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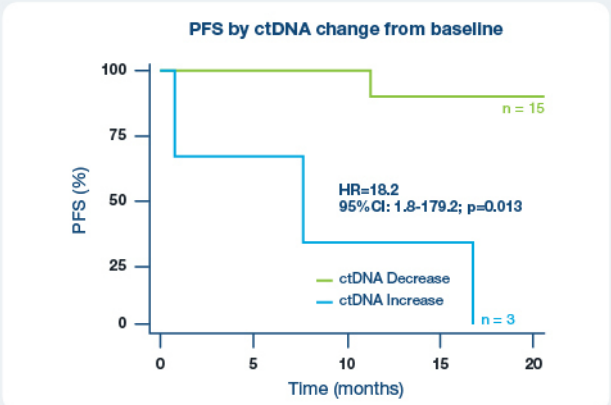

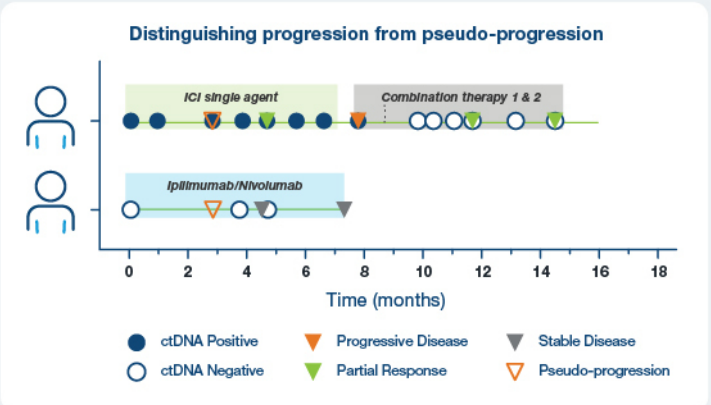

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- Signatera™ was able to help distinguish between true vs pseudo-progression

Should treatment be changed or escalated?

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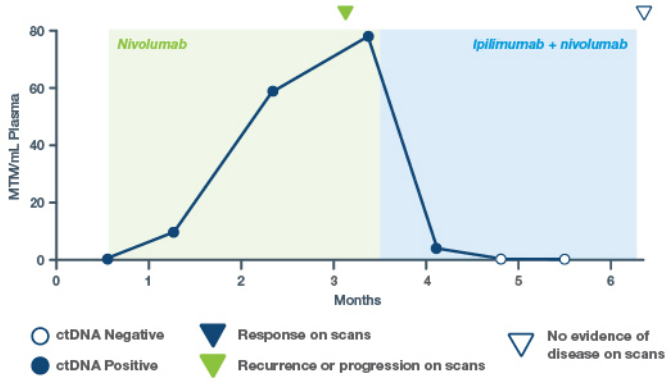

60-year-old stage IV metastatic melanoma patient[2]

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PFS = Progression-free survival

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ORIGINAL ARTICLE

Depression, anxiety, and the risk of cancer: An individual participant data meta-analysis

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Abstract

Background: Depression and anxiety have long been hypothesized to be related to an increased cancer risk. Despite the great amount of research that has been conducted, findings are inconclusive. To provide a stronger basis for addressing the associations between depression, anxiety, and the incidence of various cancer types (overall, breast, lung, prostate, colorectal, alcohol-related, and smoking-related cancers), individual participant data (IPD) meta-analyses were performed within the Psychosocial Factors and Cancer Incidence (PSY-CA) consortium.

Methods: The PSY-CA consortium includes data from 18 cohorts with measures of depression or anxiety (up to $N = 319{,}613$; cancer incidences, 25,803; person-years

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of follow-up, 3,254,714). Both symptoms and a diagnosis of depression and anxiety were examined as predictors of future cancer risk. Two-stage IPD meta-analyses were run, first by using Cox regression models in each cohort (stage 1), and then by aggregating the results in random-effects meta-analyses (stage 2).

Results: No associations were found between depression or anxiety and overall, breast, prostate, colorectal, and alcohol-related cancers. Depression and anxiety (symptoms and diagnoses) were associated with the incidence of lung cancer and smoking-related cancers (hazard ratios [HRs], 1.06–1.60). However, these associations were substantially attenuated when additionally adjusting for known risk factors including smoking, alcohol use, and body mass index (HRs, 1.04–1.23).

Conclusions: Depression and anxiety are not related to increased risk for most cancer outcomes, except for lung and smoking-related cancers. This study shows that key covariates are likely to explain the relationship between depression, anxiety, and lung and smoking-related cancers.

Preregistration number: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=157677.

KEYWORDS
anxiety, cancer, depression, meta-analysis, risk

INTRODUCTION

Depression and anxiety have long been hypothesized to increase the risk for cancer. It is thought that the increased cancer risk can occur via several pathways, including health behaviors, or by influencing mutation, viral oncogenes, cell proliferation, or DNA repair.[1] Conclusions drawn in meta-analyses vary greatly, with some supporting an association between depression, anxiety, and cancer incidence[2–4] and others finding no or a negligible association.[5–7] These meta-analyses are limited by one or more of the following: inclusion of only published studies, which results in possible underrepresentation of null findings; inclusion of studies that do not use prospective designs; combination of different cancer outcomes, which may hide effects for specific cancer types; limited adjustment for potential confounding factors; or lack of consistency in measurements of depression and anxiety.

