Article

Do depressive symptoms predict cancer incidence? 17-year follow-up of the Whitehall II study

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Abbreviations: CI, confidence interval; HR, hazard ratio; pyrs, person-years; SD, standard deviation.

Abstract
Objective: To explore the association between depressive symptom history and cancer incidence.
Methods: Affective/emotional depressive symptoms were assessed using the General Health Questionnaire (GHQ-30) depression sub-scale across phase 1 (1985-1988), phase 2 (1989-1990), and phase 3 (1991-1994) of the Whitehall II prospective cohort study; 'chronic'= depressive episode at phase 1, 2 and 3; 'new'= depressive episode at phase 3 only. Cancer Incidence was obtained from the National Health Service Central Register with an average follow-up of 15.6 years (range 0.08–17.4). The study sample consisted of 6983 participants, aged 35–55 years at baseline. Results were adjusted for age, sex, socio-economic position, health behaviours, health status/conditions, medication, and social support.
Results: Over a 17.4 year follow-up, chronic depressive symptoms did not increase the risk of cancer incidence compared to those who never experienced symptoms (hazard ratio (HR)=1.03, 95% confidence interval (CI): 0.71-1.49). Participants who experienced new depressive symptoms had an increased risk of cancer incidence in the first 9 years of follow-up (HR=1.89, 95% CI: 1.23-2.90) but no increased risk in later years (HR=0.84, 95% CI: 0.52-1.35).
Conclusion: Chronic depressive symptoms were not associated with cancer incidence. In contrast, new-onset symptoms were associated with a substantially increased risk, possibly due to reverse causality.

Key words: cancer; depressive symptoms; depression; longitudinal studies; psycho-oncology.

Introduction

Meta-analyses indicate that depressive symptoms are a risk factor for both cancer incidence and mortality [1–3], although there is large disparity among associations from individual studies. Mixed findings can be attributed to methodological factors, such as failure to adequately control for potential confounders [4–6], differences in study sample characteristics [3], and inadequate measures of depression [4]. There are also potential difficulties surrounding the accuracy of depression diagnosis among those with physical illnesses due to somatic symptom overlap. For example, symptoms such as fatigue, loss of appetite, and general malaise, could be due to depression, or 'sickness behaviour' as a result of cancer or comorbid illness. [7–9]. In addition, no study has taken into account a participants' history of depression, which could be an important determinant of cancer incidence. For example, new-onset/recent depressive symptoms have been shown to increase the risk of cardiovascular events [10,11] and all-cause mortality [12].

There are several possible biological and behavioural pathways by which the association between depression and cancer incidence may be explained. Firstly, depression may have a direct effect on the immune system through dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis [4,13–15]. Secondly, depression may indirectly lead to cancer through behavioural pathways, such as smoking, alcohol consumption, and low levels of physical activity [16–19]. Equally, depressed patients may be less likely to attend routine health checks, and have poorer adherence to treatment regimens [20,21]. A third consideration is the possibility of reverse causality whereby sub-clinical cancer may cause depression as a result of an inflammatory response [22–25].

This is the first study known to the authors to use repeated measures of depression to explore the association between depressive symptom history and cancer incidence. It is also the first to isolate the role of affective/emotional depressive symptoms, which are less likely to be confounded by somatic symptoms of poor physical health, such as fatigue or tiredness. A further strength includes data on a wide range of potential confounders and mediators.

Methods

Participants

The target population for the Whitehall II study was all London-based office staff aged 33-55 working in 20 civil service departments, covering a wide range of employment grades from low to high incomes. With a response rate of 73%, the study recruited 10,308 participants; 6895 men and 3413 women at phase 1 (1985-1988) [26]. Phase 2 (1989-1990) comprised of 8132 participants (79% of phase 1 responders), and phase 3 (1991-1994) comprised of 8815 participants (86% of phase 1 responders). Mean follow-up for cancer incidence after phase 3 was 15.6 years (range 0.08 to 17.4), with a total 109,209 person-years and 776 incident cancers.

Depressive Symptoms

At phases 1, 2 and 3, participants completed the 30-item General Health Questionnaire (GHQ-30) [27,28] which is used to detect minor psychiatric disorders in non-psychiatric populations [29,30]. A four-item depressive symptom sub-scale was derived (Cronbach's α: 0.88) based-on principal components factor analysis [31,32]. The scale has been compared with the validated seven-item depression subscale of the 28-item GHQ [33], and the test-

retest reliability was r=0.78 in a sample of 286 participants who repeated the GHQ depression sub-scale within 1 month [33]. Participants were asked whether, over the last few weeks, they had: 'been thinking of yourself as a worthless person'; 'felt that life is entirely hopeless'; 'felt that life isn't worth living'; and, 'found at times you couldn't do anything as your nerves were so bad'. These 4-items assess the affective/emotional symptoms of depression only, and do not cover somatic symptoms, such as tiredness, pain, or sleep disturbance. Items were scored on a four-point scale (0= 'not at all', 1= 'no more than usual', 2= 'rather more than usual', 3= 'much more than usual'), giving a range from 0 – 12. Participants were defined as experiencing an 'episode of depressive symptoms', if they had a sum score of 4 or more. This cut point, as used in previous studies, results in a prevalence rate similar to that of clinical depression in the general UK population [33–35]. The dichotomised GHQ depression sub-scale was used to create the following two exposure variables: Depression Incidence and Depression History.

'Depression Incidence' indicates the number of times a participant experienced an episode of depressive symptoms across phases 1 to 3. Participants who did not experience an episode of depressive symptoms at phase 1, 2 or 3, were classed as having 'never' experienced depressive symptoms. Those who reported an episode at all three phases were classed as experiencing 'chronic' depressive symptoms, as defined previously by Penninx *et al.* [10].

'Depression History' refers to the temporal arrangement of depressive symptom episodes. Over three-quarters of depressive and anxiety disorders begin prior to age twenty-four, whilst new-onset disorder in adulthood remains relatively rare [36–38]. To ensure the highest probability of capturing emerging depressive symptoms, participants who had a depressive episode at phase 3, but not at phase 1 or 2 were classified as experiencing 'new' depressive symptoms, as previously defined by Penninx *et al.* [10]. 'Never' and 'chronic' depressive symptoms were defined in the same way as the Depression Incidence variable. All other participants who experienced a depressive symptom episode once or twice across phases 1 to 3 were classified as experiencing a history of 'non-chronic' depressive symptoms.

