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Depression and anxiety during the year before death from cancer

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ABSTRACT

Objective: Previous studies of depression and anxiety during the year before death have reported different findings. We therefore aimed to study depression and anxiety in patients who had died from cancer and had previously attended cancer clinics.

Methods: We analysed routine data on 4869 deceased patients who had completed the Hospital Anxiety and Depression Scale (HADS) as part of their routine cancer care. The HADS data were linked with demographic, cancer and mortality data from national registries. We used data from all HADS completed in the last year of life to investigate the relationships between mean depression (HADS-D) and anxiety (HADS-A) scores and the percentages of high scores (≥11 on each subscale) and time to death (Analysis 1). This analysis used multivariable linear regression with cubic splines and robust standard errors to allow for multiple HADS from the same patients. We also investigated within-patient changes in scores (Analysis 2) in a subset of patients who had completed more than one HADS.

Results: In Analysis 1, modelled mean HADS-D scores increased by around 2.5 and the percentage of high HADS-D scores increased from 13% at six months before death to 30% at one month before death. Changes in HADS-A were smaller and occurred later. In Analysis 2, similar patterns were observed in individual patients' HADS scores.

Conclusion: Depression should be looked for and treated in patients with cancer and a prognosis of six months or less, in order to maximise the quality of patients' remaining life.

1. Introduction

Depression and anxiety are common in patients with cancer [1–3]. These psychiatric comorbidities not only indicate distress, but are also associated with worse quality of life, higher symptom burden, reduced ability to tolerate anticancer treatments and worse survival [4–6].

The degree of depression and anxiety that patients experience is likely to vary during their cancer journey. Whilst this variation will ultimately depend on each individual's circumstances, it has been suggested that there may be 'high-risk' periods when patients are more likely to experience clinically significant depression and/or anxiety and should be screened for these symptoms [7]. It has been assumed that one of these high-risk periods is the last months of life, as during this time patients' health is likely to deteriorate and they may become increasingly aware of their impending death. However, it is not clear, from the modest research literature on this topic, whether substantial and clinically significant increases in depression and anxiety do in fact occur during this period.

Previous studies of depression and anxiety, in patients who have died from cancer, have reported findings ranging from substantial increases to no increases in the last months of life. Some studies analysed single-item measures of depression and anxiety obtained from large administrative healthcare databases [8–11]. They reported that average depression and anxiety both appeared to increase to some degree in the last one to three months of life, but the size of these increases varied and were of uncertain clinical significance. Other studies used more robust measures of depression and/or anxiety in smaller, more selected samples of patients with advanced cancer. They reported clinically significant

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increases in depression but not in anxiety [12–15]. One study that used diagnostic interviews found no increase in the prevalence of either major depressive disorder or anxiety disorders in those closer to death [16]. To summarise, there is still uncertainty about changes in depression and anxiety in the months before death from cancer.

We therefore aimed to test the null hypothesis that depression and anxiety do not substantially change in the one-year period before death from cancer, using a robust measure of depression and anxiety in a large clinically representative sample of patients. To do this we analysed routine data on patients who had died from cancer and who had previously attended cancer clinics. The dataset comprised data on self-reported symptoms of depression and anxiety (for brevity hereafter referred to as 'depression' and 'anxiety') measured using the Hospital Anxiety and Depression Scale (HADS) [17,18], which patients had completed at clinic attendances as part of their routine care, linked with data from national registries on their demographic and cancer characteristics and dates of death.

We took two complementary approaches to analysis: The first analysis took a clinic perspective and used the data from all HADS completed at clinic attendances in the last year of life (if an individual had attended the clinic and completed the HADS multiple times these were all included). In this analysis we investigated the relationships between: (a) mean depression and anxiety scores and time to death and (b) the percentage of high depression and anxiety scores and time to death. The second analysis took an individual patient perspective and used only data from the subset of patients who had completed the HADS on more than one occasion during their last year of life. In this analysis we investigated whether individual patients' depression and anxiety scores changed with increasing proximity to their death.

2. Methods

2.1. Study design

We analysed depression and anxiety data from a large sample of patients who had died from cancer. These data had been collected during the patients' routine clinical care.

2.2. Patients

The data were on patients who had attended outpatient cancer clinics of the Edinburgh, Glasgow and Dundee National Health Service (NHS) cancer centres in Scotland, UK. Together these three centres serve a geographically defined area of approximately four million people and provide specialist care for the vast majority of patients who have been diagnosed with cancer in this region. Patients attending these clinics between May 12, 2008 and August 24, 2011 (which may have been for confirmation of their cancer diagnosis, for anticancer treatment or for follow-up) were asked to complete a self-report measure of depression and anxiety (the Hospital Depression and Anxiety Scale, HADS) as part of their routine clinic assessment. They did this at each clinic visit, prior to their oncology consultation. Most (80%) of the patients attending the clinics completed the HADS (the main reason that patients did not complete it was that their oncology appointment had begun before they could do so).

We included a patient's data in Analysis 1 if: (a) they had died (with a date of death before April 30, 2012 which was the latest date on which mortality data were available) and their primary cause of death was recorded as cancer and (b) they had a primary breast, colorectal, gynaecological, lung or prostate cancer (in order to provide estimates for the population of patients with common cancers) and (c) they had attended a cancer clinic and completed the HADS at least once in the year before death.

We included a patient's data in Analysis 2 if they met the criteria described above for Analysis 1 and: (a) they had completed a HADS between zero and three months before death ("final HADS") and (b) they had completed a HADS between three and twelve months before death ("previous HADS") and (c) they had completed these two HADS at least one month apart.

