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Psychosocial factors, health behaviors and risk of cancer incidence: Testing interaction and effect modification in an individual participant data meta-analysis

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Abstract

Depression, anxiety and other psychosocial factors are hypothesized to be involved in cancer development. We examined whether psychosocial factors interact with or modify the effects of health behaviors, such as smoking and alcohol use, in relation to cancer incidence. Two-stage individual participant data meta-analyses were performed based on 22 cohorts of the PSYchosocial factors and CAncer (PSY-CA) study. We examined nine psychosocial factors (depression diagnosis, depression symptoms, anxiety diagnosis, anxiety symptoms, perceived social support, loss events, general distress, neuroticism, relationship status), seven health behaviors/behavior-related factors (smoking, alcohol use,

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For affiliations refer to page 1757

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physical activity, body mass index, sedentary behavior, sleep quality, sleep duration) and seven cancer outcomes (overall cancer, smoking-related, alcohol-related, breast, lung, prostate, colorectal). Effects of the psychosocial factor, health behavior and their product term on cancer incidence were estimated using Cox regression. We pooled cohort-specific estimates using multivariate random-effects meta-analyses. Additive and multiplicative interaction/effect modification was examined. This study involved 437,827 participants, 36,961 incident cancer diagnoses, and 4,749,481 person years of follow-up. Out of 744 combinations of psychosocial factors, health behaviors, and cancer outcomes, we found no evidence of interaction. Effect modification was found for some combinations, but there were no clear patterns for any particular factors or outcomes involved. In this first large study to systematically examine potential interaction and effect modification, we found no evidence for psychosocial factors to interact with or modify health behaviors in relation to cancer incidence. The behavioral risk profile for cancer incidence is similar in people with and without psychosocial stress.

KEYWORDS
cancer incidence, health behaviors, individual participant data meta-analysis, interaction/effect modification, psychosocial factors

What's new?

Depression, anxiety, and other psychosocial factors can affect behavior and physiological function in ways that potentially contribute to cancer. Whether these factors serve an etiological role in cancer development, however, remains uncertain. The present study investigated whether psychosocial factors interact with or modify the effects of health behaviors in relation to cancer incidence. A total of 744 combinations of psychosocial factors, health behaviors, and cancer outcomes were analyzed, and no interaction or effect modification was identified. The results suggest that people who experience psychosocial stress are not particularly vulnerable to the negative effects of unhealthy behaviors on cancer development.

1 | INTRODUCTION

Cancer development is a multifactorial process where multiple environmental and genetic factors are involved and are hypothesized to interact with each other. Factors that may be involved in this multifactorial process include depression, anxiety and other psychosocial factors, such as the experience of a loss event or poor social support. These factors have long been hypothesized to be related to increased cancer incidence.[2–10] Although results have been inconclusive, several meta-analyses have identified a relation between, for example, depression and overall cancer incidence[2,4,7,9] or site-specific cancer incidence, including lung cancer.[2,4,9] To date, the potential interacting and modifying mechanisms between psychosocial factors and health behaviors in relation to cancer incidence remain poorly investigated and understood.[11–13]

In 2017, the PSYchosocial factors and CAncer (PSY-CA) consortium, involving 18 prospective cohort studies, was launched to perform individual participant data (IPD) meta-analyses on the association of depression, anxiety and other psychosocial factors with cancer incidence.[14] This consortium was established to overcome shortcomings of previous meta-analyses, including large differences in conceptualization and assessment of psychosocial factors across studies, limited adjustment for potential confounders and the likelihood of publication bias. In addition, the aim was to create a large study population to be able to study potential mechanisms leading to cancer incidence. So far, the PSY-CA study indicated that depression and anxiety were associated with higher risk of lung cancer and smoking-related cancer, but not with breast, prostate, colorectal, alcohol-related or overall cancer.[15]

Depression, anxiety and psychosocial stress may lead to changes in neuroendocrine regulation and immune response which may subsequently affect mutation, viral oncogenes, cell proliferation and DNA repair.[16,17] These hypothesized biological pathways overlap with those of health behaviors leading to cancer incidence.[18–21] Psychosocial factors and health behaviors may each reinforce the same biological mechanisms or act at different stages in the same disease process. Subsequently, this may lead to *interaction*, that is an increased combined risk among people with depression, anxiety or psychosocial stress and unhealthy behavior.[22] Identification of statistical interaction between psychosocial factors and health behaviors may guide the development of hypotheses regarding potential biological interaction in cancer development.

Alternatively, in the absence of a direct association between psychosocial factors and cancer incidence, psychosocial factors may *modify* the relation between health behaviors and cancer incidence. For

example, the effect of smoking on the risk of cancer incidence may be stronger among those who experience depression compared to those without depression. Such a modifying role of depression may be explained by stronger inhalation among individuals with depression[23] or by clustering of smoking and other health behaviors related to cancer incidence within this group.[23–27] Investigating potential modification effects will indicate whether individuals who experience depression, anxiety, or psychosocial stress should be prioritized in cancer prevention or screening programs.

We aimed to examine interaction and effect modification of psychosocial factors and health behaviors/behavior-related factors in their association with incident cancer within the large PSY-CA consortium. We hypothesized that, either through interaction or effect modification, the risk of developing cancer among people with depression, anxiety or psychosocial stress (low social support or the experience of a recent loss event) and unhealthy behavior (smoking, alcohol use, low physical activity or high body mass index (BMI)) is greater than the sum of the individual effects of psychosocial factors and unhealthy behaviors on cancer incidence. We also explored interaction and effect modification for several additional psychosocial factors and health behaviors/behavior-related factors.

2 | MATERIALS AND METHODS

2.1 | Study design

This study involved pre-planned two-stage IPD meta-analyses performed by the PSY-CA consortium. The PSY-CA study consists of 18 prospective cohort studies from the Netherlands, UK, Norway, and Canada. Three cohorts included multiple sub cohorts that were considered separately, resulting in 22 cohorts for analysis (Table 1) Cohort references are presented in Supplementary text S50). All cohorts harmonized their data to obtain consistent coding of variables using cohort-specific data harmonization instructions following the MAELSTROM guidelines.[28] The first stage of the meta-analysis involved running standardized analyses on harmonized datasets for each cohort. In the second stage, meta-analyses were performed to pool the effect estimates of all cohorts. A detailed description of the PSY-CA study, including ethics approval, study protocol and power calculations, has been published previously.[14] Details of the protocol for this meta-analysis were registered on PROSPERO (www.crd.york.ac.uk/PROSPERO) under ID: CRD42020181623 (submitted at 13 October 2020).

2.2 | Study population

Cohort studies were selected for the PSY-CA consortium based on the following criteria: (1) a valid and reliable measure of one or more psychosocial factors ascertained from validated measures or from measures used in previously published studies; (2) a reliable measure of cancer diagnosis derived through linkage with national or regional cancer registries during follow-up or possible to attain; and (3) availability of data on sex, age, smoking and alcohol. All relevant cohorts in the Netherlands were approached and invited to take part in PSY-CA. In order to increase the number of cohorts, international cohorts that fulfilled the inclusion criteria were identified through the BioShare consortium (which is now linked to the Public Population Project in Genomics and Society; http://www.p3gconsortium.org/about-p3g) and Integrative Analysis of Longitudinal Studies of Aging and Dementia network (www.ialsa.org/). More details on cohort selection are provided elsewhere.[14] For each cohort, we excluded participants based on the following criteria: (1) missing data on all psychosocial factors, (2) refusal of linkage to external cancer registries, and (3) history of cancer at baseline (except for non-melanoma skin cancer). Additionally, to reduce the risk of reverse causation, participants with any cancer incidence during the first year of follow-up were excluded from the analysis.

2.3 | Psychosocial factors

The following psychosocial factors were considered for our primary analyses: depression symptoms, depression diagnosis (yes/no), anxiety symptoms, anxiety diagnosis (y/n), recent loss event (y/n) and perceived social support. These factors were chosen for our primary analyses given the rather clear distinction between concepts and the focus on these factors in prior research.[14] In exploratory analyses we also studied relationship status (in a relationship vs. single), general distress, and neuroticism. Depression symptoms, anxiety symptoms, perceived social support and neuroticism included continuous sum scores which were ascertained from validated measures or measures previously published by the cohort. Depression diagnosis (including major depressive disorder and dysthymia) and anxiety diagnosis (generalized anxiety disorder, social anxiety, panic disorder and agoraphobia) were based on clinical interviews or, if not available, on symptom questionnaires using validated clinical cut-offs. General distress was assessed using the five-item Mental Health Inventory total score (MHI-5) obtained from the Short-form health survey (SF-36) or the RAND36.[29] Recent loss event was defined as the loss of an immediate family member or partner in the past 12 months. Cohort-specific details on psychosocial factor assessments are provided in Supplementary Tables S1 and S2. To improve comparison of various questionnaires used across cohorts, all continuous scores were converted to z-scores.

2.4 | Health behaviors

The following health behaviors and behavior-related factors (here together described as health behaviors) were considered for our primary analyses given the consistent evidence of their association with cancer[14]: number of cigarettes per week (or equivalent of other tobacco smoking), number of alcoholic drinks per week, assessed or self-reported BMI and hours of physical activity per week. In exploratory analyses, we also studied pack years, current smoker (y/n), ever smoker (y/n), hours of sedentary behavior per week (or hours of TV watching per week), sleep quality, short sleep duration (≤6 h per night), and long sleep duration (≥9 h per night). For number of

alcoholic drinks, we created two variables, one including non-drinkers and one excluding non-drinkers. Physical activity and sleep quality were reversely coded so that a higher score represents less physical activity/lower sleep quality. Continuous scores were converted to z-scores in each cohort. Extreme values were truncated to three times the interquartile range above the third quartile or below the first quartile. Cohort-specific details on the availability and assessment of health behaviors are provided in Supplementary Table S3.