Individual participant data (IPD) meta-analysis uses crude data from studies. This has several key advantages that lead to more reliable results than traditional meta-analyses.[8] First, via the harmonization of data, constructs across studies are, conceptually, as similar as possible. Second, there is more consistency across studies with regard to the statistical model tested and the covariates adjusted for.[9] Third, data can be included that have not previously been published or used to test the research hypothesis, which reduces the risk of overestimating effects due to publication bias. In the present study, we tested whether depression and anxiety were associated with increased cancer risk by means of IPD meta-analysis. In addition to looking at overall cancers, we also consider the four most prevalent cancers (breast, lung, prostate, and colorectal) and cancers with established common lifestyle risk factors (smoking-related cancers and alcohol-related cancers). We hypothesized that both depression and anxiety are associated with increased risk for overall cancers and breast, prostate, lung, colorectal, smoking-related, and alcohol-related cancers.

MATERIALS AND METHODS

PSY-CA consortium

The international Psychosocial Factors and Cancer Incidence (PSY-CA) consortium was established to investigate whether psychosocial factors are associated with an increased risk of cancer. The present study focuses specifically on depression and anxiety. An overview of the various research questions can be found in the preregistration in PROSPERO (http://www.crd.york.ac.uk/PROSPERO) with the following IDs: CRD42020157677, CRD42020181623, and CRD42020193716.

Inclusion/exclusion criteria

Fourteen cohorts and four subcohorts (10 [sub]cohorts in the Netherlands and eight [sub]cohorts[1] in the United Kingdom,

[1] In some cohorts, inclusion criteria or depression/anxiety instruments changed over time or there was a long recruitment period over many years. In these instances, the cohorts divided their data into subcohorts to increase homogeneity within cohorts.

Norway, and Canada) were included on the basis of the following criteria: (1) a valid and reliable measure of depression or anxiety (or another psychosocial factor[10]; in the present article, we focus on depression and anxiety); (2) an objective measure of cancer diagnosis during follow-up is available or possible to attain; (3) an assessment of smoking behavior, alcohol use, sex, and age; and (4) a prospective design (i.e., depression, anxiety, or other psychosocial factors were measured before cancer incidence). A thorough overview of the design of PSY-CA is provided in the protocol paper.[10]

Study design

A two-stage approach to IPD meta-analysis was used in PSY-CA. During the first stage, cohort-specific data harmonization instructions, based on Maelstrom guidelines, were provided to each cohort.[11] Subsequently, local researchers from each cohort ran standardized R scripts over their harmonized data sets and sent the output to the central researcher (L.A.v.T.) who, during the second stage, pooled the estimated effects from stage 1 using random-effects meta-analyses.

Variables

Assessment of depression and anxiety

Depression and anxiety were conceptualized and analyzed in two ways: diagnoses and symptoms. Diagnoses were based on clinical interviews (if available) or scoring above a clinically validated cutoff on self-report questionnaires.[2] Depression diagnosis was based on meeting the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) criteria for a current major depressive disorder or dysthymia. Anxiety diagnosis was based on the presence of a current generalized anxiety disorder, social anxiety, panic disorder (with or without agoraphobia), and/or agoraphobia, according to *DSM* criteria. Depression and anxiety symptoms were assessed by using self-report questionnaires that covered symptoms in the previous week(s). Continuous sum scores were converted to *z* scores in each cohort, with higher scores indicative of more severe symptoms (see Supplementary Materials 1).

Cancer incidence

Cohorts based in the Netherlands obtained information about cancer incidence including site, morphology, and diagnosis date from the Netherlands Cancer Registry. Cohorts outside of the Netherlands obtained information from country/province-specific registries. In four cohorts (RS1, RS2, RS3, and CARTaGENE), information from registries was supplemented with data on hospital visits, insurance claims, and general practitioner records.

Participants who had a history of cancer or cancer at baseline were excluded, except when the cancer was (nonmelanoma) skin cancer. Participants diagnosed with any cancer (including carcinoma in situ and tumors where malignancy could not be determined) within 1 year from baseline were also excluded to reduce the likeliness of reverse causality.

In the main analyses, cancer incidence included malignant tumors, tumors where malignancy could not be determined (i.e., borderline), and carcinoma in situ. Seven cancer outcomes were analyzed: overall cancers and breast, lung, prostate, colorectal, smoking-related, and alcohol-related cancers as listed by the International Agency for Research on Cancer[12] (see Supplementary Materials 2 for *International Classification of Diseases* codes).

Covariates

In the minimally adjusted models, we adjusted for birth year (age-period cohort effects), sex, country of birth, and education level across all cohorts. In the maximally adjusted models, we further adjusted for a number of health-related covariates depending on cancer outcome and availability within the cohort:

- all outcomes: weekly alcohol intake, current antidepressant use, body mass index, hours of physical activity per week (metabolic equivalent, if available), smoking status (former, current, or never), pack-years (or current number smoked), and family history of cancer;
- breast cancer: parity (0 pregnancies, 1 or 2 pregnancies, or 3+ pregnancies), (hormonal) contraceptive use, age at menarche, menopause status, and family history of breast cancer;
- colorectal cancer: sedentary behavior and family history of colorectal cancer; and
- lung and prostate cancer: family history of lung or prostate cancer, respectively.

A full overview of covariates in the maximally adjusted models per cohort is given in Supplementary Materials 3.

