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The mediating role of health behaviors in the association between depression, anxiety and cancer incidence: an individual participant data meta-analysis

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Original Article

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Abstract

Background. Although behavioral mechanisms in the association among depression, anxiety, and cancer are plausible, few studies have empirically studied mediation by health behaviors. We aimed to examine the mediating role of several health behaviors in the associations among depression, anxiety, and the incidence of various cancer types (overall, breast, prostate, lung, colorectal, smoking-related, and alcohol-related cancers).

Methods. Two-stage individual participant data meta-analyses were performed based on 18 cohorts within the Psychosocial Factors and Cancer Incidence consortium that had a measure of depression or anxiety ($N = 319\,613$, cancer incidence = 25 803). Health behaviors included smoking, physical inactivity, alcohol use, body mass index (BMI), sedentary behavior, and sleep duration and quality. In stage one, path-specific regression estimates were obtained in each cohort. In stage two, cohort-specific estimates were pooled using random-effects multivariate meta-analysis, and natural indirect effects (i.e. mediating effects) were calculated as hazard ratios (HRs).

Results. Smoking (HRs range 1.04–1.10) and physical inactivity (HRs range 1.01–1.02) significantly mediated the associations among depression, anxiety, and lung cancer. Smoking was also a mediator for smoking-related cancers (HRs range 1.03–1.06). There was mediation by health behaviors, especially smoking, physical inactivity, alcohol use, and a higher BMI, in the associations among depression, anxiety, and overall cancer or other types of cancer, but effects were small (HRs generally below 1.01).

Conclusions. Smoking constitutes a mediating pathway linking depression and anxiety to lung cancer and smoking-related cancers. Our findings underline the importance of smoking cessation interventions for persons with depression or anxiety.

Introduction

It has been long debated whether depression and anxiety increase the risk of cancer. Previous meta-analytic evidence of population-based studies has shown mixed results (Ahn, Bae, Ahn, & Hwang, 2016; Jia et al., 2017; Oerlemans, van den Akker, Schuurman, Kellen, & Buntinx, 2007; Sun et al., 2015; Wang et al., 2020). However, these meta-analyses had several limitations, such as variations across studies included in the assessments of depression and anxiety, cancer diagnosis and assessment, and the covariates considered. To address these limitations, we previously performed individual participant data (IPD) meta-analyses of 18 cohort studies

($N = 319\,613$, cancer incidence = 25 803) and found that depression and anxiety were associated with increased risk of lung and smoking-related cancers independent of demographic factors. This association was attenuated after further adjustment for health behaviors, such as smoking and physical activity. In contrast, depression and anxiety were not associated with the risk of overall cancer, or breast, prostate, colorectal, or alcohol-related cancers (van Tuijl et al., 2023).

Health behaviors may explain part of the association among depression, anxiety, and cancer risk. Previous evidence indicates that individuals with a diagnosis of depression or anxiety are more likely to smoke cigarettes, to drink alcohol heavily, to have a higher body mass index (BMI), and be more physically inactive compared with those without such a diagnosis (Penninx, 2017; Strine et al., 2008). These health behaviors and health-related factors (e.g. BMI, here collectively described as health behaviors) are known risk factors for various types of cancer. Smoking is a risk factor for lung, breast, and colorectal cancer, while high alcohol consumption and a high BMI have been linked to breast and colorectal cancer (Dekker, Tanis, Vleugels, Kasi, & Wallace, 2019; National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health, 2014; Rojas & Stuckey, 2016). Physical inactivity is a risk factor for breast, colorectal, and lung cancer (Dekker et al., 2019; Friedenreich, Ryder-Burbidge, & McNeil, 2021; Kerr, Anderson, & Lippman, 2017; Rojas & Stuckey, 2016). Physical inactivity has also been related to prostate cancer, although the evidence for this is weaker (Friedenreich et al., 2021; Kerr et al., 2017).

In addition, depression and anxiety disorders have been linked to sedentary behavior (Hiles, Lamers, Milaneschi, & Penninx, 2017), abnormal sleep duration, and poor sleep quality (van Mill, Hoogendijk, Vogelzangs, van Dyck, & Penninx, 2010). These health behaviors may also be related to a higher risk of cancer. For example, sedentary behavior, independent of physical inactivity, has been shown to increase the risk of colon and lung cancer (Friedenreich et al., 2021; Kerr et al., 2017; Schmid & Leitzmann, 2014). There is meta-analytical evidence linking a long sleep duration to a higher risk of colorectal cancer but not with overall cancer (Chen et al., 2018), while a large epidemiological cohort study in elderly found poor sleep quality to be linked with a higher risk of overall cancer (Song et al., 2021). These findings suggest that both sedentary behavior and sleep are potential mediators of the association among depression, anxiety, and cancer.

Although behavioral mechanisms in the association among depression, anxiety, and cancer are plausible, few studies have empirically studied mediation by health behaviors. To the best of our knowledge, only one study to date has shown that smoking mediates the association between depressive symptoms and lung cancer in the Nurses' Health Study (Trudel-Fitzgerald, Zevon, Kawachi, Tucker-Seeley, & Kubzansky, 2022). This study ($N = 42\,913$ women) identified 1009 cases of lung cancer over 24 years, finding that smoking partially mediated the association between depressive symptoms and lung cancer.

Our previous IPD meta-analyses found associations of depression and anxiety with the incidence of lung cancer and smoking-related cancers, but not with the incidence of overall cancer or breast, prostate, colorectal, or alcohol-related cancers (van Tuijl et al., 2023). In the present study, we also considered the cancer outcomes for which no significant main effect was observed. While the causal steps approach for mediation analysis requires a significant total effect of a predictor on the outcome, the counterfactual approach suggests that the absence of a main effect does not preclude mediation. This is because there may be inconsistent mediation, such that the direct and indirect effects may point in opposite direction and thus may cause the total effect to be close to zero (Fairchild & McDaniel, 2017; Mackinnon & Fairchild, 2009).

Our aim was to evaluate if health behaviors (smoking, physical inactivity, alcohol use, a high BMI, sedentary behavior, sleep duration, and sleep quality) mediate the relationships between depression, anxiety, and risk of cancer (overall cancer, breast, prostate, lung, colorectal, smoking-related, and alcohol-related cancers). Based on the literature, our hypotheses were as follows (van Tuijl et al., 2021): (1) smoking and physical inactivity mediate the association among depression, anxiety, and lung cancer; (2) smoking mediates the association among depression, anxiety, and smoking-related cancers; (3) smoking, physical inactivity, alcohol use, and a high BMI mediate the association among depression, anxiety, and overall cancer; (4) smoking, physical inactivity, alcohol use, and a high BMI mediate the association among depression, anxiety, and breast cancer; (5) physical inactivity mediates the association among depression, anxiety, and prostate cancer; (6) smoking, physical inactivity, alcohol use, and a high BMI mediate the association among depression, anxiety, and colorectal cancer; (7) alcohol use mediates the association among depression, anxiety, and alcohol-related cancers. Analyses other than these hypotheses were considered exploratory.

