Title: "Openness" personality trait associated with benefit from a non-pharmacological breathlessness intervention in people with intra-thoracic cancer: an exploratory analysis

Running title: Openness, breathing training and lung cancer

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ABSTRACT

Context: Breathlessness is common in people with lung cancer. Non-pharmacological breathlessness interventions reduce 'distress due to' and increase 'mastery over' breathlessness.

Objectives: Identify patient characteristics associated with response to breathlessness interventions.

Methods: Exploratory secondary trial data analysis. Response defined as a 1-point improvement in 0-10 numerical rating scale of worst breathlessness/last 24 hours (Response-Worst) or a 0.5-point improvement in the Chronic Respiratory Questionnaire (CRQ) Mastery (Response-Mastery) at 4 weeks. Univariable regression explored relationships with plausible demographic, clinical and psychological variables followed by multivariable regression for associated (P-value <0.05) variables.

Results: 158 participants with intrathoracic cancer (mean age 69.4 [SD: 9.35] years; 40% women) were randomised to one or three breathlessness training sessions. 91 had evaluable data for Response-Worst, and 107 for Response-Mastery. In the univariable analyses, the personality trait "openness" was associated with Response-Worst (Odds Ratio (OR) 1.99 [95% CI 1.08 to 3.67]; P-value=0.028) and Response-Mastery (OR = 1.84 [95% CI 1.04 to 3.23]; P-value=0.035). Higher CRQ-Fatigue (OR 0.61 [95% CI 0.41 to 0.91]: P=0.015), CRQ-Emotion (OR =0.68 [95% CI 0.47 to 0.96]: P-value=0.030) and worse CRQ-Mastery (OR =0.61 [95% CI 0.42 to 0.88]; P-value=0.008), and presence of metastases and fatigue were associated with reduced odds of Response-Mastery. In the adjusted Response-Mastery model, only "openness" remained (OR 1.73 [95% CI 0.95 to 3.15]; P-value = 0.072).

Conclusions: Worse baseline health, worse breathlessness mastery, but not severity, and "openness" were associated with a better odds of response. Breathlessness services must be easy to access and patients encouraged and supported to attend.

KEY MESSAGE This planned exploratory secondary trial data analysis shows some evidence that the personality trait "openness" and worse breathlessness mastery are associated with benefit from a breathlessness intervention in people with intrathoracic malignancy.

INTRODUCTION

Chronic breathlessness (disabling and persistent despite optimised treatment for the causative condition[1]) has widespread impacts on those living with it and those who care for them. [2; 3;4;5] Breathlessness is a multidimensional symptom that encompasses sensory, affective and cognitive components[6;7] which interact with biological, psychological, social and environmental factors to influence behaviour.[2]

Breathlessness is common in people with lung cancer, affecting almost all with advanced disease.[8] Despite appropriate use of anti-cancer treatments and management of complications, chronic breathlessness and frightening acute-on-chronic breathlessness[9] remain the daily experience of many. Non-pharmacological interventions reduce distress due to and increase mastery over breathlessness,[10] even with single training sessions.[11] However, given that engaged self-management by the patient is important, little is known about the characteristics of individuals more likely to benefit. The way a person copes with and seeks help for chronic breathlessness seems to be related to their ability to experience the best quality of life despite their limitations.[2;12]

A recent secondary pooled data analysis of three randomised controlled trials (RCT) of complex breathlessness interventions[13] explored predictors of better breathlessness outcomes. Overall, about one-third of participants had lung cancer. The only predictor of improvement in mastery was worse baseline mastery and the only predictor of improvement in distress due to breathlessness was worse baseline distress. However, candidate variables were limited by those available in the contributing datasets; the only psychological variables measured were mastery and emotional domains of the Chronic Respiratory Questionnaire and anxiety and depression (Hospital Anxiety Depression Scale).

We evaluated the cost-effectiveness of a single or three breathing training session(s) in people with intrathoracic cancer; the single session was as effective as three for breathlessness severity and was better in terms of distress due to breathlessness.[11] An *a priori* objective was to explore the relationship between patient psychological characteristics at baseline and their response to breathing training. The null hypothesis was that there would be no evidence of association between personality, coping or psychological characteristics and breathlessness benefit.

METHODS

Study design
Secondary data analysis
The parent trial is reported in detail elsewhere[11] but is summarised here. Consecutive patients with chronic breathlessness due to active intra-thoracic malignancy, were recruited into a phase III multi-centre, pragmatic, individually randomised, non-blinded parallel arm RCT of single session versus three hour-long sessions of breathing training at weekly intervals. Patients with chronic breathlessness, self-reported breathlessness ≥3/10 (0 = no breathlessness; 10 = worst imaginable breathlessness), and a clinician-estimated prognosis ≥3 months were eligible. Patients with intercurrent illness or co-morbidities making trial completion unlikely, or prior breathing training were excluded. All participants gave written informed consent.