2.5 | Cancer outcomes

Cancer cases, including cancer type and date of diagnosis, were identified through linkage with data from national or regional cancer registries. In two cohorts (Rotterdam Study and CARTaGENE), information from registries was supplemented with data on hospital visits, insurance claims, and General Practitioner records. Seven cancer incidences were considered: overall cancer, breast cancer, colorectal cancer, lung cancer, prostate cancer, smoking-related cancers and alcohol-related cancers as listed by the International Agency for Research on Cancer[14,30] (Supplementary Table S4).

2.6 | Covariates

The following sociodemographic characteristics were available for all cohorts: sex, country of birth (whether or not the participant or their parents were born in the country in which the study was carried out), education (categorized into "low," "medium" and "high") and birth year. For HUNT 3, profession level was used as a proxy indicator for education. Birth year was included in regression models as a categorical variable to adjust for cohort effects, with the number of categories depending on the range of birth years and number of cancer cases for each cohort. Additionally, the following potential confounders for the association between either psychosocial factors and/or health behaviors and cancer incidence were considered: self-reported history of antidepressants use, as it has previously been found to be associated with site-specific cancer incidence,[31–34] and self-reported family history of cancer (any, breast, prostate, lung, or colorectal cancer of the participant's parents, siblings, and/or children). For breast cancer as outcome, the following covariates were additionally included: parity (categorized into 0, 1–2 and ≥3 pregnancies), age at menarche, menopausal status (pre-menopausal vs. postmenopausal), and oral contraceptive pill use (number of years used, ever use [y/n] or baseline use [y/n], depending on the data available). The availability and assessment of these covariates differed across cohorts, see Supplementary Table S5.

2.7 | Statistical analysis

In stage one of the IPD meta-analysis, regression analyses were conducted separately for each cohort by local researchers using pre-programmed R scripts. Multivariable Cox regression models were used in all analyses with age as the underlying time variable (allowing for left truncation and right censoring of event times due to diagnosis of another type of cancer, death, loss to follow-up, or end of follow-up) and cancer diagnosis as outcome. To examine the potential interaction or effect modification between psychosocial factors and health behaviors, we included the psychosocial factor, the health behavior and the product term of the psychosocial factor and health behavior as independent variables into the model. Two models were tested for each combination of psychosocial factor, health behavior and cancer outcome: (1) a minimally-adjusted model including sociodemographic covariates available across all cohorts: birth year, sex, education, and country of origin; and (2) a maximally-adjusted model including sociodemographic covariates, other health behaviors (smoking, alcohol use, physical activity and BMI) and other potential confounders depending on cancer outcome and availability within the cohort. For each model, effect estimates of the psychosocial factor, health behavior, their product term and their variances and covariances were saved for stage two. Our primary analyses included 168 combinations of six psychosocial factors, four health behaviors and seven cancer outcomes involved. In exploratory analyses 588 models were tested including additional psychosocial factors and health behaviors.

Stage two involved meta-analyses, aggregating the results from all cohorts. For each meta-analytic model, we included the effect estimates of all cohorts which were considered to have enough cancer events to provide reliable estimates for that specific cancer outcome. Therefore, we selected models including at least 10 cancer events and, for categorical psychosocial factors and health behaviors, at least five expected events in the smallest category of either the psychosocial factor and/or health behavior category (based on the observed cohort-specific cancer incidence). Additionally, models were excluded if they did not converge or where infinite betas for the psychosocial factor, health behavior or the product term were estimated (3%). These issues were predominantly due to overfitting and occurred most often in maximally-adjusted models and in the smaller cohorts.

For each combination of psychosocial factor, health behavior and cancer outcome, the estimated cohort-specific regression coefficients for the psychosocial factor (B_1), health behavior (B_2) and product term (B_3) and their variances and covariances were entered into a multivariate random-effects meta-analysis. Between-cohort variation was estimated using restricted maximum likelihood (REML) and was quantified using I^2 and Cochrane's Q. Interaction and effect modification were studied on a multiplicative and additive scale.[35] Positive *multiplicative* interaction is present if the combined effect of two exposures is larger than the *product* of the individual effects. Positive *additive interaction* is present if the combined effect of two exposures is larger than the *sum* of the individual effects of the two exposures. Examination of multiplicative interaction was based on the pooled effect estimate of the product term (B_3). To test interaction and effect modification on an additive scale we calculated the Relative Excess Risk due to Interaction (RERI) based on the pooled coefficients, using the following formula: $\text{RERI} = e^{B1+B2+B3} - e^{B1} - e^{B2} + 1$.[35,36] The RERI can range from minus infinity to infinity. RERI = 0 reflects no interaction; RERI >0 reflects positive interaction; and a RERI <0 reflects negative interaction. As a measure of the magnitude of the interaction effect, we calculated the attributable proportion

TABLE 1 Cohort characteristics.

(Sub)Cohorts	*N*	Age, *M* (SD)	Sex, % female	Education, % high	Smoking, % yes	Alcoholic drinks p/w, *M* (SD)	BMI, *M* (SD)	Depression, %	Anxiety, %	Loss event, %	Other psychosocial factors
ALSPAC	12,772	27.6 (5.0)	100.0	17.6	34.5[a]	2.9 (3.2)[a]	22.9 (3.6)[a]	23.1	21.6	–	DS AS PS ReS
AMIGO	13,857	50.8 (9.3)	55.0	38.1	17.0	7.0 (7.5)	26.0 (4.4)	–	–	6.3	GD ReS
Atlantic PATH	2258	50.2 (8.8)	67.3	38.1	13.3	3.4 (5.3)	30.3 (4.7)	7.1	5.4	–	DS AS ReS
CARTaGENE	32,472	52.9 (7.8)	53.3	57.1	17.5	5.3 (7.5)	27.5 (5.5)	4.5	3.9	–	DS AS PS ReS
ELSA	10,282	63.5 (10.8)	55.2	12.7	18.1	3.2 (5.0)	–	23.5	–	–	DS PS ReS
EPIC-MORGEN	20,153	42.5 (11.2)	53.6	24.0	36.4	8.4 (11.3)	25.4 (3.9)	–	–	–	PS GD ReS
EPIC-Prospect	15,649	57.6 (6.0)	100.0	16.0	22.3	4.8 (6.3)	26.0 (4.1)	–	–	–	ReS
HELIUS	19,405	44.7 (13.2)	56.8	26.2	24.2	3.2 (6.6)	27.1 (5.2)	14.7	–	9.6	DS PS Ne ReS
HUNT 2	62,345	49.5 (17.1)	52.9	20.1	29.3	1.6 (2.1)	26.3 (4.1)	3.1	5.1	–	DS AS ReS
HUNT 3	13,304	39.1 (14.5)	53.0	39.5	22.9	2.5 (2.8)	26.5 (4.6)	2.3	6.0	8.2	DS AS PS Ne ReS
LASA	3556	67.9 (9.1)	48.8	17.2	25.5	9.0 (11.1)	27.0 (4.2)	2.7	3.4	–	DS AS PS Ne ReS
Lifelines	148,866	44.8 (13.0)	58.4	30.0	21.2	5.3 (6.4)	26.0 (4.3)	3.4	7.9	9.0	DS GD Ne ReS
NESDA	2296	41.7 (13.1)	65.5	35.8	37.0	7.7 (9.9)	25.6 (4.9)	36.1	41.5	2.2	DS AS PS Ne ReS
OHS	48,597	49.7 (14.3)	62.7	77.8	10.4	4.2 (6.3)	26.8 (5.5)	9.8	11.1	–	DS AS ReS
OMEGA-II	7871	47.2 (4.5)	100.0	34.7	18.7	3.1 (4.5)	25.2 (4.5)	–	–	–	GD ReS
RS 1	2852	75.7 (6.4)	61.4	10.8	13.4	7.4 (9.3)	27.5 (4.1)	4.2	7.0	3.5	DS PS ReS
RS 2	2107	67.9 (7.3)	56.7	17.0	16.5	8.7 (10.4)	27.9 (4.1)	2.3	8.5	3.2	DS PS ReS
RS 3	3496	56.7 (6.9)	55.9	26.7	28.3	6.0 (6.1)	27.7 (4.5)	2.1	7.0	2.2	DS PS ReS
UCC-SMART-2	1823	64.8 (10.0)	24.7	26.5	18.2	7.4 (8.0)	27.6 (4.2)	7.1	–	–	DS GD ReS
UHP 1	4558	38.7 (12.1)	55.2	38.0	24.2	6.6 (9.0)	25.4 (4.2)	–	–	–	DS AS GD ReS
UHP 2	2913	39.1 (11.7)	54.0	56.3	17.0	6.4 (8.1)	25.1 (4.1)	4.4	1.9	5.7	DS PS GD ReS
Whitehall-II	6395	61.0 (6.0)	28.9	35.4	11.7	11.9 (12.7)	26.7 (4.3)	15.4	–	–	DS PS GD ReS

Note: Cohort references are presented in Supplementary Text S50.

Abbreviations: ALSPAC, Avon Longitudinal Study of Parents and Children; AMIGO, Dutch Occupational and Environmental Health Cohort Study; AS, anxiety symptoms; DS, depression symptoms; ELSA, English Longitudinal Study of Ageing; EPIC, European Prospective Investigation into Cancer and Nutrition; GD, general distress; HELIUS, Healthy Life in an Urban Setting; HUNT, Nord-Trøndelag Health Study; LASA, Longitudinal Aging Study Amsterdam; Ne, neuroticism; NESDA, Netherlands Study of Depression and Anxiety; OHS, Ontario Health Study; PS, perceived social support; ReS, relationship status; RS, Rotterdam Study; UCC-SMART-2, Utrecht Cardiovascular Cohort—Second Manifestations of Arterial Disease 2; UHP, Utrecht Health Project.

[a]Self-reported smoking/alcohol use/BMI before pregnancy.

