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

Running title: Mental health, cardiovascular health, and cancer

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

4 Cancer is associated with increased long-term cardiovascular risks[1] 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

2

1 validated screening tool with possible total scores of 0-24.[9] Severe psychological distress (SPD) was

2 defined as K6≥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 ($p_{interaction}$=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

3

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 ($p_{interaction}<0.05$; **Figure**

6 **2**) or female ($p_{interaction}=0.014$), but did not differ significantly by family income ($p_{interaction}=0.992$), race

7 ($p_{interaction}=0.147$), or the presence of known cardiac conditions ($p_{interaction}=0.187$). 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-

4

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.

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

Data availability statement:

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Figure legend

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

7

1 **Figure 2.** Forest plot showing the results of pre-specified subgroup analyses amongst cancer survivors.

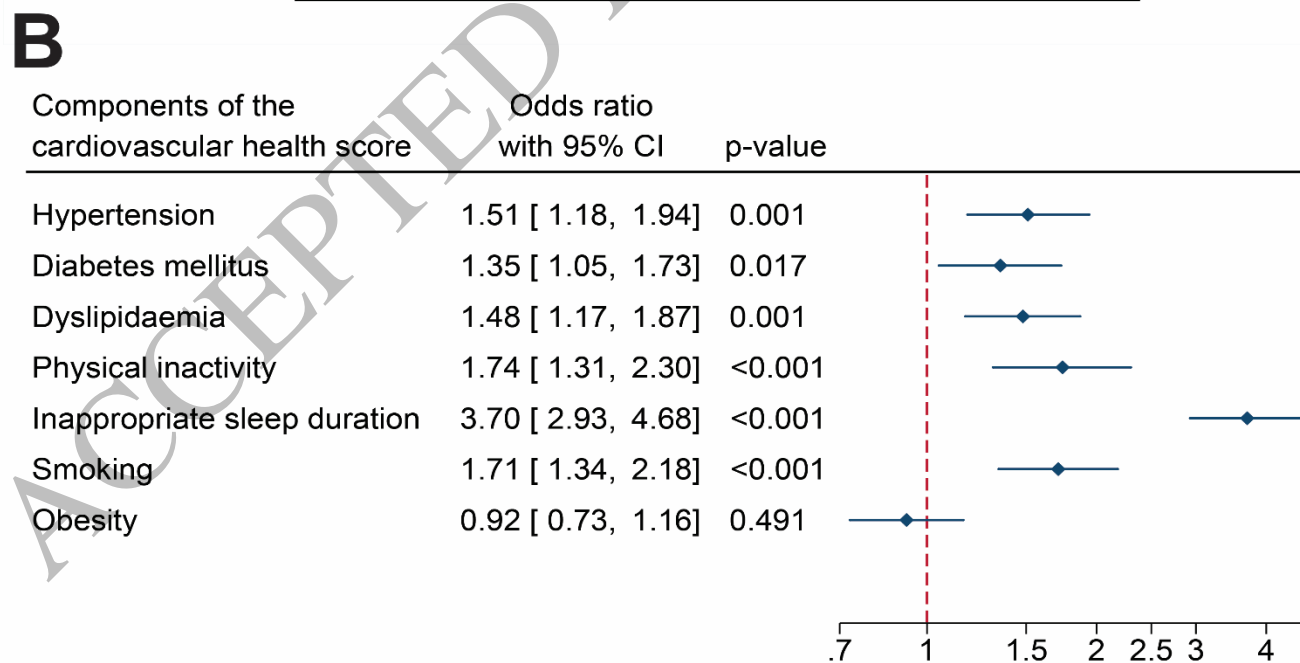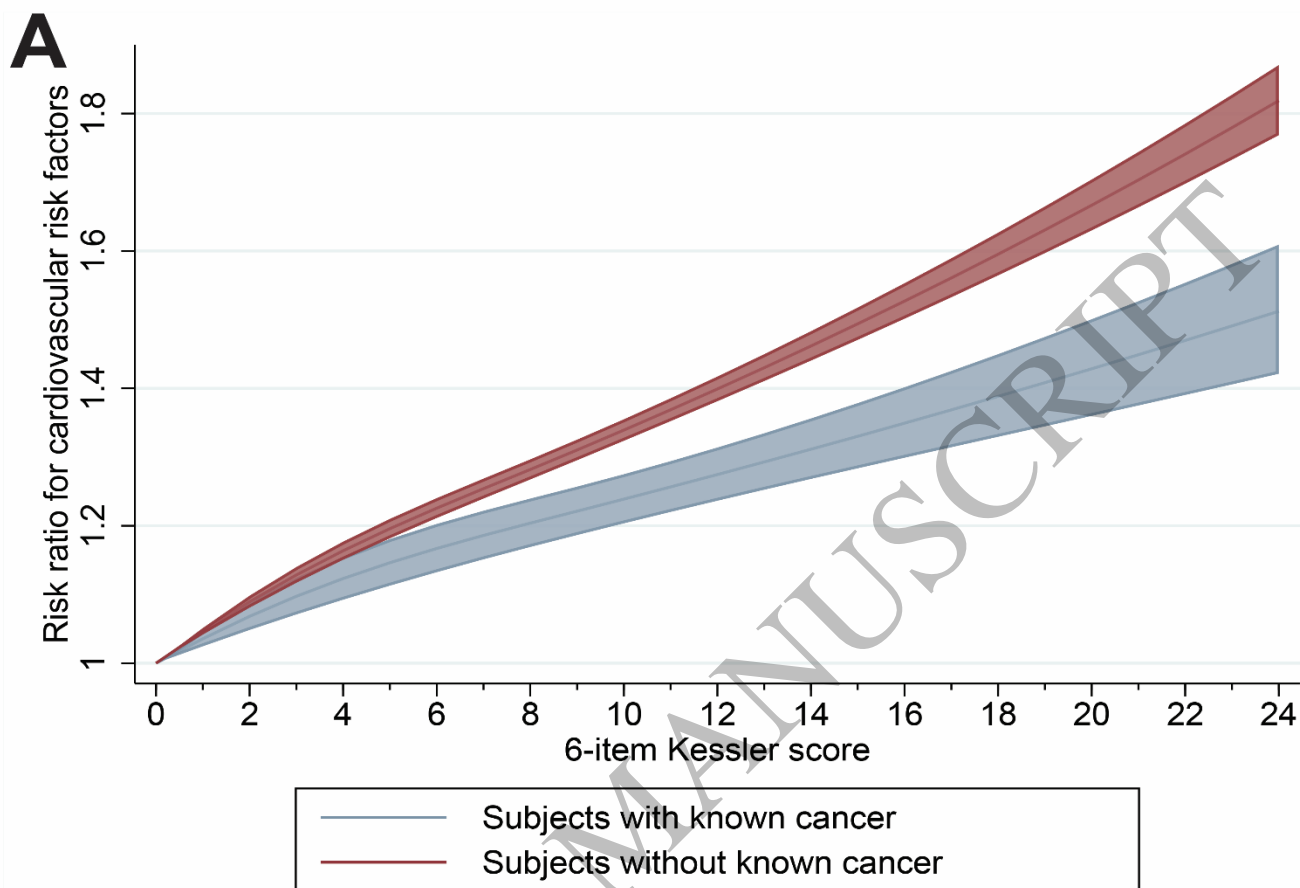2 Adjusted risk ratios and 95% confidence intervals (CIs) are shown.
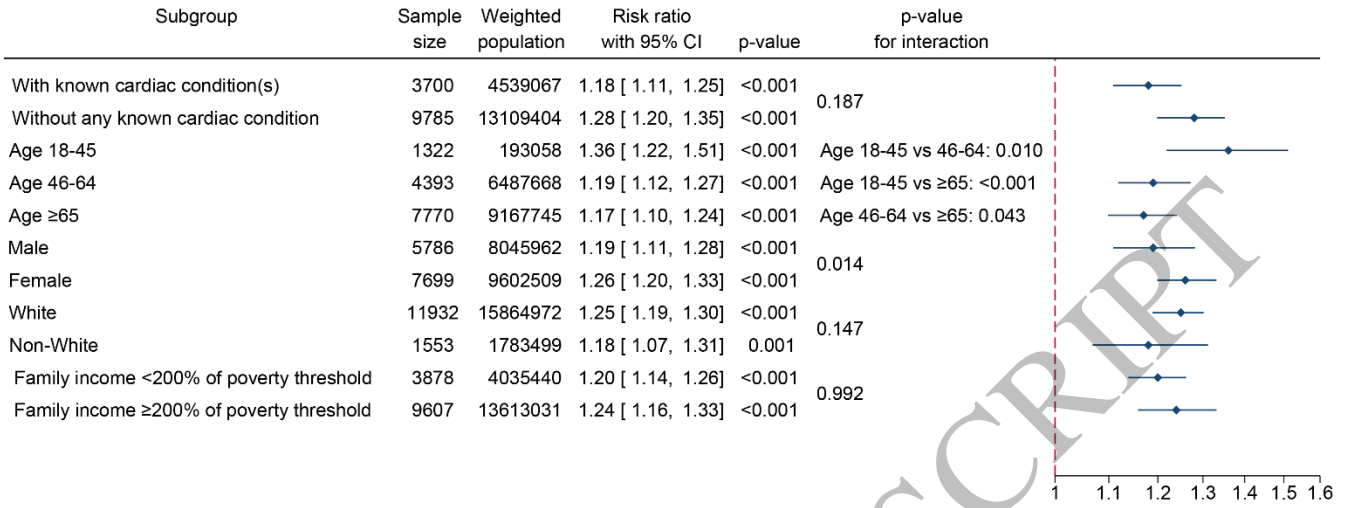
Figure 1
300x373 mm (x DPI)