Methods

Study design

The Psychosocial Factors and Cancer Incidence (PSY-CA) study consists of 18 prospective cohort studies in the Netherlands, the UK, Norway, and Canada. Three cohorts included multiple subcohorts that were considered separately, resulting in 22 cohorts for analysis. A detailed description of the PSY-CA study can be found elsewhere (van Tuijl et al., 2021, 2023). We undertook two-stage IPD meta-analyses. In the first stage, standardized analyses were performed on harmonized datasets of participating cohorts. In the second stage, meta-analyses were performed to pool cohort-specific effect estimates. The present study was pre-registered on PROSPERO (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020193716).

Study population

We used data from cohort studies that had information on depression (symptoms or diagnosis) or anxiety (symptoms or diagnosis), including 14 cohorts and 4 subcohorts. We excluded participants who had a history of cancer at baseline, except when the cancer was non-melanoma skin cancer. Participants with any cancer diagnosis in the first year of follow-up were excluded to reduce the risk of reverse causality.

Depression and anxiety

Symptoms of depression and anxiety were assessed using validated, self-report questionnaires. As various questionnaires were used across cohorts, continuous sum scores were converted to *z*-scores in each cohort. Depression diagnosis (including major depressive disorder and dysthymia) and anxiety diagnosis (generalized anxiety disorder, social anxiety, panic disorder, and

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agoraphobia) were based on clinical interviews or, if not available, on questionnaires using clinically validated cut-offs. Several cohorts used depression and anxiety symptom questionnaires as a screener to identify and invite participants to a clinical interview. Participants with scores below the screening cut-off were considered to not meet the diagnostic criteria for either depression or anxiety. Cohort-specific details on depression and anxiety variables are provided in online Supplementary Table S1.

Cancer incidence

Seven cancer types were considered: overall cancer, breast cancer, colorectal cancer, lung cancer, prostate cancer, smoking-related cancers, and alcohol-related cancers. Online Supplementary Table S2 provides the ICD codes of these cancer outcomes. Cancer cases, including cancer type and date of diagnosis, were identified through linkage with national or regional registries in all cohorts. In two cohorts (CARTaGENE and Rotterdam study) data from hospital visits, insurance claims, and general practitioner records were also taken into account.

Health behaviors

All health behaviors were assessed at baseline. The four main health behaviors included in the hypotheses were: number of cigarettes per week (or equivalent of other tobacco smoking), hours of physical activity per week, number of alcoholic drinks per week, and assessed or self-reported BMI.

The three health behaviors in exploratory analyses were: hours of sedentary behavior per week (or hours of TV watching per week), sleep quality, and night-time sleep duration. Cohort-specific details on the availability and assessment of health behaviors are provided in online Supplementary Table S3.

We operationalized most health behaviors as continuous variables in the main analyses and as categorical variables in sensitivity analyses. Continuous variables were converted to z-scores in each cohort. Sleep duration was only used as a categorical variable with the categories short (<7 h), normal (≥7 to <9 h), and long (≥9 h) sleep (Chen et al., 2018). Smoking status was dichotomized as current smoker and non-current smoker. Excessive alcohol use was defined as more than seven drinks per week based on recommendations of the Dutch Health Council (Kromhout, Spaaij, de Goede, & Weggemans, 2016). Overweight is defined as a BMI of 25 or higher. Physical activity, sedentary behavior, and sleep quality were categorized into tertiles.

Covariates

Sociodemographic covariates were available in all cohorts, including birth year, age, sex, country of origin (whether the participant and his or her parents were born in the country in which the study was carried out), and educational level (low, medium, and high). For HUNT3, instead of educational level, profession was used as an alternative socioeconomic indicator.

Availability of additional covariates differed across cohorts, which is summarized in online Supplementary Table S4. Current or a history of anti-depressant use was self-reported. Depending on the cancer outcome and data availability in each cohort, self-reported family history of (overall, breast, prostate, lung, and colorectal) cancer referred to the cancer history of the participant's parents, siblings, and/or children. In analyses with breast cancer as the outcome, the following covariates were additionally included if available: parity (nulliparity, 1–2 pregnancies, and ≥3 pregnancies), menarche age, menopausal status, and oral contraceptive use.

Statistical analysis

We performed a meta-analysis of causal mediation analysis following procedures outlined by Zhu, Centorrino, Jackson, Fitzmaurice, & Valeri, (2021). The meta-analysis was carried out in two stages: (1) local analysis in each cohort to retrieve estimates of pathways in mediation models (Fig. 1) and (2) meta-analysis to pool pathways estimated in the first stage and perform causal mediation analysis. Mediation effects were estimated for both single mediator models (Fig. 1b) and parallel multiple mediator models using the four hypothesized health behaviors (Fig. 1c). In the parallel multiple mediator models, we included 15 cohorts where all four health behaviors were available. We explored a parallel multiple mediator model that included all seven health behaviors which were available in four cohorts (online Supplementary Fig. S1).

Stage one: local analysis

First, we estimated the association between depression/anxiety and the incidence of cancer using Cox models in which no health behavior was entered (i.e. path c; Figure 1a), and entry age (age at baseline) and exit age (age at diagnosis, death, or drop-out/study end) were used as the underlying time scale (van Tuijl et al., 2023). Next, we estimated the association between depression/anxiety and each health behavior (i.e. path a; Figure 1b) using linear regression models for continuous health behaviors or (multinomial) logistic regression models for categorical health behaviors. For single mediator models, we estimated the associations between a single health behavior and cancer (i.e. path b; Figure 1b) and the associations between depression/anxiety and cancer while controlling for a single health behavior (i.e. path c'; Figure 1b) using Cox models. For the parallel multiple mediator models, we estimated Cox models that contained the associations between all health behaviors and cancer (i.e. paths b; Figure 1c; Online Supplementary Fig. S1) and the associations between depression/anxiety and cancer while controlling for all health behaviors simultaneously (i.e. path c'; Figure 1c; Online Supplementary Fig. S1). Intercepts, coefficients, and variance–covariance matrices of regression models were extracted for stage two.

The estimated models were adjusted for two confounder sets: (1) a minimally adjusted model included sociodemographic covariates available across all cohorts: birth year, sex, educational attainment, and country of origin; (2) a maximally adjusted model included other potential confounders depending on cancer outcome and availability within the cohort. Online Supplementary Table S4 gives an overview of covariates added to each model in each cohort.

Considering the heterogeneous characteristic of alcohol non-drinkers (Rosansky & Rosenberg, 2020), we additionally performed a subgroup analysis focusing on alcohol use among those who consumed at least one alcoholic drink a week.

To test exposure–mediator interaction, we estimated the associations among depression/anxiety, health behavior, and their product term with each cancer outcome in Cox models. As summarized in another study of PSY-CA (Basten et al., 2024), the exposure–mediator interaction was generally not statistically significant and therefore omitted from the mediation analyses.