TABLE 2 Follow-up duration and cancer incidence per cohort.

Cohort	Follow-up time		Cancer incidence						
	Maximum years of follow-up	Total person years	Overall cancer	Breast cancer	Lung cancer	Prostate cancer	Colorectal cancer	Smoking-related cancers	Alcohol-related cancers
ALSPAC	23.9	281,117	367	172	8	–	8	49	186
AMIGO	5.6	68,616	381	85	28	46	40	129	142
Atlantic PATH	9.8	14,036	73	20	5	7	7	24	28
CARTaGENE	10.4	239,614	3901	530	397	434	299	1348	1046
ELSA	15.9	118,140	2269	221	200	262	223	797	529
EPIC-MORGEN	20.0	364,018	2522	472	225	304	323	986	881
EPIC-Prospect	23.9	266,996	3287	984	235	–	443	1179	1502
HELIUS	8.5	103,017	424	81	31	53	32	143	126
HUNT 2	24.0	1,173,206	10,488	1185	895	1805	1560	4314	3001
HUNT 3	12.6	145,252	619	95	43	109	66	212	181
LASA	26.2	39,168	879	80	106	101	111	423	236
Lifelines	12.6	1,123,699	6139	1431	313	553	599	1739	2218
NESDA	14.9	29,567	223	35	19	10	20	85	63
OHS	39.0	434,377	2341	451	123	423	166	779	691
OMEGA-II	9.3	50,424	352	155	10	–	10	44	167
RS 1	12.9	25,202	513	48	87	53	84	311	160
RS 2	13.0	18,519	309	48	38	58	39	146	103
RS 3	8.9	25,214	219	39	25	22	34	113	94
UCC-SMART-2	12.0	9711	208	4	22	25	20	86	39
UHP 1	19.2	60,897	289	64	19	30	30	98	102
UHP 2	16.4	23,053	113	29	6	11	6	33	39
Whitehall-II	13.1	67,566	1045	90	34	248	105	283	226
Total	–	**4,749,481**	**36,961**	**4594**	**2369**	**4183**	**3395**	**10,954**	**9029**

Abbreviations: ALSPAC, Avon Longitudinal Study of Parents and Children; AMIGO, Dutch Occupational and Environmental Health Cohort Study; ELSA, English Longitudinal Study of Ageing; EPIC, European Prospective Investigation into Cancer and Nutrition; HELIUS, Healthy Life in an Urban Setting; HUNT, Nord-Trøndelag Health Study; LASA, Longitudinal Aging Study Amsterdam; UHP, Utrecht Health Project; 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.

(AP), that is the proportion of the effect of both exposures on the additive scale that is attributable to interaction, using the following formula: $AP = (e^{B1+B2+B3} - e^{B1} - e^{B2} + 1)/(e^{B1+B2+B3})$.[35] The 95% CI of the RERI and AP were calculated using the Delta method based on the pooled variance–covariance matrix.[37] The RERI and AP were not calculated if a psychosocial factor or health behavior was associated with decreased risk of cancer (i.e., a preventive effect) as these measures can only be validly calculated if both exposures increase the risk of cancer.[38] Furthermore, a preventive effect of the psychosocial factor or health behavior provides sufficient evidence to reject our hypothesis on interaction or effect modification.

Interpretation of results was done at the aggregate level by examining patterns for certain psychosocial factors, health behaviors or cancer outcomes across models and was not based on single significant associations. We therefore did not adjust *p*-values for multiple comparisons and used a conventional *p*-value cutoff of .05 for identifying associations. Interaction was determined if both the psychosocial factor and the health behavior were associated with the cancer outcome independently of each other in combination with a significant positive RERI estimate. The psychosocial factor was considered as an effect modifier if only the health behavior was associated with the cancer outcome and a significant positive RERI estimate was found.

3 | RESULTS

3.1 | Cohort characteristics

Combining the 22 cohorts and sub cohorts resulted in a total of 437,827 participants involved. Mean age at baseline per cohort ranged between 28 and 76 years and 25% to 100% were female (Table 1). Maximum time of follow-up ranged between 6 and 39 years across cohorts with a total of 4,749,481 person years of follow-up and 36,961 cancer incidences (Table 2).

Predictor	k	PY (events)	Psychosocial factor	Cigarettes	Product term	RERI (95% CI)	I^2
			B (95% CI)	B (95% CI)	B (95% CI)		
All cancers							
Depression diagnosis	16	2902753 (23712)	0.01 (-0.04, 0.07)	0.11 (0.08, 0.14)	-0.01 (-0.05, 0.03)	-0.01 (-0.05, 0.03)	53
Depressive symptoms	17	2491512 (21440)	-0.02 (-0.05, 0.02)	0.11 (0.08, 0.14)	0.00 (-0.01, 0.01)	0.00 (-0.01, 0.01)	58
Anxiety diagnosis	11	2539883 (19026)	-0.01 (-0.07, 0.06)	0.12 (0.08, 0.15)	0.02 (-0.03, 0.06)	0.02 (-0.03, 0.07)	56
Anxiety symptoms	8	1702487 (13820)	0.00 (-0.03, 0.02)	0.11 (0.08, 0.14)	0.00 (-0.01, 0.01)	0.00 (-0.01, 0.01)	34
Perceived social support	12	1243363 (11840)	0.00 (-0.03, 0.02)	0.12 (0.09, 0.16)	0.03 (0.01, 0.04)	0.03 (0.01, 0.05)	54
Recent loss event	9	1256212 (7117)	0.08 (-0.07, 0.23)	0.12 (0.07, 0.16)	0.02 (-0.15, 0.19)	0.03 (-0.17, 0.24)	57
Breast cancer							
Depression diagnosis	8	1538252 (3112)	-0.02 (-0.17, 0.13)	0.04 (0.00, 0.08)	-0.04 (-0.15, 0.06)	-0.04 (-0.15, 0.06)	0
Depressive symptoms	16	1460270 (2940)	-0.02 (-0.09, 0.05)	0.06 (0.02, 0.10)	-0.03 (-0.06, 0.00)	-0.03 (-0.07, 0.00)	33
Anxiety diagnosis	5	917908 (1666)	-0.10 (-0.29, 0.10)	0.04 (-0.02, 0.11)	-0.07 (-0.24, 0.10)	-0.07 (-0.23, 0.09)	0
Anxiety symptoms	7	964437 (1778)	-0.04 (-0.09, 0.01)	0.04 (-0.02, 0.10)	-0.02 (-0.07, 0.03)	NA (NA, NA)	0
Perceived social support	12	768944 (1722)	0.00 (-0.07, 0.07)	0.01 (-0.05, 0.06)	0.00 (-0.07, 0.07)	0.00 (-0.07, 0.07)	51
Recent loss event	3	609105 (1269)	0.03 (-0.14, 0.21)	0.02 (-0.04, 0.08)	0.01 (-0.13, 0.16)	0.01 (-0.14, 0.17)	0
Prostate cancer							
Depression diagnosis	5	719201 (2454)	-0.08 (-0.37, 0.20)	-0.09 (-0.16, -0.02)	0.00 (-0.17, 0.17)	NA (NA, NA)	19
Depressive symptoms	15	882156 (2892)	-0.02 (-0.07, 0.02)	-0.07 (-0.13, 0.00)	0.02 (-0.03, 0.06)	NA (NA, NA)	21
Anxiety diagnosis	3	607486 (1896)	0.10 (-0.38, 0.59)	-0.04 (-0.09, 0.02)	0.11 (-0.05, 0.28)	NA (NA, NA)	0
Anxiety symptoms	7	685197 (2079)	-0.03 (-0.08, 0.03)	-0.12 (-0.25, 0.01)	-0.09 (-0.30, 0.12)	NA (NA, NA)	60
Perceived social support	10	465350 (1465)	-0.02 (-0.07, 0.03)	-0.05 (-0.11, 0.01)	-0.01 (-0.09, 0.07)	NA (NA, NA)	45
Recent loss event	2	103695 (153)	0.37 (-0.22, 0.96)	-0.07 (-0.50, 0.35)	-0.07 (-0.82, 0.69)	NA (NA, NA)	38
Colorectal cancer							
Depression diagnosis	5	1450957 (1854)	0.13 (-0.06, 0.32)	0.05 (0.00, 0.09)	0.02 (-0.10, 0.15)	0.03 (-0.11, 0.18)	0
Depressive symptoms	15	2246371 (2427)	-0.11 (-0.25, 0.03)	0.07 (0.03, 0.11)	-0.06 (-0.13, 0.01)	-0.06 (-0.13, 0.01)	61
Anxiety diagnosis	5	2077507 (1949)	-0.27 (-0.57, 0.03)	0.03 (-0.02, 0.08)	0.11 (-0.01, 0.23)	0.09 (-0.02, 0.19)	13
Anxiety symptoms	7	1480531 (1615)	0.00 (-0.05, 0.06)	0.08 (-0.05, 0.20)	-0.03 (-0.11, 0.04)	-0.03 (-0.12, 0.05)	42
Perceived social support	11	1025932 (1181)	0.00 (-0.06, 0.06)	0.07 (0.02, 0.13)	0.01 (-0.03, 0.05)	0.01 (-0.03, 0.05)	0
Recent loss event	1	128363 (64)	0.08 (-0.68, 0.84)	0.09 (-0.13, 0.31)	-0.37 (-1.03, 0.29)	-0.36 (-0.94, 0.22)	
Lung cancer							
Depression diagnosis	6	2323592 (1482)	0.24 (-0.06, 0.54)	0.45 (0.31, 0.59)	-0.07 (-0.15, 0.02)	0.02 (-0.13, 0.18)	93
Depressive symptoms	15	2246371 (1751)	0.09 (-0.01, 0.20)	0.44 (0.37, 0.51)	-0.02 (-0.04, 0.00)	0.02 (-0.03, 0.07)	80
Anxiety diagnosis	5	2077507 (1264)	0.35 (0.10, 0.60)	0.43 (0.26, 0.61)	-0.03 (-0.11, 0.05)	0.16 (-0.01, 0.34)	94
Anxiety symptoms	7	1480531 (1189)	0.08 (0.02, 0.14)	0.45 (0.34, 0.56)	-0.02 (-0.04, 0.00)	0.01 (-0.03, 0.05)	83
Perceived social support	11	1025932 (1057)	0.06 (-0.01, 0.12)	0.47 (0.40, 0.54)	0.01 (-0.02, 0.04)	0.05 (0.01, 0.09)	60
Recent loss event	1	850018 (147)	0.60 (0.21, 1.00)	0.19 (0.13, 0.25)	-0.03 (-0.18, 0.12)	0.12 (-0.21, 0.44)	
Smoking related cancers							
Depression diagnosis	11	2744341 (7975)	0.16 (0.06, 0.26)	0.26 (0.22, 0.31)	-0.05 (-0.10, 0.00)	-0.02 (-0.09, 0.04)	75
Depressive symptoms	17	2491512 (7875)	0.02 (-0.04, 0.08)	0.25 (0.21, 0.29)	-0.01 (-0.02, 0.00)	-0.01 (-0.03, 0.01)	64
Anxiety diagnosis	11	2539883 (6800)	0.06 (-0.08, 0.19)	0.24 (0.18, 0.29)	0.02 (-0.04, 0.07)	0.04 (-0.04, 0.12)	71
Anxiety symptoms	8	1702487 (5196)	0.03 (0.00, 0.07)	0.26 (0.21, 0.30)	-0.01 (-0.03, 0.01)	0.00 (-0.03, 0.02)	47
Perceived social support	12	1243363 (4295)	0.01 (-0.02, 0.04)	0.27 (0.23, 0.31)	0.01 (-0.02, 0.04)	0.01 (-0.03, 0.05)	50
Recent loss event	5	1168479 (1909)	0.18 (-0.07, 0.44)	0.21 (0.14, 0.27)	-0.02 (-0.22, 0.18)	0.01 (-0.25, 0.28)	70
Alcohol related cancers							
Depression diagnosis	9	2627933 (6258)	0.07 (-0.04, 0.17)	0.09 (0.06, 0.12)	-0.03 (-0.10, 0.04)	-0.03 (-0.11, 0.05)	0
Depressive symptoms	17	2491512 (6116)	-0.01 (-0.06, 0.04)	0.10 (0.07, 0.13)	-0.02 (-0.04, 0.00)	-0.02 (-0.04, 0.00)	34
Anxiety diagnosis	11	2539883 (5839)	-0.07 (-0.18, 0.04)	0.09 (0.06, 0.12)	0.02 (-0.07, 0.10)	0.01 (-0.07, 0.09)	0
Anxiety symptoms	8	1702487 (3972)	-0.01 (-0.04, 0.02)	0.09 (0.06, 0.12)	0.00 (-0.03, 0.02)	-0.01 (-0.03, 0.02)	0
Perceived social support	12	1243363 (3399)	0.00 (-0.04, 0.05)	0.11 (0.07, 0.15)	0.01 (-0.02, 0.05)	0.02 (-0.03, 0.06)	23
Recent loss event	5	1168479 (2249)	0.01 (-0.12, 0.14)	0.06 (0.01, 0.10)	-0.06 (-0.20, 0.07)	-0.07 (-0.20, 0.07)	0

