Journal of Affective Disorders 316 (2022) 1–9

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Depressive symptomology and cancer incidence in men and women: Longitudinal evidence from the HUNT study

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ARTICLE INFO

Keywords:
Cancer
Oncology
cancer risk
Depressive symptoms
Depression
Psychiatry
Mental health
Neuroscience
Psychology

ABSTRACT

Background: Depressive symptoms and mood disorders are associated with a host of physical conditions. However, it is inconclusive whether depressive symptoms are also associated with cancer onset. The aim of this study was to investigate whether depressive symptoms are associated with cancer incidence in a large population-based sample of men and women.

Methods: This study examined data from waves two (HUNT 2, 1995–97) and three (HUNT 3, 2006–08) of the Trøndelag Health Study (HUNT). Depressive symptoms were ascertained using the Hospital Anxiety and Depression Scale (HADS-D $\geq$ 8), cancer onset was identified via linkage with the Cancer Registry of Norway, death records by the national Cause of Death Register (CDR), and information on lifestyle and demographic factors was self-reported. Cox-proportional hazard regression models were used to test associations. Unadjusted, age-adjusted and multivariable best models accounting for smoking, education, marital status and current employment are presented.

Results: Men and women (n = 61,985; 46.0 % men) were followed from baseline over a period of 778,802 person-years. During the 20-year study period, there were 6856 (11.1 %) individuals with incident cancers and 12,480 (20.1 %) deaths (n = 2498 attributed to cancer). For men with depressive symptoms, 505 (15.3 %) developed incident cancer during the follow-up period, whereas among those without depressive symptoms, 3164 (12.5 %) developed incident cancer. Following adjustment for age, depressive symptomology was not significantly associated with risk of overall cancer onset, nor among prostate, colon or melanoma subtypes. Depressive symptoms were associated with an increased risk of bronchus and lung cancer both before (HR 1.90, 95 % CI 1.43–2.50, $p \leq 0.001$) and after adjustment for age (HR 1.38, 95 % CI 1.04–1.80, p = 0.025). However, further adjustment for additional possible confounders explained this association. For women with depressive symptoms, 384 (11.2 %) developed incident cancer during the follow-up period, whereas among those with no depressive symptomology, 2803 (9.3 %) developed incident cancer. After accounting for age, depressive symptomology was not associated with risk of overall cancer onset, nor among breast, colon, lung and bronchus, or melanoma subtypes. Additional analyses evaluating relationship of depression symptom severity and cancer onset did not alter findings for men or women.

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https://doi.org/10.1016/j.jad.2022.08.002
Received 28 February 2022; Received in revised form 21 July 2022; Accepted 1 August 2022
Available online 4 August 2022

Limitations: This report is limited by the post-hoc study design and subsequent non-randomised nature. Future prospective studies are required.
Conclusion: These results suggest that depressive symptoms are not associated with an increased risk of overall or site-specific cancer onset in these men and women. Given the increased co-occurrence of other medical conditions such as cardiovascular disease, diabetes, stroke and musculoskeletal disorders in people with depression, the role of clinically diagnosed depression and other psychiatric disorders in association with cancer onset necessitates further consideration.

1. Background

Mental disorders are a major cause of disease burden globally, consistently accounting for >14 % of the age-standardised years lived with disability, with >10 % prevalence worldwide (James et al., 2018). Following anxiety, mood disorder is the second most prevalent mental disorder yet is associated with the highest rate of disability (Steel et al., 2014). Furthermore, mood disorders are associated with increased healthcare utilisation and reduced life expectancy compared to the general population (Moon et al., 2019; Vigo et al., 2016). This increase in morbidity and mortality is largely attributed to associated lifestyle factors and physical comorbidities.

Research has shown that both clinically-diagnosed depression and self-reported depressive symptoms are associated with a number of chronic physical conditions including cardiovascular disease (CVD) (Ariyo et al., 2000; Egede et al., 2005; Hazuda et al., 2019; Lett et al., 2004), musculoskeletal disorders (Jacka et al., 2005; Pasco et al., 2008), stroke (Bos et al., 2008; Li et al., 2012; Péquignot et al., 2016; Zhao et al., 2019), heart failure (Gustad et al., 2014a) and diabetes mellitus (Bai et al., 2013; Deschênes et al., 2018; Luo et al., 2019; Vancampfort et al., 2015). Additionally, there is a growing body of evidence linking depression with cancer onset (McGee et al., 1994; Penninx et al., 1998; Zaidan et al., 2014; Huang et al., 2015). The latest global cancer data indicate an increased burden with approximately 18.1 million new cases and 9.6 million deaths in 2018, with the current number of people alive within five years of a cancer diagnosis estimated to be 43.8 million (International Agency for Research on Cancer and WHO, 2018). These figures, combined with the prevalence and morbidity associated with depression (James et al., 2018), highlights the need to explore associations between these prevalent disorders.

Therefore, our aim was to investigate the longitudinal association between depressive symptomology and cancer incidence (overall and among particular anatomical subtypes) in a large population-based sample of men and women.

2. Methods

2.1. Study population and setting

The Trøndelag Health (HUNT) study is a large, population-based study of residents of Trøndelag county, Norway. All citizens of this area, aged ≥20 years were invited by mail to participate in each of the four study waves, carried out roughly every decade from 1984 to 2019. Detailed descriptions of the HUNT study cohorts, including participation, emigration and mortality have been published elsewhere (Krokstad et al., 2013). Assessments at both HUNT 2 and HUNT 3 included questionnaires covering self-reported health, quality of life, behavioural, lifestyle and sociodemographic factors. Additionally, anthropometry and a wide range of other clinical measures were taken during a clinical examination performed by especially trained nurses (Krokstad et al., 2013).