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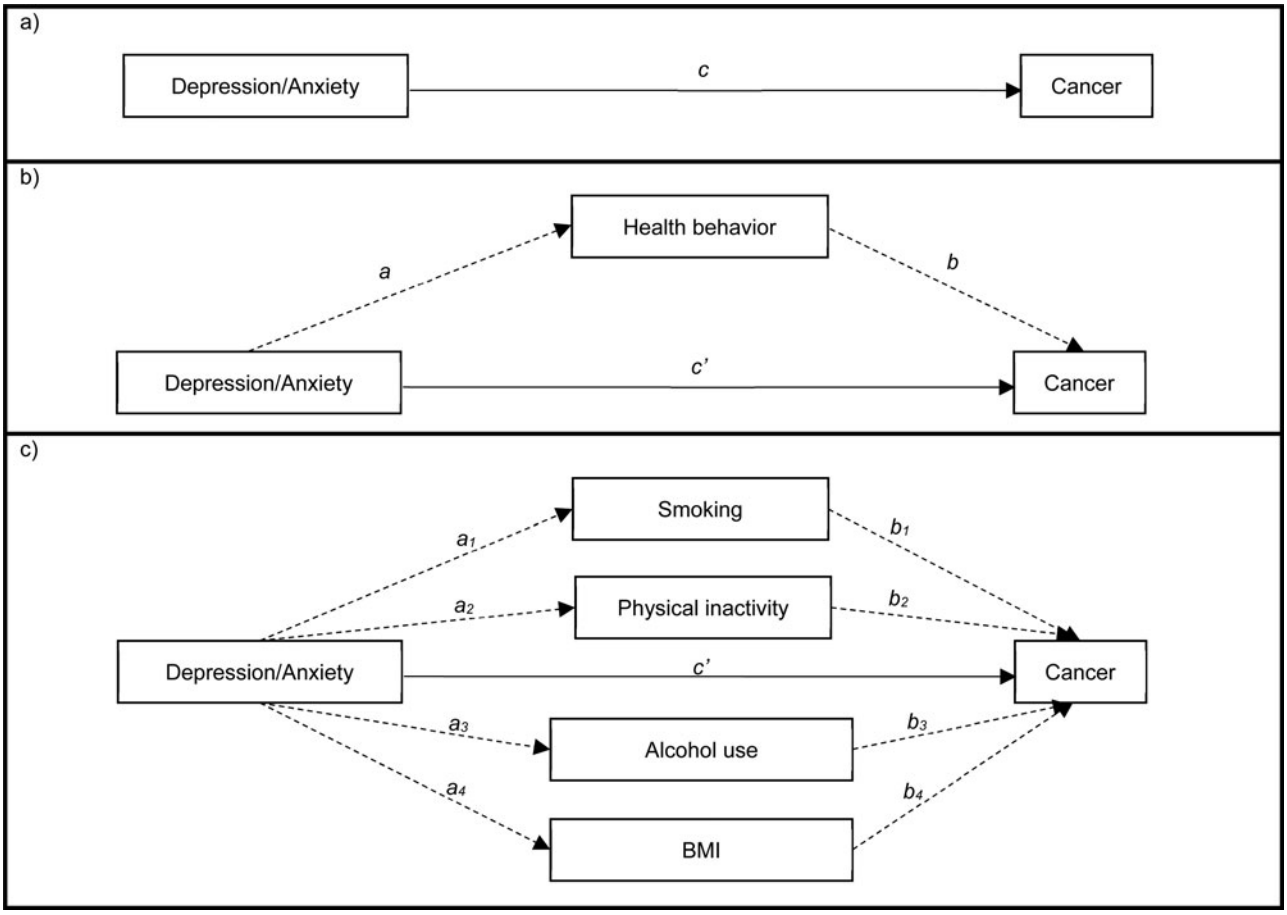

Figure 1. Theoretical framework of mediation analysis.

The inclusion of cohort-level results from stage one into stage two was based on two criteria to avoid the inclusion of unreliable estimates due to low number of cases: (1) each model should include at least ten cancer cases and (2) the a priori expected number of cancer cases among individuals with a depression/anxiety diagnosis should be at least five. The expected number of cases was calculated by multiplying the proportion of depression/anxiety diagnosis by the number of cases in the cohort.

Stage two: meta-analysis

The estimated intercept, path *a*, path *b*, and path *c*′, as well as the corresponding variances and covariances, from each cohort were entered into a random-effects multivariate meta-analysis. We estimated between-cohort heterogeneity in path *a*, *b* and *c*′ using I^2 for each path (Higgins & Thompson, 2002), with the restricted maximum likelihood (REML) estimator.

Based on the pooled coefficients, we calculated natural direct effects, natural indirect effects (i.e. mediating effects), and total effects in hazard ratios (HRs) (VanderWeele, 2011). We obtained 95% Monte-Carlo confidence intervals (CIs) of these effect estimates based on the pooled variance–covariance matrices. Effects were statistically significant when a HR of 1 was not included in the CI. In multiple mediator models with categorical variables, we used the pooled path *c* to represent total effect, as little guidance is available on the computation of total effect for this scenario. We obtained the pooled path *c* using random-effects univariate meta-analysis.

Sensitivity analysis

Models were rerun with continuous health behaviors converted to categorical variables (see health behaviors above).

Results

Cohort characteristics

Table 1 shows characteristics of each cohort included in the current study, and Table 2 shows follow-up duration and number of cancer outcomes of each cohort. In total, there were 319 613 participants involved in the study, including 25 803 cancer diagnoses and 3 254 714 person years of follow-up. Mean age at baseline per cohort ranged between 27.6 and 75.7 years, and 24.8–100% of participants were female.

Lung cancer and smoking-related cancers

We report results from maximally adjusted models only because they were largely similar to those from minimally adjusted models. For lung cancer, in single-mediator models, number of cigarettes smoked mediated the associations among depression (symptoms and diagnosis), anxiety (symptoms and diagnosis), and lung cancer (HRs range 1.04–1.10). Physical inactivity mediated the associations among diagnoses of depression, anxiety, and lung cancer, with small mediating effects (HRs 1.02 and 1.01, respectively). In exploratory analyses, individuals with more depression symptoms or a depression diagnosis had a

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Table 1. Baseline characteristics of each cohort