Cancer incidence

Cancer incidence data for 1971-2008 were obtained from the National Health Service Central Register (NHSCR) for nearly all participants (n=10,297). Cancer sites in cancer registry data were coded according to International Classification of Diseases revision 9 (ICD-9) in 1971-1994, and revision 10 (ICD-10) from 1995 onwards. Incidence of malignant cancer was defined as ICD-9 codes 140-208 or ICD-10 codes COO-C97. Follow-up time was from phase 3 to first incident cancer, or censored at death or end 2008. Total incident cancer was 776, this included 109 smoking-related, 311 hormone-related, and 356 other. Hormone related cancers were breast (ICD9 174; ICD10 C50), cervix (180; C53), corpus uteri (182; C54), ovary (183; C56), and prostate (185; C61). Smoking-related cancers were considered to be oral cavity (ICD9 140-149; ICD10 C00-C06, C09-C14), oesophagus (150; C15), pancreas (157; C25), respiratory and intrathoracic organs (160-163; C30-C34, C38), and urinary tract (188-189; C64-C68) [39].

Covariates

Variables believed to be associated with both depression and cancer incidence were included as covariates in the analysis, and were obtained at phase 3 unless otherwise indicated.

Demographic data included age and sex. Socio-economic position was indexed by civil service employment grade, ranging from 1 (highest) to 6 (lowest) [26].

Measures of health status obtained from clinical screening included body-mass-index (BMI in kg/m^2, grouped into quintiles) and systolic blood pressure (mmHg, grouped into quintiles). Self-reported 'health in the last year' was assessed using a 5 point scale (very good, good, average, poor, very poor).

Health conditions included self-reported respiratory illness (yes/no), and presence of longstanding illness (yes/no).

Medication use included self-reported 'antidepressant use in the last 14 days' at phase 1 (yes/no).

Health behaviours were categorised as follows: smoking (non-smoker, ex-smoker, 1-10 per day, 11-20 per day, and 21+ per day); alcohol consumption (units per week, grouped into quintiles); fruit and vegetable consumption (0-2 per week, 3-4 per week, 5-6 per week, daily, and 2+ per day); meat consumption (0-3 per month, 1-2 per week, 3-4 per week, 5-6 per week, and daily); and physical activity (number of hours of mild/moderate/vigorous physical activity per week).

Social support measures were obtained from phase 2, and included 'emotional support' (seven-item scale measuring confiding, boosting self-esteem, sharing interests and reciprocity), 'practical support' (four-item scale measuring the level of practical help received), and 'negative aspects of social support' (four-item scale measuring the inadequacy of the closest person to deliver support [31]. These measures were based on the person nominated as closest in the Close Persons Questionnaire [40], which has been validated against the Self Evaluation and Social Support Interview in a sample of 201 Civil Servants [40]. Social support measures were grouped into tertiles representing low, medium and high support.

Missing data

There were missing data for the following covariates: employment grade (n=6, 0.1%); smoking (n=232, 3.3%); alcohol consumption (n=6, 0.1%); meat consumption (n=10, 0.1%); body mass index (n=310, 4.4%); systolic blood pressure (n=306, 4.4%), fruit and vegetable consumption (n=7, 0.1%);respiratory illness (n=5, 0.1%), health in the last year (n=8, 0.1%); antidepressant use (question introduced only partway through phase 1 data collection, n=1748, 25.0%); practical support (n=258, 3.7%); emotional support (n=277, 4.0%); and negative aspects of social support (n=278, 4.0%). Overall 12.8% of records had missing covariate data (34.7% if including antidepressant use); therefore, multiple imputation (*mi* command in Stata 12.0) [41,42] was used to impute missing data for covariates. Analysis models were run with ten imputations.

Statistical Analysis

All analyses were conducted using Stata 12.0. To assess the characteristics of the study sample, continuous variables were grouped to allow the calculation of rate-ratios using the Mantel-Haenszel method. Kaplan-Meier graphs were produced to show the unadjusted

relationship between Depression Incidence/Depression History and cancer incidence over time. Log-rank tests were used to test the equality of survival curves.

The relationship between Depression Incidence/Depression History and cancer incidence was explored using Cox Regression models [43]. All models were first adjusted for age and sex. Second, covariates were grouped into measures of socio-economic position, health behaviours, health status, health conditions, social support and medication (defined previously) and the impact of each group was assessed in turn. Third, all covariates were then added into the model and likelihood ratio χ2 tests (LRT) were used to assess whether covariates were independent predictors of cancer incidence. Finally, if a covariate did not predict cancer incidence, and its removal from the model did not affect the Depression Incidence/Depression History hazard-ratios, then it was excluded from the final model.

The proportional hazards assumption was assessed using the Schoenfeld Residuals method. Where there was evidence against the proportional hazards assumption, piecewise Cox regression was used to estimate separate hazard ratios for early and later follow up. Interactions coefficients were examined between Depression Incidence/Depression History and each of the covariates. If necessary, covariates were reclassified into fewer categories to ensure cancer incidence was not zero among interaction sub-categories.

Sensitivity analyses involved the inclusion of a 3-year wash-out period to test whether depressive symptoms occurred as a result of suspected cancer prior to diagnosis. The association between Depression Incidence/History and cancer incidence was also examined by cancer type.

Results

Excluded participants

Of the 10,308 participants in the Whitehall II study, 3325 were excluded from analysis leaving a study sample of 6983. Reasons for exclusion were non-response (n=2176) or death (n=125) before phase 3, no link to cancer registry (n=11), previous cancer incidence (cancer registry n=139; self-reported n=12), and missing GHQ data at either phase 1, 2 or 3 (n=987). Participants were not included if they had GHQ data at two phases only as it was considered questionable to make assumptions about the chronicity or history of depressive symptoms based on only two time points.

Cox regression analysis showed there was no difference in cancer incidence risk between excluded participants and study sample participants after adjustment for age and sex (hazard ratio (HR)=1.08, 95% confidence interval (CI): 0.95, 1.23); however inclusion/exclusion was associated with employment grade, smoking, self-reported health, fruit and vegetable consumption and physical activity (χ^2 all $P < 0.002$). Excluded participants were more likely to smoke, be clerical and support staff, eat fewer fruit and vegetables, do fewer hours of physical activity, and report poorer health in the last year.

Table 1. Descriptive characteristics of the study sample and crude cancer incidence rates (n=6983, 776 incident cancer).