A total of 65,237 adults participated in HUNT 2 and 50,807 in HUNT 3 (participation rate of 69.5 % and 54.1 %, respectively). Of those participating in HUNT 3, 37,071 had also participated in HUNT 2. For those who participated in HUNT 2 and/or HUNT 3 ($n = 79{,}387$; 74.6 %), linkage was performed via the unique Norwegian 11-digit personal identification number with the Cancer Registry of Norway for this study. Exclusions were made where a *de-novo* cancer diagnosis was i) not certified (i.e., international classification of diseases-10th revision (ICD-10) code D00-D46) ($n = 113$), ii) occurred prior to the HUNT 2 start date in 1995 ($n = 2296$), iii) prior to participants baseline assessment (HUNT 2 or HUNT 3) ($n = 459$), or (iv) within <1 year or > 10-years following baseline assessment ($n = 2722$). Of the remaining 73,797 participants, an additional 11,812 cases were excluded, as they did not complete the HADS questionnaire or were missing ≥3 of the seven questions pertaining to depressive symptoms (Fig. 2). Thus, 61,985 (46.0 % men) participants were included in final analyses.

The study was approved by the Human Research Ethics Committee at the Norwegian University of Science and Technology, the National Directorate of Health, the Norwegian Data Inspectorate and the HUNT data access committee. All participants provided informed, written consent (Fig. 1).

2.2. Outcome: incident cancer

The Cancer Registry of Norway was established in 1951. All medical physicians in Norway are required by law to notify new cancer cases to the registry. The registry database contains information regarding date of birth, sex, age and county at time of diagnosis and disease specific information pertaining to each new case, including year of diagnosis, localisation, topography, morphology, stage and any metastases (Research, 2019). All *de-novo* malignant neoplasms with an International Classification of Diseases-10th revision (ICD-10) code ranging from C00-C96 (all malignant neoplasms) were included. Cases with an ICD.10 code ranging from D00-D49 (which represent in-situ, benign and uncertain neoplasms (Organisation, 2013)) were checked for a subsequent diagnosis; if the subsequent diagnosis had an ICD.10 code of C00-C96, then this was considered the *de-novo* case, otherwise, they were excluded. Further details concerning cancer diagnoses within the HUNT study have been described elsewhere (Fossa et al., 2015).

2.3. Exposure: depressive symptomology

The Hospital Anxiety and Depression Rating Scale (HADS) (Zigmond, 1983) is a validated self-reported measure of clinically significant anxiety and depression symptoms, utilized in both clinical and research settings (Stafford et al., 2007). A Norwegian translation of the HADS was used in this study (Mykletun et al., 2001a). The HADS consists of a four-point Likert scale, which indicates symptoms severity, from 0 (no symptom) to 3 (highest symptom level), based on seven items assessing for core anxiety symptoms (HADS-A) and seven items assessing core depressive symptoms (HADS-D) occurring during the last week. We included all participants who responded to ≥5 items on the HADS-D subscale; missing scores were substituted based on sum of completed items multiplied by 7/5 or 7/6, respectively, for $n = 3092$ participants at HUNT 2 and $n = 1024$ participants at HUNT 3. Participants with a HADS-D score at baseline of ≥8 were considered as having 'depressive symptoms' (at a moderate to severe level) and participants with a HADS-D score < 8 as having 'no or mild depressive symptoms'. Participants were also grouped into three categories; not depressed (score < 8), moderately depressed (score between 8 and 10), and severely depressed (score ≥ 11) (Zigmond and Snaith, 1983) to evaluate a dose response

association.

2.4. Covariates

Body weight and height were measured to the nearest 0.5 kg and 1.0 cm, respectively. Body mass index (BMI) was calculated (kg/m^2).

Smoking habits were ascertained at the time of study assessment via self-report and participants were categorized as never, previous or current smokers. Physical activity was reported as light or hard, defined respectively as activity excluding or including sweating and/or feelings of breathlessness (Gustad et al., 2014b). The participants were categorized as inactive (<1 h of strenuous activity and < 3 h of light physical activity per week), moderately active (1–3 h of strenuous activity or > 3 h of light activity per week), and as physically active (>3 h of strenuous physical activity per week). Participants were asked to record the average number of glasses of alcohol (beer/wine/spirits) consumed during a two-week period. Responses were summed and a daily average number of glasses calculated. Participants were then categorized as abstainers, very light drinkers (0–1 drinks per day), light to moderate drinkers (1–2 drinks per day), or moderate to heavy drinkers (>2 drinks per day).

Marital status was dichotomized and grouped as married/registered partner versus not married/no registered partner (includes unmarried, widow(er), divorced, separated, separated partner, divorced partner and surviving partner). Education was self-reported and categorized as low (≤ 9 years), medium (between 10 and 12 years), or high (over 12 years). Employment status (current) was self-reported at time of assessment and data dichotomised to employed (paid work/self-employed) or unemployed.

Blood was collected from participants at HUNT 3 (as well as a subsample of 10,000 in HUNT 2). Following collection, serum was separated from blood cells (centrifugation at 1010 ×*g*) and stored in a refrigerator at 4 °C. All samples were transported via cooler on the same day to the central laboratory, located at Levanger Hospital. At the laboratory, samples entered the HUNT biobank and were stored at −70 °C. Serum micro/high-sensitive C-reactive protein (CRP) was analysed using Architect cSystem ci8200, by latex immunoassay method. The measurement range was 0.1–160 mg/L. Measurements above or below instrument range were assigned values of 0 or 160.1, respectively.