Statistical analysis

Stage 1: Local analyses

Cox regression models (minimally or maximally adjusted; see the Covariates section) were used in all analyses to calculate hazard ratios (HRs) and 95% confidence intervals (CIs), with entry age (age

[2]Although diagnoses cannot be made on the basis of self-report questionnaires alone, we apply validated cutoffs that have been found to show a sufficient degree of sensitivity and specificity. We refer to scores above the cutoff as "diagnosis."

at baseline) and exit age (age at diagnosis, death, or dropout/study end) as timescale.

Only participants without missing information on depression or anxiety were included in the analyses. Covariates were included if they were available for at least 60% of the sample. Extreme values for continuous covariates were truncated to three times the interquartile range above the third quartile or below the first quartile. For the covariates related to physical activity, alcohol use, and smoking, only upper extreme outliers were truncated because a substantial number reported 0 (e.g., never smokers).

Stage 2: Meta-analyses

For each meta-analysis, we selected models (from stage 1) that included at least 10 cancer events and, for depression and anxiety diagnosis, at least five expected events (cancer incidences) in the smallest category of depression/anxiety diagnosis (based on the observed cohort-specific cancer incidence) (Table 2).

Beta coefficients and robust standard errors from stage 1 were entered into a random-effects meta-analysis separately for each exposure and cancer outcome. Between-study heterogeneity was estimated by using restricted maximum likelihood (REML). The Hartung–Knapp–Sidik–Jonkman approach was used to adjust test statistics and CIs to more fully account for the estimation uncertainty.[13] To examine between-cohort heterogeneity, we report I^2 using the following general rule[14]: 0%–25%, low heterogeneity; 26%–50%, moderate heterogeneity; and 51%–75%, substantial heterogeneity. Because the value of I^2 depends critically on the size of the studies included,[15] we also looked at Tau^2 (estimated by using REML) and Cochrane's *Q*. For ease of reading, only I^2 is reported, as Tau^2 and Cochrane's *Q* were essentially similar to I^2. Given the number of meta-analyses conducted that increases the likelihood of type I errors, we focused our conclusions on consistent patterns of results, as stated in the PSY-CA protocol.[10]

Additional analyses

Several additional analyses were conducted in both stages of the analyses to explore the robustness of our findings.

Stage 1. First, to explore the effect of follow-up duration, analyses were rerun when capping the follow-up duration at four cutoff points: 5, 10, 15, and 20 years. Second, the main analyses were rerun in which carcinoma in situ or borderline tumors were not considered a cancer event and were censored at the time of diagnosis. Third, the minimally adjusted models were rerun with the sample for the corresponding maximally adjusted model to test whether change in effects from the minimally adjusted to the maximally adjusted models could be explained by sample-size reduction because of missing values on covariates. Fourth, given the correlation between anxiety and depression, when both depression and anxiety showed a statistically significant association with a cancer outcome in the maximally adjusted model, a final model was run that included both depression and anxiety. Finally, analyses were repeated within males and females separately when sex modified the effects of depression or anxiety on the basis of the relative excess risk due to interaction, a measure for additive interaction.

Stage 2. First, to explore the effect of measurement type in depression and anxiety diagnoses, subgroup analyses were conducted that compared the effects observed between cohorts using self-report questionnaires and cohorts using clinical interviews. Second, to examine influential cohorts, we conducted leave-one-out analyses across all models and present the range of pooled effects and I^2 when excluding each cohort in turn. We looked at the effect of influential cohorts in a particular model only when there was at least substantial heterogeneity (>50% for I^2). In these cases, influential studies were identified with the R package Meta[16] on the basis of the criteria outlined by Viechtbauer and Cheung[17] and by considering the change in I^2 as reported in the range.

Changes from protocol

Initially, we had planned to report univariable models.[10] However, the conclusions were very similar to those of the minimally adjusted models and therefore we do not report these results. Furthermore, we had initially planned to run subgroup analyses that looked at differences between cancer stages at diagnosis. This turned out not to be possible because few cohorts had sufficient information. Finally, we applied extra exclusion criteria at stage 2 on the basis of the number of expected cases (see the Stage 2: Meta-analyses section) because models with few cancer incidences resulted in convergence issues.

RESULTS

Descriptive statistics

The percentage of participants with a diagnosis of depression or anxiety in each cohort, along with other descriptives, is displayed in Table 1. Table 2 conveys the number of cancer diagnoses per cohort.

Main results

We found no evidence for an association between depression or anxiety and overall cancer incidence at follow-up (HRs, 0.98–1.05; Figure 1). When looking at specific cancer types, we found that depression and anxiety were associated with an increased risk of lung cancer in the minimally adjusted models (HRs, 1.12–1.60). In

TABLE 1 Prevalence of anxiety and depression along with descriptives of each cohort.