Cohort	Total number	Age mean (S.D.)	Female %	High education %	Smoker %	Alcoholic drinks p/w Mean (S.D.)	BMI mean (S.D.)	Depression diagnosis %	Anxiety diagnosis %
ALSPAC (Boyd et al., 2013; Fraser et al., 2013)	10 276	27.6 (5.0)	100.0	17.6	34.2	1.8 (4.8)	–	23.1	21.6
Atlantic PATH (Borugian et al., 2010; Sweeney et al., 2017)	2141	50.2 (8.8)	67.3	38.1	13.3	3.4 (5.3)	30.3 (4.7)	7.1	5.4
CARTaGENE (Awadalla et al., 2013; Borugian et al., 2010; Dummer et al., 2018)	32 093	52.9 (7.8)	53.2	57.1	17.5	5.3 (7.5)	27.5 (5.5)	4.5	3.9
ELSA (Steptoe, Breeze, Banks, & Nazroo, 2013)	9248	63.4 (10.6)	55.3	12.8	18.1	3.2 (5.0)	–	23.5	–
HELIUS (Snijder et al., 2017; Stronks et al., 2013)	19 103	44.7 (13.2)	56.8	26.3	24.2	3.2 (6.6)	27.1 (5.2)	14.7	–
HUNT2 (Krokstad et al., 2013)	54 697	48.3 (16.5)	52.5	20.9	29.7	1.6 (2.2)	26.3 (4.0)	3.1	5.1
HUNT3 (Krokstad et al., 2013)	8602	40.2 (14.6)	55.8	42.5	22.9	2.4 (2.8)	26.6 (4.6)	2.3	6.0
LASA (Hoogendijk et al., 2016; Huisman et al., 2011)	3506	67.8 (9.0)	48.9	17.2	25.4	9.0 (11.1)	27.0 (4.2)	2.7	3.4
Lifelines (Scholtens et al., 2015)	141 134	44.5 (12.7)	58.4	29.9	20.5	5.3 (6.5)	26.0 (4.3)	3.4	7.9
NESDA (Penninx et al., 2008)	2296	41.7 (13.1)	65.5	35.8	37.0	7.7 (10.0)	25.6 (4.9)	36.1	41.5
OHS (Borugian et al., 2010; Dummer et al., 2018)	14 384	49.7 (14.8)	64.2	71.1	14.3	3.7 (6.1)	27.0 (5.8)	9.8	11.1
RS1 (Hofman et al., 2015)	2812	75.7 (6.4)	61.5	10.9	13.4	7.4 (9.3)	27.5 (4.1)	4.2	7.0
RS2 (Hofman et al., 2015)	1981	67.9 (7.3)	56.7	17.0	16.5	8.7 (10.4)	27.9 (4.1)	2.3	8.5
RS3 (Hofman et al., 2015)	2968	56.7 (6.9)	55.9	26.6	28.4	6.0 (6.1)	27.7 (4.5)	2.1	7.0
UCC-SMART-2 (Simons, Algra, van de Laak, Grobbee, & van der Graaf, 1999)	1810	64.8 (10.0)	24.8	26.6	18.1	7.4 (8.0)	27.6 (4.2)	7.1	–
UHP 1[a] (Grobbee et al., 2005)	4385	38.6 (12.1)	55.2	38.2	24.2	6.6 (9.0)	25.4 (4.2)	–	–
UHP 2 (Grobbee et al., 2005)	2660	39.0 (11.6)	54.1	56.4	17.0	6.4 (8.2)	25.1 (4.1)	4.4	1.9
Whitehall II (Marmot & Brunner, 2005)	5517	60.9 (5.9)	27.8	36.0	11.6	11.9 (12.6)	26.8 (4.3)	15.4	–

ALSPAC, Avon Longitudinal Study of Parents and Children (mothers cohort); Atlantic PATH, Atlantic Partnership for Tomorrow's Health; BMI, body mass index; 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]Only contributed to analyses related to symptoms of depression and anxiety.

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

Cohort	Maximum years of follow-up	Overall cancer	Breast cancer	Lung cancer	Prostate cancer	Colorectal cancer	Smoking-related cancers	Alcohol-related cancers
ALSPAC	20	307	150	8	0	8	36	160
Atlantic PATH	10	67	18	5	7	7	24	26
CARTaGENE	10	3875	528	393	429	297	1336	1040
ELSA	16	2038	190	173	249	201	705	466
HELIUS	8	421	80	31	51	32	143	125
HUNT2	24	8998	1046	778	1581	1292	3640	2555
HUNT3	13	452	79	34	78	54	153	141
LASA	26	874	80	104	100	111	420	236
Lifelines	13	5587	1332	274	503	549	1569	2058
NESDA	15	223	35	19	10	20	85	63
OHS	10	482	103	33	73	28	163	151
RS1	13	507	47	87	53	83	306	157
RS2	13	293	46	37	57	38	140	96
RS3	9	183	34	18	20	26	89	76
UCC-SMART-2	12	207	4	22	25	20	86	39
UHP 1	19	277	61	18	28	29	96	98
UHP 2	16	104	27	6	10	6	30	36
Whitehall II	13	908	66	30	221	92	245	181
Total	–	25 803	3926	2070	3495	2893	9266	7704

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.

higher BMI, which in turn was associated with a lower risk of lung cancer (HRs 0.99 and 0.97, respectively). Sedentary behavior mediated the associations among depression (symptoms and diagnosis), anxiety (symptoms and diagnosis), and lung cancer (HRs range 1.01–1.02). These results were similar in multiple mediator models (Table 3 and online Supplementary Table S5). Alcohol use (among drinkers) mediated the associations among depression (symptoms and diagnosis), anxiety (symptoms and diagnosis), and lung cancer in single mediator models, but not in multiple mediator models (Table 3).

For smoking-related cancers, in single mediator models, smoking (HRs range 1.03–1.06) mediated the associations among depression (symptoms and diagnosis), anxiety (symptoms and diagnosis), and smoking-related cancers. In exploratory analyses, physical inactivity (HRs range 1.001–1.01), alcohol use (among drinkers; HRs range 1.004–1.02), and sedentary behavior (HRs range 1.002–1.01) also mediated the associations. Again, these results were similar in multiple mediator models (Table 4 and online Supplementary Table S6).

Overall cancer and other types of cancer

In line with our hypotheses, smoking, physical inactivity, alcohol use, and a higher BMI mediated the associations among depression, anxiety, and overall cancer and colorectal cancer, and alcohol use mediated the associations among depression, anxiety, and alcohol-related cancers. However, except for smoking, the mediating effects of health behaviors were generally small (HRs below 1.01). Contrary to our hypotheses, health behaviors did not mediate the associations among depression, anxiety, and breast cancer and prostate cancer. Detailed results for these cancer outcomes are reported in online Supplementary text and Tables S7–S26.

Between-cohort heterogeneity

Between-cohort heterogeneity was high in the associations between depression/anxiety and health behaviors, with I^2 generally above 75% (substantial heterogeneity). Between-cohort heterogeneity was relatively low in the association between depression/anxiety and cancer and the association between health behaviors and cancer, with I^2 generally below 50% (moderate heterogeneity) (Tables 3 and 4; Online Supplementary Tables S5–S28).

Sensitivity analysis

Mediating effects of health behaviors operationalized as categorical variables were generally consistent with those of continuous variables reported above (online Supplementary Tables S5–S28).

Discussion

In this pooled analysis of 18 prospective cohort studies we found that (1) cigarette smoking mediated the associations among depression, anxiety, and lung cancer and smoking-related cancers; (2) physical inactivity and sedentary behavior also mediated these associations, but to a much lesser degree than smoking;

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Table 3. Mediation of smoking, physical inactivity, alcohol use, and BMI in the associations of depression and anxiety with lung cancer