Mortality data was obtained for all participants in HUNT 2 and 3 by data linkage (via personal identification number) with the national Cause of Death Register (CDR) (Health, n.d.). This national registry was established in 1951 by the Norwegian Institute of Public Health (NIPH) and covers all deaths in Norway, regardless of whether the deceased is a

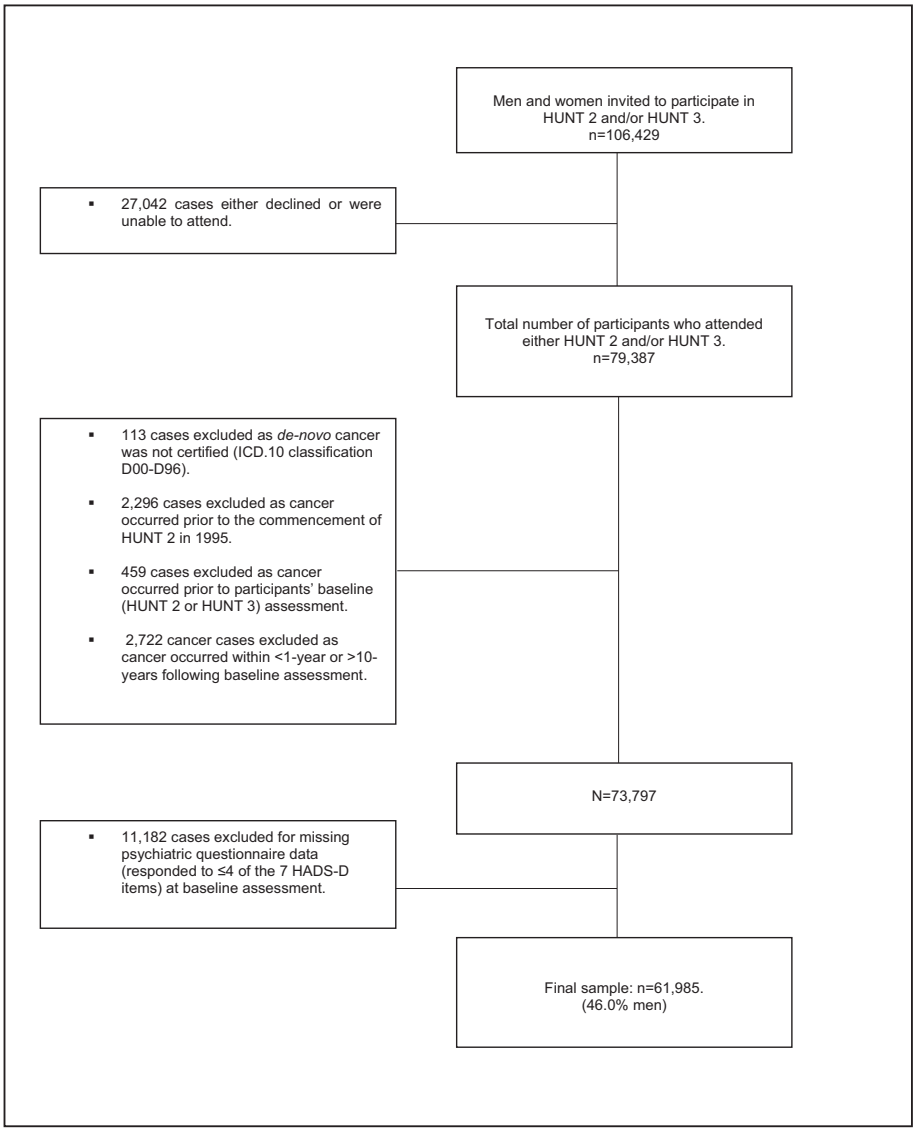

Fig. 1. Flow diagram depicting participant selection.

native inhabitant of Norway, via mandatory reporting by doctors with accompanying death certificate. Deaths occurring in other countries are also reported to the registry. Official causes of death are based on death certificates in accordance with the ICD-10, as outlined by the World Health Organisation (WHO).

2.5. Statistical analyses

Statistical analyses were completed using SPSS (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp) and Stata (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.). Person years were calculated by summing the time (in years) between date of baseline assessment (participation in either HUNT 2 or HUNT 3) to date of cancer onset [event], death, or the end of the study period (31 December 2016). Differences in baseline characteristics between those with depressive symptoms (HADS-D $\geq$ 8) and without depressive symptoms (HADS-D $<$ 8) at baseline were compared using *t*-tests for normally distributed continuous data, Mann–Whitney for non-normally distributed continuous data and chi-squared tests for categorical data.

The association between depressive symptoms (exposure of interest) and *de-novo* cancer onset (outcome) was investigated using Cox proportional hazards regression models. Separate models were employed for each sex. Participants were followed from baseline until cancer onset, death or until the end of the study period (31 December 2016). For cancer cases who attended both HUNT 2 and HUNT 3, data from the clinical examination closest to the event (cancer) was selected; for non-cancer cases (controls), data from the most recent appointment was selected. All measures were collected prior to cancer onset. Unadjusted (Model I) and age-adjusted (Model II) models are reported. All models were tested sequentially for confounding and/or effect modification and retained if significant (Model III). Hazard ratio (HR) and its 95 % confidence interval (95 % CI) are presented. A two-sided significance level alpha of 0.05 was the cut off value for all tests.