Characteristic		N	%	Inciden	Rate (per	Rate ratio
Depression	0 - Never	5167	74.0	589	7.29	1 (ref)
Incidence[a]	1 occasion	1084	15.5	114	6.75	0.93 (0.76 to 1.13)
	2 occasions	470	6.7	42	5.68	0.78 (0.57 to 1.07)
	3 - Chronic	262	3.8	31	7.61	1.04 (0.73 to 1.50)
Depression	Never	5,167	74.0	589	7.29	1 (ref)
History[b]	New	346	5.0	42	7.94	1.09 (0.80 to 1.49)
	Non-	1,208	17.3	114	6.00	0.82 (0.67 to 1.00)
	Chronic	262	3.8	31	7.61	1.04 (0.73 to 1.50)
Age group	35-39	1932	27.7	106	3.40	1.0
	40-44	1794	25.7	166	5.79	1.70 (1.33 to 2.17)
	45-49	1419	20.3	160	7.25	2.13 (1.67 to 2.73)
	50-56	1838	26.3	344	12.62	3.71 (2.99 to 4.62)
Sex	Male	4856	69.5	507	6.66	1.0
	Female	2127	30.5	269	8.14	1.22 (1.06 to 1.42)
Employment	1 - High	1217	17.4	163	8.57	1 (ref)
grade	2	1510	21.6	158	6.66	0.78 (0.63 to 0.97)
	3	990	14.2	102	6.54	0.76 (0.60 to 0.98)
	4	1198	17.2	126	6.71	0.78 (0.62 to 0.99)
	5	983	14.1	103	6.70	0.78 (0.61 to 1.00)
	6 - Low	1079	15.5	122	7.34	0.86 (0.68 to 1.08)
	Missing	6	0.1			
Smoking	Non-	3489	50.0	376	6.84	1 (ref)
	Ex-smoker	2455	35.2	268	7.01	1.03 (0.88 to 1.20)
	1-10/day	293	4.2	38	8.37	1.22 (0.88 to 1.71)
	11-20/day	336	4.8	38	7.32	1.07 (0.77 to 1.49)
	>21/day	178	2.6	25	9.28	1.36 (0.91 to 2.04)
	Missing	232	3.3			
Longstanding	No	4603	65.9	484	6.68	1.0
illness	Yes	2380	34.1	292	7.95	1.19 (1.03, 1.38)

Abbreviation: pyrs, person years.

[a]Depression Incidence: Number of depressive symptom episodes across phases 1 to 3.

[b] Depression History: Never = no depressive symptom episodes phase 1, 2 or 3; New =

episode phase 3 only; Non-chronic = episode once/twice from phase 1 or 2; Chronic = episode phase 1, 2, and

Descriptive characteristics

Table 1 presents the characteristics of the study sample and crude cancer incidence rates for selected covariates (see Appendix A for full table). The majority (69.5%) of the sample are male. The sample is relatively evenly distributed across each of the age groups, with a mean age of 44.4 years (SD=6.04) at phase 1. 74% of the sample had never experienced an episode of depressive symptoms.

Log-rank tests showed an association between cancer incidence and age, sex, BMI, longstanding illness, physical activity, alcohol consumption (all $p<0.05$, not shown). The rate-ratios (table 1; see Appendix A for full table) indicate that the risk of cancer incidence increases with age, if participants are female, report longstanding illness, and have a BMI greater than 22.4. Those doing 2-5 hours of physical activity appear to have a lower risk of cancer incidence than those doing higher or lower levels, whilst those who drink lightly to moderately (1-16 units/week) have an increased risk of cancer incidence compared to those who never drink and heavier drinkers (17+ units/week).

Log-rank tests for all other covariates were not statistically significant (all $p>0.05$, not shown); although the rate-ratios suggest that those in the highest employment grade (grade 1) appear to have an increased risk of cancer incidence compared to those in lower grades.

Figure 1. Kaplan-Meier survival curves by Depression Incidence (1985-1994), 17.4 year follow-up.

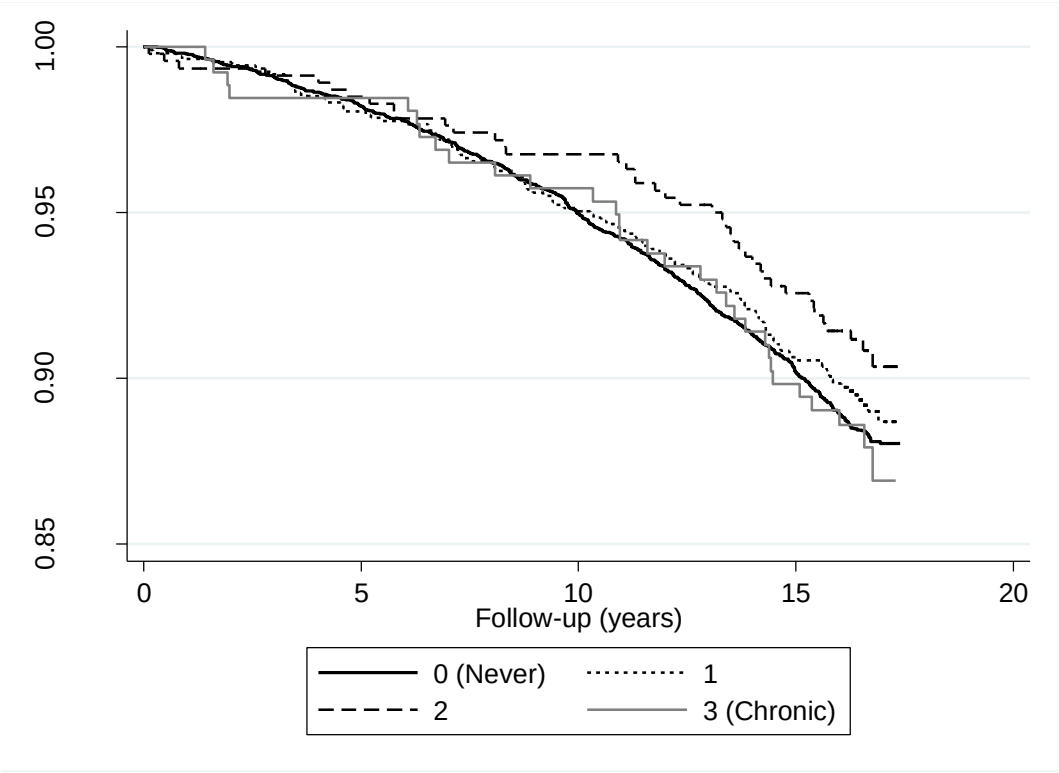

Figure 2. Kaplan-Meier survival curves by Depression History (1985-1994), 17.4 year follow-up.