2.3. Measures

2.3.1. Depression and anxiety

The Hospital Anxiety and Depression Scale (HADS) was routinely given to patients each time they attended the cancer clinic, in order to assess their depression and anxiety symptoms over the preceding week [17]. The HADS is a widely used, validated, self-report scale with a total of 14 items; seven items make up the HADS-depression subscale (HADS-D) and seven make up the HADS-anxiety subscale (HADS-A) [18]. The individual items are each scored from zero to three, resulting in maximum subscale scores of 21, with higher scores indicating greater severity. We defined a high score as $\geq$11 on each subscale as recommended by the designers of the HADS [17].

2.3.2. Demographic and cancer data

We obtained data on patients' demographic and cancer characteristics from the NHS Scotland Cancer Registry, which systematically collects information from hospitals throughout Scotland for all recorded cases of cancer. These data included sex, date of cancer diagnosis (the date on which the cancer was first diagnosed whether by histopathological, radiological or other clinical methods), age at cancer diagnosis, primary cancer (see Appendix A for details) and socioeconomic status (defined using the Scottish Index of Multiple Deprivation, based on area of residence at the time of cancer diagnosis; see Appendix B for details).

2.3.3. Mortality data

We obtained data on patients' dates and causes of death from the National Records of Scotland database. The database includes data on all deaths that occur in Scotland.

2.4. Data linkage

To ensure data security and confidentiality the depression and anxiety data were sent to the Information Services Division of NHS Scotland for linkage with demographic, cancer and mortality data. Data linkage was done using unique patient identification numbers (Community Health Index numbers) and dates of birth. All identifying data were then removed (one-way linkage) to produce an anonymised dataset.

2.5. Ethical approval

All patients whose data were included had given consent for these to be used for research (by selecting 'yes' to a consent statement either on paper or on a touchscreen computer). This procedure and the creation of the dataset for analysis were approved by the South East Scotland Research Ethics Committee, the NHS Scotland Caldicott Guardian Forum, and the NHS Scotland Privacy Advisory Committee.

2.6. Statistical analyses

We separately analysed data on depression (using HADS-D scores) and anxiety (using HADS-A scores). We only included scores from HADS with no missing items.

2.6.1. Analysis 1a

In this analysis we investigated the relationships between mean HADS-D and mean HADS-A scores and time to death using multivariable linear regression. Some patients had completed the HADS multiple times in the year before their death. For these patients, we included all of their HADS scores, giving them equal weight, and accounted for correlations between them using the clustered Huber-White sandwich estimator of variance [19,20]. We used restricted cubic splines (with four knots,

positioned at 5th, 35th, 65th and 95th percentiles) to model HADS-D and HADS-A scores flexibly over time, adjusting for age, sex and primary cancer. We plotted the mean modelled HADS-D and HADS-A scores against time for a population of patients with the distribution of age, sex and cancer in the dataset and used sunflower plots to show the density-distributions of the observed scores [21]. We then estimated the difference between the mean HADS-D and HADS-A scores at each of the last six months before death and the mean of the mean scores at seven, eight, nine, ten, 11 and 12 (7–12) months before death. We repeated this analysis, dividing the sample by primary cancer to determine whether any patterns observed were seen in all cancers (in these cancer-specific analyses, we adjusted only for age and sex).

2.6.2. Analysis 1b

We also investigated the relationships between the percentage of high HADS-D scores and the percentage of high HADS-A scores (defined as HADS subscale scores ≥11) and time to death using multivariable linear regression, again including all HADS scores and accounting for correlations between HADS completed by the same person using the clustered Huber-White sandwich estimator of variance [19,20]. We used linear regression in order to model the percentage additively, the use of Huber-White standard errors making inferences from this model valid. We again used restricted cubic splines (with four knots, positioned at 5th, 35th, 65th and 95th percentiles), in this case to model the percentage of patients with high HADS-D and HADS-A scores flexibly over