The trial was prospectively registered (ISRCTN49387307). Ethical approval was given by Sheffield Research Ethics Committee (ref 10/H1308/66) including for the method of consent. Institutional approval was gained from each site prior to recruitment.

Baseline and outcome measures

In addition to the primary outcome, measure of patient-reported intensity of the worst breathlessness over the past 24 hours ('worst'), specific psychological measures of interest at baseline (Box 1) were the Big Five Inventory (BFI)[14] and Mental Toughness Questionnaire (MTQ-48)[15], Chronic Respiratory Questionnaire-Self-Administered-Survey (CRQ-SAS)[16], Hospital Anxiety and Depression Scale (HADS)[17], Brief COPE[18], Catastrophic thinking and perceived Injustice Experiences Questionnaire (CIEQ-Chr – 1-5 IEQ, 6-12 PCS)[19] and numerical rating scales (NRS) for coping with and distress due to breathlessness. Health status (Euroqol [EQ-5D] and EQ-visual analogue scale (EQVAS)[20], and the Karnofsky Performance Scale (KPS)[21] were also measured.

<<insert Box 1 about here>>

Definition of response for this study

We considered two binary outcome measures. Firstly, Response-worst (yes/no) was derived using an improvement of 1 point or more (yes) from baseline assessment to week 4 on the 'worst' breathlessness scale over past 24 hours .[22] Secondly, CRQ-SAS Mastery was used to determine patient response (Response-mastery: yes/no), using an improvement of 0.5 from baseline assessment to week 4 (yes).[23]

Explanatory variables

Explanatory variables with rationale for use are shown in Box 2.

<<insert Box 2 about here>>

Statistical analysis

Percentages of responders (Yes) and non-responders (No) by baseline characteristics are presented for categorical variables. Whereas, means and standard deviations are presented for continuous variables. Furthermore, we present summary statistics for baseline characteristics for those whose outcome was missing.

We used logistic regression to explore univariable associations of response at baseline. The primary dependent variables were Response-Worst and Response-Mastery. Explanatory independent variables included 'Demographic characteristics', 'Intervention characteristics', 'Cancer-related variables' and 'Psychological Variables' as shown in Box 2, drawn from the literature or from plausible biological explanation. A multiple logistic regression model was then built from significantly associated variables (P-value <0.05). Odds ratios were provided in addition to 95% Confidence Intervals (CI) and P-values. In this exploratory analysis, we did not adjust for multiple hypotheses testing or impute missing data.

RESULTS

One hundred and fifty-six participants (mean age 69.4 [9.35] years; 40% women) were randomised (1:2 randomisation, 52 to three sessions, 104 to single session). Primary lung cancer was the most common diagnosis in 133 (85.3 %), 12 (8%) had mesothelioma (data not shown). Two withdrew from each arm prior to the intervention and were excluded from the analysis. At 4 weeks 124/156 (79%) participants were still in the trial. Details are presented elsewhere.[11]

There were 91 participants with baseline and week 4 data evaluable for Response-Worst, of whom 47/91 (60%) were responders, and 107 for Response-Mastery (49/107; 46% responders). Characteristics according to response are shown in Online Supplementary Table 1. The univariable analyses showing a relationship between variables and Response –Worst or Response-Mastery with evidence of a statistically significant relationship are shown in Table 1.

<<insert Table 1 about here>>

Predictors of Response-Worst breathlessness

No demographic, intervention or cancer variables showed evidence of relationship to response at the statistical significance level of 0.05. Participants who were more open and saw things as a challenge were more likely to respond to the intervention, in addition to those who employed denial or sought out emotional support as a way of coping. Some evidence (P-values between 0.05 and 0.1) of a relationship was observed for the explanatory variable "Openness".

Predictors of Response-Mastery over breathlessness

As with Response-worst, we had no evidence that demographic or intervention variables were predictive of Response-mastery. With this outcome, some disease characteristics did show some evidence of relationship. People with worse self-reported health status, no metastases, and less fatigue were more likely to respond.

When considering the psychological variables, BFI "Openness" was again predictive of response. With the CRQ, worse baseline breathlessness levels and worse emotional function were associated with a better response. Those who used "humour" as a way of coping, were less likely to respond.