Cohorts	Total N[a]	Age, mean (SD), years	Female, %	Low education, %	High education, %	Nonnative, %	Depression diagnosis clinical interview, %	Depression diagnosis questionnaire, %	Anxiety diagnosis clinical interview, %	Anxiety diagnosis questionnaire, %
ALSPAC[18,19]	10,276	27.6 (5.0)	100	18	17.6	2	–	23	–	22
Atlantic PATH[20,21]	2141	50.2 (8.8)	67	3	38	2	–	7	–	5
CARTaGENE[20,22,23]	32,093	52.9 (7.8)	53	22	57	15	–	5	–	4
ELSA[24]	9248	63.4 (10.6)	55	40	12	6	–	24	–	–
HELIUS[25,26]	19,103	44.7 (13.2)	57	44	26	79	–	15	–	–
HUNT2[27]	54,697	48.3 (16.5)	53	67	20	1	–	3	–	5
HUNT3[27]	8602	40.2 (14.6)	56	28	40	5	–	2	–	6
LASA[28,29]	3506	67.8 (9.0)	49	66	17	1	3	14	3	3
Lifelines[30]	141,134	44.5 (12.7)	58	29	30	6	3	3	8	–
NESDA[31]	2296	41.7 (13.1)	66	30	36	7	36	52	42	22
OHS[20,22]	14,384	49.7 (14.8)	64	1	71	49	–	10	–	11
RS1[32]	2812	75.7 (6.4)	61	59	11	2	4	12	7	–
RS2[32]	1981	67.9 (7.3)	57	52	17	3	2	9	9	–
RS3[32]	2968	56.7 (6.9)	56	46	27	3	2	10	–	7
UCC-SMART-2[33]	1810	64.8 (10.0)	25	26	27	10	–	7	–	–
UHP1[34]	4385	38.6 (12.1)	55	30	37	22	–	No validated cutoff	–	No validated cutoff
UHP2[34]	2660	39.0 (11.6)	54	17	55	21	–	4	–	2
Whitehall II[35]	5517	60.9 (5.9)	28	12	35	9	–	15	–	–

Abbreviations: ALSPAC, Avon Longitudinal Study of Parents and Children (mothers cohort); Atlantic PATH, Atlantic Partnership for Tomorrow's Health; ELSA, English Longitudinal Study of Ageing; HELIUS, Healthy Life in an Urban Setting; HUNT, Nord-Trøndelag Health Study; LASA, Longitudinal Aging Study Amsterdam; NESDA, Netherlands Study of Depression and Anxiety; OHS, Ontario Health Study; RS, Rotterdam Study; UCC-SMART-2, Utrecht Cardiovascular Cohort–Second Manifestations of Arterial Disease 2; UHP, Utrecht Health Project.

[a]Based on the maximum *N* in a minimally adjusted model. The number of missing participants per cohorts varies per model, and the final number in a particular model may be lower than the frequencies reported. The final *N* and number of incidences per cohort in the meta-analysis can be seen in the individual forest plots in Supplementary Materials 4.

TABLE 2 Follow-up duration and number of cancer events per type and cohort.

Cohort (country)	Follow-up duration, years	All cancers[a]	Breast cancer[a]	Lung cancer[a]	Prostate cancer[a]	Colorectal cancer	Smoking-related cancers[a]	Alcohol-related cancers[a]
ALSPAC (UK)	20	307	150	8[b,c]	0	8[b,c]	36	160
Atlantic PATH (CAN)	10	67[c]	18[b,c]	5[b,c]	7[b,c]	7[b,c]	24[b,c]	26[b,c]
CARTaGENE (CAN)	10	3875	528	393	429	297	1336	1040
ELSA (UK)	16	2038	190	173	249	201	705	466
HELIUS (NL)	8	421	80	31	51	32	143	125
HUNT2 (NOR)	24	8998	1046	778	1581	1292	3640	2555
HUNT3 (NOR)	13	452	79[b]	34[b,c]	78[b]	54[b,c]	153[b]	141[b]
LASA (NL)	26	874	80[b,c]	104[b,c]	100[b,c]	111[b,c]	420	236
Lifelines (NL)	13	5587	1332	274	503	549	1569	2058
NESDA (NL)	15	223	35	19[b]	10[b,c]	20	85	63
Ontario Health Study (CAN)	10	482	103	33[b,c]	73	28[b]	163	151
RS1 (NL)	13	507	47[b,c]	87[b]	53[b,c]	83[b]	306	157
RS2 (NL)	13	293	46[b,c]	37[b,c]	57[b]	38[b,c]	140[b]	96[b]
RS3 (NL)	9	183	34[b,c]	18[b,c]	20[b,c]	26[b,c]	89[b]	76[b]
UCC-SMART-2 (NL)	12	207	4[b]	22[b]	25[b]	20[b]	86	39[b]
UHP1 (NL)	19	277	61	18	28	29	96	98
UHP2 (NL)	16	104[c]	27[b,c]	6[b,c]	10[b,c]	6[b,c]	30[b,c]	36[b,c]
Whitehall II (UK)	13	908	66	30	221	92	245	181
Total	—	25,803	3926	2070	3495	2893	9266	7704

Abbreviations: ALSPAC, Avon Longitudinal Study of Parents and Children (mothers cohort); Atlantic PATH, Atlantic Partnership for Tomorrow's Health; CAN, Canada; ELSA, English Longitudinal Study of Ageing; HELIUS, Healthy Life in an Urban Setting; HUNT, Nord-Trøndelag Health Study; LASA, Longitudinal Aging Study Amsterdam; NESDA, Netherlands Study of Depression and Anxiety; NL, the Netherlands; NOR, Norway; OHS, Ontario Health Study; RS, Rotterdam Study; UCC-SMART-2, Utrecht Cardiovascular Cohort–Second Manifestations of Arterial Disease 2; UHP, Utrecht Health Project; UK, United Kingdom.

[a]Based on the maximum number of incidences in a minimally adjusted model.

[b]Fewer than five expected cancer cases in participants with a depression diagnosis.