3. Results

Participants (n = 61,985; 46.0 % men) were followed from baseline over a period of 778,802 person-years. During the 20-year study period [mean follow up 11.1 ± 5.6 for years for men; 11.1 ± 5.2 years for women], 242 participants emigrated and 12,480 died (n = 2498 attributed to cancer). There were 6856 (11.1 %) incident cancers. Cancer subtypes included prostate (n = 1227; 17.9 %), breast (n = 824; 12.0 %), colon (n = 728; 10.6 %), bronchus and lung (n = 532, 7.8 %), melanoma (n = 340, 5.0 %) and other (n = 3205, 46.7 %) [Fig. 2]. Characteristics of the study population and according to those with and without depressive symptoms by sex are presented in Table 1.

3.1. Men

3.1.1. Characteristics

For men, those with depressive symptoms tended to be older, have a higher BMI, were more likely to be current or prior smokers, consume alcohol, be physically inactive, have higher serum hs-CRP levels and have a lower level of education, were less likely to be married or have a registered partner, or be currently employed/self-employed compared, and had a shorter follow-up time to those who did not have depressive symptoms. For those with depressive symptoms, 505 (15.3 %) developed incident cancer during the follow-up period, whereas among those who did not have depressive symptoms, 3164 (12.5 %) developed incident cancer ($p \leq 0.001$; Cohen's d 0.1).

3.1.2. Any cancer

Over the follow-up period, 3669 (12.9 %) men were diagnosed with an incident cancer. Depressive symptoms were associated with an increased likelihood of cancer onset (1.34, 95 % CI 1.22–1.48, p $\leq$0.001). However, after accounting for age, this relationship was no longer significant (HR: 1.00, 95 % CI 0.91–1.10, p = 0.926) [Model II, Table 2]. Further adjustment [model III] did not substantially change RR estimate(s) or add to model precision.

Severity of depressive symptoms did not modify the above findings. Compared with no depressive symptoms, having moderate depressive symptoms (HR: 1.36, 1.22–1.51, $p \leq 0.001$) or severe depressive symptoms (HR:1.31, 1.10–1.56, p = 0.002) increased likelihood of cancer onset, however these relationships were not sustained following adjustment for age (adj HR: 1.01, 0.90–1.12, p = 0.907 and HR: 1.00, 95 % CI 0.84–1.19, p = 0.991, respectively).

3.1.3. Cancer subtypes

Table 2 presents longitudinal associations between baseline depressive symptoms and the major cancer subtypes. Following adjustment for age, depressive symptoms were not associated with onset of prostate, colon or melanoma cancer. However, depressive symptoms were associated with an increased risk of bronchus/lung cancer both before (HR 2.06, 95%CI 1.56–2.72, p $\leq$0.001) and after adjustment for age (RR 1.50, 95 % CI 1.14–1.99, p = 0.004), although this relationship was not sustained in the fully adjusted model (RR: 1.24, 95 % CI 0.84–1.82, p = 0.273).

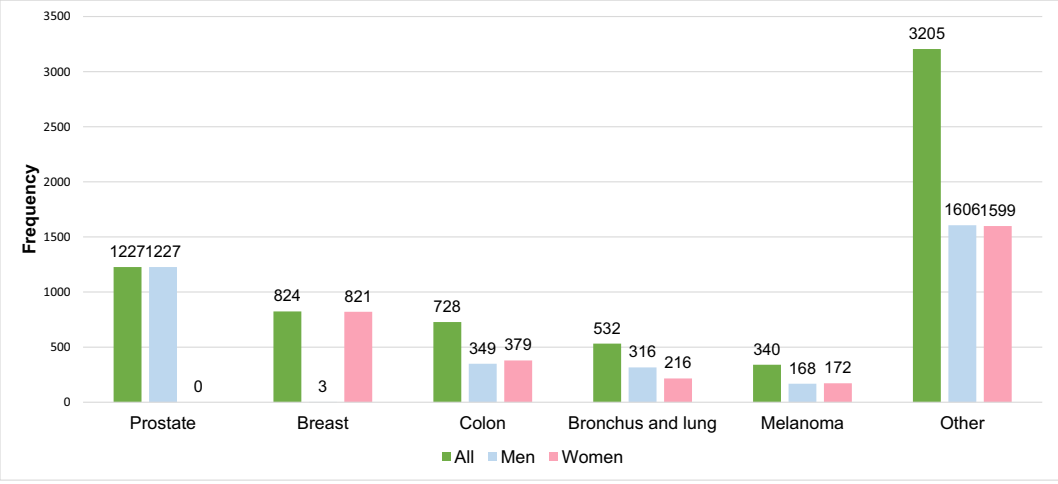

Fig. 2. Frequency of registry confirmed *de-novo* cancer cases according to ICD.10 classification. [All ICD.10 cancer categories with a percentage representing <5.0 % of cases are included in the 'other' category.]

Table 1
Baseline characteristics for all men and women and according to depressive symptoms. Values are given as n (%), median (IQR), or mean (standard deviation)[a].