A multiple regression model (see Table 3) was only built for Response-Mastery as only 'Openness' was significantly associated with Response-worst. In the adjusted analysis, none of the explanatory variables had a P-value < 0.05. In addition, a correlation matrix was prepared for the explanatory variables included in the multiple logistic model. Openness was not correlated to any CRQ SAS variables whereas the CRQ scales were statistically significantly correlated to each other although not highly (data not shown, available on request).

<<insert Table 2 about here>>

DISCUSSION

In this planned exploratory analysis, we found some evidence that the personality trait of "openness" was associated with both response in severity of breathlessness and mastery over breathlessness. Cancer metastases and presence of fatigue, and worse baseline CRQ mastery and emotional function also predicted better gains in mastery in the univariable analyses. Some ways of coping showed weak relationships with better severity response in those using denial and emotional support but a worse mastery response in those using humour.

Brighton *et al*, found a similar proportion of responders (60% "worst"; 50% "mastery") and that worse baseline mastery predicted greater likelihood of response.[13] As the authors discuss, this could be regression to the mean, but is unlikely to be the sole explanation given the effect sizes observed and consistent findings across similar trials,[10] and similar interventions (some improvements from pulmonary rehabilitation were greatest in those with worse baseline disease burden).[26] It is also consistent with our finding that those with worse self-reported health were more likely to respond, although the extent of cancer and degree of fatigue appeared to limit potential; intuitively understandable given the physical effort needed to practice the self-management techniques. It is also notable that in the parent trial, distress due to breathlessness was worse in the group attending three sessions, which may indicate a burden of intervention.[11] Some sites delivered home-intervention to minimise this, but the findings remained despite stratification by site.

Patients' ways of coping, approach to seeking help and their expectations of both the symptom and of success of self-management affect how well people live with chronic breathlessness due to a number of cardio-respiratory causes.[2;27] An engaged style of coping (problem solving, findings ways to maintain role and activities despite limitations) appears to support daily living well,[2] and "optimism" and "hardiness" helps promote resilience and self-management in people with acute-on-chronic breathlessness crises.[12] This narrative is consistent with our finding that patients with a higher level of "challenge" (the extent to which people identify problems as ways for self-development; arguably an important attribute in being "hardy") and "openness" to trying new things were more likely to respond for both outcomes. Such open-mindedness could protect against the assumption that "nothing will help".[28] Of note, we found that those using "denial" also may be more likely to be a responder (worst breathlessness). Although counterintuitive, perhaps, as denial can be seen as a way of protecting oneself from being overwhelmed by the stressor, those who can use denial with regard to breathlessness, may be more likely to engage with training. For example, even though training could make breathlessness worse in the immediate term, patients might use denial to overcome that threatening situation,[29] although if this is so, it is surprising not to see an association with active coping as well. However, use of denial to protect against threat, combined with "openness" and "challenge", would make an interesting psychological profile. Personality and coping also seem to be integrally related.[30] Personality may affect type of coping strategy used, or nuance and effectiveness of use directly through biological drives, or in response to experiences of stressors.[31] In patients with lung cancer the trait of neuroticism and helplessness/hopelessness coping styles were strongly linked with increased anxiety;[32] a driver for breathlessness.

Functional imaging has increased our understanding of the role of prior bad experiences and mood in forming brain networks, and how they influence the perception of breathlessness in a "Bayesian" manner.[27] Thus the inference of what the brain expects and the sensory inputs the brain actually receives will result in the patient's perception of breathlessness. People who are less likely to automatically "fear the worst" may therefore gain more benefit from interventions.

Strengths and limitations

The *a priori* design, prospectively collecting a range of personality traits and coping style data at baseline is a strength. The main limitation is the exploratory nature of the design and the number of tests conducted. Also, for these observational data, only association rather than causation can be apportioned. As a secondary analysis of data collected from trial participants, the representativeness of the findings are limited by the trial's eligibility criteria. Although these were broad, the same characteristics that may help patients do well with self-management interventions, may also be associated with those prepared to be enrolled in a clinical trial. However, we did have a range of personality and coping styles represented in the dataset.[11]

Implications for clinical practice and research

The patients who benefited most, seem to be those with the worst self-reported health status and breathlessness. However, these may be those most reluctant to attend, and services should be easy to get to and patients encouraged and supported. Compassionately challenging fears and negative expectations may help improve benefit to that seen in people with a more open, positive view of life. These data are exploratory and therefore not directly clinically-translatable, but provide sufficient signal to warrant further investigation of the impact of personality and coping on responses to complex interventions that require self-management efficacy. In particular, the combination of "openness", "challenge" and "denial" would be interesting to examine in more depth.