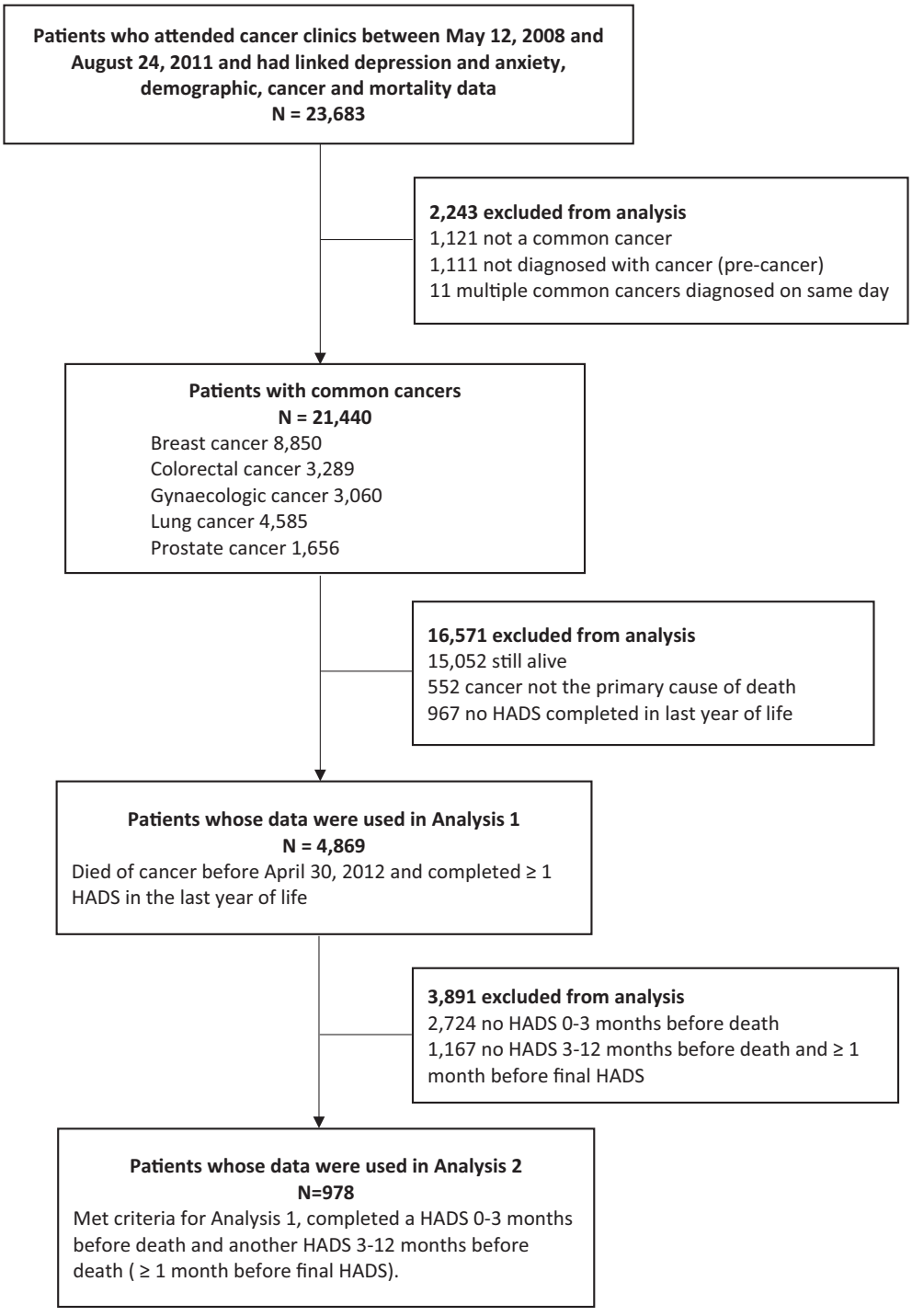

Fig. 1. Flowchart showing how patients' data were selected for inclusion in each analysis.

time, adjusting for age, sex and primary cancer. We plotted the modelled percentages of high scores against time for a population of patients with the distribution of age, sex and cancer in the dataset. We then estimated the difference in percentages of high scores between each of the last six months before death and the mean of the percentages at seven, eight, nine, ten, 11 and 12 (7–12) months before death. We repeated this analysis, dividing the sample by primary cancer (in these cancer-specific analyses, we adjusted only for age and sex).

2.6.3. Analysis 2

In this analysis we determined whether individual patients' HADS-D and HADS-A scores changed with time to death using a within-patient change-in-scores analysis, using data from the subset of patients described above. Each patient contributed one measure of change to the analysis: if a patient had completed the HADS more than once in the intervals described, we used the latest final HADS and the earliest previous HADS scores to maximise the difference in time between the two scores. We calculated changes for HADS-D and HADS-A (the difference between each patient's final HADS-D and previous HADS-D and between their final HADS-A and previous HADS-A) and tested the means of these changes using *t*-tests.

We performed subgroup analyses, classifying each change according to the timing of the two relevant HADS: (a) <1 month before death and > 6 months before death; (b) <1 month before death and 3–6 months before death; (c) 1–3 months before death and > 6 months before death; and (d) 1–3 months before death and 3–6 months before death. We produced plots of changes in scores, for both HADS-D and HADS-A, for each subgroup. We used linear regression models to investigate the effects of the timing of the final HADS and the previous HADS on the size of the change in HADS-D and HADS-A scores. We tested whether these effects were statistically significant using Wald tests. We then fitted the models including an interaction between the timing of the final and previous HADS in order to estimate the mean change in score (and 95% confidence intervals) for each of these groups.

All analyses were conducted in Stata version 17 [22].

3. Results

3.1. Patient characteristics

Fig. 1 shows how patients' data were selected for inclusion in each analysis. Data on 4869 patients were used for Analysis 1 (see Appendix C for details of the number of HADS completed within each monthly interval in the last year of life). Data from a subset of 978 patients were used for Analysis 2.

Table 1 shows the characteristics of patients whose data were used in the two analyses (see Appendices D and E for these by each primary cancer). The 4869 clinic attendees had a mean age of 68 years and 57% were female. 54% had a diagnosis of lung cancer, reflecting the poor prognosis associated with this primary cancer. The median time period between cancer diagnosis and death was 1.3 years. The subset of patients whose data were used for Analysis 2 had similar characteristics to those whose data were used for Analysis 1.

Table 1
Characteristics of patients whose data were included in the analyses.

	Patients whose data were used for Analysis 1	Subset of patients whose data were used for Analysis 2[a]
	N = 4869	*N* = 978
Sex		
Female	2787 (57%)	528 (54%)
Male	2082 (43%)	450 (46%)
Primary Cancer		
Lung	2625 (54%)	595 (61%)
Colorectal	752 (15%)	119 (12%)
Gynaecological	695 (14%)	116 (12%)
Breast	621 (13%)	119 (12%)
Prostate	176 (4%)	29 (3%)
Age at death (years)		
Mean [SD]	68.0 (11.1)	67.1 (10.6)
Socioeconomic status[b]		
1	1371 (28%)	271 (28%)
2	1070 (22%)	210 (21%)
3	822 (17%)	158 (16%)
4	731 (15%)	141 (14%)
5	875 (18%)	198 (20%)
Time interval between cancer diagnosis & death (years)		
Median [IQR]	1.3 [0.7, 2.6]	1.2 [0.8, 2.6]

[a] Analysis 2 only included patients who had completed a Hospital Anxiety and Depression Scale between 0 and 3 months before death and another between 3 and 12 months before death.

[b] Scottish Index of Multiple Deprivation quintile score: 1 = most deprived, 5 = least deprived.