	Men (n = 28,521)				Women (n = 33,464)			
	All	No depressive symptoms	Depressive symptoms	p	All	No depressive symptoms	Depressive symptoms	p
Incident Cancer								
Any	3669 (12.9 %)	3164 (12.5 %)	505 (15.3 %)	<0.001	3187 (9.5 %)	2803 (9.3 %)	384 (11.2 %)	<0.001
Prostate	1227 (4.3 %)	1058 (4.2 %)	169 (5.1 %)	0.013	–	–	–	–
Breast	–	–	–	–	821 (2.5 %)	739 (2.5 %)	82 (2.4 %)	0.789
Colon	349 (1.2 %)	302 (1.2 %)	47 (1.4 %)	0.263	379 (1.1 %)	331 (1.1 %)	48 (1.4 %)	0.122
Bronchus and lung	316 (1.1 %)	254 (1.0 %)	62 (1.9 %)	<0.001	216 (0.6 %)	182 (0.6 %)	34 (1.0 %)	0.008
Melanoma	168 (0.6 %)	151 (0.6 %)	17 (0.5 %)	0.557	172 (0.5 %)	151 (0.5 %)	21 (0.6 %)	0.400
Age (year)	53.0 ± 17.1	52.1 ± 17.0	59.1 ± 16.0	<0.001	52.8 ± 17.8	52.1 ± 17.7	59.5 ± 17.0	<0.001
Married/registered partner	17,019 (59.8 %)	15,045 (59.8 %)	1974 (59.9 %)	0.838	17,989 (53.9 %)	16,253 (54.2 %)	1736 (50.6 %)	<0.001
Employed (current)	17,748 (62.2 %)	16,285 (64.6 %)	1463 (44.4 %)	<0.001	18,561 (55.5 %)	17,342 (57.8 %)	1219 (35.5 %)	<0.001
Education level				<0.001				<0.001
Low (<9 years)	7259 (30.8 %)	6013 (28.9 %)	1246 (45.3 %)		10,511 (39 %)	8969 (37.1 %)	1542 (55.4)	
Medium (10–12 years)	11,461 (48.7 %)	10,306 (49.5 %)	1155 (42.0 %)		10,857 (40.2 %)	9956 (41.1 %)	901 (32.4)	
High (>12 years)	4838 (20.5 %)	4489 (21.6 %)	349 (12.7 %)		5609 (20.8 %)	5270 (21.8 %)	339 (12.2 %)	
BMI (kg/m^2)	27.1 ± 3.8	27.0 ± 3.7	27.3 ± 4.0	0.001	26.8 ± 4.8	26.7 ± 4.8	27.5 ± 5.2	<0.001
Smoking history				<0.001				<0.001
Never	10,574 (38.0 %)	9663 (39.2 %)	911 (28.5 %)		15,022 (46.3 %)	13,605 (46.7 %)	1417 (42.6 %)	
Previous	9852 (35.4 %)	8593 (34.8 %)	1259 (39.4 %)		8453 (26.1 %)	7637 (26.2 %)	816 (24.5 %)	
Current	7436 (26.7 %)	6407 (26.0 %)	1029 (32.2 %)		8951 (27.6 %)	7860 (27.0 %)	1091 (32.8)	
Physical activity				<0.001				<0.001
Inactive	11,557 (43.0 %)	9900 (41.4 %)	1657 (55.8 %)		13,755 (44.8 %)	11,900 (43.0 %)	1855 (62.1 %)	
Moderate active	10,806 (40.2 %)	9819 (41.1 %)	987 (33.2 %)		13,506 (44.0 %)	12,549 (45.3 %)	957 (32.0 %)	
Active	4496 (16.7 %)	4170 (17.5 %)	326 (11.0 %)		3423 (11.2 %)	3248 (11.7 %)	175 (5.9 %)	
Alcohol consumption				0.010				0.988
0–1 drinks per day	23,655 (92.1 %)	21,050 (92.0 %)	2605 (92.6 %)		27,902 (98.2 %)	25,354 (98.2 %)	2584 (98.2 %)	
1–2 drinks per day	1751 (6.8 %)	1587 (6.9 %)	164 (5.8 %)		470 (1.7 %)	428 (1.7 %)	42 (1.6 %)	
>2 drinks per day	289 (1.1 %)	246 (1.1 %)	43 (1.5 %)		45 (0.2 %)	41 (0.2 %)	4 (0.2 %)	
Serum CRP (mg/L)	2.5 ± 5.5	2.5 ± 5.4	3.1 ± 6.8	<0.001	2.8 ± 5.8	2.7 ± 5.9	3.2 ± 5.2	<0.001
Follow-up (person year)	11.1 ± 5.6	11.3 ± 5.6	10.0 ± 5.6	<0.001	11.1 ± 5.2	11.2 ± 5.2	10.5 ± 5.3	<0.001

[Missing data; married/registered partner (n = 118; 0.2 %), employed (n = 21; 0.0 %), education (n = 11,450; 18.5 %), BMI (n = 557; 0.9 %), smoking (n = 1697; 2.7 %), physical activity (n = 4442; 7.2 %), alcohol (n = 7873; 12.7 %) and CRP (n = 24,458; 39.5 %)].

[a] A two-sided significance level alpha of 0.05 was the cut off value for all tests.

3.2. Women

3.2.1. Characteristics

For women, those with depressive symptoms tended to be older, have a higher BMI, were more likely to be current or prior smokers, be physically inactive, have higher serum hsCRP, were more likely to have a lower level of education, were less likely to be married or have a registered partner, or be currently employed/self-employed, and had a shorter follow-up time compared to those who did not have depressive symptoms. Alcohol consumption did not differ between the groups. For those with depressive symptoms, 384 (11.2 %) developed incident cancer during the follow-up period, whereas among those with no depressive symptoms, 2803 (9.3 %) developed incident cancer ($p \leq 0.001$).