Mediator	N cohort	Person-year (N incidence)	Indirect effect (95% CI)	Direct effect (95% CI)	Total effect (95% CI)	I^2 – path *a*	I^2 – path *b*	I^2 – path *c'*
Depression symptoms								
Single mediator model								
N. smoking	15	2 092 982 (1631)	1.042 (1.033–1.052)	1.08 (0.97–1.19)	1.12 (1.02–1.24)	0.90	0.91	0.57
Physical inactivity	12	2 049 557 (1488)	1.005 (0.998–1.014)	1.14 (1.08–1.19)	1.14 (1.09–1.20)	0.98	0.24	0.04
N. alcohol use	15	2 153 042 (1678)	0.998 (0.996–0.999)	1.15 (1.10–1.21)	1.15 (1.10–1.20)	0.66	0.17	0.38
N. alcohol use (drinker)	15	1 515 158 (1118)	1.005 (1.002–1.010)	1.12 (1.05–1.19)	1.12 (1.06–1.19)	0.89	<0.01	0.25
BMI	14	2 064 345 (1522)	0.988 (0.981–0.994)	1.17 (1.11–1.23)	1.15 (1.09–1.21)	0.93	0.41	0.45
Sedentary behavior	6	1 686 153 (1149)	1.008 (1.003–1.015)	1.14 (1.08–1.21)	1.15 (1.09–1.22)	0.98	<0.01	<0.01
Poor sleep quality	10	644 666 (736)	0.967 (0.931–1.004)	1.15 (1.03–1.29)	1.11 (0.99–1.26)	0.98	0.05	0.30
Sleep duration	9	1 846 361 (1409)						
Long sleep			1.009 (0.999–1.022)	1.16 (1.10–1.22)	1.17 (1.11–1.23)	0.94	0.65	0.38
Short sleep			1.001 (0.984–1.021)	1.16 (1.10–1.22)	1.17 (1.11–1.23)	0.95	0.46	0.38
Multiple mediator model								
N. smoking	11	1 746 735 (1155)	1.038 (1.026–1.052)	1.11 (1.04–1.18)	1.14 (1.08–1.21)	0.92	0.92	0.22
Physical inactivity	11	1 746 735 (1155)	1.004 (0.996–1.012)	1.11 (1.04–1.18)	1.14 (1.08–1.21)	0.97	0.13	0.22
N. alcohol use	11	1 746 735 (1155)	0.999 (0.998–1.001)	1.11 (1.04–1.18)	1.14 (1.08–1.21)	0.56	0.59	0.22
N. alcohol use (drinker)	11	1 210 721 (738)	1.005 (1.000–1.012)	1.09 (1.00–1.19)	1.09 (1.00–1.20)	0.91	0.68	0.14
BMI	11	1 746 735 (1155)	0.991 (0.983–0.997)	1.11 (1.04–1.18)	1.14 (1.08–1.21)	0.93	<0.01	0.22
Depression diagnosis								
Single mediator model								
N. smoking	7	2 226 671 (1391)	1.104 (1.064–1.154)	1.15 (0.92–1.44)	1.27 (1.00–1.61)	0.88	0.97	<0.01
Physical inactivity	7	2 315 706 (1454)	1.022 (1.006–1.043)	1.42 (1.10–1.83)	1.45 (1.12–1.88)	0.97	<0.01	0.19
N. alcohol use	7	2 342 598 (1505)	0.992 (0.986–0.997)	1.48 (1.15–1.90)	1.47 (1.14–1.89)	0.63	0.30	0.16
N. alcohol use (drinker)	7	1 662 426 (969)	1.012 (0.996–1.032)	1.23 (0.95–1.58)	1.24 (0.96–1.60)	0.88	0.43	<0.01
BMI	6	2 335 278 (1365)	0.974 (0.951–0.992)	1.76 (1.40–2.21)	1.71 (1.37–2.15)	0.89	0.55	<0.01
Sedentary behavior	4	2 094 418 (1262)	1.021 (1.008–1.037)	1.75 (1.38–2.21)	1.78 (1.41–2.25)	0.85	<0.01	<0.01
Poor sleep quality	3	321 534 (440)	0.957 (0.881–1.038)	1.73 (1.20–2.49)	1.66 (1.16–2.36)	0.92	<0.01	<0.01
Sleep duration	5	2 288 113 (1346)						
Long sleep			1.025 (0.983–1.083)	1.56 (1.20–2.04)	1.60 (1.26–2.05)	0.90	0.82	0.30
Short sleep			1.008 (0.958–1.071)	1.56 (1.20–2.04)	1.60 (1.26–2.05)	0.86	0.65	0.30
Multiple mediator model								
N. smoking	6	1 886 711 (1060)	1.097 (1.051–1.155)	1.37 (1.14–1.64)	1.72 (1.44–2.06)	0.88	0.97	<0.01
Physical inactivity	6	1 886 711 (1060)	1.017 (1.004–1.034)	1.37 (1.14–1.64)	1.72 (1.44–2.06)	0.92	<0.01	<0.01
N. alcohol use	6	1 886 711 (1060)	0.997 (0.990–1.002)	1.37 (1.14–1.64)	1.72 (1.44–2.06)	0.62	0.53	<0.01
N. alcohol use (drinker)	6	1 321 032 (662)	1.012 (0.997–1.038)	1.12 (0.75–1.69)	1.14 (0.76–1.71)	0.86	0.75	<0.01
BMI	6	1 886 711 (1060)	0.981 (0.962–0.995)	1.37 (1.14–1.64)	1.72 (1.44–2.06)	0.90	0.29	<0.01
Anxiety symptoms								
Single mediator model								
N. smoking	7	1 338 187 (1091)	1.049 (1.035–1.064)	1.05 (0.99–1.12)	1.10 (1.04–1.17)	0.85	0.94	<0.01
Physical inactivity	7	1 315 557 (1065)	1.001 (0.997–1.004)	1.14 (1.07–1.22)	1.14 (1.07–1.22)	0.71	0.49	<0.01
N. alcohol use	7	1 319 289 (1091)	1.002 (1.000–1.004)	1.13 (1.07–1.20)	1.14 (1.07–1.20)	0.91	<0.01	0.29
N. alcohol use (drinker)	7	866 581 (649)	1.010 (1.006–1.015)	1.14 (1.05–1.23)	1.15 (1.06–1.25)	0.44	<0.01	0.06

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Table 3. (*Continued.*)