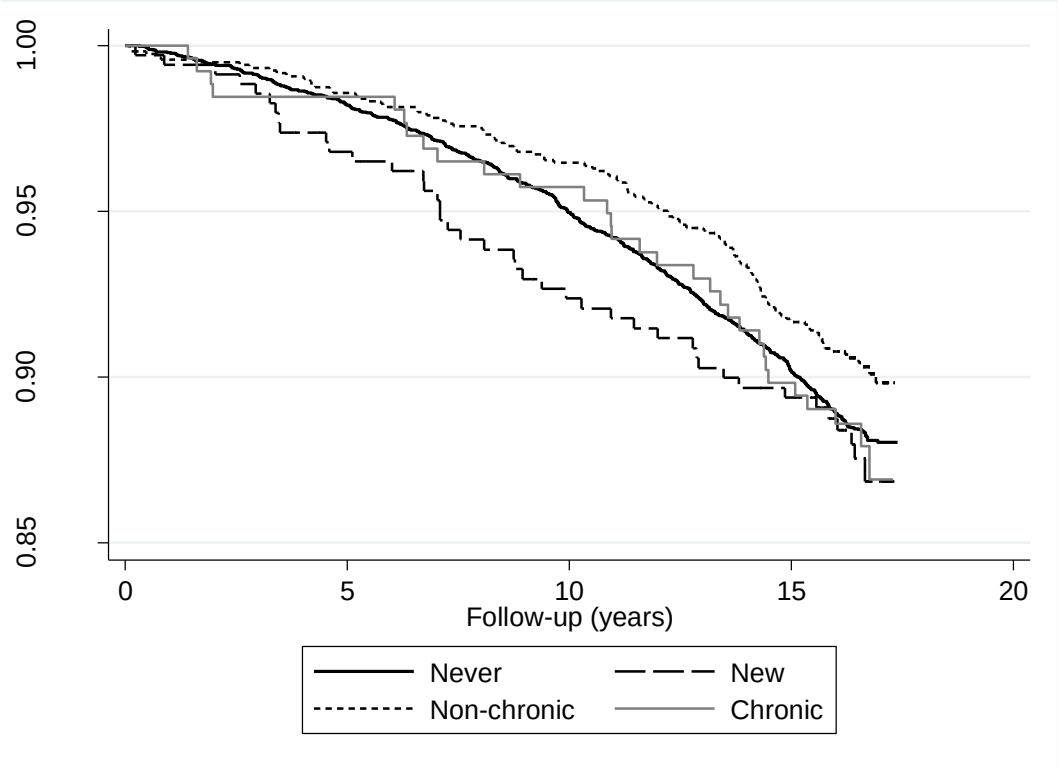

Figure 1 and 2 show unadjusted cumulative cancer free survival curves with respect to Depression Incidence and Depression History. There was no overall difference in survival curves with respect to Depression Incidence, Log Rank $\chi^2(3)=3.0$, $P=0.38$, and Depression History, LR$\chi^2(3)=4.5$, $P=0.21$.

The proportional hazard assumption was borderline violated with regard to 'new' depressive symptoms (LR$\chi^2(3)$, $P=0.05$) therefore analysis of Depression History was conducted on the first and second half of follow-up: less than 9 years and greater than 9 years. Figure 2 indicates that participants with 'new' depressive symptoms had the lowest survival probability until approximately 9 to 10 years of follow-up when survival probability appears to increase relative to the other groups.

Table 2. Hazard Ratios (HR) for the association between Depression Incidence/Depression History and cancer incidence over a 17.4 year follow-up; 776 incident cancer, n=6983.

	Hazard ratio (95% CI)			
	Model A: Adjusted for age and sex	**Model A + employment grade**	**Fully Adjusted**[a]	**Fully adjusted** + 3 year wash-out[b]
Depression Incidence[c]				
0 (Never)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
1	0.95 (0.78, 1.16)	0.95 (0.78, 1.16)	0.94 (0.77, 1.15)	0.95 (0.77, 1.18)
2	0.81 (0.59, 1.11)	0.82 (0.60, 1.12)	0.79 (0.58, 1.09)	0.78 (0.57, 1.08)
3 (Chronic)	1.02 (0.71, 1.47)	1.07 (0.75, 1.54)	1.05 (0.73, 1.52)	1.09 (0.75, 1.57)
Depression History[d]				
Never	1 (ref)	1 (ref)	1 (ref)	1 (ref)
New	1.21 (0.89, 1.66)	1.23 (0.90, 1.68)	1.23 (0.89, 1.68)	1.18 (0.85, 1.66)
Non-chronic	0.83 (0.68, 1.02)	0.83 (0.68, 1.02)	0.82 (0.67, 0.99)	0.83 (0.67, 1.02)
Chronic	1.02 (0.71, 1.47)	1.07 (0.75, 1.54)	1.05 (0.73, 1.51)	1.01 (0.68, 1.49)

[a] Adjusted for age sex, employment grade smoking, alcohol consumption, meat consumption, mild physical activity, body-mass-index, systolic blood pressure, respiratory illness, and longstanding illness.

[b] 713 incident cancer, n=6887

[c] Depression Incidence: Number of depressive symptom episodes across phases 1 to 3.

[d] Depression History: Never = no depressive symptom episodes phase 1, 2 or 3; New = episode phase 3 only; Non-chronic = episode once/twice from phase 1or 2; Chronic = episode phase 1, 2, and 3.

Table 3. Hazard ratios (HR) for the association between Depression History and cancer incidence by follow-up time.

	< **9 years**			≥ **9 years**	
	Hazard Ratio (95% CI)			**Hazard Ratio (95% CI)**	
	Age and sex adjusted	**Fully adjusted**[a]	**Fully adjusted** + 3 year wash out[b]	**Age and sex adjusted**	**Fully adjusted**[a]
	(285 incident cancer, n= 6983)			(491 incident cancer, n= 6582)	
Depression history[c]					
Never	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
New	1.88 (1.23, 2.88)	1.89 (1.23, 2.90)	1.95 (1.21, 3.17)	0.82 (0.51, 1.31)	0.84 (0.52, 1.35)
Non-chronic	0.76 (0.54, 1.08)	0.73 (0.52, 1.04)	0.75 (0.50, 1.10)	0.87 (0.68, 1.12)	0.86 (0.67, 1.11)
Chronic	1.00 (0.55, 1.83)	0.98 (0.53, 1.82)	0.83 (0.38, 1.77)	1.03 (0.66, 1.62)	1.09 (0.69, 1.73)

[a] Adjusted for age, sex, employment grade, smoking, alcohol consumption, meat consumption, mild physical activity, body-mass-index, systolic blood pressure, respiratory illness, and longstanding illness.