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Subgroup	Sample size	Weighted population	Risk ratio with 95% CI	p-value	p-value for interaction
With known cardiac condition(s)	3700	4539067	1.18 [1.11, 1.25]	<0.001	0.187
Without any known cardiac condition	9785	13109404	1.28 [1.20, 1.35]	<0.001	
Age 18-45	1322	193058	1.36 [1.22, 1.51]	<0.001	Age 18-45 vs 46-64: 0.010
Age 46-64	4393	6487668	1.19 [1.12, 1.27]	<0.001	Age 18-45 vs ≥65: <0.001
Age ≥65	7770	9167745	1.17 [1.10, 1.24]	<0.001	Age 46-64 vs ≥65: 0.043
Male	5786	8045962	1.19 [1.11, 1.28]	<0.001	0.014
Female	7699	9602509	1.26 [1.20, 1.33]	<0.001	
White	11932	15864972	1.25 [1.19, 1.30]	<0.001	0.147
Non-White	1553	1783499	1.18 [1.07, 1.31]	0.001	
Family income <200% of poverty threshold	3878	4035440	1.20 [1.14, 1.26]	<0.001	0.992
Family income ≥200% of poverty threshold	9607	13613031	1.24 [1.16, 1.33]	<0.001	

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Figure 2
276x109 mm (x DPI)

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