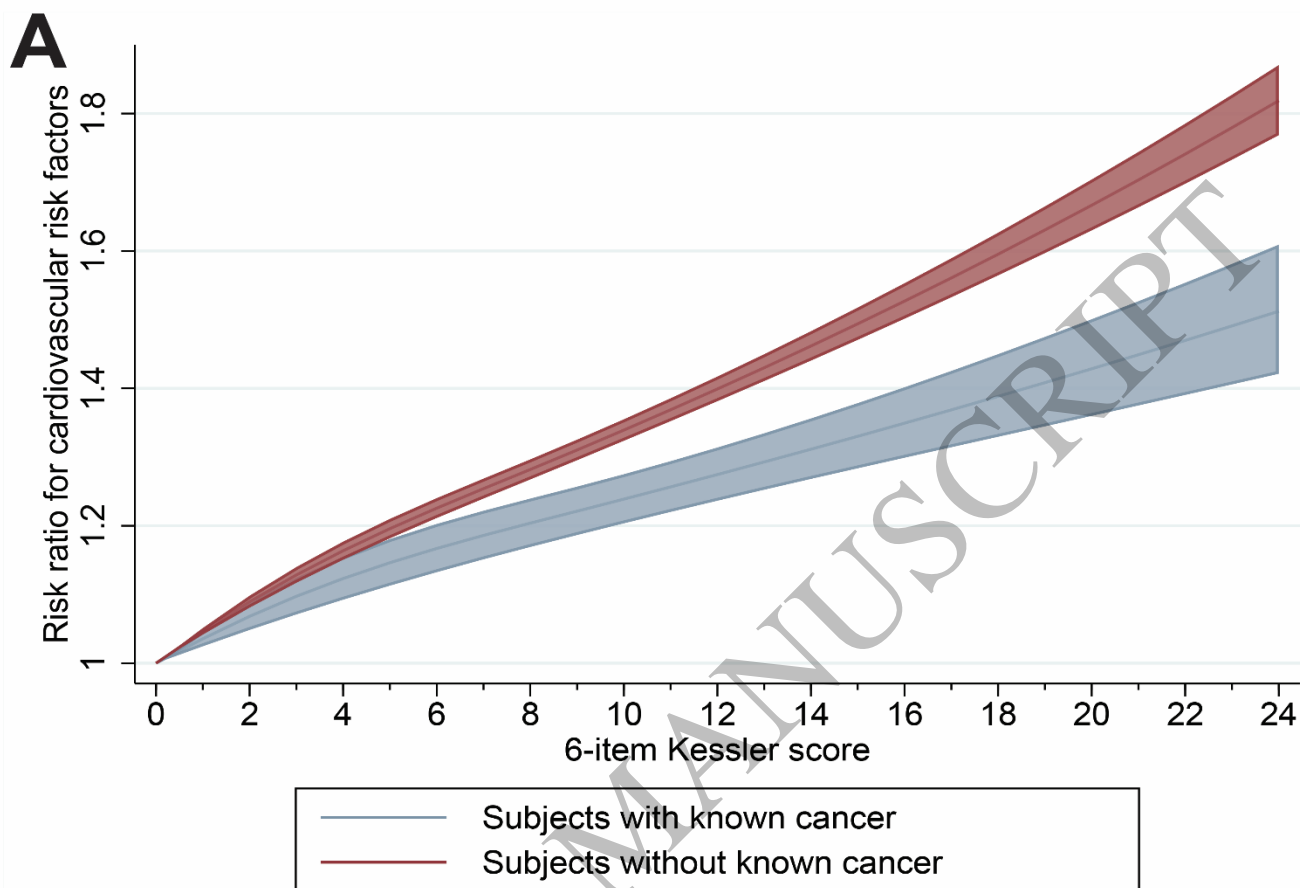


Figure 1
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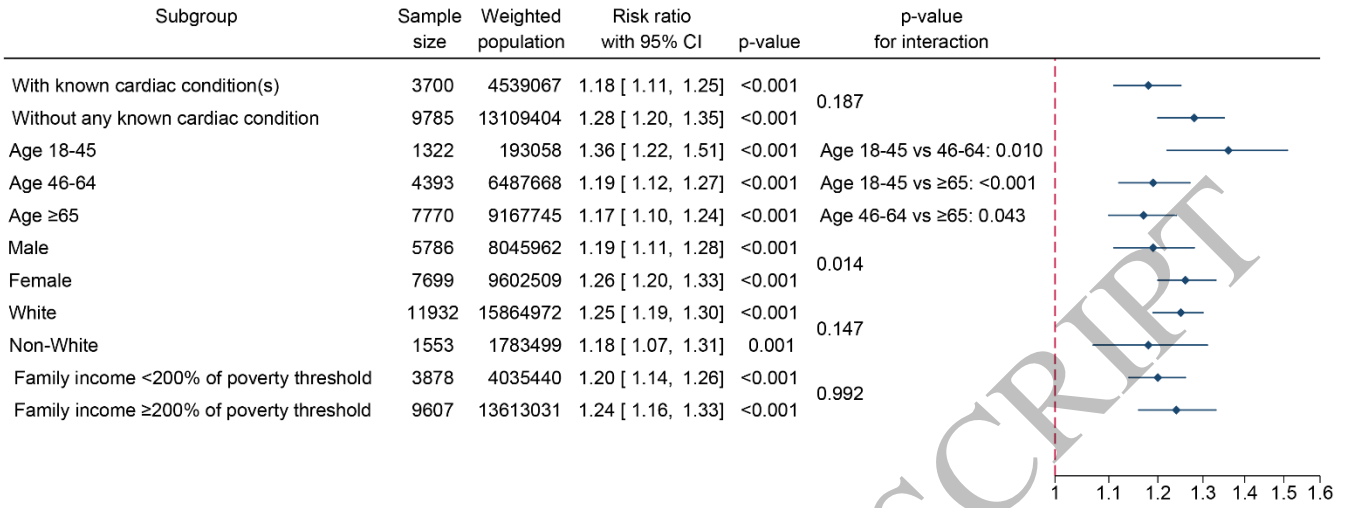


Figure 2
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