CONCLUSIONS

Patients with worse subjective health status, worse baseline breathlessness mastery, but not severity, and the personality trait "openness" are most likely to respond to worst breathlessness and mastery following a breathlessness intervention. Presence of metastases and worse fatigue reduce the likelihood of benefit. Breathlessness services must be easy to get to and patients encouraged and supported to attend.

AUTHOR CONTRIBUTION

Concept: MJJ, SN; Design: All; Analysis: MK; Interpretation: All; First draft of manuscript: MJJ; Revisions and agreement with final version; All

DATA SHARING

Relevant anonymised patient level data available on reasonable request to the corresponding author.

ROLE OF THE SPONSOR

The sponsors did not have any role in the design, conduct, interpretation, review, approval, or control of this article.

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BOXES

Box 1 Psychological measures

Measure	Description
Big Five Inventory[14]	46 item statements with 5 point Likert scale to assess degree of agreement (1 disagree strongly; 5 strongly agree) Self-report inventory intended to measure an individual on the Big Five Factors (dimensions) of personality (Extraversion, Neuroticism, Agreeableness, Conscientiousness and Openness)
Mental Toughness Questionnaire[15]	48 item statements with a 5 point Likert scale to assess degree of agreement. (1 disagree strongly; 5 strongly agree) Intended to measure the proposed four core components of mental toughness (control, challenge, commitment and confidence)
Chronic Respiratory Questionnaire[16]	20- items. A list of 5 standardised activities is given and the patients asked to rate the level of breathlessness caused by these on a 7 point Likert scale. The patient is then asked in a similar manner regarding energy levels, mood and feeling of control over their illness and breathing. Total score and subscores on 4 categories (dyspnoea, fatigue, emotional function, mastery); Higher scores indicate better health-related quality of life.
Hospital Anxiety and Depression Scale[17]	A widely used 14 item (7 for depression scoring 0 -3, 7 for anxiety scoring 0 - 3) screening tool for depression and anxiety. Higher scores indicate worse anxiety or depression.
Brief COPE[18]	A 28-item multidimensional measure of strategies used for coping or regulating cognitions in response to stressors, each rated (1 = I haven't been doing this at all to 4 = I have been doing this a lot) No overall scores – item level scores only

Catastrophic thinking and perceived Injustice Experiences Questionnaire [19]	A 12-item scale that asks respondents to indicate the frequency with which they experience different thoughts concerning the sense of unfairness in relation to their injury on a 5-point scale with the endpoints (0) *never* and (4) *all the time*.
Numerical Rating Scale – COPE*	0 to 10 numerical rating scale, "How well have you *coped* with your breathlessness on average over the past 24 hours?"; 0 =I have not coped at all; 10 = I have coped very well
Numerical Rating Scale – DISTRESS*	0 to 10 numerical rating scale, How much *distress* has your breathlessness caused you on average over the past 24 hours?"; 0 = No distress at all; 10 = The worst imaginable distress

*Non-validated scales

Box 2. Explanatory variables with rationale

	Variable	Rationale
Demographic characteristics	• Age • Sex	• Breathlessness is more prevalent in older people[24] • Breathlessness is more commonly reported, and at higher levels in women[25]
Intervention characteristics	• Study arm – low/high • Study site	• Some individuals may respond to different intensities of intervention even though the group estimate was of no difference • Study sites varied with the composition of their breathlessness intervention teams and components although all provided the study core components.
Cancer related variables	• Performance/health status: ○ KPS* ○ EQ-5D* • Physical extent of disease: ○ Presence of metastases (yes/no) ○ Smoking (never/ever) • Symptoms: ○ NRS Average* ○ CRQ-Dyspnoea*, CRQ-Fatigue*	All of these may affect the ability of the patient to respond due to physical restriction

Psychological factors	• Study arm Preference • CRQ-Emotion, CRQ-Mastery • NRS Cope, • NRS Distress • BFI domains * • HADS (Anxiety, depression) • MTQ-48 (Commitment, Control, Challenge, Confidence) * • Brief COPE (All 14 scales)* • Catastrophizing and Injustice	All of these factors may affect the ability of the patient to engage with the intervention
* KPS - Karnofsky Performance Scale; EQ-5D – Euroqol; BFI - Big Five Inventory; MTQ-48 - Mental Toughness Questionnaire, CRQ-SAS - Chronic Respiratory Questionnaire; HADs - Hospital Anxiety and Depression Scale; NRS – numerical rating scale		

TABLES
Online Supplementary Table 1: Descriptive statistics by response status for worst breathlessness and mastery and for those with missing outcomes.