[c]Fewer than five expected cancer cases in participants with an anxiety diagnosis.

maximally adjusted models, all effect estimates were attenuated (HRs, 1.07–1.23; Figure 2). Similarly, for smoking-related cancers, depression diagnosis, anxiety diagnosis, and anxiety symptoms were associated with an increased risk of incidence (HRs, 1.06–1.24). Again, these effect estimates were attenuated in the maximally adjusted models (HRs, 1.04–1.08; Figure 3). We found no evidence for an association between depression or anxiety and the incidence of colorectal cancer (HRs, 0.88–1.13; Figure 4), prostate cancer (HRs, 0.97–1.17; Figure 5), or alcohol-related cancers (HRs, 0.97–1.06; Figure 6). For breast cancer, all pooled HRs were consistently negative but mean pooled HRs were close to 1 (HRs, 0.92–0.98; Figure 7) and the upper limit of the 95% CIs all exceeded 1 (with the exception of anxiety symptoms). Across all outcomes, conclusions were similar for diagnoses and symptoms unless indicated otherwise. Forest plots for each meta-analysis are presented in Supplementary Materials 4.

Additional analyses

Analyses with different times of follow-up showed similar HRs for overall, smoking-related, and alcohol-related cancer incidence when capping at 10 and 15 years (Supplementary Materials 5). Other capping points and cancer forms could not be analyzed because of too few cancer incidences and limited follow-up. Analyses excluding carcinomas in situ and borderline tumors did not change the previously observed associations regarding lung cancer and smoking-related cancers (Supplementary Materials 6). The reduction in HRs from the minimally adjusted to maximally adjusted models was not explained by reduced power because conclusions did not change when rerunning minimally adjusted models with the samples used in maximally adjusted models (Supplementary Materials 7). Because neither depression nor anxiety was significantly related to cancer incidence in maximally adjusted models, we did not run meta-analyses with both anxiety and depression in the models. No sex

differences were identified in the associations between depression/anxiety and cancer incidence (Supplementary Materials 8).

The analysis for anxiety and depression diagnosis by measurement type (clinical interview vs. self-report questionnaire) indicated in most cases no differences related to measurement type (Supplementary Materials 9). The exception to this was the association between depression diagnosis and breast cancer, which was associated with increased risk when measured by clinical interview (two studies) compared to decreased risk when measured by self-report questionnaire (seven studies; Figures S9.21 and S9.22). Leave-one-out ranges shown in the figures indicated consistent HRs when excluding each cohort in turn. Further leave-one-out analysis in meta-analyses where $I^2 > 50\%$ did not reveal any influential cohorts.

DISCUSSION

The current study is the first IPD meta-analysis regarding the association between depression and anxiety and cancer risk. Methodological strengths are the use of validated measures of depression or anxiety, the harmonization of data to reach conceptually similar variables, the use of the same statistical procedure across all cohorts, and the control of key confounders in the Cox regression models. In our IPD meta-analyses, on the basis of 18 prospective cohorts, we observed that (1) anxiety and depression were not associated with an increased risk for overall cancers, nor for breast, prostate, colorectal, or alcohol related-cancers; and (2) anxiety and depression were associated with an increased risk for lung cancer and smoking-related cancers after adjustment for sociodemographic factors only but not after additionally adjusting for health-related covariates and other potential confounders. Furthermore, our findings were robust because conclusions did not change when accounting for the reduced power in the maximally adjusted models or the type of measurement for anxiety and depression diagnoses, nor when excluding in situ or borderline tumors, nor when comparing 10- to 15-year follow-up. Finally, we observed no evidence of sex differences in any associations.

The lack of association between anxiety and depression and all cancers is not consistent with several previous meta-analyses.[2–4] These differences are likely to be explained by the higher consistency in the covariates included in our models across all cohorts via data harmonization, the unlikely presence of publication bias in our meta-analysis because inclusion was not restricted to published studies, and the large sample size in our study. Furthermore, cancer diagnosis was based on registry information in all cohorts. Therefore, data on malignancy, site, and time of diagnosis are less influenced by recall bias.[36] Also, we used age as the timescale in the Cox regression model whereas previous studies tended to use time on study, which can lead to bias given the nonparametric confounding effect of age in cancer.[37]

For lung cancer, in minimally adjusted models, depression and anxiety diagnoses were related to increased risk (58% and 60% increased risk, respectively). Furthermore, depression symptoms and anxiety symptoms (for each SD increase) were related to 15% and 12% increased risk, respectively. Similar patterns were seen for smoking-related cancers, although the effect estimates were smaller. Because effects attenuated considerably when further adjusting for health behaviors and other potential confounders (including smoking-related variables), it is possible that tobacco smoking or other unhealthy behaviors play a more crucial role, via mediation or interaction. Indeed, previous studies have attributed the association between depression and smoking-related cancers to increased prevalence of smoking among depressed persons.[38–40] To understand the link between depression, anxiety, and the incidence of lung and smoking-related cancers, further research on the mediating and interactive effects of health behaviors is needed. The residual effect in maximum models may be explained by imperfect adjustment for unhealthy behaviors. Another possibility is a common Ras proto-oncogene that increases the risk for both depression and cancers related to the Ras oncogene family such as lung cancer.[41]

A few limitations exist in the current study. We did not use multiple imputation to deal with missing data[42] because it was not feasible to do this in a standardized way in all 18 cohorts. Furthermore, we did not consider specific subtypes of cancer (e.g., non–small cell lung cancer vs. other types of lung cancer) that may be differentially related to depression and anxiety.[41] Other cohorts may have met the inclusion and exclusion criteria but were neither known to the consortium nor came up in a literature search. PSY-CA is set up in such a way that information from additional cohorts can be added in the future. To reduce the likeliness of type I errors, we focused our conclusions on consistent findings, but it is possible that small, sporadic effects relate to true effects that require even more power to detect. Finally, we looked at current depression or anxiety at baseline, whereas individuals with a history of depression and anxiety, or more chronic forms of depression and anxiety, may be at a higher risk of cancer.[43]

In conclusion, our study does not support the hypothesis that depression and anxiety are related to an increased risk for overall cancers nor breast, prostate, colorectal, or alcohol-related cancers. Although we found support for an association with smoking-related cancers such as lung cancer, when we adjusted for additional covariates the effect was substantially reduced. The results from the current study may help health professionals to alleviate feelings of guilt and self-blame in patients with cancer who attribute their diagnosis to previous depression or anxiety. However, further research is required to test whether depression and anxiety interact with or moderate the effects of health behaviors on the incidence of lung and smoking-related cancers.