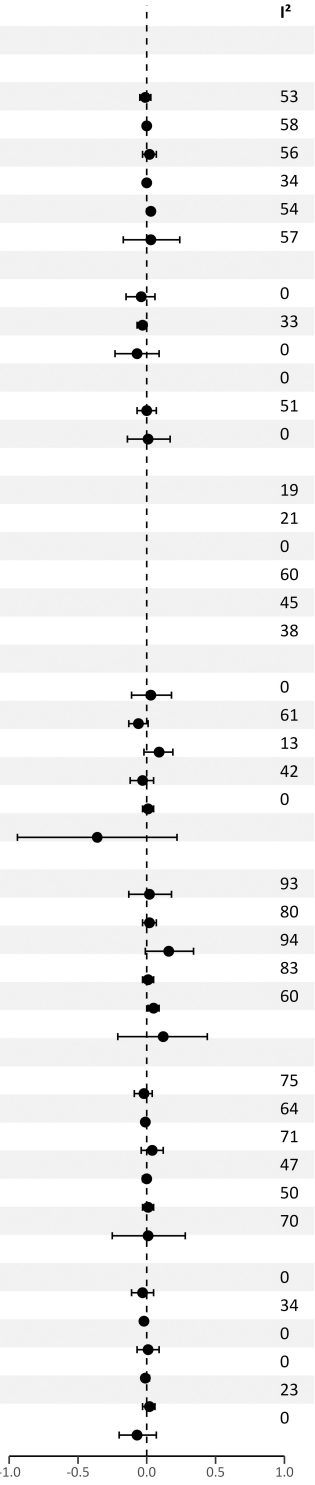

FIGURE 1 Depression, anxiety, psychosocial stress and number of cigarettes per week and their interaction in relation to cancer incidences, based on minimally-adjusted models. All models were adjusted for sex, birth year, country of origin and education. The RERI was not calculated if a psychosocial factor or health behavior was associated with decreased risk of cancer (i.e., a preventive effect). k: number of cohorts and sub cohorts included in meta-analysis; PY (events): total person years and number of cancer incidences for all cohorts combined; B: beta coefficient; RERI: Relative Excess Risk due to Interaction (with graphically displayed 95% CI); I^2: statistical measure of between study heterogeneity. NA, not available.

3.2 | Interaction and effect modification

Figures 1–4 present the results for psychosocial factors interacting with number of cigarettes (Figure 1), number of alcoholic drinks (Figure 2), physical activity (Figure 3) and BMI (Figure 4) based on the minimally-adjusted models correcting for sex, birth year, education and country of origin. Results for maximally-adjusted models are provided in Supplementary Figures S6–S9. Out of 168 models, we found