	Response_Worst					Response_Mastery		
	Responders (Yes)	Non-responders (No)	Total	Missing		Responders (Yes)	Non-responders (No)	Total
N (%)	47 (48)	44 (52)	91	64		49 (46)	57 (54)	107
Age *	69.5 (9.93)	70 (9.95)	69.7 (9.89)	68.5 (8.41)		68.8 (8.44)	69.9 (10.39)	69.4 (9.52)
Sex								
Female	23 (50)	16 (37)	39 (43)	22 (33.85)		18 (37)	26 (46)	44 (42)
Male	23 (50)	28 (64)	51 (57)	41 (63)		31 (63)	31 (54)	62 (59)
Study Arm								
High	14 (30)	18 (41)	32 (35)	20 (31)		19 (39)	18 (31)	37 (35)
Low	33 (70)	26 (59)	59 (65)	45 (69)		30 (61)	40 (69)	70 (65)
Study Site								
Cambridge	5 (10.64)	2 (5)	7 (8)	5 (8)		4 (8)	3 (5)	7 (7)
Cardiff	9 (19.15)	7 (16)	16 (18)	8(12)		7 (14)	9 (16)	16 (15)
Coventry	3 (6.38	8 (18)	11 (12)	4 (6)		5 (10)	6 (10)	11 (10)
East Kent	14 (29.79)	9 (21)	23 (25)	5 (8)		11 (22)	12 (21)	22 (22)
Edinburgh	0 (0)	1 (2)	1 (1)	1 (2)		0 (0)	1 (2)	1 (1)
Glasgow	5 (10.64)	1 (2)	6 (7)	19 (29)		11 (22)	11 (19)	22 (21)
Hull	6 (12.77)	10 (23)	16 (18)	17 (26)		5 (10)	11(19)	16 (15)
West Kent	5 (10.64)	6 (14)	11 (12)	6 (9)		6 (12)	5 (9)	11 (10)

Performance/health status: mean score (SD)

KPS*	72.33 (7.82)	73.41 (9.11)	72.86 (8.44)	66.9 (10.17)		72.77 (7.72)	72.83 (8.18)	72.8 (7.92)
EQ5D VAS	57.78 (18.05)	59.27 (18.76)	58.52 (18.30)	55.5 (18.75)		55.15 (16.74)	61.77 (18.48)	58.70 (17.92)
Metastases: N (%)								
Yes	9 (21)	4 (10)	13 (15)	10 (15)		3 (7)	11 (21)	14 (14)
No	33 (79)	38 (90)	71 (85)	47 (72)		43 (94)	42 (79)	85 (86)
Smoking: N (%)								
Ever	39 (85)	41 (93)	80 (89)	60 (92)		44 (90)	50 (86)	94 (89)
Never	7 (15)	3 (7)	10 (11)	3 (5)		5 (10)	7 (12)	12 (11)
Numerical Rating Scales for breathlessness: mean score (SD)								
Average	5.24 (1.72)	5.32 (1.39)	5.28 (1.56)	6.04 (1.77)		5.50 (1.57)	5.10 (1.50)	5.38 (1.54)
Cope	7.00 (2.03)	7.00 (2.09)	7 (2.05)	6.44 (2.24)		6.88 (1.96)	7.12 (2.15)	7.01 (2.06)
Distress	4.70 (2.80)	3.95 (2.71)	4.34 (2.76)	5.18 (3.31)		4.66 (2.82)	3.98 (2.77)	4.28 (2.80)
Chronic Respiratory Questionnaire: mean score (SD)								
Dyspnea	4.56 (1.33)	4.52 (1.22)	4.54 (1.27)	4.18 (1.26)		4.52 (1.12)	4.47 (1.33)	4.49 (1.23)
Fatigue	3.28 (0.94)	3.35 (1.00)	3.31 (1.00)	3.07 (1.18)		3.08 (1.01)	3.58 (1.03)	3.35 (1.25)
Emotion	4.57 (1.12)	4.62 (1.07)	4.59 (1.09)	4.08 (1.34)		4.33 (1.17)	4.81 (1.06)	4.59 (1.13)
Mastery	4.46 (1.16)	4.56 (1.06)	4.51 (1.10)	3.96 (1.25)		4.16 (1.05)	4.75 (1.11)	4.48 (1.12)
Arm Preference: N (%)								
High	11 (23)	9 (20)	14 (22)	20 (22)		10 (20)	16 (28)	26 (24)
Low	14 (30)	8 (18)	22 (24)	14 (22)		10 (20)	13 (22)	23 (22)
None	22 (47)	27 (61)	49 (54)	36 (55)		29 (60)	29 (50)	58 (54)
Big Five Inventory: mean score (SD)								