3.2.2. Any cancer

Over the follow-up period, 3187 (9.5 %) women were diagnosed with an incident cancer. Depressive symptoms were associated with an increased likelihood of cancer onset (RR 1.27, 95 % CI 1.14–1.41, p = 0.001). However, after accounting for age, this relationship was no longer significant (RR: 1.01, 95 % CI 0.92–1.14, p = 0.723). [Model II, Table 2]. Further adjustment [model III] did not substantially change RR estimate(s) or add to model precision.

Severity of depressive symptoms did not modify the above findings. Compared with no depressive symptoms, having moderate depressive symptoms (HR:1.28, 1.13–1.45, p ≤0.001) or severe depressive symptoms (HR: 1.26, 1.04–1.53, p = 0.019) increased likelihood of cancer onset, however these relationships were not sustained following adjustment for age (adj HR: 1.03, 95 % CI 0.91–1.17, p = 0.650 and HR: 1.00, 95 % CI 0.82–1.21, p = 0.966, respectively).

3.2.3. Cancer subtypes

Table 2 presents Cox regression models showing associations between depressive symptoms and the major cancer subtypes. Depressive symptoms were associated with an increased odds of bronchus/lung cancer (unadjusted HR, 1.74 95%CI 1.21–2.51, p = 0.003). However, following adjustment for age, depressive symptoms were not associated with onset of breast, colon, bronchus and lung, or melanoma cancer (all $p > 0.05$).

4. Discussion

Results from this large population-based study of >61,000 adults free of cancer at baseline suggest that self-reported depressive symptoms are not associated with any or site-specific cancer onset, including malignant neoplasms of the breast (women), prostate (men), colon, lung and bronchus, or malignant melanoma of the skin, in both men and women. Whilst these findings are consistent with other population-based studies examining depressive symptoms and cancer onset (Hahn and Petitti, 1988; Zonderman et al., 1989; Kaplan and Reynolds, 1998;

Table 2
Depressive symptoms as a predictor of any cancer and subtypes among men (n = 28,521) and women (n = 33,464).

	Men		Women	
	Model I[a]	Model II[b]	Model I	Model II
	HR (95 % CI)	HR (95 % CI)	HR (95 % CI)	HR (95 % CI)
Cancer (any)				
Depressive symptoms	1.34 (1.22–1.48)	1.00 (0.91–1.10)	1.27 (1.14–1.41)	1.01 (0.92–1.14)
Age (year)	–	1.06 (1.06–1.06)	–	1.04 (1.03–1.04)
Prostate				
Depressive symptoms	1.35 (1.14–1.58)	0.98 (0.84–1.16)	–	–
Age (year)	–	1.07 (1.06–1.07)	–	–
Breast				
Depressive symptoms	–	–	1.03 (0.82–1.29)	0.90 (0.72–1.13)
Age (year)	–	–	–	1.02 (1.02–1.03)
Colon				
Depressive symptoms	1.31 (0.96–1.78)	0.95 (0.69–1.29)	1.34 (0.99–1.81	0.97 (0.72–1.32)
Age (year)	–	1.07 (1.06–1.08)	–	1.06 (1.05–1.07)
Bronchus/lung				
Depressive symptoms	2.06 (1.56–2.72)	1.50 (1.14–1.99)	1.74 (1.21–2.51)	
Age (year)	–	1.07 (1.06–1.07)	–	
Melanoma				
Depressive symptoms	0.94 (0.57–1.56)	0.80 (0.48–1.32)	1.30 (0.83–2.06)	
Age (year)	–	1.03 (1.02–1.04)	–	

[a] Unadjusted.
[b] Age-adjusted.

Dalton et al., 2002; Kroenke et al., 2005; Gross et al., 2010; Lemogne et al., 2013; Kessing et al., 2015; Archer et al., 2015; Martinsson et al., 2016; Lai et al., 2013), this is, to the best of our knowledge, one of the only well-designed large-scale population-based studies to investigate the association between depressive symptoms and incident cancer across clinical subtypes measured, and to account for a range of demographic, lifestyle and potential risk factors including serum markers of inflammation.