3.2. Relationship between mean depression scores and mean anxiety scores and time to death (Analysis 1a)

Fig. 2 shows the relationships between mean depression and anxiety scores and time to death. The lines show the modelled mean HADS-D and HADS-A scores from 12 months before death onwards for a population of patients with the distribution of age, sex and cancer in the dataset. The sunflower plots show the observed HADS-D and HADS-A scores. Table 2 shows the differences between mean HADS-D and HADS-A scores at each of the last six months before death and 7–12 months before death.

At 12 months before death the mean HADS-D score was 5.37 (95% CI 5.04 to 5.70) and the mean HADS-A score was 5.62 (95% CI 5.27 to 5.97). Mean HADS-D started to materially increase from six months before death and mean HADS-A from three months before death (see Fig. 2). The differences between mean HADS-D at each of the six months before death and at 7–12 months before death were all statistically significant, whereas the differences in mean HADS-A were only statistically significant from three months before death onwards (see Table 2). For both HADS-D and HADS-A the size of these differences became larger with increasing proximity to death. Each of the cancer-specific analyses had similar findings (see appendix).

3.3. Relationship between the percentage of high depression scores and the percentage of high anxiety scores and time to death (Analysis 1b)

Fig. 3 shows the modelled percentages of high HADS-D scores and high HADS-A scores (defined as scores ≥11 on each subscale) from 12 months before death onwards. At 12 months before death, the modelled percentage of high HADS-D scores was 11% (95% CI 9% to 14%) and of high HADS-A scores was 15% (95% CI 12% to 17%). Table 3 shows the differences between percentages of high HADS-D and HADS-A scores at each of the last six months before death and 7–12 months before death.

The observed changes were similar to those described above for mean scores. The percentage of high HADS-D scores started to materially increase at six months before death and the percentage of high HADS-A scores at three months before death (see Fig. 3). The differences between the percentages of high scores at each of the six months before death and at 7–12 months before death were statistically significant from four months before death onwards for HADS-D and from two months before death onwards for HADS-A (see Table 3). At one month before death the modelled percentage of high HADS-D scores was 30% (95% CI 27% to 32%) and the percentage of high HADS-A scores was 22% (95% CI 20% to 25%). The results of each of the cancer-specific analyses were again similar (see Appendices F, G and H).

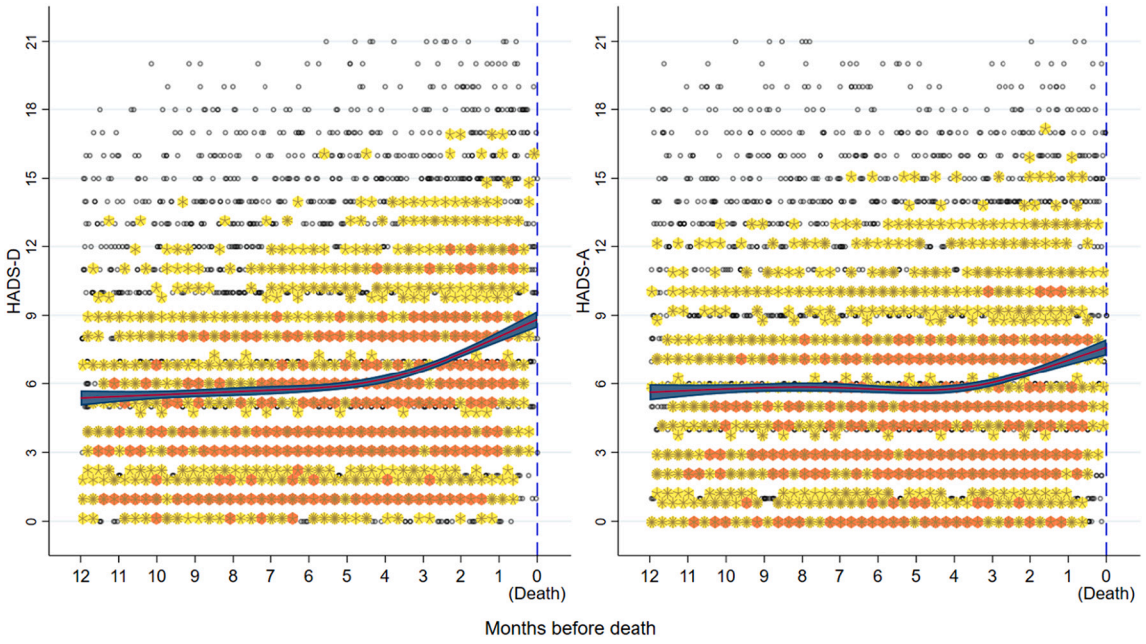

Fig. 2. The relationships between mean depression and anxiety scores and time to death.
The left panel shows the relationship between mean depression scores and time to death. The right panel shows the relationship between mean anxiety scores and time to death (Analysis 1a). Red lines show modelled mean scores against time, with 95% confidence bands, for a population of patients with the distribution of age, sex and cancer in the dataset. Sunflower plots show observed scores. A black circle represents one to four completed HADS; a light hexagon with: five radii represents five completed HADS, six radii represents six completed HADS… 14 radii represents 14 completed HADS. A dark hexagon with five radii represents 15 to 17 completed HADS, six radii represents 18 to 20 patients etc.
HADS-D = Hospital Anxiety and Depression Scale-Depression subscale; HADS-A = Hospital Anxiety and Depression Scale-Anxiety subscale.

Table 2
Modelled differences between mean depression and anxiety scores at each of the last six months before death and the mean of the mean scores at 7–12 months before death (Analysis 1a).