Extraversion	3.21 (0.88)	3.31 (0.80)	3.26 (0.84)	3.15 (0.75)	3.23 (0.75)	3.277 (0.87)	3.25 (0.81)
Agreeableness	4.32 (0.49)	4.19 (0.54)	4.26 (0.52)	4.05 (0.69)	4.14 (0.57)	4.29 (0.51)	4.22 (2.67)
Conscientiousness	4.16 (0.58)	4.11 (0.58)	4.14 (0.58)	3.99 (0.68)	4.14 (0.64)	4.05 (0.61)	4.09 (0.63)
Neuroticism	2.44 (0.87)	2.39 (0.80)	2.42 (0.83)	2.76 (0.89)	2.54 (0.77)	2.40 (0.86)	2.46 (0.82)
Openness	3.60 (0.68)	3.25 (0.75)	3.42 (0.73)	3.10 (0.65)	3.54 (0.69)	3.24 (0.71)	3.38 (0.72)

Hospital Anxiety Depression Scale: mean score (SD)

Anxiety	6.02 (4.07)	5.82 (3.71)	5.92 (3.88)	7.43 (4.85)	6.59 (3.99)	5.74 (3.8)	6.13 (3.90)
Depression	6.00 (3.31)	5.64 (3.70)	5.82 (3.49)	6.75 (3.95)	6.43 (3.51)	5.64 (3.36)	6.00 (3.44)

Mental Toughness Questionnaire: mean score (SD)

Commitment	3.84 (0.61)	3.75 (0.66)	3.79 (0.63)	3.61 (0.64)	3.81 (0.53)	3.74 (0.70)	3.77 (0.63)
Challenge	3.94 (0.67)	3.68 (0.62)	3.81 (0.65	3.66 (0.67)	3.86 (0.61)	3.69 (0.65)	3.77 (0.63)
Emotion	3.20 (0.61)	3.34 (0.60	3.26 (0.61)	3.28 (0.68)	3.30 (0.67)	3.29 (0.62)	3.29 (0.64)
Life	3.72 (0.67)	3.69 (0.65)	3.70 (0.66)	3.62 (0.70)	3.78 (0.64)	3.66 (0.73)	3.71 (0.65)
Abilities	3.61 (0.62)	3.78 (0.53)	3.69 (0.58)	3.58 (0.64)	3.64 (0.58)	3.68 (0.61)	3.66 (0.59)
Interpersonal	3.86 (0.82)	3.77 (0.72)	3.81 (0.77)	3.76 (0.79)	3.84 (0.72)	3.79 (0.80)	3.81 (0.76)

BriefCOPE questionnaire: mean score (SD)

self-distraction	4.83 (1.95)	4.79 (1.97)	4.80 (1.95)	4.85 (1.69)	4.84 (1.77)	4.70 (1.95)	4.76 (1.86)
active coping	4.74 (1.84)	4.49 (2.02)	4.61 (1.92)	4.78 (1.53)	4.96 (1.68)	4.40 (1.96)	4.66 (1.85)
denial	3.36 (1.86)	2.79 (1.06)	3.09 (1.55)	3.3 (1.75)	3.12 (1.67)	3.16 (1.59)	3.14 (1.62)
substance use	2.53 (1.21)	2.35 (0.95)	2.44 (1.09)	2.7 (1.59)	2.35 (0.95)	2.57 (1.33)	2.47 (1.17)
emotional support	6.35 (1.85)	5.58 (1.93)	5.98 (1.91)	6.2 (1.67)	6.24 (1.94)	5.70 (1.83)	5.95 (1.89)
instrumental support	5.15 (1.93)	4.91 (1.80)	5.03 (1.86)	4.95 (1.79)	5.18 (1,81)	4.88 (1.8)	5.02 (1.90)

