REVIEW

Depression and anxiety predict health-related quality of life in chronic obstructive pulmonary disease: systematic review and meta-analysis

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Background: The causal association between depression, anxiety, and health-related quality of life (HRQoL) in chronic obstructive pulmonary disease (COPD) is unclear. We therefore conducted a systematic review of prospective cohort studies that measured depression, anxiety, and HRQoL in COPD.

Methods: Electronic databases (Medline, Embase, Cumulative Index to Nursing and Allied Health Literature [CINAHL], British Nursing Index and Archive, PsycINFO and Cochrane database) were searched from inception to June 18, 2013. Studies were eligible for inclusion if they: used a nonexperimental prospective cohort design; included patients with a diagnosis of COPD confirmed by spirometry; and used validated measures of depression, anxiety, and HRQoL. Data were extracted and pooled using random effects models.

Results: Six studies were included in the systematic review; of these, three were included in the meta-analysis for depression and two were included for the meta-analysis for anxiety. Depression was significantly correlated with HRQoL at 1-year follow-up (pooled $r=0.48$, 95% confidence interval 0.37–0.57, $P<0.001$). Anxiety was also significantly correlated with HRQoL at 1-year follow-up (pooled $r=0.36$, 95% confidence interval 0.23–0.48, $P<0.001$).

Conclusion: Anxiety and depression predict HRQoL in COPD. However, this longitudinal analysis does not show cause and effect relationships between depression and anxiety and future HRQoL. Future studies should identify psychological predictors of poor HRQoL in well designed prospective cohorts with a view to isolating the mediating role played by anxiety disorder and depression.

Keywords: long-term conditions, COPD, quality of life, panic

Background

Chronic obstructive pulmonary disease (COPD) is responsible for approximately 5% of deaths worldwide and is predicted to become the third leading cause of death by 2030.[1] It is a chronic respiratory disease that typically results in a wide range of extrapulmonary comorbidities, such as cardiovascular disease, skeletal muscle dysfunction, osteoporosis, diabetes, anemia, and depression.[2,3] COPD severity has traditionally been assessed using measures of airflow obstruction, such as forced expiratory volume in one second (FEV_1). However, the therapeutic focus in COPD has started to shift away from an emphasis on lung function and mortality to management of comorbidities and more patient-centered outcomes related to functioning and health status. This trend is reflected in the increased use and reliance on patient-centered outcomes such as health-related quality of life (HRQoL) to assess the impact of therapeutic strategies in COPD.[4]

HRQoL is a multidimensional concept that refers to quality of life that is directly related to health or illness. It often includes domains related to the physical, social, and psychological impact of illness.[5] HRQoL is concerned with a patient's experience of illness and can be defined as the subjective perception of the impact of health status on satisfaction with daily life.[5–7] COPD severity is associated with impaired HRQoL,[8–10] but poor HRQoL can also exacerbate symptoms of COPD (such as breathlessness) and can have a significant impact on physical functioning, the probability of hospital admission, and mortality.[11–18]

There are a range of psychological factors that might explain variation in respiratory-specific HRQoL over and above markers of disease severity, such as FEV_1. Depression and anxiety have both been found to be important predictors of HRQoL in cross-sectional studies,[19–24] with anxiety explaining over 40% of the variance in HRQoL in some cases.[20] Tsiligianni et al conducted a meta-analysis of cross-sectional studies and reported that depression and anxiety were highly correlated with respiratory-specific HRQoL; a higher correlation was only found between dyspnea and HRQoL.[25] Further studies conducted since this review have confirmed this finding,[26] with one population-based study in Singapore showing that the impact of depression on HRQoL in COPD was significantly greater than in people without COPD.[27] Some cross-sectional studies have also examined the association between psychological health and more generic measures of HRQoL, such as the Medical Outcomes Study Short Form.[28] However, even when HRQoL is measured using these generic measures, depression and anxiety still account for a significant proportion of the variance in people with COPD.[29,30]

Findings to date are thus mainly derived from cross-sectional studies, and although results suggest that there is a significant association between depression, anxiety, and HRQoL in COPD, they are not able to determine causal associations between these factors. It is important to consider the temporal and causal association between depression and/or anxiety and HRQoL in order to inform the development of future interventions aimed at improving HRQoL. We have therefore conducted a systematic review with meta-analysis of longitudinal prospective studies to assess the ability of depression and anxiety to predict future HRQoL in patients with COPD.

Methods

The methods and results for this review are reported in line with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[31]

Information sources and search strategy

Studies were identified for inclusion in this review by searching the following electronic databases from inception to June 18, 2013: Medline, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), British Nursing Index and Archive, PsycINFO, and Cochrane database. The search strategy was designed using Medical Subject Headings (MeSH) terms and key words relating to COPD, depression, anxiety, panic, HRQoL, and longitudinal cohort studies for each database. Electronic searches were supplemented by hand searches of reference lists of included papers and relevant reviews.