Time before death	Mean score[a]	95% confidence interval	Difference between mean score and mean of values at 7–12 months[b]	95% confidence interval	*P*-value
Depression					
7–12 months	5.54	5.37, 5.71	–	–	–
6 months	5.79	5.62, 5.95	0.25	0.07, 0.42	0.005
5 months	5.93	5.76, 6.10	0.39	0.20, 0.59	<0.001
4 months	6.21	6.03, 6.39	0.67	0.45, 0.90	<0.001
3 months	6.69	6.52, 6.86	1.15	0.93, 1.38	<0.001
2 months	7.34	7.17, 7.50	1.80	1.57, 2.02	<0.001
1 month	8.07	7.83, 8.31	2.53	2.25, 2.82	<0.001
Anxiety					
7–12 months	5.76	5.57, 5.95	–	–	–
6 months	5.75	5.57, 5.92	−0.01	−0.20, 0.17	0.904
5 months	5.70	5.53, 5.87	−0.06	−0.26, 0.15	0.586
4 months	5.78	5.60, 5.96	0.02	−0.21, 0.25	0.875
3 months	6.05	5.88, 6.22	0.29	0.06, 0.53	0.012
2 months	6.50	6.34, 6.67	0.74	0.51, 0.98	<0.001
1 month	7.05	6.81, 7.28	1.29	1.00, 1.58	<0.001

[a] Mean modelled scores for a population of patients with the distribution of age, sex and cancer in the dataset.
[b] Modelled differences between mean scores at each of the last six months before death and the mean of the mean scores at 7, 8, 9, 10, 11 and 12 (7–12) months before death.

3.4. Within-patient changes in depression and anxiety scores (analysis 2)

In the analysis of within-patient changes, statistically significant increases in HADS-D and HADS-A were observed in the period between 3 and 12 months before death and 0–3 months before death. HADS-D scores increased by a mean of 1.93 (95% CI 1.67 to 2.20, $p < 0.001$) and HADS-A scores increased by a mean of 0.49 (95% CI 0.25 to 0.73, $p < 0.001$).

Figs. 4 and 5 show the within-patient changes, displayed in subgroups according to when patients had completed their final and previous HADS. The lines indicate which pairs of HADS are from the same patient. In an analysis relating the within-patient change in HADS-D to the two binary timing variables used to form the subgroups, the size of the change was significantly associated with the timing of both the final HADS and the previous HADS ($p = 0.007$ and $p = 0.004$ respectively). The largest changes were observed for patients who completed their final HADS <1 month before death and their previous HADS >6 months before death (mean change in HADS-D score 3.00; 95% CI 2.21 to 3.79, $p < 0.001$). For HADS-A, the size of the change was not significantly associated with the timing of the final or previous HADS (p

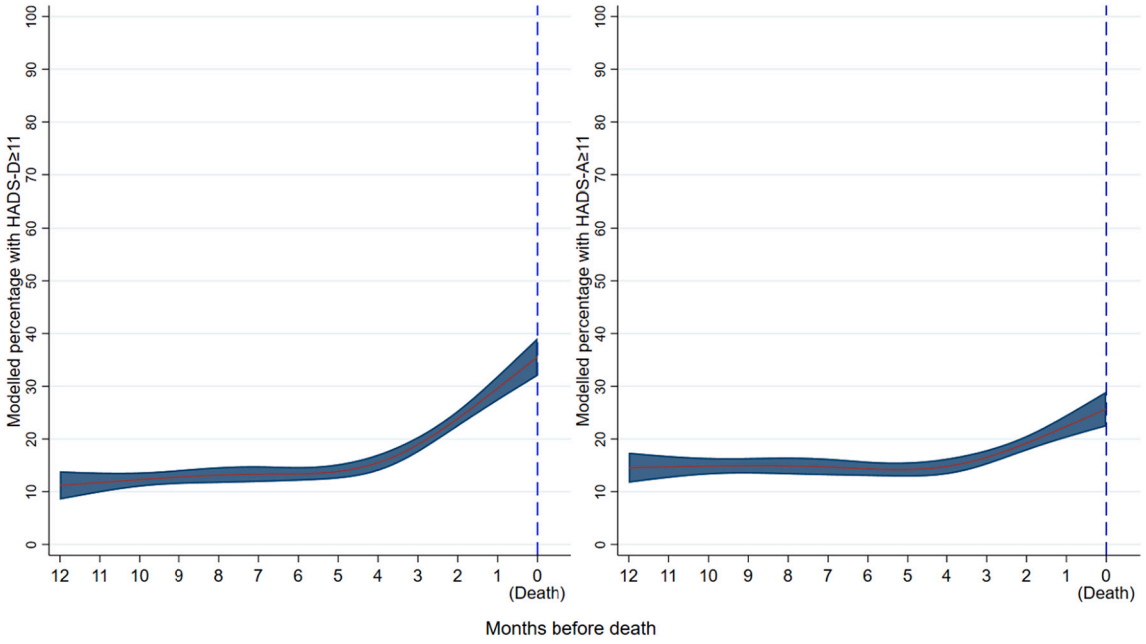

Fig. 3. The relationships between the percentages of high depression and anxiety scores and time to death.
Left panel shows modelled percentage of high depression scores (HADS-D ≥ 11) against time and right panel shows modelled percentage of high anxiety scores (HADS-A ≥ 11) against time (Analysis 1b), both with 95% confidence bands, for a population of patients with the distribution of age, sex and cancer in the dataset. HADS-D = Hospital Anxiety and Depression Scale-Depression subscale; HADS-A = Hospital Anxiety and Depression Scale-Anxiety subscale.

Table 3
Modelled differences between percentages of high scores at each of the last six months before death and the mean of the percentages at 7–12 months before death (Analysis 1b).