behavioural disengagement	2.41 (1.11)	2.30 (0.74)	2.36 (0.94)	2.75 (1.30)		2.45 (1.02)	2.40 (1.07)	2.42 (1.04)
venting	3.17 (1.52)	2.88 (1.38)	3.03 (1.46)	3.27 (1.36)		3.14 (1.51)	2.95 (1.39)	3.04 (1.48)
positive reframing	4.07 (1.85)	3.86 (1.70)	3.98 (1.77)	3.87 (1.55)		4.20 (1.78)	3.84 (1.61)	4.01 (1.69)
planning	4.00 (1.80)	3.93 (1.80)	3.96 (1.79)	4.22 (1.69)		4.16 (1.87)	3.95 (1.66)	4.05 (1.76)
humour	4.33 (2.04)	4.37 (2.10)	4.35 (2.06)	4.63 (2.28)		3.98 (2.15)	4.70 (2.00)	4.37 (2.09)
acceptance	7.07 (1.14)	6.60 (1.69)	6.84 (1.45)	6.66 (1.40)		6.84 (1.50)	6.77 (1.34)	6.80 (1.41)
religion	3.78 (2.08)	3.28 (2.06)	3.53 (2.07)	3.02 (2.00)		3.39 (2.13)	3.40 (1.95)	3.40 (2.03)
self-blame	3.27 (1.66)	3.21 (1.64)	3.24 (1.64)	3.47 (1.70)		3.45 (1.56)	3.09 (1.64)	3.26 (1.60)
Catastrophic thinking and perceived Injustice Experiences Questionnaire mean score (SD)								
Injustice	4.34 (2.61)	3.73 (2.75)	4.04 (2.68)	4.23 (2.74)		4.20 (2.54)	3.88 (2.51)	4.03 (2.52)
Catastrophising	4.45 (3.06)	3.77 (3.09)	4.12 (3.07)	5.12 (3.98)		4.14 (3.10)	4.19 (3.05)	4.17 (3.06)

Table 1. Univariable analyses (P values at the P <0.05 level shown in bold.)

	Baseline values	Response - Worst Odds Ratio (95% CIs) P value	Response – Mastery Odds Ratio (95% CIs) P value
Demographic			
Age		0.99 (0.95 to 1.04); p = 0.797	0.99 (0.95 to 1.03); P = 0.551
Sex (man vs woman [ref])		0.57 (0.25 to 1.33); p = 0.193	1.44 (0.66 to 3.15); P = 0.356
Smoking (never vs ever[ref])		2.45 (0.59 to 10.17); P = 0.216	0.81 (0.24 to 2.74); P = 0.737
Intervention			
	Study arm (High vs low)	0.61 (0.26 to 1.46); P = 0.268	1.41 (0.63 to 3.13); P = 0.402
	Study site vs Cambridge [ref]	P=0.181	P=0.888
	Cardiff	0.51 (0.08 to 3.49); P = 0.496	0.58 (0.10 to 3.51); P = 0.556
	Coventry	0.15 (0.02 to 1.24); P = 0.078	0.63 (0.09 to 4.22); P = 0.630
	East Kent	0.62 (0.10 to 3.92); P = 0.614	0.69 (0.12 to 3.79); P = 0.667
	Glasgow	2 (0.13 to 29.81); P = 0.615	0.75 (0.14 to 4.17); P = 0.742
	Hull	0.24 (0.03 to 1.65); P = 0.147	0.34 (0.05 to 2.13); P = 0.250
	West Kent	0.33 (0.04 to 2.52); P = 0.287	0.90 (0.13 to 6.08); P = 0. 914
Cancer related			
	Karnofsky Performance Status	0.98 (0.94 to 1.04); P = 0.553	1.0 (0.95 to 1.05); P = 0.968
	EuroQol- VAS	1.0 (0.97 to 1.02); P = 0.711	0.98 (0.96 to 1.00) ; P = 0.07
	Metastases (Yes vs No [ref])	2.59 (0.73 to 9.20); P = 0.141	0.27 (0.07 to 1.02) ; P= 0.054
	Symptoms		
	NRS average	0.97 (0.74 to 1.26); P = 0.809	1.19 (0.90 to 1.57); P = 0.220
	CRQ-Dyspnea	1.03 (0.74 to 1.42); P = 0.876	1.04 (0.76 to 1.41); P = 0.827

CRQ-Fatigue	0.93 (0.60 to 1.43); P = 0.727	0.61 (0.41 to 0.91); **P = 0.015**

Psychological factors

Arm preference	P = 0.321	P=0.597
low vs high [ref]	1.43 (0.42 to 4.93); P = 0.570	1.23 (0.39 to 3.86); P = 0.722
None vs high [ref]	0.67 (0.23 to 1.90); P = 0.447	1.60 (0.62 to 4.11); P = 0.329
NRS cope	1.0 (0.82 to 1.22); P = 1.000	0.94 (0.77 to 1.16); P = 0.576
NRS distress	1.11 (0.95 to 1.29); P = 0.200	1.09 (0.94 to 1.27); P = 0.258
CRQ-Emotion	0.96 (0.66 to 1.41); P = 0.842	0.68 (0.47 to 0.96); **P = 0.030**
CRQ-Mastery	0.92 (0.63 to 1.35); P = 0.681	0.61 (0.42 to 0.88); **P = 0.008**