Predictor	k	PY (events)	Psychosocial factor	Alcoholic drinks	Product term	RERI (95% CI)	I^2
			B (95% CI)	B (95% CI)	B (95% CI)		
All cancers							
Depression diagnosis	16	3011239 (24325)	0.01 (-0.07, 0.10)	0.05 (0.02, 0.08)	-0.01 (-0.07, 0.06)	-0.01 (-0.08, 0.07)	47
Depressive symptoms	17	2546339 (21651)	0.00 (-0.04, 0.03)	0.04 (0.02, 0.07)	-0.01 (-0.02, 0.01)	-0.01 (-0.02, 0.01)	52
Anxiety diagnosis	11	2650784 (19688)	0.06 (0.00, 0.13)	0.05 (0.01, 0.09)	0.05 (-0.01, 0.10)	0.06 (-0.01, 0.12)	46
Anxiety symptoms	8	1679168 (13717)	0.00 (-0.03, 0.02)	0.04 (0.00, 0.08)	0.00 (-0.02, 0.01)	0.00 (-0.02, 0.02)	39
Perceived social support	12	1268382 (12134)	0.00 (-0.03, 0.03)	0.05 (0.01, 0.09)	0.00 (-0.01, 0.02)	0.00 (-0.01, 0.02)	56
Recent loss event	10	1607533 (8158)	0.08 (-0.03, 0.19)	0.05 (0.00, 0.10)	0.05 (-0.26, 0.36)	0.07 (-0.30, 0.44)	59
Breast cancer							
Depression diagnosis	9	1659980 (3381)	-0.05 (-0.23, 0.12)	0.06 (0.00, 0.11)	-0.04 (-0.23, 0.15)	-0.04 (-0.23, 0.14)	21
Depressive symptoms	16	1486793 (2995)	-0.01 (-0.08, 0.06)	0.06 (-0.02, 0.13)	0.00 (-0.04, 0.05)	0.00 (-0.04, 0.05)	41
Anxiety diagnosis	7	1536624 (3016)	-0.09 (-0.25, 0.06)	0.04 (-0.03, 0.11)	0.04 (-0.09, 0.16)	0.03 (-0.09, 0.15)	0
Anxiety symptoms	8	1003013 (1873)	-0.04 (-0.08, 0.01)	0.03 (-0.03, 0.09)	0.01 (-0.04, 0.06)	NA (NA, NA)	0
Perceived social support	12	778369 (1743)	0.02 (-0.06, 0.10)	0.07 (-0.03, 0.16)	0.03 (-0.02, 0.09)	0.04 (-0.02, 0.10)	48
Recent loss event	4	749717 (1524)	0.05 (-0.13, 0.22)	0.08 (-0.02, 0.17)	0.00 (-0.21, 0.21)	0.00 (-0.24, 0.25)	0
Prostate cancer							
Depression diagnosis	7	1122165 (2964)	-0.05 (-0.25, 0.15)	-0.01 (-0.06, 0.03)	0.01 (-0.15, 0.17)	0.01 (-0.14, 0.17)	0
Depressive symptoms	16	1057147 (3078)	-0.02 (-0.07, 0.02)	0.00 (-0.06, 0.06)	0.01 (-0.02, 0.05)	0.01 (-0.02, 0.05)	0
Anxiety diagnosis	6	1018711 (2470)	0.19 (-0.14, 0.51)	0.04 (-0.04, 0.12)	0.04 (-0.10, 0.18)	0.06 (-0.12, 0.23)	32
Anxiety symptoms	7	676155 (2060)	-0.05 (-0.14, 0.03)	0.03 (-0.04, 0.11)	0.01 (-0.03, 0.05)	0.01 (-0.03, 0.05)	0
Perceived social support	11	490013 (1534)	-0.01 (-0.06, 0.04)	0.01 (-0.06, 0.07)	0.02 (-0.02, 0.06)	0.02 (-0.02, 0.06)	17
Recent loss event	3	491257 (617)	0.15 (-0.38, 0.69)	0.06 (-0.01, 0.13)	0.04 (-0.24, 0.33)	0.07 (-0.26, 0.39)	39
Colorectal cancer							
Depression diagnosis	7	2489679 (2354)	0.13 (-0.05, 0.31)	0.03 (-0.02, 0.09)	0.05 (-0.09, 0.19)	0.06 (-0.11, 0.24)	0
Depressive symptoms	15	2300488 (2424)	-0.04 (-0.10, 0.01)	0.07 (0.02, 0.13)	-0.03 (-0.08, 0.03)	-0.03 (-0.08, 0.03)	15
Anxiety diagnosis	5	2189885 (1980)	-0.08 (-0.31, 0.15)	0.04 (-0.01, 0.09)	0.16 (-0.03, 0.36)	0.17 (-0.06, 0.40)	0
Anxiety symptoms	7	1456309 (1587)	0.01 (-0.03, 0.06)	0.05 (0.00, 0.10)	0.02 (-0.02, 0.06)	0.02 (-0.02, 0.06)	0
Perceived social support	11	1049845 (1209)	-0.01 (-0.07, 0.05)	0.02 (-0.04, 0.08)	0.00 (-0.05, 0.06)	0.00 (-0.05, 0.06)	0
Recent loss event	2	1106636 (570)	-0.11 (-0.37, 0.15)	0.10 (0.02, 0.18)	-0.15 (-0.40, 0.10)	-0.15 (-0.37, 0.07)	0
Lung cancer							
Depression diagnosis	7	2489679 (1619)	0.45 (0.23, 0.68)	0.15 (0.07, 0.22)	-0.10 (-0.32, 0.12)	-0.08 (-0.43, 0.27)	24
Depressive symptoms	15	2300488 (1793)	0.16 (0.07, 0.24)	0.16 (0.09, 0.22)	-0.01 (-0.05, 0.02)	0.01 (-0.04, 0.05)	28
Anxiety diagnosis	5	2189885 (1367)	0.43 (0.21, 0.65)	0.16 (0.07, 0.24)	-0.04 (-0.25, 0.16)	0.01 (-0.35, 0.38)	29
Anxiety symptoms	7	1456309 (1186)	0.13 (0.06, 0.21)	0.09 (0.01, 0.16)	-0.02 (-0.07, 0.03)	-0.01 (-0.08, 0.05)	16
Perceived social support	11	1049845 (1089)	0.09 (0.03, 0.15)	0.15 (0.07, 0.24)	0.01 (-0.03, 0.05)	0.03 (-0.02, 0.07)	0
Recent loss event	1	977495 (259)	0.41 (0.08, 0.74)	0.20 (0.07, 0.33)	0.17 (-0.08, 0.42)	0.45 (-0.02, 0.92)	
Smoking related cancers							
Depression diagnosis	12	2861008 (8277)	0.17 (0.06, 0.28)	0.08 (0.04, 0.13)	-0.05 (-0.15, 0.05)	-0.05 (-0.17, 0.07)	35
Depressive symptoms	17	2546339 (7939)	0.03 (-0.02, 0.08)	0.08 (0.05, 0.12)	0.00 (-0.02, 0.02)	0.00 (-0.02, 0.02)	44
Anxiety diagnosis	11	2650784 (7052)	0.16 (0.03, 0.30)	0.08 (0.03, 0.13)	0.04 (-0.06, 0.13)	0.06 (-0.06, 0.19)	38
Anxiety symptoms	8	1679168 (5159)	0.05 (0.00, 0.10)	0.07 (0.02, 0.11)	-0.01 (-0.04, 0.02)	-0.01 (-0.04, 0.02)	20
Perceived social support	12	1268382 (4437)	0.03 (-0.01, 0.06)	0.11 (0.06, 0.16)	0.01 (-0.02, 0.04)	0.02 (-0.01, 0.05)	25
Recent loss event	5	1293657 (2191)	0.23 (0.03, 0.44)	0.11 (0.06, 0.15)	0.04 (-0.08, 0.15)	0.08 (-0.07, 0.24)	34
Alcohol related cancers							
Depression diagnosis	11	2851390 (6836)	0.07 (-0.04, 0.17)	0.07 (0.02, 0.11)	0.02 (-0.07, 0.12)	0.03 (-0.08, 0.15)	27
Depressive symptoms	17	2546339 (6182)	0.00 (-0.05, 0.05)	0.08 (0.04, 0.12)	0.00 (-0.03, 0.02)	-0.01 (-0.03, 0.02)	35
Anxiety diagnosis	11	2650784 (6098)	-0.02 (-0.13, 0.08)	0.07 (0.02, 0.12)	0.13 (0.01, 0.25)	0.14 (0.00, 0.28)	12
Anxiety symptoms	8	1679168 (3944)	-0.01 (-0.05, 0.03)	0.07 (0.02, 0.12)	0.02 (-0.01, 0.05)	0.02 (-0.02, 0.05)	0
Perceived social support	12	1268382 (3473)	0.03 (-0.01, 0.06)	0.09 (0.03, 0.15)	0.02 (-0.01, 0.05)	0.02 (-0.01, 0.06)	33
Recent loss event	5	1293657 (2515)	0.06 (-0.06, 0.18)	0.12 (0.07, 0.16)	0.01 (-0.11, 0.13)	0.02 (-0.12, 0.17)	0

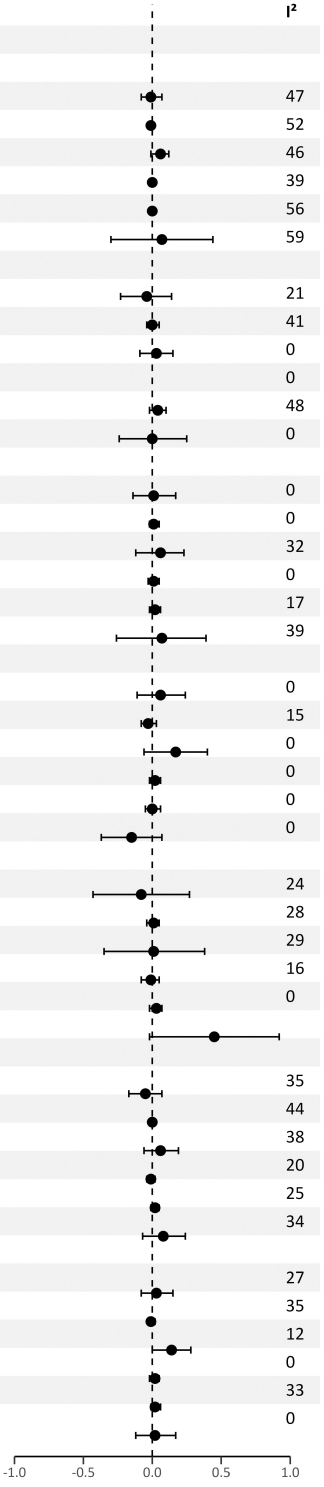

FIGURE 2 Depression, anxiety, psychosocial stress and number of alcoholic drinks per week and their interaction in relation to cancer incidences, based on minimally-adjusted models. All models were adjusted for sex, birth year, country of origin and education. The RERI was not calculated if a psychosocial factor or health behavior was associated with decreased risk of cancer (i.e., a preventive effect). k: number of cohorts and sub cohorts included in meta-analysis; PY (events): total person years and number of cancer incidences for all cohorts combined; B: beta coefficient; RERI: Relative Excess Risk due to Interaction (with graphically displayed 95% CI); I^2: statistical measure of between study heterogeneity. NA, not available.

no statistical evidence for interaction effects between psychosocial factors, health behaviors and cancer incidence. We found four small modification effects that were statistically significant. First, the effect of number of cigarettes on overall cancer incidence was larger among persons with lower perceived social support (RERI: 0.03, 95% CI: 0.01 to 0.05; AP: 3%, 95% CI: 1% to 4%; multiplicative effect: HR: 1.03,