Time before death	Percentage[a]	95% confidence interval (%)	Difference between percentage and mean of percentages at 7–12 months[b]	95% confidence interval (%)	P-value
Depression					
7–12 months	12	11, 14	–	–	–
6 months	13	12, 15	1	0, 2	0.182
5 months	14	12, 15	1	0, 3	0.078
4 months	16	14, 17	3	1, 5	<0.001
3 months	19	17, 20	7	5, 8	<0.001
2 months	24	22, 25	11	10, 13	<0.001
1 month	30	27, 32	17	15, 20	<0.001
Anxiety					
7–12 months	15	13, 16	–	–	–
6 months	14	13, 16	0	−2, 1	0.581
5 months	14	13, 16	−1	−2, 1	0.526
4 months	15	13, 16	0	−2, 2	0.967
3 months	17	15, 18	2	0, 4	0.070
2 months	19	18, 21	4	3, 6	<0.001
1 month	22	20, 25	8	5, 10	<0.001

[a] Modelled percentages for a population of patients with the distribution of age, sex and cancer in the dataset.
[b] Modelled differences in percentage of high scores between each of the last six months before death and the mean of the percentages at 7, 8, 9, 10, 11 and 12 (7–12) months before death.

= 0.059 and $p = 0.348$ respectively). The largest changes were observed for patients who completed their final HADS <1 month before death and their previous HADS 3–6 months before death (mean change in HADS-A scores 1.09; 95% CI 0.34 to 1.84, $p = 0.004$). The results of each of the cancer-specific analyses were similar (see Appendix I).

4. Discussion

4.1. Main findings

Our findings provide strong evidence against the null hypothesis that depression and anxiety do not substantially increase in the one-year period before death from cancer. In our analysis of all HADS completed in the last year of life, we found that depression, and to a lesser extent anxiety, increased with proximity to death. For depression, both the mean score and the percentage of high scores started to materially increase from six months before death. For anxiety, the mean score and the percentage of high scores, increased from two to three months before death but by a smaller amount. A similar pattern was observed in the within-patient analyses, and also in each of the cancer-specific analyses, suggesting that these findings are robust.

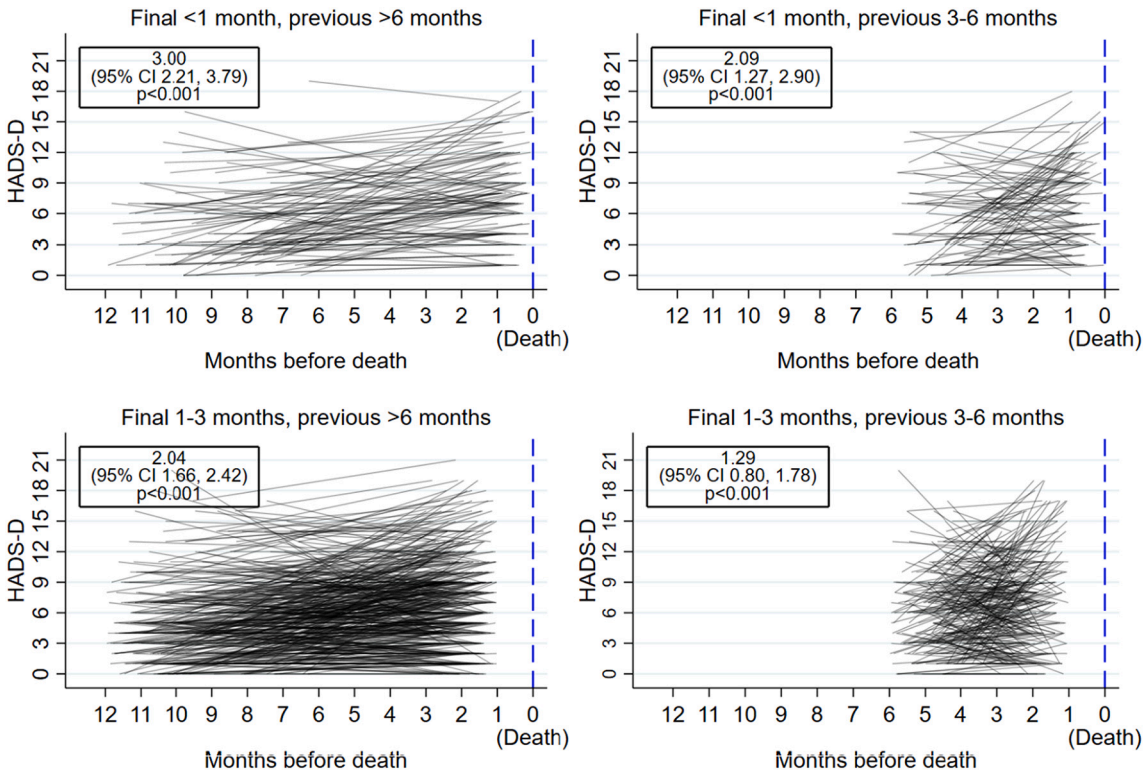

Fig. 4. Changes in individual patients' depression scores according to their timing relative to death.
Panels show changes in observed HADS-D scores (Analysis 2) for final HADS-D < 1 month before death and previous HADS-D > 6 months before death (top left), final HADS-D < 1 month before death and previous HADS-D 3–6 months before death (top right), final HADS-D 1–3 months before death and previous HADS-D > 6 months before death (bottom left), final HADS-D 1–3 months before death and previous HADS-D 3–6 months before death (bottom right). HADS-D = Hospital Anxiety and Depression Scale-Depression subscale.