AUTHOR CONTRIBUTIONS

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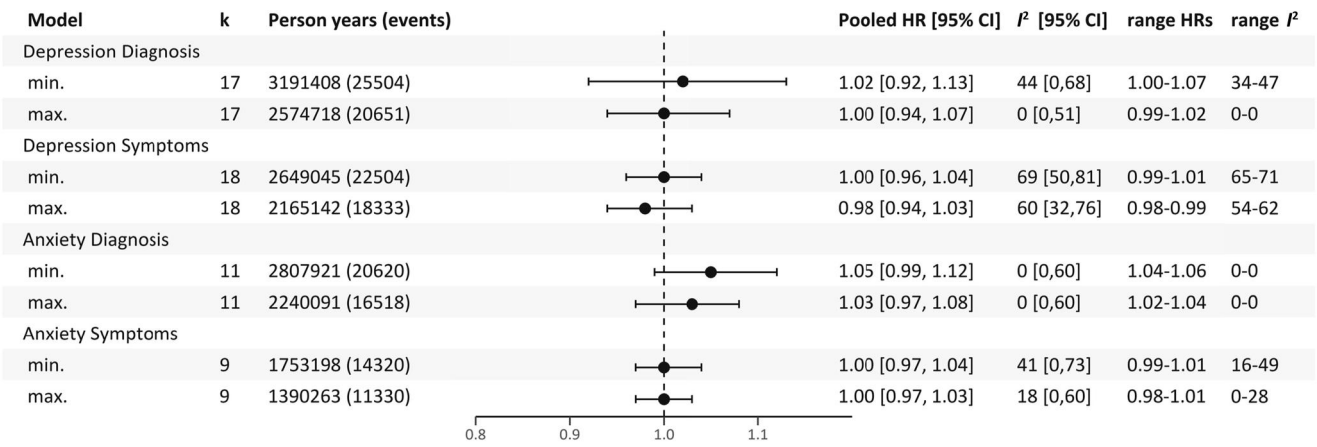

FIGURE 1 Association between depression/anxiety and all cancer types. Error bars convey the 95% confidence interval around the pooled HR. HR indicates hazard ratio; max., maximally adjusted (additionally adjusting for health-related covariates and other potential risk factors); min., minimally adjusted (demographic variables).

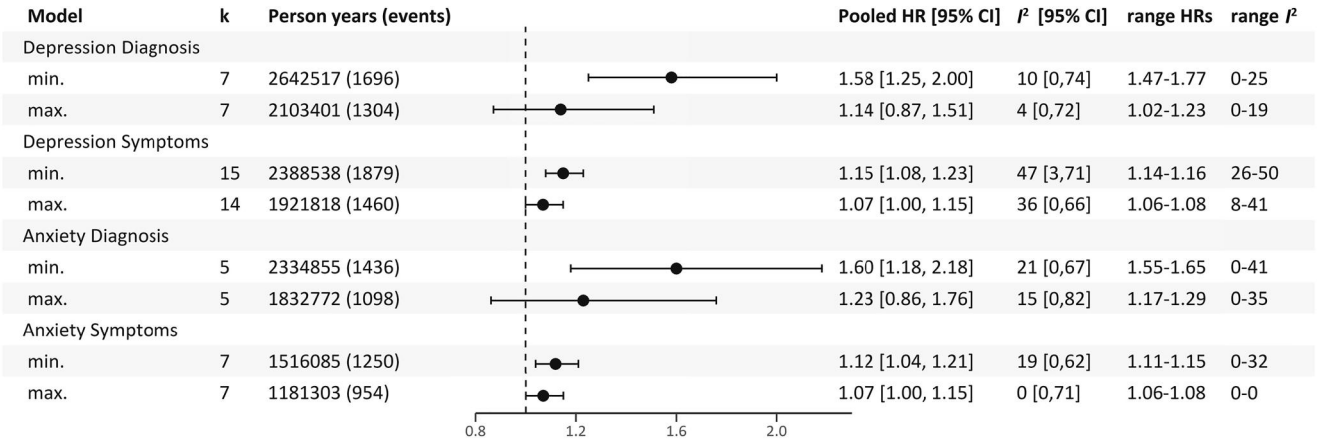

FIGURE 2 Association between depression/anxiety and lung cancer. Error bars convey the 95% confidence interval around the pooled HR. HR indicates hazard ratio; max., maximally adjusted (additionally adjusting for health-related covariates and other potential risk factors); min., minimally adjusted (demographic variables).