Big Five Inventory

BFI Extraversion	0.87 (0.53 to 1.44); P = 0.587	0.94 (0.59 to 1.51); P = 0.812
BFI Agreeableness	1.64 (0.72 to 3.72); P = 0.239	0.59 (0.29 to 1.22); P = 0.157
BFI Conscientiousness	1.19 (0.58 to 2.45); P = 0.643	1.25 (0.67 to 2.33); P = 0.482
BFI Neuroticism	1.08 (0.65 to 1.79); P = 0.759	1.23 (0.77 to 1.97); P = 0.392
BFI Openness	1.99 (1.08 to 3.67); **P = 0.028**	1.84 (1.04 to 3.23); **P = 0.035**

Hospital Anxiety Depression Scale

Anxiety	1.01 (0.91 to 1.13); P = 0.802	1.06 (0.96 to 1.17); P = 0.261
Depression	1.02 (0.92 to 1.16); P = 0.618	1.07 (0.96 to 1.20); P = 0.237

Mental Toughness Questionnaire-48

MTQ-48 Commitment	1.27 (0.65 to 2.47); P = 0.479	1.22 (0.66 to 2.26); P = 0.523
MTQ-48 Challenge	1.85 (0.95 to 3.62); P= 0.071	1.56 (0.84 to 2.91); P = 0.159
MTQ-48 Emotion	0.67 (0.33 to 1.35); P = 0.261	1.03 (0.56 to 1.87); P = 0.932
MTQ-48 Life	1.06 (0.56 to 2.00); P = 0.859	1.34 (0.73 to 2.44); P = 0.340
MTQ-48 Abilities	0.61 (0.29 to 1.27); P = 0.185	0.89 (0.47 to 1.69); P = 0.720
MTQ-48 Interpersonal	1.18 (0.69 to 2.03); P = 0.544	1.07 (0.65 to 1.78); P = 0.781

Brief COPE		
self-distraction	1.01 (0.81 to 1.25); P = 0.931	1.04 (0.85 to 1.28); P = 0.708
active coping	1.07 (0.86 to 1.33); P = 0.537	1.18 (0.95 to 1.46); P = 0.127
denial	1.29 (0.96 to 1.74); P= 0.087	0.99 (0.78 to 1.25); P = 0.917
substance use	1.17 (0.79 to 1.74); P = 0.429	0.84 (0.59 to 1.19); P = 0.332
emotional support	1.24 (0.99 to 1.56); P = 0.062	1.17 (0.95 to 1.44); P = 0.142
instrumental support	1.07 (0.86 to 1.35); P = 0.533	1.10 (0.89 to 1.36); P = 0.382
behavioural disengagement	1.14 (0.72 to 1.80); P = 0.582	1.04 (0.72 to 1.51); P = 0.822
venting	1.15 (0.86 to 1.55); P = 0.349	1.10 (0.84 to 1.43); P = 0.488
positive reframing	1.07 (0.84 to 1.35); P = 0.585	1.14 (0.90 to 1.43); P = 0.272
planning	1.02 (0.81 to 1.30); P = 0.851	1.07 (0.86 to 1.34); P = 0.527
humour	0.99 (0.81 to 1.21); P = 0.916	0.84 (0.70 to 1.02); P =0.078
acceptance	1.26 (0.93 to 1.71); P = 0.138	1.03 (0.79 to 1.36); P = 0.813
religion	1.13 (0.92 to 1.39); P = 0.253	1.0 (0.82 o 1.20); P = 0.968
self blame	1.02 (0.79 to 1.32); P = 0.869	1.15 (0.90 to 1.47); P = 0.254
Catastrophic thinking and perceived Injustice Experiences Questionnaire		
Injustice	1.09 0.93 to 1.28); P = 0.276	1.05 (0.90 to 1.23); P = 0.505
Catastrophising	1.08 (0.94 to 1.23); P = 0.296	0.99 (0.88 to 1.13); P = 0.937

Table 2. Adjusted and crude estimates using logistic regression for Response – outcome

	Crude Odds Ratios (95% CIs) P value	Adjusted Odds Ratios (95% CIs) P value
Symptoms:CRQ-Fatigue	0.61 (0.41 to 0.91): **P = 0.015**	0.72 (0.44 to 1.19); P = 0.201
CRQ-Emotion	0.68 (0.47 to 0.96): **P = 0.030**	1 (0.6 to 1.68); P = 0.995
CRQ-Mastery	0.61 (0.42 to 0.88); **P = 0.008**	0.69 (0.43 to 1.12); P = 0.132
BFI Openness	1.84 (1.04 to 3.23); **P = 0.035**	1.73 (0.95 to 3.15); P = 0.072
P values at the P <0.05 level shown in bold. The crude estimates are those reported in Table 2 but presented here for ease of comparison.		