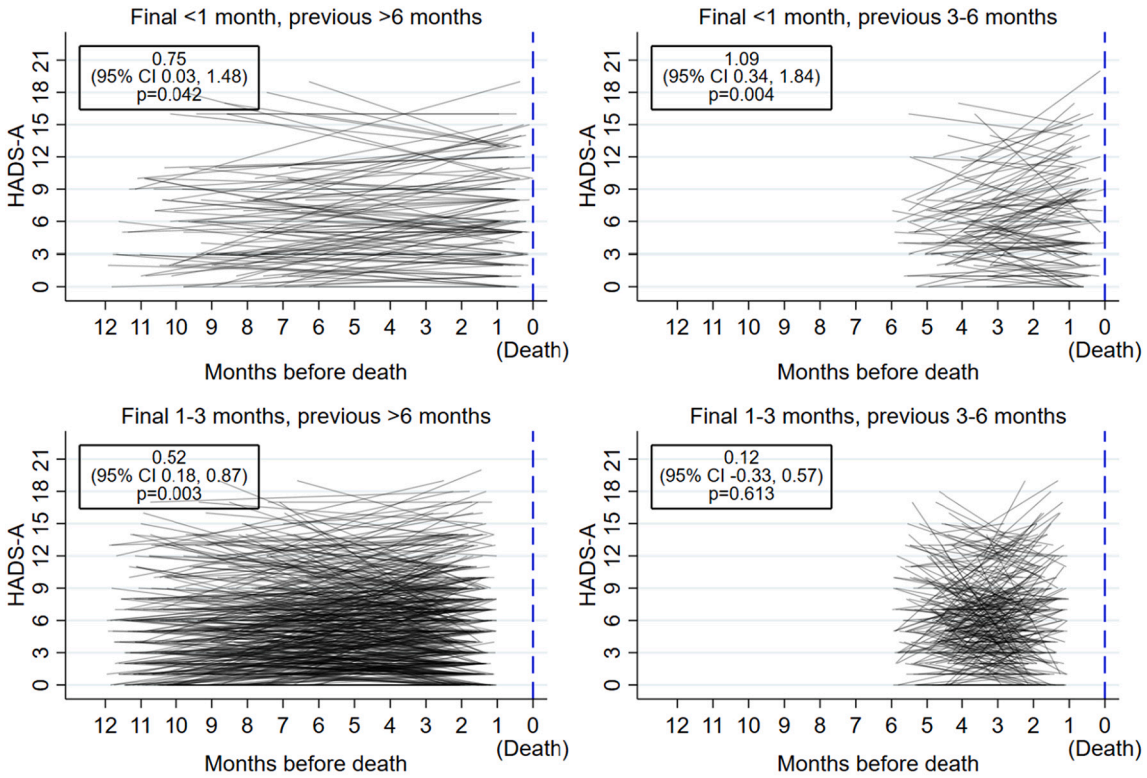

Fig. 5. Changes in individual patients' anxiety scores according to their timing relative to death.
Panels show changes in observed HADS-A scores (Analysis 2) for final HADS-A < 1 month before death and previous HADS-A > 6 months before death (top left), final HADS-A < 1 month before death and previous HADS-A 3–6 months before death (top right), final HADS-A 1–3 months before death and previous HADS-A > 6 months before death (bottom left), final HADS-A 1–3 months before death and previous HADS-A 3–6 months before death (bottom right). HADS-A = Hospital Anxiety and Depression Scale-Anxiety subscale.

4.2. Discussion of main findings

The increase in depression with proximity to death can be regarded as clinically significant. Both the increase in mean HADS-D score between 6 and 12 months and one month before death (2.53, Analysis 1a) and the mean increase in individual patients' scores between 3 and 12 months and 0–3 months before death (1.93, Analysis 2) were greater than the minimal clinically important difference reported for this measure of 1.7 [23]. The percentage of high scores increased from 12% at 7–12 months before death to 30% at one month before death. The 7–12 month prevalence, which was obtained using a conservative cut-off for high scores on the HADS, is in keeping with previous systematic reviews of the prevalence of interview-diagnosed major depression in patients with cancer [1,3]. The absolute increase in the percentage of high scores from 7 to 12 months to one month (Analysis 1b) was also substantial and, likely to be clinically meaningful. The findings of Analysis 1 tell us that mean depression and anxiety scores increase with closeness to death. Although this finding is arguably the one of most relevance from a cancer clinic perspective, it may not necessarily reflect changes in individual patients. This is because depression and/or anxiety may influence clinic attendance. However, the similarity of the findings of Analyses 1a and 2 make this explanation unlikely.

The increase in anxiety with proximity to death occurred later and is of uncertain clinical significance. The increase in mean HADS-A score (Analysis 1a) and in individual patients' scores (Analysis 2) were both smaller (1.29 and 0.49 respectively) than for depression, as was the 8% absolute increase in the percentage of high scores (Analysis 1b).

The causes of these observed increases in depression and anxiety cannot be determined from the data available to us. In particular, we do not know what information patients had received, or what they believed, about their cancer, the curative or palliative nature of their treatment, or their cancer prognosis. However, it seems likely from other studies, and from clinical experience, that patients may become more depressed as they become sicker, grow more dependent on others and start to anticipate future losses [24]. The smaller and later increase in anxiety may reflect patients' fears about dying, such as worrying that they will be in pain, or die in an undignified manner; fears that may be more prominent even closer to the time of death than our data allow us to observe [25].

4.3. Other relevant literature

Only a modest number of previous studies have provided useful information about depression and anxiety in the period before death from cancer. The paucity of studies probably reflects the considerable challenges of researching this topic.

Four publications describe retrospective studies of data on patients who died from cancer in Ontario, Canada [8–11]. These patients had completed the Edmonton Symptom Assessment System (ESAS) when they attended clinics. The publications report that both depression and anxiety increased somewhat in the last three months before death. However, the reported increases vary between the studies and are of unclear clinical significance. Whilst the major strength of these studies is that they were of very large and reasonably representative samples of over 10,000 patients, the interpretation of their findings is limited by the use of only single items from the ESAS to measure depression and anxiety [26].