[b] 222 incident cancer, n=6887

[c] Depression History: Never = no depressive symptom episodes phase 1, 2 or 3; New = episode phase 3 only; Non-chronic = episode once/twice from phase 1 or 2; Chronic = episode phase 1, 2, and 3.

Multivariable Associations

Table 2 presents associations between Depression Incidence/Depression History and cancer incidence over the full 17.4 year follow-up. Neither Depression Incidence nor Depression History were significantly associated with cancer incidence in age and sex adjusted models. Fully adjusted associations between Depression Incidence/Depression History and cancer incidence were almost identical to those adjusted for age and sex only. There was little impact on the hazard-ratios after adjusting for each group of potential mediators and confounders.

With regard to Depression Incidence, the fully adjusted model shows those who experienced one episode of depressive symptoms and those who had 'chronic' depressive symptoms were no more likely to develop cancer than those who 'never' experienced depressive symptoms. Participants who experienced two episodes of depressive symptoms appeared to have a decreased risk of cancer incidence, although this association did not reach statistical significance (HR=0.79, 95% CI: 0.58, 1.09).

With regard to Depression History, there was a borderline association between those who had a history of 'non-chronic' depressive symptoms and a decreased risk of cancer incidence (HR=0.82, 95% CI: 0.67, 0.99).

Table 3 shows that during the first 9 years of follow-up, those with 'new' depressive symptoms appeared to have an increased risk of developing cancer compared to those who 'never' experienced symptoms (HR=1.89, 95% CI: 1.23, 2.90); this association persisted after the inclusion of a 3-year wash-out period. In contrast, over >9 years of follow-up, those with 'new' depressive symptoms appeared to have a tendency for a reduced risk of developing cancer, although this was not statistically significant (HR=0.84 95% CI: 0.52, 1.35). The hazard ratios for chronic and non-chronic symptoms appear relatively consistent over time. Over both periods of follow-up, fully adjusted associations between Depression History and cancer incidence were very similar to those adjusted for age and sex only (see Appendix 2 for full multivariable models).

Across all crude and multivariable analyses, there was no evidence of an interaction between Depression Incidence/Depression History and sex (p=0.12/0.90), or other covariates (all interaction coefficients $p > 0.05$).

Sensitivity Analysis

The Depression Incidence and Depression History hazard ratios were largely unaffected after inclusion of a three-year wash out period (Tables 2 and 3).

Power was too low to present the results by cancer type, although the hazard ratios were examined to identify possible trends. Over a 17.4 year follow-up, the age and sex adjusted association between Depression Incidence/History and hormone-related cancers (n=311) was largely identical compared to all-cancers combined (n=776). However, those with chronic symptoms appeared to have an increased risk of smoking-related cancer (n=109; HR=1.74, 95% CI: 0.80, 3.76) and a lower risk of other cancers (n=356; HR=0.80, 95% CI: 0.44, 1.45), compared to hormone-related cancers (HR=1.04, 95% CI: 0.60, 1.82) and all-cancers combined.

Discussion

This study shows that over a 17.4 year follow-up, 'chronic' depressive symptoms were not associated with an increased risk of cancer incidence compared to those who 'never' experienced symptoms; there was no evidence of a dose-response relationship. The hazard ratio for 'new' depressive symptoms was different depending on follow-up time. In the first nine years of follow-up, new-onset depressive symptoms were associated with an increased risk of cancer incidence; however in later years ($\geq$ 9 year follow-up), the association was attenuated and no longer statistically significant. Unexpectedly, intermittent, or 'non-chronic' symptoms were associated with a borderline reduced risk. There was no evidence of an interaction between Depression Incidence/History and sex, which is consistent with other studies of cancer incidence and mortality [1–3,44,45].

A comparison of the Depression History and Depression Incidence variables indicates an important difference in the role a single episode of depressive symptoms depending on when it occurred. A single episode experienced at either phase 1, 2, or 3 demonstrated no apparent association with cancer incidence, whereas a 'new' episode experienced at phase 3 appeared to increase the risk of cancer incidence by 89% in the first 9 years of follow-up. This finding is consistent with reverse causality, whereby sub-clinical cancer may lead to depressive symptoms; Dantzer et al., [23] suggest that long-term exposure to proinflammatory cytokines, such as in sub-clinical cancer, may act directly on the brain to elicit sickness behaviour, and the additional development of depressive symptoms in vulnerable individuals [22,23]. Animal studies have also shown that tumours may elicit depressive and anxiety symptoms in rats, even in the absence of overt sickness behaviours [46]. Equally, those with 'new' symptoms may be less adapted to cope with emotional stress compared to those who have been previously depressed, due to differences in experience, expectations and stoicism [47]. The persistence of the association between new depressive symptoms and cancer incidence after the inclusion of a 3 year wash-out period suggests that the association is not simply due to psychological stress as a result of suspected cancer. Previous research has also shown that new depressive symptoms were a better predictor of cardiovascular events than those with a history of depressive symptoms [10] and that 'recent' affective disorder was more strongly associated with mortality than 'lifetime' affective disorder [12].

Those experiencing 'chronic' depressive symptoms did not have an increased risk of cancer incidence compared to those who 'never' experienced symptoms. This is inconsistent with previous findings which have reported risk ratios around 2.0 with respect to studies that have used measures of chronic depression [4,12,44].

It is plausible that these differential associations could be attributed to methodological factors. For example, the study reports all-site cancer incidence only. Cancers are not biologically homogenous and as such depression may influence different types of cancer in different ways [4]. Sensitivity analysis suggested that the role of chronic depressive symptoms could be more important with respect to smoking-related cancers, which made up just 14% of the sample. If the effect of chronic symptoms is mediated through behavioural pathways, then this could potentially explain the null finding.

Equally, a meta-analysis by Pinquart and Duberstein demonstrated a tendency for stronger associations between depression and cancer mortality in those aged over 70 [3]. The current

study has a mean participant age of only 44.4 years at baseline, which could help to explain the differential associations. Stronger associations observed in older cohorts could suggest that depressive scales are simply tapping somatic symptoms of co-morbid disease [3], including sub-clinical cancer. All previous studies known to the authors have used depressive scales inclusive of somatic symptoms.