Predictor	k	PY (events)	Psychosocial factor	Physical activity	Product term	RERI (95% CI)	I^2
			B (95% CI)	B (95% CI)	B (95% CI)		
All cancers							
Depression diagnosis	14	2940515 (22934)	0.01 (-0.07, 0.09)	0.00 (-0.02, 0.02)	0.02 (-0.04, 0.08)	0.02 (-0.04, 0.08)	31
Depressive symptoms	15	2463736 (20302)	-0.01 (-0.04, 0.02)	0.01 (0.00, 0.03)	-0.01 (-0.03, 0.00)	-0.01 (-0.03, 0.00)	32
Anxiety diagnosis	9	2592582 (18515)	0.04 (-0.02, 0.11)	0.00 (-0.03, 0.02)	0.01 (-0.05, 0.07)	0.01 (-0.05, 0.07)	11
Anxiety symptoms	8	1682200 (13514)	0.00 (-0.03, 0.02)	0.00 (-0.03, 0.03)	0.00 (-0.03, 0.02)	0.00 (-0.03, 0.02)	27
Perceived social support	10	1111939 (10493)	-0.02 (-0.05, 0.01)	0.01 (-0.02, 0.03)	-0.02 (-0.04, 0.00)	-0.02 (-0.04, 0.00)	0
Recent loss event	7	1457726 (6742)	0.16 (-0.02, 0.33)	-0.01 (-0.06, 0.03)	-0.09 (-0.24, 0.07)	-0.10 (-0.26, 0.07)	17
Breast cancer							
Depression diagnosis	9	1632748 (3308)	-0.01 (-0.19, 0.16)	0.00 (-0.05, 0.05)	0.04 (-0.10, 0.19)	0.04 (-0.11, 0.19)	10
Depressive symptoms	14	1438184 (2844)	-0.03 (-0.08, 0.03)	0.02 (-0.02, 0.06)	-0.01 (-0.06, 0.04)	-0.01 (-0.06, 0.03)	38
Anxiety diagnosis	7	1515815 (2964)	-0.02 (-0.16, 0.12)	-0.01 (-0.07, 0.05)	-0.05 (-0.23, 0.13)	-0.04 (-0.21, 0.12)	28
Anxiety symptoms	8	1002368 (1862)	-0.05 (-0.10, 0.00)	0.03 (-0.03, 0.08)	-0.05 (-0.13, 0.03)	NA (NA, NA)	23
Perceived social support	10	685336 (1509)	-0.02 (-0.11, 0.07)	0.05 (-0.01, 0.10)	-0.05 (-0.16, 0.06)	-0.05 (-0.16, 0.06)	54
Recent loss event	3	685266 (1418)	0.05 (-0.11, 0.21)	-0.06 (-0.12, 0.00)	0.01 (-0.14, 0.17)	0.01 (-0.15, 0.16)	0
Prostate cancer							
Depression diagnosis	7	1125719 (2898)	0.02 (-0.22, 0.26)	-0.06 (-0.10, -0.01)	0.05 (-0.10, 0.19)	0.05 (-0.10, 0.19)	10
Depressive symptoms	14	1023637 (2913)	0.00 (-0.03, 0.04)	-0.04 (-0.08, 0.00)	-0.06 (-0.10, -0.02)	-0.06 (-0.09, -0.02)	10
Anxiety diagnosis	5	1017329 (2364)	0.20 (-0.10, 0.51)	-0.07 (-0.12, -0.01)	-0.09 (-0.27, 0.09)	-0.11 (-0.32, 0.09)	24
Anxiety symptoms	7	679832 (2046)	-0.01 (-0.07, 0.04)	-0.03 (-0.07, 0.01)	-0.02 (-0.08, 0.03)	-0.02 (-0.07, 0.03)	0
Perceived social support	9	426604 (1338)	0.00 (-0.06, 0.06)	-0.01 (-0.06, 0.05)	-0.02 (-0.08, 0.04)	-0.02 (-0.07, 0.04)	12
Recent loss event	3	482153 (565)	0.17 (-0.27, 0.62)	-0.10 (-0.18, -0.03)	-0.01 (-0.19, 0.18)	-0.02 (-0.21, 0.16)	0
Colorectal cancer							
Depression diagnosis	7	2464851 (2292)	0.12 (-0.06, 0.31)	0.04 (0.00, 0.09)	0.00 (-0.15, 0.16)	0.01 (-0.17, 0.19)	0
Depressive symptoms	13	2217094 (2237)	-0.02 (-0.06, 0.03)	0.05 (0.01, 0.10)	-0.02 (-0.06, 0.02)	-0.02 (-0.06, 0.02)	0
Anxiety diagnosis	4	2150043 (1854)	-0.07 (-0.29, 0.14)	0.05 (0.00, 0.10)	-0.01 (-0.23, 0.21)	-0.02 (-0.23, 0.19)	0
Anxiety symptoms	7	1458591 (1560)	0.01 (-0.04, 0.06)	0.07 (0.00, 0.14)	-0.01 (-0.07, 0.06)	-0.01 (-0.07, 0.06)	0
Perceived social support	9	905984 (991)	-0.01 (-0.07, 0.05)	0.06 (-0.02, 0.15)	-0.03 (-0.09, 0.02)	-0.04 (-0.09, 0.02)	0
Recent loss event	2	1068303 (554)	-0.20 (-0.57, 0.17)	0.03 (-0.06, 0.12)	0.12 (-0.47, 0.70)	0.10 (-0.43, 0.63)	0
Lung cancer							
Depression diagnosis	7	2464851 (1561)	0.37 (0.15, 0.58)	0.09 (0.04, 0.15)	-0.06 (-0.27, 0.15)	-0.05 (-0.37, 0.26)	18
Depressive symptoms	12	2201824 (1607)	0.16 (0.08, 0.25)	0.07 (0.00, 0.15)	-0.06 (-0.16, 0.04)	-0.06 (-0.17, 0.05)	44
Anxiety diagnosis	4	2150043 (1244)	0.40 (0.18, 0.63)	0.09 (0.02, 0.15)	-0.10 (-0.52, 0.32)	-0.11 (-0.73, 0.51)	62
Anxiety symptoms	7	1458591 (1164)	0.14 (0.08, 0.21)	-0.06 (-0.20, 0.07)	-0.04 (-0.11, 0.03)	-0.05 (-0.13, 0.03)	49
Perceived social support	8	890720 (864)	0.10 (0.04, 0.17)	-0.04 (-0.18, 0.09)	0.00 (-0.06, 0.06)	0.00 (-0.06, 0.05)	37
Recent loss event	1	974562 (252)	0.45 (0.13, 0.77)	0.06 (-0.08, 0.20)	-0.05 (-0.33, 0.23)	-0.05 (-0.46, 0.36)	
Smoking related cancers							
Depression diagnosis	11	2812808 (7784)	0.15 (0.04, 0.26)	0.03 (0.00, 0.07)	-0.09 (-0.20, 0.02)	-0.10 (-0.22, 0.02)	22
Depressive symptoms	15	2463736 (7287)	0.04 (0.00, 0.09)	0.03 (0.00, 0.07)	-0.03 (-0.06, 0.00)	-0.03 (-0.06, 0.00)	28
Anxiety diagnosis	9	2592582 (6492)	0.19 (0.05, 0.34)	0.03 (0.00, 0.07)	-0.07 (-0.24, 0.10)	-0.07 (-0.28, 0.13)	28
Anxiety symptoms	8	1682200 (5079)	0.06 (0.01, 0.11)	0.01 (-0.05, 0.08)	-0.03 (-0.08, 0.03)	-0.03 (-0.09, 0.03)	44
Perceived social support	10	1111939 (3663)	0.01 (-0.03, 0.06)	0.00 (-0.06, 0.07)	-0.04 (-0.09, 0.00)	-0.04 (-0.08, 0.00)	43
Recent loss event	3	1167419 (1723)	0.24 (-0.03, 0.51)	0.06 (-0.02, 0.14)	-0.20 (-0.48, 0.09)	-0.23 (-0.56, 0.11)	39
Alcohol related cancers							
Depression diagnosis	10	2805518 (6562)	0.06 (-0.04, 0.17)	0.03 (-0.01, 0.06)	0.00 (-0.12, 0.11)	0.00 (-0.13, 0.12)	13
Depressive symptoms	15	2463736 (5790)	-0.01 (-0.04, 0.03)	0.04 (0.02, 0.07)	-0.02 (-0.05, 0.01)	-0.02 (-0.05, 0.01)	14
Anxiety diagnosis	9	2592582 (5750)	-0.02 (-0.13, 0.08)	0.02 (-0.02, 0.07)	-0.05 (-0.18, 0.09)	-0.05 (-0.18, 0.08)	0
Anxiety symptoms	8	1682200 (3906)	0.00 (-0.04, 0.03)	0.04 (0.01, 0.08)	-0.04 (-0.08, 0.01)	-0.04 (-0.08, 0.01)	0
Perceived social support	10	1111939 (2962)	0.01 (-0.03, 0.05)	0.07 (0.03, 0.11)	-0.05 (-0.13, 0.02)	-0.06 (-0.13, 0.02)	30
Recent loss event	3	1167419 (2180)	0.01 (-0.13, 0.15)	-0.01 (-0.07, 0.05)	-0.06 (-0.26, 0.15)	-0.06 (-0.25, 0.13)	0

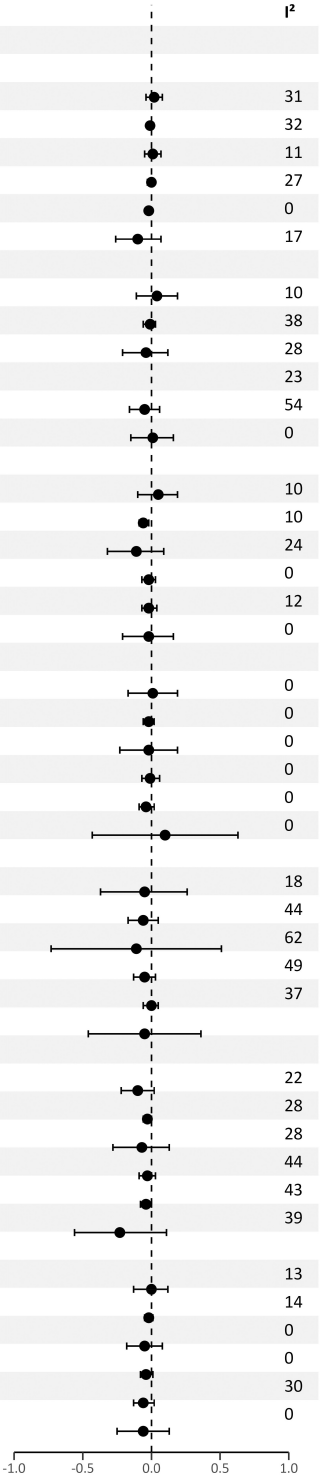

FIGURE 3 Depression, anxiety, psychosocial stress and hours of physical activity per week and their interaction in relation to cancer incidences, based on minimally-adjusted models. Physical activity was reversely coded so that a higher score represents less physical activity. All models were adjusted for sex, birth year, country of origin and education. The RERI was not calculated if a psychosocial factor or health behavior was associated with decreased risk of cancer (i.e., a preventive effect). k: number of cohorts and sub cohorts included in meta-analysis; PY (events): total person years and number of cancer incidences for all cohorts combined; B: beta coefficient; RERI: Relative Excess Risk due to Interaction (with graphically displayed 95% CI); I^2: statistical measure of between study heterogeneity. NA, not available.