Four prospective studies have used more robust measures of depression and/or anxiety in smaller, more selected samples of patients with advanced cancer, who subsequently died. Two of these studies investigated whether the proportion of patients with clinically significant depression and anxiety increases with proximity to death: One study (which recruited 325 patients in Taiwan) reported an increase in the proportion of patients with clinically significant depression, but not anxiety, in the last three months of life, using a score of $\geq$11 on the relevant HADS subscale to define clinically significant symptoms [12,13]. The other study (which assessed 289 patients in the USA) reported no increase in the proportion of patients with either depression or anxiety in the period before death, when these were defined using interview-assessed DSM-IV diagnoses [16]. The other two studies investigated the course of depression in individual patients [14,15]. These found that depression, when measured using the Beck Depression Inventory (BDI) in a study of 365 patients in Canada and using the Patient Health Questionnaire-9 (PHQ-9) in a study of 58 patients in the USA, increased with closeness to death.

Two secondary analyses of data from palliative care studies reported only modest increases in depression and anxiety scores at the end of life [27,28]. One of these analyses was of data from 341 patients in the USA and measured depression and anxiety using the Profile Of Mood States [27]. The other was of data from 116 patients in Sweden and Norway, and used the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC) [28].

From a wider perspective, an analysis of general population data from the Health and Retirement Survey of 3274 older adults in the USA, found that both the average depression score and the proportion of people with a clinically significant depression score increased in the last four months of life, when measured using the Center of Epidemiological Studies Depression Scale (CESD-8). Interestingly, these increases were especially marked in the last month of life for older adults who reported having a diagnosis of cancer [29].

In the context of this literature, our study adds weight to the evidence of a substantial and clinically significant increase in depression, but probably not anxiety, in the three months before death from cancer.

4.4. Strengths and limitations

The strengths of our study are: (a) the use of depression and anxiety data from a large number of unselected patients with common cancers, collected as part of their routine care when they attended cancer clinics; (b) the assessment of depression and anxiety using a validated scale, that was developed for use in the medically ill; (c) the analysis of systematically collected demographic, cancer and mortality data from national registries; (d) the use of two complementary approaches to analysis; one investigating the relationships between mean scores, and the percentage of high scores, and time to death and one investigating whether individual patients' depression and anxiety scores changed with increasing proximity to death.

Our study also had limitations: (a) The findings are based on data from patients who had died from cancer and who had attended cancer clinics in the last year of life. Although most patients with cancer attend such clinics in the UK, our findings may not generalize to other patient populations such as patients attending primary care or palliative care settings. Similarly, they may not generalize to patients who are able to access the newer anticancer treatments that have been available since the data were collected. Nor can we make inferences about depression and/or anxiety before the last year of life. (b) Whilst not all patients who attended the cancer clinics completed the HADS, raising the possibility of bias, the vast majority (80%) did and the main reason for non-completion was operational. (c) Approximately half of the patients whose data we analysed had lung cancer, reflecting the poor prognosis of this cancer. However, similar findings were observed in other cancers in the cancer-specific analyses. (d) The HADS has limitations [30]. In particular, it does not provide psychiatric diagnoses and is less aligned to diagnostic criteria than other measures such as the PHQ-9 (for depression) or the Generalized Anxiety Disorder-7 (for anxiety). Whilst we used a recommended cut-off of $\geq$11 to define high scorers, a variety of other cut-off scores have been proposed and each may have given somewhat different findings [30]. Furthermore, as patients completed the HADS in the cancer clinic it is possible that their scores were artificially increased by the setting. However our previous research suggests that any such effect is very small [31]. (e) We conducted an analysis of routine data, rather than recruiting participants to a prospective study.

Whilst we adjusted for age, sex and primary cancer, this meant that we did not have information on other variables such as: more detailed data on patients' cancer (e.g. stage of disease, receipt of recent anticancer treatments, reason for clinic attendance); psychological state (e.g. previous history of depression and/or anxiety, receipt of psychiatric treatments, existential distress, desire for hastened death); or their general health (e.g. comorbidities, physical symptoms, quality of life).

4.5. Implications for researchers

The study of whether patients with cancer become substantially more depressed and anxious in their last months of life presents methodological challenges. The ideal study design would probably be to recruit a large, representative sample of patients with a one-year cancer prognosis and prospectively measure their symptoms regularly using repeated diagnostic interviews, with complete data collection, until they died. However, this approach would be difficult to achieve for a number of reasons: first, prognosis can be difficult to estimate; second, the study of large well-characterized samples of patients using frequent measures, preferably diagnostic interviews, over a long period of time is highly resource-intensive; third, patients are likely to drop out of the study as they become less well and as they are closer to death. It is perhaps not surprising therefore that previous large studies have used routine data, using simple measures obtained over a long period before death, and that prospective studies using more intensive diagnostic interviews have been of small selected samples done in a short period close to death. Whilst future studies are unlikely to be able to follow an ideal design, researchers should be aware of how their design choices may limit their findings. These choices include sample, measure and approach to analysis. New research should also endeavour to better understand the nature and cause of depression and anxiety in the last year of life; their relationships with other symptoms, quality of life and existential distress; and their optimal management.

4.6. Implications for clinicians

Whilst many cancer services routinely assess depression in all their patients at least once, the findings of this study confirm that the last months of life are a 'high risk' period for depression and emphasize the need to screen for depression in patients judged to be in the last six months of their life, when this prognosis can be estimated [7]. Not only is clinically significant depression likely to become more prevalent during this time, but making an early diagnosis of a depressive disorder allows sufficient time to treat it. Both pharmacological and psychological treatments for major depression are effective in patients with poor prognosis cancers and can greatly improve their quality of life [32,33]. The implications of our findings for assessing and managing anxiety in such patients, are less clear and require further study.

4.7. Conclusions

Our analyses of routine data from a large number of deceased patients who had attended cancer clinics found clear evidence of a substantial and clinically significant increase in depression in the six months before death. We also found evidence of a later and smaller increase in anxiety that was of less clear clinical significance. These findings indicate a need to actively look for, and where appropriate treat, depression in patients with a short cancer prognosis in order to maximise the quality of their limited remaining life.

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

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