It is also possible that the GHQ-subscale cut-off captured moderate, rather than severe depressive symptoms, which could have additionally contributed to the null association. Stronger associations between depression and cancer incidence and mortality have been shown with regard to more severe depressive symptoms, and depression diagnosis [2,4,44,48].

Strengths and Limitations

The strengths of the study include a large sample, high quality prospective data on a wide range of confounders and mediators, and a long mean follow-up (15.6 years). Cancer incidence data was ascertained for nearly all participants from national cancer register linkage, available from 1971. Repeated measures of affective/emotional depressive symptoms helped to distinguish between transient and chronic episodes, and were arguably less likely to be confounded by symptoms of physical ill health compared to depressive scales incorporating somatic items.

The study has several limitations. The study had low power to explore associations with respect to different types of cancer, and also to examine potential interactions, such as increased cancer risk in sub-groups such as smokers [5,49,50]. It is also possible that UK cancer registry data was underreported during the early years of follow-up [51]; however underreporting is unlikely to be related to depressive symptoms and so should not bias results – towards the end of follow-up, coverage was estimated to be around 97% [52].

Measures of depressive symptoms in early adulthood were not available so there may be some people in the new onset group who experienced symptoms of depression prior to inclusion in the study. By restricting our definition of new onset to phase 3 only, we attempted to limit this possibility. Using the alternative definition of new onset at both phases 2 and 3 resulted in weaker associations with cancer incidence over a 9-year follow-up (fully adjusted HR=1.54, 95% CI: 1.05-2.24) so our results for new depression may be an overestimate. The GHQ depression sub-scale was also shown to have low sensitivity when compared with a measure of depression based on a structured psychiatric interview [53].

Most covariates were obtained from phase 3 only; it is possible that measures from earlier time-points could play an important role in cancer development, particularly for factors such as smoking and alcohol consumption. However, other covariates were known to follow strong trajectories, such as systolic blood pressure and BMI [54–56], or were retrospective in nature, such as ‘longstanding illness’, which suggests that accounting for earlier measures would have been of limited benefit.

There is some evidence of selection bias whereby participants with missing depressive symptom data were more likely to smoke, be in a low employment grade, eat fewer fruit and vegetables, do fewer hours of physical activity, and report poorer physical health; which

could affect external validity. A final consideration is that multiple comparisons were conducted which increases the likelihood that the results could be due to chance.

Conclusion

Previous research has demonstrated that chronic depressive symptoms increase the risk of cancer incidence when using measures of depression inclusive of somatic symptoms; yet this study found no association with regard to chronic affective/emotional depressive symptoms. These differential findings could be due to low numbers of smoking-related cancers in our study sample, but may equally emphasise the need to distinguish between affective/emotional and somatic symptoms of depression.

New-onset depressive symptoms were associated with an increased-risk of cancer incidence, which is consistent with reverse causality as a result of inflammatory processes. It is possible that the aetiology of adult 'new-onset' depression is distinct to that of chronic depression.

Overall, this study highlights the importance of further research with regard to the relationship between life course profiles of depression and cancer incidence. If new-onset depression is found to predict cancer incidence, then this could serve as an important marker for the development of the disease.

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I confirm that each author has made a valuable contribution to this work: GA, JH and HP conceived and designed the study. GA and JH undertook the data analyses. GA drafted the manuscript, and JH and HP critically revised the manuscript for important intellectual content. All authors read and approved the final version.

Conflict of interests: All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf. The authors have no competing interests to report.

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Caption titles:

Figure 1. Kaplan-Meier survival curves by Depression Incidence (1985-1994), 17.4 year follow-up.

Figure 2. Kaplan-Meier survival curves by Depression History (1985-1994), 17.4 year follow-up.

Appendix A:

Table A.1. Descriptive characteristics of the study sample and crude cancer incidence rates; n=6983, 776 incident cancer (full table).

Characteristic		N	%	Incident cancer	Rate (per 1000	Rate ratio (95% CI)
Depression	0 - Never	5167	74.0	589	7.29	1 (ref)
Incidence[a]	1 occasion	1084	15.5	114	6.75	0.93 (0.76 to 1.13)
	2 occasions	470	6.7	42	5.68	0.78 (0.57 to 1.07)
	3 - Chronic	262	3.8	31	7.61	1.04 (0.73 to 1.50)
Depression	Never	5,167	74.0	589	7.29	1 (ref)
History[b]	New	346	5.0	42	7.94	1.09 (0.80 to 1.49)
	Non-chronic	1,208	17.3	114	6.00	0.82 (0.67 to 1.00)
	Chronic	262	3.8	31	7.61	1.04 (0.73 to 1.50)
Age group	35-39	1932	27.7	106	3.40	1.0
	40-44	1794	25.7	166	5.79	1.70 (1.33 to 2.17)
	45-49	1419	20.3	160	7.25	2.13 (1.67 to 2.73)
	50-56	1838	26.3	344	12.62	3.71 (2.99 to 4.62)
Sex	Male	4856	69.5	507	6.66	1.0
	Female	2127	30.5	269	8.14	1.22 (1.06 to 1.42)
Employment	1 - High	1217	17.4	163	8.57	1 (ref)
grade	2	1510	21.6	158	6.66	0.78 (0.63 to 0.97)
	3	990	14.2	102	6.54	0.76 (0.60 to 0.98)
	4	1198	17.2	126	6.71	0.78 (0.62 to 0.99)
	5	983	14.1	103	6.70	0.78 (0.61 to 1.00)
	6 - Low	1079	15.5	122	7.34	0.86 (0.68 to 1.08)
	Missing	6	0.1			