Mediator	N cohort	Person-year (N incidence)	Indirect effect (95% CI)	Direct effect (95% CI)	Total effect (95% CI)	I^2 – path *a*	I^2 – path *b*	I^2 – path *c*′
BMI	7	1 317 143 (1105)	0.996 (0.989–1.002)	1.13 (1.06–1.21)	1.13 (1.05–1.20)	0.95	0.03	0.25
Sedentary behavior	5	1 203 519 (969)	1.004 (1.000–1.011)	1.11 (1.04–1.18)	1.11 (1.05–1.19)	0.97	<0.01	<0.01
Poor sleep quality	6	518 490 (557)	0.973 (0.936–1.011)	1.18 (1.04–1.34)	1.15 (1.00–1.32)	0.99	<0.01	<0.01
Sleep duration	5	1 189 926 (1056)						
Long sleep			1.009 (0.997–1.027)	1.20 (1.08–1.34)	1.22 (1.08–1.37)	0.95	0.81	0.17
Short sleep			1.003 (0.988–1.021)	1.20 (1.08–1.34)	1.22 (1.08–1.37)	0.89	0.51	0.17
Multiple mediator model								
N. smoking	7	1 207 738 (959)	1.049 (1.035–1.065)	1.08 (1.02–1.15)	1.12 (1.06–1.20)	0.84	0.91	<0.01
Physical inactivity	7	1 207 738 (959)	1.000 (0.997–1.003)	1.08 (1.02–1.15)	1.12 (1.06–1.20)	0.69	0.34	<0.01
N. alcohol use	7	1 207 738 (959)	1.000 (0.998–1.001)	1.08 (1.02–1.15)	1.12 (1.06–1.20)	0.91	<0.01	<0.01
N. alcohol use (drinker)	7	811 011 (596)	1.001 (0.993–1.008)	1.08 (1.00–1.17)	1.08 (1.00–1.17)	0.35	0.24	0.05
BMI	7	1 207 738 (959)	0.996 (0.991–1.001)	1.08 (1.02–1.15)	1.12 (1.06–1.20)	0.95	<0.01	<0.01
Anxiety diagnosis								
Single mediator model								
N. smoking	5	1 935 163 (1166)	1.086 (1.019–1.174)	1.34 (1.04–1.73)	1.46 (1.13–1.87)	0.97	0.98	0.29
Physical inactivity	4	2 009 926 (1155)	1.006 (1.000–1.013)	1.53 (1.22–1.91)	1.54 (1.23–1.93)	0.63	0.37	<0.01
N. alcohol use	5	2 052 866 (1272)	1.001 (0.994–1.009)	1.53 (1.19–1.95)	1.53 (1.19–1.96)	0.79	0.55	0.12
N. alcohol use (drinker)	5	1 465 212 (788)	1.028 (1.007–1.056)	1.43 (0.99–2.05)	1.47 (1.03–2.09)	0.89	0.56	0.42
BMI	5	2 144 330 (1293)	1.002 (0.988–1.018)	1.55 (1.25–1.90)	1.55 (1.25–1.91)	0.87	0.43	0.07
Sedentary behavior	4	2 051 323 (1186)	1.010 (1.003–1.020)	1.55 (1.24–1.93)	1.56 (1.25–1.95)	0.86	<0.01	<0.01
Poor sleep quality	3	286 733 (492)	0.965 (0.911–1.016)	1.62 (1.13–2.34)	1.57 (1.09–2.26)	0.95	<0.01	0.45
Sleep duration	5	2 161 166 (1312)						
Long sleep			1.015 (0.992–1.050)	1.50 (1.21–1.85)	1.52 (1.23–1.89)	0.84	0.82	<0.01
Short sleep			1.003 (0.972–1.042)	1.50 (1.21–1.85)	1.52 (1.23–1.89)	0.76	0.60	<0.01
Multiple mediator model								
N. smoking	4	1 696 403 (945)	1.092 (1.027–1.186)	1.41 (1.03–1.94)	1.58 (1.32–1.91)	0.98	0.98	0.32
Physical inactivity	4	1 696 403 (945)	1.004 (0.999–1.012)	1.41 (1.03–1.94)	1.58 (1.32–1.91)	0.74	<0.01	0.32
N. alcohol use	4	1 696 403 (945)	1.001 (0.995–1.010)	1.41 (1.03–1.94)	1.58 (1.32–1.91)	0.89	0.73	0.32
N. alcohol use (drinker)	4	1 206 975 (586)	1.021 (0.994–1.061)	1.43 (0.94–2.15)	1.46 (0.94–2.23)	0.92	0.85	0.55
BMI	4	1 696 403 (945)	0.996 (0.982–1.007)	1.41 (1.03–1.94)	1.58 (1.32–1.91)	0.91	0.47	0.32

Indirect effect is calculated based on path *a* and path *b*; direct effect refers to path *c*′; total effect is calculated based on indirect and direct effects. These effects are Hazard Ratios. Multiple mediator model includes cohorts with the four main health behaviors (smoking, physical inactivity, alcohol use, and BMI).

(3) smoking, physical inactivity, alcohol use, and a higher BMI mediated the associations among depression, anxiety and overall cancer, colorectal cancer, and alcohol-related cancers, but except for smoking, the mediating effects of health behaviors were generally very small; (4) health behaviors did not seem to mediate the associations among depression, anxiety, and breast cancer and prostate cancer.

In line with our hypotheses, smoking mediated the associations among depression, anxiety, and lung cancer and smoking-related cancers. Specifically, depression/anxiety was associated with a 3–10% increased risk of these two outcomes, and this was through smoking. Our data also confirmed the hypotheses that physical inactivity mediated the associations among depression, anxiety, and lung cancer, although its mediating effects were much smaller than smoking. In fact, the mediating effects of smoking for lung cancer and smoking-related cancers were the largest among all health behaviors and cancer outcomes studied, which highlights its important mediating role in the associations.

Furthermore, exploratory analyses showed that physical inactivity and sedentary behavior simultaneously mediated the associations among depression, anxiety, lung cancer, and smoking-related cancers, suggesting that different mechanisms in the associations may exist between time spent sitting and not engaging in physical activity. Indeed, the pooled correlation between physical inactivity and sedentary behavior was low in

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Table 4. Mediation of smoking, physical inactivity, alcohol use, and BMI in the associations of depression and anxiety with smoking-related cancers