4.1. Comparison to prior research

4.1.1. Depressive symptoms and incident cancer

One of the earliest studies reporting no association between depressive symptoms and cancer onset was conducted by Zonderman et al. who examined 5729 participants from the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study (Zonderman et al., 1989). Over a 10-year follow-up, it was reported that depressive symptoms (measured by the Center for Epidemiologic Studies Depression scale), or the depression subscale from the General Well-being Schedule, were not associated with cancer onset (data obtained from hospital records) both before and after adjustment for age, sex, marital status, smoking, family history of cancer, hypertension, and serum cholesterol level. These findings were similarly replicated in the retrospective study by Kaplan et al., and the study by Hahn and colleagues who did not detect associations between depressive symptoms and any cancer diagnoses and breast cancer specifically (Hahn and Petitti, 1988; Kaplan and Reynolds, 1998). More recently, the 2015 study by Archer and colleagues (Archer et al., 2015) also explored the association between depressive symptom history and incident cancer. Affective/emotional depressive symptoms were assessed using the General Health Questionnaire (GHQ-30) depression subscale across all three phases (1985–1988, 1989–1990, 1991–1994 respectively) of the Whitehall II prospective cohort study. 'Chronic' depression equated to a depressive episode at all three phases, and 'new' depression was a depressive episode at phase three only. Cancer incidence was obtained from the National Health Service Central Register. Among a sample of 6983 participants (age 33–35 years at baseline) and over a 17.4-year follow-up, chronic depressive symptoms were not associated with an increased risk of incident cancer (HR: 1.03, 95 % CI 0.71–1.49) compared to those with no symptoms. However, 'new' depressive symptoms were associated with an increased risk of incident cancer, but only in the first nine years (HR = 1.89, 95 % CI: 1.23–2.90). There was no association in later years, a finding potentially attributed to reverse causality. Lastly, the large prospective longitudinal study by Lemogne and colleagues (Lemogne et al., 2013) including over 14,000 adults (10,506 men, 3697 women) aged between 35 and 50 years, from the French national gas and electricity company '*Electricité de France-Gaz de Franc'e'* (GAZEL cohort) reported mixed findings. Unlike prior studies which measured depression by presence of depressive symptoms only, this study included a combination of self-reported depressive symptoms (CES—D) as well as medically certified 'sickness absences for depression' (SAD) (Radloff, 1977). Cancer data were extracted from medical records kept by the national gas and electricity company, and diagnoses occurring after retirement were captured by self-report. Following analysis and adjustment for lifestyle factors, a negative association was reported between depression and incident prostate cancer in men (HR 0.58, 95 % CI 0.37–0.91, $p = 0.02$). However, no further associations, for all cancers combined or among specific subtypes, were evident.

4.1.2. Clinical depression and incident cancer

The study by Gross et al. (Gross et al., 2010) investigated a population-based sample of over 3000 US adults from the Baltimore Catchment Area Study, this time with mixed outcomes. Depression status was obtained using the Diagnostic Interview Schedule (DIS) and cancer status was self-reported at time of interview and from the National Death Index (NDI). Over 24 years of follow-up, there were 334 incident cancers. Following adjustment for confounders (age, sex, marital status, race, socioeconomic status, parity (when evaluating breast cancer), and self-reported history of alcohol abuse/dependence and smoking status), no associations were detected between depression and risk of prostate cancer in men, or colon, lung, or skin cancers in either men or women. However, depression was associated with an increased risk of overall cancer (HR: 1.9, 95 % CI: 1.2–3.0) and breast cancer (HR: 4.4, 95 % CI: 1.08–17.6) among women. Furthermore, a meta-analysis was conducted by Ahn et al. (Ahn et al., 2016) in 2016 to investigate the association between clinically defined mood disorder rather than depressive symptoms and cancer risk. Nine studies fulfilled the eligibility criteria: including six nested case-control studies, two retrospective cohort studies and only one prospective cohort study. Results indicated that patients with depressive disorder were at increased risk for cancer (OR, 1.26; 95 % CI: 1.06–1.50, $p = 0.01$); however, this significant effect was reportedly only observed in studies considered 'low-quality' (OR, 1.31; 95 % CI, 1.05–1.63) and not in those considered 'high-quality' (OR, 1.15; 95 % CI, 0.85–1.56).

4.1.3. Potential underlying mechanisms

The heterogeneity of depression assessment (e.g., self-reported symptoms versus clinically diagnosed depression) and other psychological factors associated with depression, may contribute to the somewhat mixed findings in the current evidence base on associations between depression and incident cancer.

Whilst the HADS is a validated measure of depression in general populations (Kjærgaard et al., 2014), some studies have reported that the HADS-D subscale likely represents an anhedonic phenotype of depression, due to the comparatively high proportion of anhedonic items (which describes the inability to feel pleasure in normally pleasurable activities) (Langvik et al., 2016). Studies have shown that this

'phenotype' is more prevalent in men (Grav et al., 2012), which may be why our study, and others involving non-clinical healthy populations, have cited significantly more depressive symptoms in men than women when depression is measured via the HADS (Grav et al., 2012; Bjelland et al., 2002; Nortvedt et al., 2006; Mykletun et al., 2001b; Haug et al., 2004; Bjerkeset et al., 2005). This is counter to the known higher prevalence of depression in women than men (Vigo et al., 2016; Ageing, 2013; Statistics, 2008; Baxter et al., 2014), which may, in part, contribute to the mixed findings between depressive symptomology and incident cancer reported in the literature.

Depression is a heterogeneous disorder in relation to risk factors, underlying pathophysiology, symptom manifestations, progression, and response to pharmacotherapies (Hasler, 2010). Currently, the DSM-5 outlines six specifiers which can be applied to major depressive episodes; this includes chronic, catatonic features, melancholic features, atypical features, postpartum onset and seasonal pattern (Association, 2013). Interestingly, there is research suggesting that depression subtypes are likely to be differentially associated with different biological mechanisms. For instance, recent studies suggest that the atypical subtype is more strongly related to dysregulations of cardiometabolic (e.g., metabolic syndrome) and inflammation pathways, and the melancholic subtype to a dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis (Lasserre et al., 2021; Antonijevic, 2006; Baune et al., 2012; Lamers et al., 2013). These associations are further indexed by studies citing specific depressive subtypes, namely atypical or 'immune-metabolic depression' are linked to cardiovascular risk factors and other disorders, whilst other depressive subtypes are not (Lasserre et al., 2016; Lasserre et al., 2014; Capuron et al., 2017; Mohamed et al., 2020). As such, different subtypes of depression, which were unable to be examined in this study, might be differentially related to cancer onset. This requires confirmation and may also go some way to explaining the heterogeneous findings in the literature.