Smoking	Non-smoker	3489	50.0	376	6.84	1 (ref)
	Ex-smoker	2455	35.2	268	7.01	1.03 (0.88 to 1.20)
	1-10/day	293	4.2	38	8.37	1.22 (0.88 to 1.71)
	11-20/day	336	4.8	38	7.32	1.07 (0.77 to 1.49)
	>21/day	178	2.6	25	9.28	1.36 (0.91 to 2.04)
	Missing	232	3.3			
Alcohol units	None	1336	19.1	127	6.09	1 (ref)
grams p/wk	1 – 3	1254	18.0	149	7.60	1.25 (0.99 to 1.58)
	4 – 7	1350	19.3	170	8.05	1.32 (1.05 to 1.66)
	8 – 16	1620	23.2	189	7.48	1.23 (0.98 to 1.54)
	17+	1417	20.3	140	6.29	1.03 (0.81 to 1.31)
	Missing	6	0.1			
Physical activity	0 – 1	811	11.6	91	7.23	1 (ref)
hrs p/wk	2 – 3	1426	20.4	136	6.02	0.83 (0.64 to 1.09)
	4 – 5	1512	21.7	149	6.24	0.86 (0.67 to 1.12)
	6 – 9	1452	20.8	178	7.91	1.09 (0.85 to 1.41)
	10+	1782	25.5	222	8.04	1.11 (0.87 to 1.42)
Meat	0-3/month	707	10.1	81	7.35	1 (ref)
consumption	1-2/week	1335	19.1	146	7.03	0.96 (0.73 to 1.25)
	3-4/week	2565	36.7	289	7.19	0.98 (0.76 to 1.25)
	5-6/week	1751	25.1	185	6.72	0.91 (0.70 to 1.19)
	>7/week	615	8.8	74	7.76	1.05 (0.77 to 1.45)
	Missing	10	0.1			
Longstanding	No	4603	65.9	484	6.68	1 (ref)

Illness	Yes	2380	34.1	292	7.95	1.19 (1.03 to 1.38)
Respiratory illness	No	6508	93.2	722	7.09	1 (ref)
	Yes	470	6.7	52	7.15	1.01 (0.76 to 1.34)
	Missing	5				
Body mass index	15.0-22.39	1344	19.3	106	4.96	1 (ref)
	22.4-24.09	1344	19.3	140	6.62	1.33 (1.04 to 1.72)
	24.1-25.59	1367	19.6	170	7.95	1.60 (1.26 to 2.04)
	25.6-27.79	1331	19.1	162	7.76	1.56 (1.22 to 2.00)
	27.8+	1287	18.4	150	7.48	1.50 (1.18 to 1.93)
	Missing	310	4.4			
Systolic blood pressure, mmHg	52-108	1247	17.9	140	7.09	1 (ref)
	109-115	1240	17.8	123	6.26	0.88 (0.69 to 1.13)
	116-122	1410	20.2	149	6.72	0.95 (0.75 to 1.19)
	123-131	1393	20.0	147	6.73	0.95 (0.75 to 1.19)
	132+	1387	19.9	169	7.88	1.11 (0.88 to 1.39)
	Missing	306	4.4			

Abbreviation: pyrs, person years.

[a]Depression Incidence: Number of depressive symptom episodes across phases 1 to 3.

[b] Depression History: Never = no depressive symptom episodes phase 1, 2 or 3; New = episode phase 3 only; Non-chronic = episode once/twice from phase 1 or 2; Chronic = episode phase 1, 2, and 3.

Appendix B: Fully adjusted models for the association between Depression Incidence / Depression History and cancer incidence (full results).

Table B.1. Fully adjusted hazard Ratios for the association between Depression Incidence/covariates and cancer incidence over a 17.4 year follow-up; 776 incident cancer, n=6983.

		Hazard ratio[b] (95% CI)
Depression Incidence[a]	0 - Never	1 (ref)
	1 occasion	0.94 (0.77, 1.15)
	2 occasions	0.79 (0.58, 1.08)
	3 - Chronic	1.05 (0.73, 1.52)
Age (continuous)		1.09 (1.08, 1.10)
Sex	Male	1 (ref)
	Female	1.32 (1.10, 1.59)
Employment Grade	1 - High	1 (ref)
	2	0.90 (0.72, 1.12)
	3	0.89 (0.69, 1.14)
	4	0.87 (0.68, 1.10)
	5	0.72 (0.55, 0.94)
	6 - Low	0.66 (0.50, 0.88)
Smoking	Non-smoker	1 (ref)
	Ex-smoker	0.95 (0.81, 1.12)
	1-10/day	1.28 (0.91, 1.79)
	11-20/day	1.16 (0.82, 1.63)
	>21/day	1.57 (1.05, 2.37)
Alcohol units grams p/wk	None	1 (ref)
	1 – 3	1.27 (1.00, 1.62)
	4 – 7	1.40 (1.10, 1.77)
	8 – 16	1.35 (1.06, 1.71)
	17+	1.20 (0.93, 1.56)
Physical activity (hours p/wk)		1.01 (1.00, 1.02)
Body mass Index	15.0-22.39	1 (ref)
	22.4-24.09	1.25 (0.97, 1.63)
	24.1-25.59	1.51 (1.18, 1.93)
	25.6-27.79	1.41 (1.10, 1.82)

	27.8+	1.39 (1.08, 1.79)
Longstanding Illness	No	1 (ref)
	Yes	1.11 (0.95, 1.28)
Systolic blood pressure, mmHg	52-108	1 (ref)
	109-115	0.84 (0.66, 1.07)
	116-122	0.88 (0.69, 1.11)
	123-131	0.83 (0.65, 1.06)
	132+	0.85 (0.67, 1.07)
Respiratory illness	No	1 (ref)
	Yes	0.94 (0.7, 1.25)
Meat consumption	0-3/month	1 (ref)
	1-2/week	0.86 (0.65, 1.13)
	3-4/week	0.85 (0.66, 1.09)
	5-6/week	0.82 (0.63, 1.07)
	>7/week	0.98 (0.71, 1.36)

[a]Depression Incidence: Number of depressive symptom episodes across phases 1 to 3.
[b] Adjusted for age, sex, employment grade, smoking, alcohol consumption, meat consumption, mild physical activity, body-mass-index, systolic blood pressure, respiratory illness, and longstanding illness.

Table B.2. Fully adjusted hazard ratios for the association between Depression History/covariates and cancer incidence over a 17.4 year follow-up; 776 incident cancer, n=6983.