Mediator	N cohort	Person-year (N incidence)	Indirect effect (95% CI)	Direct effect (95% CI)	Total effect (95% CI)	I^2 – path *a*	I^2 – path *b*	I^2 – path *c'*
Depression symptoms								
Single mediator model								
N. smoking	18	2 350 387 (7433)	1.025 (1.020–1.030)	1.01 (0.95–1.06)	1.03 (0.98–1.08)	0.89	0.77	0.62
Physical inactivity	16	2 322 444 (6841)	1.004 (1.001–1.008)	1.03 (0.98–1.08)	1.03 (0.99–1.08)	0.98	0.09	0.51
N. alcohol use	18	2 400 018 (7524)	1.000 (0.998–1.001)	1.03 (0.98–1.08)	1.03 (0.98–1.08)	0.84	0.46	0.60
N. alcohol use (drinker)	18	1 606 225 (5052)	1.004 (1.002–1.008)	1.04 (0.99–1.09)	1.05 (1.00–1.09)	0.90	0.37	0.44
BMI	16	2 097 037 (6879)	1.001 (0.999–1.003)	1.02 (0.97–1.08)	1.02 (0.97–1.08)	0.93	<0.01	0.62
Sedentary behavior	7	1 697 903 (5126)	1.004 (1.001–1.009)	1.06 (1.01–1.11)	1.06 (1.01–1.12)	0.98	<0.01	0.56
Poor sleep quality	11	657 975 (2918)	1.000 (0.982–1.020)	1.01 (0.93–1.09)	1.01 (0.94–1.08)	0.98	0.30	0.65
Sleep duration	12	1 938 013 (6524)						
Long sleep			1.001 (0.999–1.003)	1.04 (0.98–1.10)	1.04 (0.98–1.10)	0.92	<0.01	0.60
Short sleep			1.006 (0.999–1.014)	1.04 (0.98–1.10)	1.04 (0.98–1.10)	0.94	0.10	0.60
Multiple mediator model								
N. smoking	14	1 793 155 (5531)	1.023 (1.017–1.029)	1.00 (0.96–1.05)	1.02 (0.96–1.09)	0.90	0.77	0.39
Physical inactivity	14	1 793 155 (5531)	1.002 (0.999–1.005)	1.00 (0.96–1.05)	1.02 (0.96–1.09)	0.97	<0.01	0.39
N. alcohol use	14	1 793 155 (5531)	1.000 (0.999–1.000)	1.00 (0.96–1.05)	1.02 (0.96–1.09)	0.50	0.32	0.39
N. alcohol use (drinker)	14	1 247 996 (3589)	1.003 (1.001–1.005)	1.01 (0.97–1.05)	1.02 (0.98–1.06)	0.89	0.25	0.35
BMI	14	1 793 155 (5531)	1.003 (1.001–1.006)	1.00 (0.96–1.05)	1.02 (0.96–1.09)	0.93	<0.01	0.39
Depression diagnosis								
Single mediator model								
N. smoking	12	2 600 476 (7599)	1.062 (1.046–1.080)	1.14 (1.03–1.25)	1.21 (1.10–1.33)	0.83	0.89	0.13
Physical inactivity	11	2 658 983 (7318)	1.007 (0.999–1.017)	1.17 (1.05–1.31)	1.18 (1.05–1.32)	0.96	0.42	<0.01
N. alcohol use	12	2 702 286 (7842)	0.997 (0.993–1.001)	1.19 (1.06–1.34)	1.19 (1.06–1.33)	0.87	0.52	0.19
N. alcohol use (drinker)	12	1 821 130 (5265)	1.011 (1.002–1.023)	1.18 (1.04–1.33)	1.19 (1.05–1.35)	0.91	0.54	<0.01
BMI	10	2 480 289 (7304)	1.003 (0.999–1.008)	1.20 (1.07–1.34)	1.20 (1.07–1.35)	0.92	<0.01	0.17
Sedentary behavior	5	2 163 088 (5855)	1.013 (1.003–1.025)	1.28 (1.13–1.46)	1.30 (1.14–1.48)	0.91	0.33	<0.01
Poor sleep quality	6	457 837 (2438)	1.012 (0.976–1.049)	1.02 (0.77–1.37)	1.04 (0.79–1.36)	0.89	<0.01	0.49
Sleep duration	9	2 480 501 (7203)						
Long sleep			1.002 (0.993–1.011)	1.16 (1.01–1.34)	1.17 (1.01–1.34)	0.85	<0.01	0.25
Short sleep			1.016 (1.002–1.031)	1.16 (1.01–1.34)	1.17 (1.01–1.34)	0.68	<0.01	0.25
Multiple mediator model								
N. smoking	9	1 997 661 (5764)	1.059 (1.039–1.083)	1.09 (0.97–1.22)	1.22 (1.08–1.40)	0.86	0.89	<0.01
Physical inactivity	9	1 997 661 (5764)	1.004 (0.997–1.011)	1.09 (0.97–1.22)	1.22 (1.08–1.40)	0.90	0.25	<0.01
N. alcohol use	9	1 997 661 (5764)	0.998 (0.995–1.000)	1.09 (0.97–1.22)	1.22 (1.08–1.40)	0.56	0.49	<0.01
N. alcohol use (drinker)	9	1 389 027 (3751)	1.008 (1.000–1.020)	1.05 (0.87–1.28)	1.06 (0.88–1.28)	0.88	0.59	<0.01
BMI	9	1 997 661 (5764)	1.009 (1.003–1.018)	1.09 (0.97–1.22)	1.22 (1.08–1.40)	0.92	<0.01	<0.01
Anxiety symptoms								
Single mediator model								
N. smoking	9	1 573 026 (4809)	1.028 (1.022–1.034)	1.03 (1.00–1.07)	1.06 (1.03–1.10)	0.82	0.74	<0.01
Physical inactivity	9	1 550 933 (4674)	1.001 (1.000–1.003)	1.06 (1.02–1.11)	1.06 (1.02–1.11)	0.74	0.36	<0.01
N. alcohol use	9	1 544 048 (4789)	1.001 (1.000–1.003)	1.05 (1.00–1.10)	1.05 (1.00–1.10)	0.87	0.33	0.12
N. alcohol use (drinker)	9	940 299 (2895)	1.006 (1.004–1.009)	1.07 (1.01–1.13)	1.08 (1.02–1.14)	0.57	<0.01	0.09

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Table 4. (*Continued.*)

Mediator	N cohort	Person-year (N incidence)	Indirect effect (95% CI)	Direct effect (95% CI)	Total effect (95% CI)	I^2 – path *a*	I^2 – path *b*	I^2 – path *c*′
BMI	8	1 330 264 (4801)	1.000 (0.999–1.002)	1.06 (1.01–1.11)	1.06 (1.01–1.11)	0.95	<0.01	0.12
Sedentary behavior	6	1 215 269 (4181)	1.002 (1.000–1.005)	1.07 (1.02–1.12)	1.07 (1.02–1.13)	0.97	<0.01	0.15
Poor sleep quality	7	531 800 (2106)	0.997 (0.979–1.017)	1.08 (1.01–1.14)	1.07 (1.02–1.13)	0.99	0.06	<0.01
Sleep duration	6	1 203 035 (4550)						
Long sleep			1.002 (0.999–1.005)	1.06 (1.02–1.11)	1.07 (1.02–1.12)	0.94	<0.01	<0.01
Short sleep			1.006 (1.001–1.014)	1.06 (1.02–1.11)	1.07 (1.02–1.12)	0.88	<0.01	<0.01
Multiple mediator model								
N. smoking	8	1 220 483 (4269)	1.027 (1.021–1.034)	1.04 (1.01–1.07)	1.06 (1.02–1.10)	0.81	0.63	<0.01
Physical inactivity	8	1 220 483 (4269)	1.000 (0.999–1.002)	1.04 (1.01–1.07)	1.06 (1.02–1.10)	0.76	0.40	<0.01
N. alcohol use	8	1 220 483 (4269)	1.000 (1.000–1.001)	1.04 (1.01–1.07)	1.06 (1.02–1.10)	0.86	0.34	<0.01
N. alcohol use (drinker)	8	819 403 (2663)	1.003 (1.001–1.006)	1.05 (1.00–1.10)	1.05 (1.01–1.10)	0.50	<0.01	0.03
BMI	8	1 220 483 (4269)	1.001 (1.000–1.003)	1.04 (1.01–1.07)	1.06 (1.02–1.10)	0.95	<0.01	<0.01
Anxiety diagnosis								
Single mediator model								
N. smoking	11	2 396 968 (6389)	1.053 (1.030–1.080)	1.07 (0.95–1.20)	1.12 (1.00–1.27)	0.95	0.89	0.08
Physical inactivity	9	2 447 836 (6063)	1.004 (1.000–1.008)	1.16 (1.04–1.29)	1.16 (1.04–1.30)	0.76	0.39	<0.01
N. alcohol use	11	2 502 159 (6658)	1.001 (0.998–1.004)	1.16 (1.02–1.33)	1.16 (1.02–1.33)	0.75	0.54	0.08
N. alcohol use (drinker)	11	1 692 986 (4372)	1.017 (1.007–1.028)	1.06 (0.89–1.25)	1.07 (0.91–1.27)	0.83	0.44	0.27
BMI	10	2 382 387 (6763)	1.001 (0.999–1.004)	1.18 (1.05–1.33)	1.18 (1.05–1.33)	0.88	<0.01	0.06
Sedentary behavior	6	2 206 636 (5652)	1.007 (1.001–1.016)	1.15 (0.99–1.34)	1.16 (1.00–1.34)	0.92	0.25	0.36
Poor sleep quality	8	524 527 (2533)	1.001 (0.974–1.029)	1.28 (1.08–1.51)	1.28 (1.08–1.51)	0.95	0.18	<0.01
Sleep duration	9	2 306 080 (6621)						
Long sleep			1.001 (0.994–1.009)	1.16 (1.02–1.33)	1.17 (1.02–1.33)	0.85	<0.01	0.04
Short sleep			1.008 (0.996–1.020)	1.16 (1.02–1.33)	1.17 (1.02–1.33)	0.74	0.12	0.04
Multiple mediator model								
N. smoking	8	1 897 346 (5268)	1.056 (1.029–1.090)	1.07 (0.95–1.21)	1.19 (1.03–1.36)	0.96	0.90	<0.01
Physical inactivity	8	1 897 346 (5268)	1.003 (0.999–1.007)	1.07 (0.95–1.21)	1.19 (1.03–1.36)	0.77	0.29	<0.01
N. alcohol use	8	1 897 346 (5268)	1.000 (0.997–1.002)	1.07 (0.95–1.21)	1.19 (1.03–1.36)	0.75	0.52	<0.01
N. alcohol use (drinker)	8	1 343 928 (3436)	1.009 (1.000–1.021)	0.93 (0.73–1.19)	0.94 (0.74–1.20)	0.88	0.57	0.22
BMI	8	1 897 346 (5268)	1.005 (1.001–1.012)	1.07 (0.95–1.21)	1.19 (1.03–1.36)	0.89	<0.01	<0.01