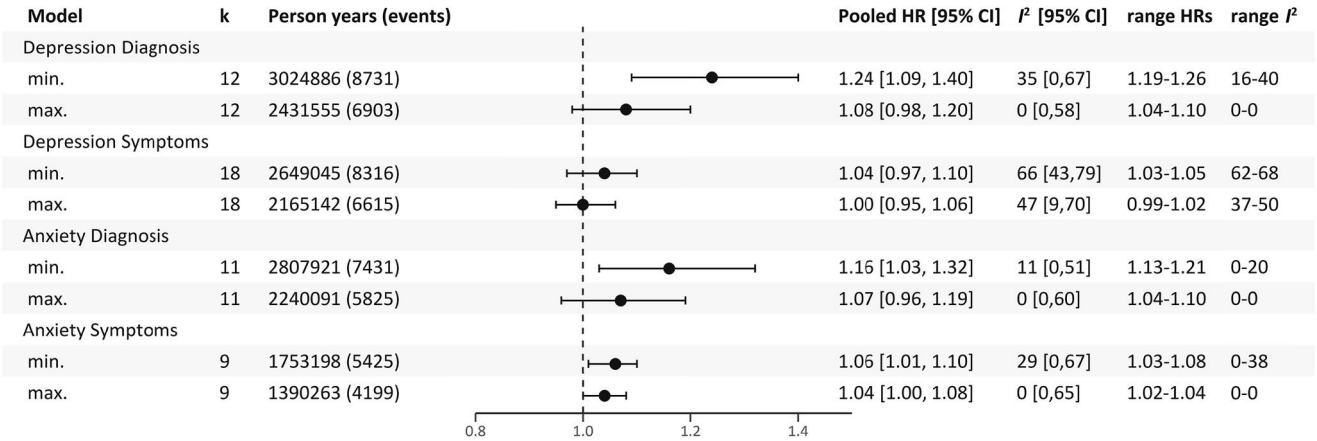

FIGURE 3 Association between depression/anxiety and smoking-related cancers. Error bars convey the 95% confidence interval around the pooled HR. HR indicates hazard ratio; max., maximally adjusted (additionally adjusting for health-related covariates and other potential risk factors); min., minimally adjusted (demographic variables).

Model	k	Person years (events)	Pooled HR [95% CI]	I^2 [95% CI]	range HRs	range I^2
Depression Diagnosis						
min.	7	2642517 (2483)	1.12 [0.99, 1.28]	0 [0,71]	1.10-1.16	0-0
max.	7	2018983 (1848)	1.13 [0.94, 1.34]	0 [0,71]	1.05-1.17	0-0
Depression Symptoms						
min.	15	2388538 (2534)	0.98 [0.93, 1.03]	18 [0,55]	0.97-0.99	0-23
max.	15	1862610 (1898)	0.97 [0.92, 1.02]	0 [0,54]	0.96-0.98	0-0
Anxiety Diagnosis						
min.	5	2334855 (2090)	0.88 [0.69, 1.14]	0 [0,79]	0.79-0.94	0-0
max.	5	1753137 (1534)	0.89 [0.57, 1.41]	29 [0,72]	0.76-0.97	0-46
Anxiety Symptoms						
min.	7	1516085 (1669)	1.01 [0.98, 1.04]	0 [0,71]	1.01-1.02	0-0
max.	7	1128988 (1184)	1.01 [0.91, 1.11]	11 [0,74]	0.96-1.03	0-24

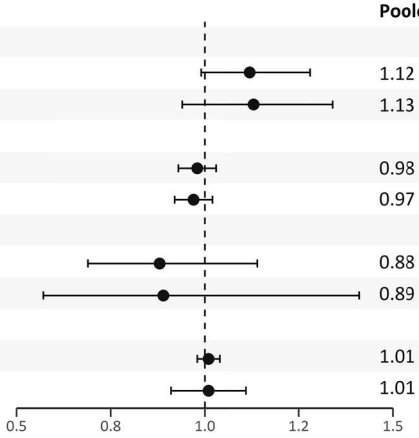

FIGURE 4 Association between depression/anxiety and colorectal cancer. Error bars convey the 95% confidence interval around the pooled HR. HR indicates hazard ratio; max., maximally adjusted (additionally adjusting for health-related covariates and other potential risk factors); min., minimally adjusted (demographic variables).

Model	k	Person years (events)	Pooled HR [95% CI]	I^2 [95% CI]	range HRs	range I^2
Depression Diagnosis						
min.	7	1204801 (3104)	0.97 [0.74, 1.26]	24 [0,66]	0.89-1.03	0-36
max.	7	934543 (2395)	1.04 [0.80, 1.36]	19 [0,63]	0.98-1.09	0-33
Depression Symptoms						
min.	16	1095536 (3193)	0.98 [0.95, 1.01]	0 [0,52]	0.96-0.98	0-0
max.	15	872476 (2514)	1.00 [0.97, 1.03]	0 [0,54]	0.97-1.00	0-0
Anxiety Diagnosis						
min.	6	1099375 (2584)	1.11 [0.73, 1.70]	41 [0,76]	0.99-1.20	25-49
max.	6	839929 (1972)	1.17 [0.92, 1.50]	0 [0,75]	1.10-1.23	0-0
Anxiety Symptoms						
min.	7	703041 (2141)	0.99 [0.93, 1.05]	7 [0,73]	0.95-1.00	0-23
max.	7	542175 (1638)	0.99 [0.93, 1.05]	0 [0,71]	0.97-0.99	0-0

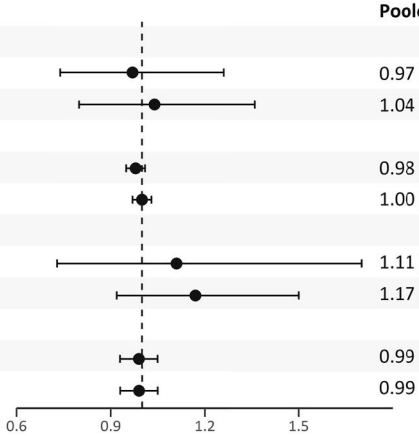

FIGURE 5 Association between depression/anxiety and prostate cancer. Error bars convey the 95% confidence interval around the pooled HR. HR indicates hazard ratio; max., maximally adjusted (additionally adjusting for health-related covariates and other potential risk factors); min., minimally adjusted (demographic variables).