95% CI: 1.01 to 1.04; Figure 1). Similarly, the effect of number of cigarettes on lung cancer incidence was also larger among persons with lower perceived social support (RERI: 0.05, 95% CI: 0.01 to 0.09; AP: 3%, 95% CI: 0% to 5%; multiplicative effect: HR: 1.01, 95% CI: 0.98 to 1.04; Figure 1). Both modification effects remained in the maximally-adjusted models (Supplementary Figure S6). Third, the effect of

Predictor	k	PY (events)	Psychosocial factor	BMI	Product term	RERI (95% CI)	I^2
			B (95% CI)	B (95% CI)	B (95% CI)		
All cancers							
Depression diagnosis	15	2985697 (22786)	-0.01 (-0.12, 0.10)	0.03 (0.01, 0.04)	-0.01 (-0.09, 0.07)	-0.01 (-0.09, 0.07)	29
Depressive symptoms	16	2441532 (19783)	-0.01 (-0.05, 0.03)	0.02 (0.01, 0.04)	0.00 (-0.02, 0.02)	0.00 (-0.02, 0.02)	46
Anxiety diagnosis	11	2726406 (20039)	0.06 (0.00, 0.12)	0.03 (0.01, 0.05)	-0.01 (-0.09, 0.07)	-0.01 (-0.09, 0.07)	0
Anxiety symptoms	8	1660918 (13750)	0.00 (-0.03, 0.03)	0.02 (0.00, 0.04)	0.00 (-0.01, 0.02)	0.00 (-0.02, 0.02)	21
Perceived social support	11	1123989 (9789)	-0.01 (-0.04, 0.02)	0.02 (0.00, 0.05)	0.02 (-0.01, 0.04)	0.02 (-0.01, 0.04)	0
Recent loss event	10	1661799 (8405)	0.14 (0.01, 0.27)	0.03 (0.01, 0.06)	-0.09 (-0.17, -0.01)	-0.09 (-0.19, 0.00)	25
Breast cancer							
Depression diagnosis	8	1619895 (3267)	0.02 (-0.14, 0.17)	0.02 (-0.01, 0.05)	-0.02 (-0.14, 0.09)	-0.02 (-0.14, 0.09)	0
Depressive symptoms	15	1410707 (2810)	0.00 (-0.06, 0.07)	0.06 (0.00, 0.12)	-0.01 (-0.04, 0.03)	-0.01 (-0.04, 0.03)	44
Anxiety diagnosis	7	1551629 (3081)	-0.09 (-0.25, 0.07)	0.05 (-0.03, 0.12)	-0.16 (-0.42, 0.10)	-0.15 (-0.36, 0.07)	30
Anxiety symptoms	8	974958 (1857)	-0.05 (-0.10, -0.01)	0.03 (-0.04, 0.11)	-0.01 (-0.06, 0.05)	NA (NA, NA)	32
Perceived social support	11	691141 (1495)	-0.02 (-0.09, 0.05)	0.06 (-0.01, 0.13)	0.01 (-0.04, 0.06)	0.01 (-0.04, 0.06)	30
Recent loss event	4	777798 (1592)	-0.01 (-0.21, 0.19)	0.04 (-0.02, 0.11)	0.06 (-0.07, 0.19)	0.07 (-0.08, 0.21)	0
Prostate cancer							
Depression diagnosis	6	1141086 (2813)	-0.01 (-0.26, 0.23)	-0.07 (-0.13, 0.00)	0.02 (-0.28, 0.33)	NA (NA, NA)	44
Depressive symptoms	15	1028425 (2890)	-0.02 (-0.05, 0.02)	-0.03 (-0.07, 0.02)	0.01 (-0.05, 0.06)	NA (NA, NA)	0
Anxiety diagnosis	6	1083079 (2542)	0.17 (-0.07, 0.40)	-0.07 (-0.12, -0.01)	0.15 (-0.13, 0.43)	NA (NA, NA)	45
Anxiety symptoms	7	685960 (2097)	-0.03 (-0.09, 0.03)	-0.07 (-0.12, -0.01)	-0.02 (-0.08, 0.05)	NA (NA, NA)	0
Perceived social support	10	432849 (1254)	0.00 (-0.06, 0.06)	-0.04 (-0.11, 0.04)	0.04 (-0.02, 0.09)	NA (NA, NA)	31
Recent loss event	3	543386 (655)	0.16 (-0.22, 0.54)	-0.08 (-0.19, 0.02)	-0.24 (-0.55, 0.07)	NA (NA, NA)	0
Colorectal cancer							
Depression diagnosis	6	2488829 (2249)	0.14 (-0.07, 0.35)	0.09 (0.02, 0.16)	-0.09 (-0.38, 0.20)	-0.09 (-0.42, 0.23)	17
Depressive symptoms	14	2218210 (2278)	-0.05 (-0.13, 0.03)	0.09 (0.01, 0.17)	0.04 (0.00, 0.08)	0.04 (0.00, 0.08)	20
Anxiety diagnosis	5	2286783 (2052)	-0.11 (-0.35, 0.13)	0.08 (0.01, 0.14)	-0.17 (-0.43, 0.09)	-0.16 (-0.37, 0.05)	0
Anxiety symptoms	7	1459597 (1623)	0.01 (-0.04, 0.06)	0.09 (0.04, 0.14)	0.00 (-0.05, 0.04)	0.00 (-0.05, 0.04)	0
Perceived social support	10	917106 (988)	-0.02 (-0.09, 0.05)	0.04 (-0.06, 0.14)	0.08 (0.01, 0.15)	0.09 (0.02, 0.15)	33
Recent loss event	2	1183421 (603)	-0.13 (-0.40, 0.14)	0.17 (0.09, 0.26)	0.00 (-0.25, 0.25)	-0.02 (-0.27, 0.23)	0
Lung cancer							
Depression diagnosis	6	2488829 (1487)	0.61 (0.40, 0.81)	-0.22 (-0.36, -0.08)	-0.08 (-0.29, 0.12)	NA (NA, NA)	29
Depressive symptoms	14	2218210 (1645)	0.19 (0.07, 0.31)	-0.21 (-0.30, -0.11)	-0.05 (-0.09, 0.00)	NA (NA, NA)	52
Anxiety diagnosis	5	2286783 (1393)	0.49 (0.29, 0.69)	-0.20 (-0.33, -0.07)	0.14 (-0.07, 0.34)	NA (NA, NA)	41
Anxiety symptoms	7	1459597 (1205)	0.13 (0.06, 0.20)	-0.19 (-0.32, -0.05)	-0.02 (-0.08, 0.04)	NA (NA, NA)	28
Perceived social support	10	917106 (899)	0.08 (0.02, 0.14)	-0.23 (-0.32, -0.13)	-0.02 (-0.09, 0.05)	NA (NA, NA)	15
Recent loss event	1	1054501 (270)	0.46 (0.16, 0.77)	-0.07 (-0.22, 0.09)	-0.17 (-0.49, 0.15)	NA (NA, NA)	
Smoking related cancers							
Depression diagnosis	11	2837126 (7801)	0.20 (0.09, 0.32)	0.03 (0.00, 0.06)	-0.12 (-0.23, -0.02)	-0.14 (-0.26, -0.03)	0
Depressive symptoms	16	2441532 (7356)	0.04 (-0.02, 0.10)	0.03 (0.00, 0.05)	-0.02 (-0.04, 0.01)	-0.02 (-0.04, 0.01)	46
Anxiety diagnosis	11	2726406 (7207)	0.17 (-0.02, 0.36)	0.03 (0.00, 0.07)	0.01 (-0.15, 0.18)	0.02 (-0.17, 0.21)	27
Anxiety symptoms	8	1660918 (5221)	0.06 (0.01, 0.11)	0.02 (-0.01, 0.06)	-0.01 (-0.04, 0.01)	-0.01 (-0.04, 0.02)	17
Perceived social support	11	1123989 (3628)	0.02 (-0.02, 0.05)	0.03 (0.00, 0.07)	0.02 (-0.01, 0.05)	0.02 (-0.01, 0.05)	0
Recent loss event	5	1371826 (2268)	0.23 (0.01, 0.45)	0.06 (-0.04, 0.16)	-0.16 (-0.34, 0.03)	-0.18 (-0.40, 0.04)	41
Alcohol related cancers							
Depression diagnosis	10	2827513 (6548)	0.06 (-0.05, 0.18)	0.07 (0.04, 0.09)	-0.05 (-0.15, 0.05)	-0.06 (-0.16, 0.05)	0
Depressive symptoms	16	2441532 (5777)	0.00 (-0.06, 0.05)	0.06 (0.03, 0.09)	0.00 (-0.03, 0.03)	0.00 (-0.03, 0.03)	42
Anxiety diagnosis	11	2726406 (6231)	-0.03 (-0.15, 0.08)	0.08 (0.03, 0.12)	-0.10 (-0.28, 0.07)	-0.10 (-0.27, 0.06)	21
Anxiety symptoms	8	1660918 (3956)	-0.01 (-0.05, 0.03)	0.06 (0.02, 0.09)	-0.02 (-0.06, 0.02)	-0.02 (-0.06, 0.02)	11
Perceived social support	11	1123989 (2911)	0.00 (-0.05, 0.04)	0.07 (0.03, 0.12)	0.03 (-0.01, 0.06)	0.03 (-0.01, 0.07)	0
Recent loss event	5	1371826 (2616)	0.02 (-0.10, 0.14)	0.10 (0.03, 0.16)	-0.05 (-0.19, 0.10)	-0.05 (-0.20, 0.10)	0