Indirect effect is calculated based on path *a* and path *b*; direct effect refers to path *c*′; total effect is calculated based on indirect and direct effects. These effects are Hazard Ratios. Multiple mediator model includes cohorts with the four main health behaviors (smoking, physical inactivity, alcohol use, and BMI).

our study ($r = 0.17$, 95% CI 0.05–0.27). Physical inactivity may increase the risk of lung cancer and smoking-related cancers through reduced pulmonary function, forced expiratory volume, and forced vital capacity which likely increase the duration of exposure to carcinogenic agents in the lungs (Cannioto et al., 2018; Garcia-Aymerich, Lange, Benet, Schnohr, & Antó, 2007). Although the underlying mechanisms are unclear, sedentary behavior reduces the activity of weight-bearing skeletal muscles, which may alter anti-cancer responses of myokines in the skeletal muscles and activate inflammatory pathways that are important for cancer development (Aoi et al., 2013; Hojman et al., 2011).

We observed inconsistent mediation patterns regarding depression, BMI, and lung cancer in exploratory analyses, where a higher BMI was related to a lower risk of lung cancer, even after controlling for smoking. This negative association between BMI and lung cancer was also observed in previous meta-analyses (Duan et al., 2015; Renehan, Tyson, Egger, Heller, & Zwahlen, 2008). Several mechanisms have been proposed, such as smoking being an explanatory factor or weight loss representing a preclinical event prior to lung cancer; however, these mechanisms were proven unaccountable for the inverse association between BMI and lung cancer (Abdel-Rahman, 2019). A recent review summarized that several studies showed increased central adiposity associated with a higher risk of lung cancer and argued that body compositions assessed using anthropometric indicators or image-based techniques should be considered when estimating

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the risk of lung cancer (Vedire et al., 2023). While few cohorts involved in our study have such information, further studies are warranted to investigate the mediating role of body compositions in the association between depression and lung cancer.

As mentioned before, we did not find an association of depression and anxiety with the risk of overall cancer, or colorectal or alcohol-related cancers in the previous study (van Tuijl et al., 2023), but nevertheless examined mediation for these outcomes for reasons outlined in the introduction. Our results generally confirmed the hypotheses for these outcomes. Exploratory analyses also revealed the mediating role of sedentary behavior in the associations among depression, anxiety and overall cancer and colorectal cancer. Notably, mediating effects of these health behaviors, except for smoking, were very small, and thus the clinical implications of these findings are likely to be limited.

Contrary to our hypothesis, we did not find consistent mediating effects of health behaviors in the associations among depression, anxiety, and breast cancer. Our findings may suggest that behavioral mechanisms play a lesser role in the associations among depression, anxiety, and breast cancer. On the other hand, it has been suggested that depression and anxiety may be related to lower estrogen levels (Wharton, Gleason, Olson, Carlsson, & Asthana, 2012), which may decrease the risk of breast cancer (Clemons & Goss, 2001). While testing the mediation by hormone in the associations among depression, anxiety and breast cancer was not planned in PSY-CA, we hypothesized that menopausal status may moderate the associations. However, our analyses based on PSY-CA study did not find menopausal status moderating the associations.

In addition, against our hypothesis, we found that individuals with depression or anxiety were more physically inactive, which in turn was related to a lower risk of prostate cancer in single mediator models, but not in multiple mediator models. However, we found that depressed individuals smoked more, which was related to a lower risk of prostate cancer in both single and multiple mediator models. Besides unmeasured confounding, a possible explanation could be that non-smokers are more likely to receive prostate-specific antigen screening compared with smokers. A similar explanation was posted by the authors of a previous meta-analysis, finding that lower physical activity was related to a lower risk of prostate cancer (Moore et al., 2016). The authors suggested that this positive association may be biased by screening behavior: physically active men are more likely to receive prostate-specific antigen screening than inactive men, which may increase the likelihood of diagnosing indolent prostate cancers (Moore et al., 2016). Another meta-analysis showed that smokers appeared to have an increased risk of developing aggressive prostate cancer than non-smokers (Foerster et al., 2018). We were unable to further distinguish these mediating effects by prostate cancer stage or behavior due to the limited number of cohorts with such information.

Methodological strengths of the present study include 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 addition, the present study is among the largest to date which provided sufficient statistical power to extensively investigate mediation by several health behaviors in the associations among depression, anxiety, and cancer. A few limitations nevertheless need to be acknowledged. First, we used information on depression/anxiety and health behaviors collected at the same time, making their temporal order unclear. Indeed, bidirectional associations between depression/anxiety and health behaviors have been shown in previous studies (Azevedo Da Silva et al., 2012; Hiles et al., 2017). While lagged data may have provided a more accurate representation of the association between depression/anxiety and health behaviors, such data were available in only a limited number of cohorts. Second, we did not consider different types (e.g. major depressive disorder or dysthymia in depression; generalized anxiety disorder or social anxiety in anxiety) or remission of depression and anxiety because most cohorts included did not have such information. Third, we were unable to directly assess between-cohort heterogeneity in indirect effects due to the limited methodology available for the meta-analysis of causal mediation analysis. We instead assessed path-specific heterogeneity and found high heterogeneity in the association between depression/anxiety and health behaviors. Fourth, availability of health behaviors, especially sedentary behavior and sleep, and the number of cancer cases differed across cohorts. As a result, the pooled indirect effect sizes may not be directly comparable because they may stem from meta-analyses of different numbers of cohorts. Fifth, the results of single and multiple mediator models were based on complete-case analyses as participants with missing values on health behaviors were excluded from the models. This means that there was reduction in the analytical sample from single to multiple mediator models. Although multiple imputation was considered to deal with missing values under the missing not at random assumption, developing cohort-specific multiple imputation models and running long scripts for 22 cohorts was considered unfeasible. However, since effect estimates were generally the same across single and multiple mediator models, it is unlikely that the reduction of sample size in multiple mediator models due to missing data in health behaviors accounted for the results. Finally, although we included a number of potential confounders, including cancer-specific ones, there might be unmeasured confounders that bias the mediation effect estimates reported in this paper.

In conclusion, smoking constitutes a prominent mediating pathway linking depression and anxiety to the risk of lung cancer and smoking-related cancers. Our findings underline the importance of smoking cessation interventions in clinical practice for persons with depression or anxiety (Gierisch, Bastian, Calhoun, McDuffie, & Williams, 2012; Rüther et al., 2014; Taylor et al., 2021).

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291724000850.

Data availability statement. The data that support the findings of this study are owned by 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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