Model	k	Person years (events)	Pooled HR [95% CI]	I^2 [95% CI]	range HRs	range I^2
Depression Diagnosis						
min.	11	3015245 (7185)	1.06 [0.96, 1.16]	0 [0,60]	1.04-1.07	0-0
max.	11	2424303 (5888)	1.02 [0.94, 1.12]	0 [0,60]	1.00-1.03	0-0
Depression Symptoms						
min.	18	2649045 (6452)	1.00 [0.94, 1.06]	55 [23,74]	0.99-1.01	37-58
max.	18	2165142 (5283)	0.99 [0.92, 1.06]	53 [19,72]	0.98-1.00	42-55
Anxiety Diagnosis						
min.	11	2807921 (6403)	0.97 [0.89, 1.07]	0 [0,60]	0.96-0.98	0-0
max.	11	2240091 (5204)	0.98 [0.87, 1.10]	0 [0,60]	0.96-1.01	0-0
Anxiety Symptoms						
min.	9	1753198 (4133)	1.00 [0.97, 1.03]	0 [0,65]	0.99-1.00	0-0
max.	9	1390263 (3304)	0.99 [0.95, 1.04]	6 [0,67]	0.97-1.00	0-18

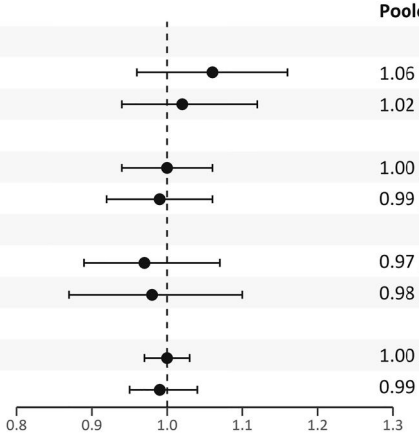

FIGURE 6 Association between depression/anxiety and alcohol-related cancers. Error bars convey the 95% confidence interval around the pooled HR. HR indicates hazard ratio; max., maximally adjusted (additionally adjusting for health-related covariates and other potential risk factors); min., minimally adjusted (demographic variables).

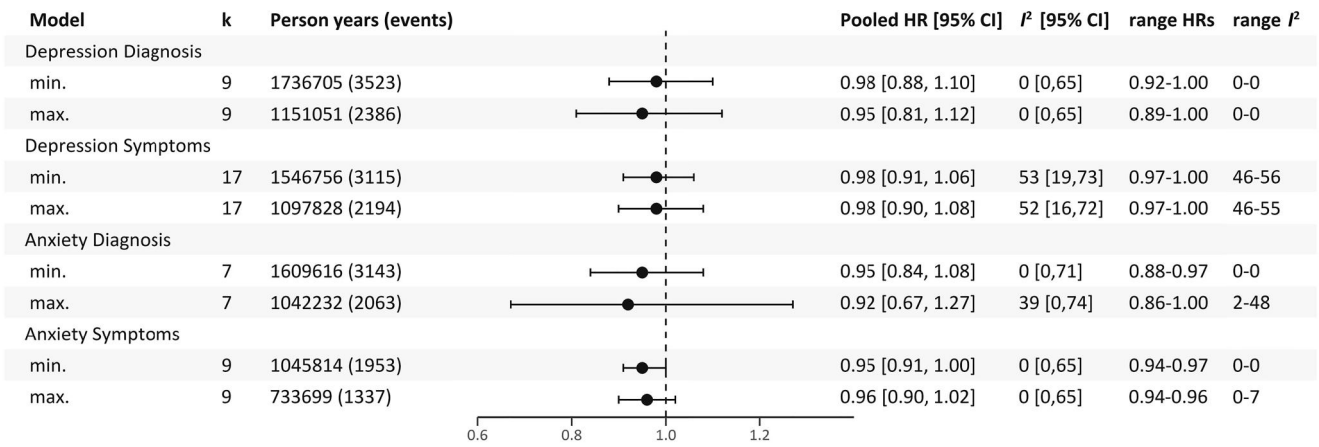

FIGURE 7 Association between depression/anxiety and breast cancer. Error bars convey the 95% confidence interval around the pooled HR. HR indicates hazard ratio; max., maximally adjusted (additionally adjusting for health-related covariates and other potential risk factors); min., minimally adjusted (demographic variables).

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Lifelines is a multidisciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviors of 167,729 persons living in the north of the Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, sociodemographic, behavioral, physical, and psychological factors that contribute to the health and disease of the general population, with a special focus on multimorbidity and complex genetics. The Lifelines initiative has been made possible by a subsidy from the Dutch Ministry of Health, Welfare and Sport, the Dutch Ministry of Economic Affairs, University Medical Center Groningen, Groningen University, and the provinces in the north of the Netherlands (Drenthe, Friesland, Groningen).

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are owned by the participating cohort studies. Data are not publicly available but may be shared upon reasonable request at each cohort depending on cohort-specific regulations.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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