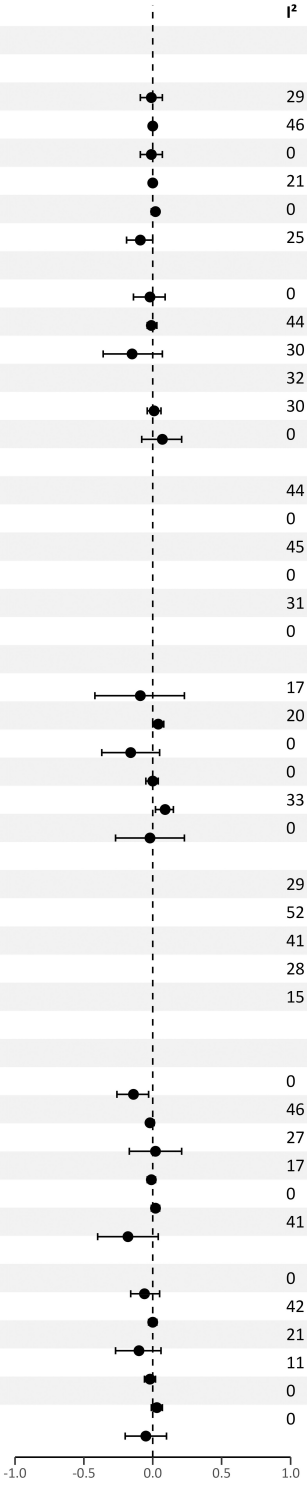

FIGURE 4 Depression, anxiety, psychosocial stress and body mass index (BMI) and their interaction in relation to cancer incidences, based on minimally-adjusted models. All models were adjusted for sex, birth year, country of origin and education. The RERI was not calculated if a psychosocial factor or health behavior was associated with decreased risk of cancer (i.e., a preventive effect). k: number of cohorts and sub cohorts included in meta-analysis; PY (events): total person years and number of cancer incidences for all cohorts combined; B: beta coefficient; RERI: Relative Excess Risk due to Interaction (with graphically displayed 95% CI); I^2: statistical measure of between study heterogeneity. NA, not available.

alcoholic drinks on alcohol-related cancer incidence was larger among people with an anxiety diagnosis (RERI: 0.14, 95% CI: 0.00 to 0.28; AP: 12%, 95% CI: 1% to 22%; multiplicative effect: HR: 1.14, 95% CI: 1.01 to 1.28; Figure 2). This modification effect did not reach significance in the maximally-adjusted model (Supplementary Figure S7). Fourth, the effect of BMI on colorectal cancer incidence was larger

among persons with higher depressive symptoms, but only when the multiplicative scale was considered (RERI: 0.04, 95% CI: −0.001 to 0.08; AP: 4%, 95% CI: −0.03% to 7%; multiplicative effect: HR: 1.04, 95% CI: 1.001 to 1.08; Figure 4) and this effect remained in the maximally-adjusted model (Supplementary Figure S9).

Substantial between-study heterogeneity (I^2 >50%) was found predominantly for models including number of cigarettes and lung, smoking-related or overall cancer as outcome. In all cohorts number of cigarettes was associated with increased risk of these cancer outcomes, but effect sizes varied.

In exploratory analyses, including an additional 576 models, we tested potential interaction/effect modification for additional psychosocial factors (general distress, neuroticism and relationship status) and health behaviors (smoking, ever smoked, pack years, sedentary behavior, short sleep duration, long sleep duration, sleep quality and alcohol use among persons who consume at least one alcoholic drink per week). For 12 exploratory models involving either sleep quality or sleep duration, interaction and effect modification could not be tested due to insufficient data across cohorts. Two small additive interaction effects were identified in the minimally-adjusted models: the combined effects of depression symptoms and pack years on lung cancer incidence (RERI: 0.04, 95% CI: 0.00 to 0.08; AP: 2%, 95% CI: 0% to 4%; HR: 0.98, 95% CI: 0.96 to 1.00) and of anxiety diagnosis and pack years on lung cancer incidence (RERI: 0.22, 95% CI: 0.02 to 0.43; AP: 9%, 95% CI: 2% to 17%; HR: 0.97, 95% CI: 0.88 to 1.05) were larger than the sum of the individual effects (Supplementary Figure S22). For depression symptoms and pack years, this additive effect remained significant in the maximally-adjusted model (RERI: 0.05, 95% CI: 0.00 to 0.09; Supplementary Figure S23). Modification effects of psychosocial factors on health behaviors were found for 13 minimally-adjusted models. Five psychosocial factors increased the effect of ever smoked on lung cancer incidence, but only for depression symptoms this modification effect remained significant in the maximally-adjusted model (Supplementary Figures S20, S21, S44 and S45). All other modification effects were small and did not show a distinct pattern of certain combinations of psychosocial factors, health behaviors or cancer outcomes involved (see Supplementary Figures S10–S49).

4 | DISCUSSION

This IPD meta-analysis of 22 cohorts and sub cohorts is the first large study to systematically examine potential interaction and effect modification of various psychosocial factors and health behaviors, in relation to cancer incidence. We examined a large number of potential interactions for seven cancer outcomes but found only support for one of them in exploratory analyses. A few instances of effect modification of psychosocial factors on the relation between health behaviors and cancer incidence were found but effect estimates were small and results were inconsistent across factors and cancer outcomes involved. Overall, these results provide no support for different effects of health behaviors on cancer risks in people with and without depression, anxiety or psychosocial stress.

To date, few studies have examined interaction or effect modification between depression or other psychosocial factors and health behaviors in relation to cancer incidence and reported inconclusive findings.[11–13] Previous studies were limited by only examining effects of psychosocial factors within subgroups without formally testing for subgroup differences. In addition, when interaction or effect modification was tested in these studies, this was done on a multiplicative scale, while interaction on an additive scale often better reflects biological interaction and is more relevant to public health.[35,39] Most previous research contained too small samples to study interaction or effect modification as much larger sample sizes are required to identify interaction effects compared to main effects.[40,41]

The absence of interaction between psychosocial factors and health behaviors leading to cancer incidence is contrary to our hypothesis. One potential explanation is that the pathways of psychosocial factors leading to cancer incidence do not overlap with biological pathways of health behaviors leading to cancer development. The role of previously hypothesized biological mechanisms[16,17] may be limited. Instead, the relation between psychosocial factors and cancer incidence may be more likely to be explained by behavioral pathways. For example, depression and anxiety may lead to increased smoking, alcohol use and other unhealthy behaviors[23–27] which subsequently increase the risk of cancer incidence.[18–21] Within the PSY-CA study we indeed found evidence for such a behavioral pathway: smoking, and to a lesser extent also physical inactivity, partially mediated the relation of depression and anxiety with lung and smoking-related cancer incidence.[42]

An alternative explanation may be that interaction between psychosocial factors and health behaviors may only appear when people suffer from psychosocial stress and have unhealthy behaviors for a prolonged period of time.[43] In the present study, psychosocial factors and health behaviors were assessed only one point in time. Longitudinal studies using repeated measures of psychosocial stress and health behaviors may be able to shed light on this potential explanation. However, we regard this an unlikely explanation for the current results given the substantial stability of depression and anxiety symptom scores over time as previously reported.[44] In addition, we also examined interaction effects for relatively stable factors, like neuroticism, which is considered a trait, or for pack years, which is a summary measure of history of smoking behavior.

Regarding the modifying role of psychosocial factors, we found that for a few specific combinations our (statistical) definition of effect modification was met. However, these are likely chance findings given the absence of multiple testing correction, the small effect sizes and the absence of a distinct pattern for specific psychosocial factors, health behaviors or cancer types. Based on our findings, there is no indication that individuals who experience depression, anxiety or psychosocial stress are particularly vulnerable to the negative effects of unhealthy behaviors on cancer development. The behavioral risk profile for cancer incidence is similar to those without depression, anxiety or psychosocial stress. As unhealthy behaviors are more prevalent among these individuals,[23–27] and unhealthy behaviors are risk factors for a range of health outcomes beyond cancer, they nevertheless are an important target population for promotion of healthy lifestyles.

A major strength of this study is the utilization of harmonized IPD of multiple large cohort studies, which provided sufficient statistical power to study potential interaction and effect modification for a large number of psychosocial factors and health behaviors.[14] Second, all cohorts had a prospective study design and excluded individuals with a diagnosed cancer at baseline. Third, assessment of depression, anxiety and other psychosocial factors were predominantly based on validated instruments. Fourth, site-specific cancers as well as smoking-related, alcohol-related and overall cancers were examined. Fifth, cancer incidence was derived through linkage with national or regional cancer registries with high levels of coverage. Finally, we included a wide range of health behaviors and behavior-related factors and adjusted for many potential confounding factors.

Limitations include that the results are based on complete-case analyses as participants with missing values on psychosocial factors, health behaviors and covariates were excluded from the models. Although multiple imputation was considered to deal with missing values under the Missing At Random assumption, developing cohort-specific multiple imputation models for 22 cohorts was considered being unfeasible. Second, for some combinations of psychosocial factors (such as loss events), health behaviors and cancer outcomes, statistical analyses were underpowered to detect potentially small effects, or models could not be tested at all due to too few cancer cases within cohorts. Finally, other cohorts may have met the inclusion criteria for the PSY-CA consortium but were unknown to the consortium members, did not come up in the literature review or were not included due to cost-related or ethical issues. PSY-CA is set-up in such a way that additional cohorts can be added in the future.

In conclusion, within the large PSY-CA study, we found no evidence that depression, anxiety, and other psychosocial factors interact with or modify the effects of health behaviors in relation to cancer incidence. In addition, this study suggests that people who experience depression, anxiety or psychosocial stress are not particularly vulnerable to the negative effects of unhealthy behaviors on cancer development.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are owned by participating cohort studies. Data may be shared upon reasonable request at each cohort depending on cohort-specific regulations. Further information is available from the corresponding author upon request.

ETHICS STATEMENT

The ethics approval for PSY-CA was waived by the Medical Ethics Review Committee of VU University Medical Center (2018.101). For inclusion in PSY-CA, ethics approval was granted for each study by the local institution or through appropriate national research governance frameworks.

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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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