Other psychological constructs associated with depression may also contribute to the mixed evidence base. For example, several HUNT studies of the HADS have shown low help seeking for mental problems in those with depression compared to anxiety (Roness et al., 2005), which may also corelate with overall reduced healthcare utilisation and opportunity for cancer screening. This is further supported by the study by Stewart et al. (Stewart et al., 2020), which found depression (HADS-D) without anxiety, to be associated with later help-seeking in cancer and significantly increased incidence of beyond-local extent of disease at diagnosis, which may in part, explain the often-reported increased cancer mortality for patients with cancer and depression, compared to patients with cancer without depression (Mykletun et al., 2007; Satin et al., 2009; Kim et al., 2015). Anxiety disorders have been associated with increased help-seeking and a potential increase in cancer survival (Stewart et al., 2020; Cuijpers et al., 2014). This is in contention with the findings on depression alone. Given depression and anxiety often co-occur, future studies investigating depression, anxiety, and comorbid depression and anxiety are warranted. Additionally, many of the somatic symptoms of depression (fatigue, sleep disturbances and loss of appetite) overlap with early symptoms of cancer (Kapfhammer, 2006). Thus, there is the possibility that symptoms of early-stage cancers may be similarly pronounced to, and potentially interpreted as, depressive symptomology, resulting in a negative association between depression and cancer onset. However, this would likely also result in a survival bias, and as cancer progresses and symptoms are fully expressed, accurate cancer detection will doubtlessly occur (Nikendei et al., 2018; Die Trill, 2012; Reich et al., 2008). Overall, investigation of depressive phenotype, chronicity, and comorbid depression and anxiety, as well as stage at diagnosis, may further elucidate the null and/or negative associations between depression and incident cancer described within the literature.

4.2. Strengths and limitations

The large sample size, which included relatively equal spread of both sexes across the adult lifespan, representative of the general population, is a clear strength in this study. Furthermore, cancer data were obtained via a registry and therefore free of recall and other associated bias. The Cancer Registry of Norway is a member organisation under the umbrella of the International Association of Cancer Registries and subject to strict quality control measures and evaluations authorised by the World Health Organisation. Moreover, data concerning a large range of confounding variables were available. The HADS has been verified as an effective tool in the screening of mood disorder in general populations (Kjærgaard et al., 2014). Additionally, as the HADS has been specifically designed to detect both anxiety and depression in patients with physical disorders, potentially reducing the likelihood of reverse causality. Moreover, examining depressive symptoms has the potential to capture a wider scope of individuals experiencing depressive symptoms in the general population, including those with minor to moderate yet subthreshhold diagnostic symptomology, less clinicically severe presentations, or those on the trajectory to developing full diagnostic criteria. However, it is noteworthy that the HADS only assesses symptoms occuring within the previous week of assessment. As a clinical diagnosis requires symptoms to be present for a minimum of two weeks, individuals with baseline depressive symptomology in this study may not reflect clinically significant depression at other time points. Moreover, there is a likelihood of incresed nonattendance in HUNT among the most severely depressed. These factors may, at least in part, explain why our study and studies similar to ours, have reported no association, whereas other studies and those examining clinical depression have reported associations.

There are limitations to acknowledge. Power limitations meant only select cancer subtypes could be investigated. Additionally, given the small effect size and increased probability of a type-2-error, null findings should be interpreted with caution. Likewise, cancer is a blanket term for a multitude of diseases characterised by uncontrolled division of abnormal cells. Each disease has its own neoplastic pathway, as well as its own set of risk factors and treatments. Site-specific risk factors for the selected subtypes were not considered. Moreover, detailed information on depression such as chronicity, severity, subtype, or whether participants are taking antidepressants or another adjuvant medication, were not examined. Lastly, findings may not be generalisable to other populations of men, women, or other anatomical cancer subtypes.

5. Conclusion

These data provide evidence to suggest that depressive symptoms are not associated with an increased risk of overall or site-specific cancer onset in this population-based study of men and women. Given the increased comorbidity of other medical conditions such as cardiovascular disease, diabetes, stroke and musculoskeletal disorders in patients with depression, the role of clinically diagnosed depression and other psychiatric disorders in association with cancer onset necessitates further consideration.

Ethics approval and consent to participate

The Human Research Ethics Committee at the Norwegian University of Science and Technology have approved the study. Furthermore, the Norwegian Data Inspectorate, the Regional Committee for Ethics in Medical Research and the HUNT Publication Review Board approved the use of HUNT data. All participants provided informed, written consent.

Consent for publication

Not applicable.

Availability of data and material

The data that support the findings of this study are available from the HUNT study, but restrictions apply to the availability of these data. Data are however available from the authors upon reasonable request and with permission from the HUNT study CEO and laboratory manager Marit Naess.

Funding

SPC is supported by a PhD stipend from IMPACT at Deakin University; MB is supported by NHMRC Senior Principal Research Fellowships (1156072); and LJW is supported by a NHMRC Investigator grant (1174060).

CRediT authorship contribution statement

SPC took part in the conception and design of the study, data cleaning and statistical analysis, interpretation of the analysis and takes primary responsibility for writing of the manuscript. ER and MM were consulted on data manipulation, analysis and interpretation of the data and critically revised the manuscript. LJW and OB took part in the conception and design of the study, interpretation of the data and critically revised the manuscript. JAP, DC and MB took part in the interpretation of data and critically revised the manuscript. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare that they have no competing interests.

Acknowledgements

The Trøndelag Health Study (HUNT) is a collaboration between HUNT Research Centre (Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology NTNU), Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health.

We acknowledge the men and women who participated in the HUNT study.

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