		Hazard ratio[b] (95% CI)
Depression History[a]	Never	1 (ref)
	New	1.23 (0.89, 1.68)
	Non-chronic	0.82 (0.67, 1.00)
	Chronic	1.05 (0.73, 1.52)
Age (continuous)		1.09 (1.08, 1.11)
Sex	Male	1 (ref)
	Female	1.33 (1.11, 1.59)
Employment Grade	1 - High	1 (ref)
	2	0.90 (0.72, 1.13)
	3	0.89 (0.69, 1.14)
	4	0.87 (0.68, 1.10)
	5	0.72 (0.55, 0.94)
	6 - Low	0.66 (0.50, 0.87)
Smoking	Non-smoker	1 (ref)
	Ex-smoker	0.95 (0.81, 1.12)
	1-10/day	1.27 (0.91, 1.78)
	11-20/day	1.15 (0.82, 1.62)
	>21/day	1.56 (1.04, 2.35)
Alcohol units grams p/wk	None	1 (ref)
	1 – 3	1.27 (1.00, 1.62)
	4 – 7	1.40 (1.11, 1.78)
	8 – 16	1.36 (1.07, 1.72)
	17+	1.21 (0.93, 1.58)
Physical activity (hours p/wk)		1.01 (1.00, 1.02)
Body mass Index	15.0-22.39	1 (ref)
	22.4-24.09	1.26 (0.97, 1.63)
	24.1-25.59	1.52 (1.19, 1.94)
	25.6-27.79	1.41 (1.10, 1.81)

	27.8+	1.39 (1.08, 1.80)
Longstanding Illness	No	1 (ref)
	Yes	1.11 (0.95, 1.28)
Systolic blood pressure, mmHg	52-108	1 (ref)
	109-115	0.84 (0.66, 1.07)
	116-122	0.88 (0.70, 1.11)
	123-131	0.83 (0.65, 1.06)
	132+	0.85 (0.67, 1.07)
Respiratory illness	No	1 (ref)
	Yes	0.94 (0.70, 1.25)
Meat consumption	0-3/month	1 (ref)
	1-2/week	0.86 (0.65, 1.13)
	3-4/week	0.85 (0.66, 1.10)
	5-6/week	0.82 (0.62, 1.07)
	>7/week	0.98 (0.71, 1.36)

[a] Depression History: Never = no depressive symptom episodes phase 1, 2 or 3; New = episode phase 3 only; Non-chronic = episode once/twice from phase 1 or 2; Chronic = episode phase 1, 2, and 3

[b] Adjusted for age, sex, employment grade, smoking, alcohol consumption, meat consumption, mild physical activity, body-mass-index, systolic blood pressure, respiratory illness, and longstanding illness.

Table B.3. Fully adjusted hazard ratios for the association between Depression History/covariates and cancer incidence by follow-up time.

		Hazard ratio[b] (95% CI)	
		< 9 year (285 incident cancer, n= 6983)	**≥ 9 year** (491 incident cancer, n= 6582)
Depression History[a]	Never	1 (ref)	1 (ref)
	New	1.89 (1.23, 2.90)	0.84 (0.52, 1.35)
	Non-chronic	0.73 (0.52, 1.04)	0.86 (0.67, 1.11)
	Chronic	0.98 (0.53, 1.82)	1.09 (0.69, 1.73)
Age (continuous)		1.10 (1.07, 1.12)	1.09 (1.07, 1.11)
Sex	Male	1 (ref)	1 (ref)
	Female	1.75 (1.31, 2.34)	1.11 (0.88, 1.41)
Employment Grade	1 - High	1 (ref)	1 (ref)
	2	0.99 (0.66, 1.47)	0.87 (0.67, 1.13)
	3	1.10 (0.71, 1.69)	0.80 (0.59, 1.09)
	4	1.06 (0.70, 1.60)	0.79 (0.58, 1.06)
	5	1.00 (0.64, 1.55)	0.59 (0.41, 0.83)
	6 - Low	0.77 (0.48, 1.21)	0.62 (0.44, 0.88)
Smoking	Non-smoker	1 (ref)	1 (ref)
	Ex-smoker	1.13 (0.87, 1.47)	0.86 (0.70, 1.05)
	1-10/day	1.04 (0.57, 1.89)	1.41 (0.94, 2.12)
	11-20/day	1.12 (0.64, 1.97)	1.17 (0.77, 1.79)
	>21/day	1.48 (0.71, 3.08)	1.61 (0.97, 2.65)
Alcohol units grams p/wk	None	1 (ref)	1 (ref)
	1 – 3	1.35 (0.93, 1.97)	1.23 (0.90, 1.67)
	4 – 7	1.36 (0.92, 2.00)	1.43 (1.05, 1.93)
	8 – 16	1.45 (0.99, 2.14)	1.30 (0.95, 1.76)
	17+	1.13 (0.72, 1.76)	1.25 (0.90, 1.73)
Physical activity (hours p/wk)		1.01 (1.00, 1.03)	1.01 (1.00, 1.02)
Body mass Index	15.0-22.39	1 (ref)	1 (ref)
	22.4-24.09	1.24 (0.82, 1.88)	1.27 (0.89, 1.80)
	24.1-25.59	1.17 (0.78, 1.74)	1.78 (1.29, 2.46)

	25.6-27.79	1.06 (0.71, 1.58)	1.67 (1.20, 2.33)
	27.8+	1.10 (0.73, 1.65)	1.61 (1.15, 2.27)
Longstanding Illness	No	1 (ref)	1 (ref)
	Yes	1.14 (0.89, 1.45)	1.09 (0.9, 1.31)
Systolic blood pressure, mmHg	52-108	1 (ref)	1 (ref)
	109-115	0.90 (0.59, 1.37)	0.80 (0.59, 1.09)
	116-122	1.13 (0.76, 1.68)	0.76 (0.57, 1.02)
	123-131	1.02 (0.68, 1.52)	0.74 (0.55, 1.00)
	132+	1.06 (0.71, 1.57)	0.75 (0.56, 1.00)
Respiratory illness	No	1 (ref)	1 (ref)
	Yes	0.85 (0.52, 1.41)	0.99 (0.69, 1.41)
Meat consumption	0-3/month	1 (ref)	1 (ref)
	1-2/week	0.76 (0.50, 1.14)	0.95 (0.65, 1.38)
	3-4/week	0.68 (0.47, 1.00)	1.00 (0.71, 1.41)
	5-6/week	0.61 (0.40, 0.93)	0.99 (0.69, 1.42)
	>7/week	0.77 (0.46, 1.30)	1.15 (0.76, 1.76)

[a] Depression History: Never = no depressive symptom episodes phase 1, 2 or 3; New = episode phase 3 only; Non-chronic = episode once/twice from phase 1 or 2; Chronic = episode phase 1, 2, and 3

[b] Adjusted for age, sex, employment grade, smoking, alcohol consumption, meat consumption, mild physical activity, body-mass-index, systolic blood pressure, respiratory illness, and longstanding illness.