Eligibility criteria

Studies were eligible for inclusion in this review if they:
- used a nonexperimental prospective cohort design
- did not include any standardized experimental intervention; this was to ensure that samples included in the review had not been exposed to any intervention which may have modified the association between depression, anxiety, and HRQoL over the duration of the study
- included patients with a diagnosis of COPD confirmed by spirometry as an FEV_1/forced vital capacity ratio <0.70 or FEV_1 <80% of the predicted values according to GOLD (Global initiative for chronic Obstructive Lung Disease) criteria;[32] studies that included a cohort of patients with a range of chronic physical health problems including COPD were eligible only where data for COPD confirmed by spirometry were reported separately
- used validated self-report measures of either general or respiratory-specific HRQoL
- used validated diagnostic clinical interviews or self-report measures of depression and anxiety; clinical and subthreshold symptoms of depression and anxiety were included.

Studies where depression and anxiety were measured using a subscale of a quality of life measure were excluded. Studies were not excluded by date of publication, sample size, or follow-up period. However, studies that were unpublished, published in abstract form only, or were not published in the English language were not included in this review.

Study selection

Titles and abstracts were screened (by AB) and full papers of potentially relevant abstracts were retrieved. Full text versions of abstracts were independently screened and final decisions about eligibility were made at a consensus meeting with all review authors. Further information was requested from authors of seven papers, of whom five responded to provide additional information on their papers.

Data extraction

An electronic form was developed in Microsoft Excel for the purpose of data extraction. Data were extracted independently by two researchers (AB, CA) who each looked at all studies. Data were extracted on study design, method and place of recruitment, sample age, sex, smoking history, method of COPD diagnosis, and severity classification (FEV_1). Scores for HRQoL depression and anxiety were extracted at both baseline and follow-up. Any disagreements between researchers were resolved by discussion.

The main aim of this review was to assess the strength of the longitudinal association between anxiety, depression, and HRQoL in COPD. Where these data were not available in the published papers, authors were contacted by email or letter to request the appropriate data. Where the length of follow-up varied, data were extracted and included in the meta-analysis for the time point closest to 12 months after the baseline measures were taken.

Quality assessment

Studies were rated for their quality by two researchers (AB, CA) using criteria adapted from guidance on the assessment of observational studies[33] and the Quality Assessment Tool for Quantitative Studies.[34] Any disagreements were resolved by discussion.

The quality review included assessment of selection bias, response bias, the reliability and validity of data collection methods, withdrawals and dropouts, and whether confounding variables were adequately controlled for. Three key criteria were deemed as essential to the quality review and each study was awarded one point for each criterion met; this was then used as a framework for narrative synthesis of the results. These key criteria were: response rate of 70% or greater at baseline; control for confounding factors in analysis; and response rate greater than 70% at follow-up.[34]

Data analysis and synthesis

Data analysis was conducted in Stata (version 12.1; StataCorp LP, College Station, TX, USA) and Comprehensive Meta-analysis (version 2.2.064; BioStat International, Inc., Tampa, FL, USA). Where possible, indices of association between depression or anxiety and total scores for HRQoL measures were included in the meta-analysis. However, where total scores were not available, the most appropriate subscale score was used. For the St George's Respiratory Questionnaire (SGRQ)[35] the Impact subscale was used because it provides a measure of social functioning and psychological disturbance associated with respiratory disease.[35] We aimed to extract regression coefficients where possible. However, since regression coefficients were not available in any of the studies, correlation coefficients were extracted and transformed for meta-analysis using Fisher's Z transformation in order to normalize the distribution of r, making the variance independent of the unknown true value of the correlation.[36] The Z scores were then pooled across the studies using a random effects model to account for variation between studies. The pooled effect size was then converted back to a correlation coefficient.[37] A pooled correlation coefficient of $r=0.10$ was considered small, $r=0.25$ as moderate, and $r=0.40$ as large.[38] Where papers did not report either a correlation coefficient or the data required to compute a correlation coefficient, we contacted the corresponding author and requested the missing data. Two authors responded and supplied the relevant data.[39,40] Statistical heterogeneity was investigated using I^2 which measures the percentage of the variation across studies that is due to heterogeneity and cannot be explained by chance.[41] Low heterogeneity is indicated by an I^2 result of $\leq 25\%$, moderate heterogeneity by around 50%, and high heterogeneity is $\geq 75\%$.[41]

Results

Electronic and hand searches identified 380 citations excluding duplicates. Of these, 236 citations were excluded on the basis that their abstracts did not meet the eligibility criteria for this review. The full texts for 144 citations were reviewed. Six studies were identified that met the criteria for inclusion in the systematic review,[39,40,42–45] of which three were eligible for inclusion in meta-analysis for depression[39,40,43] and two for anxiety.[39,40] The flow of the studies and reasons for exclusion are presented in the PRISMA flow chart in Figure 1.[31]

Characteristics of studies and populations

The characteristics of each study are summarized in Table 1. In total, there were data for 895 COPD patients, of whom 69.8% (n=625) were male. Five of the studies included both male and female COPD patients and one was limited to male patients.[39] The mean age across the studies ranged from 64.6 years[44] to 73.5 years.[42] Length of follow-up ranged from 3 months[40] to 5 years.[39]

The majority of participants (61.1%, n=547) were recruited in hospital following admission for acute exacerbations of COPD.[42,43] The remaining 38.9% (n=348) were recruited from hospital outpatient settings. One study excluded patients who had experienced an acute exacerbation in the previous 6 weeks,[39] and another reported that none of the patients in their sample had been admitted for an acute
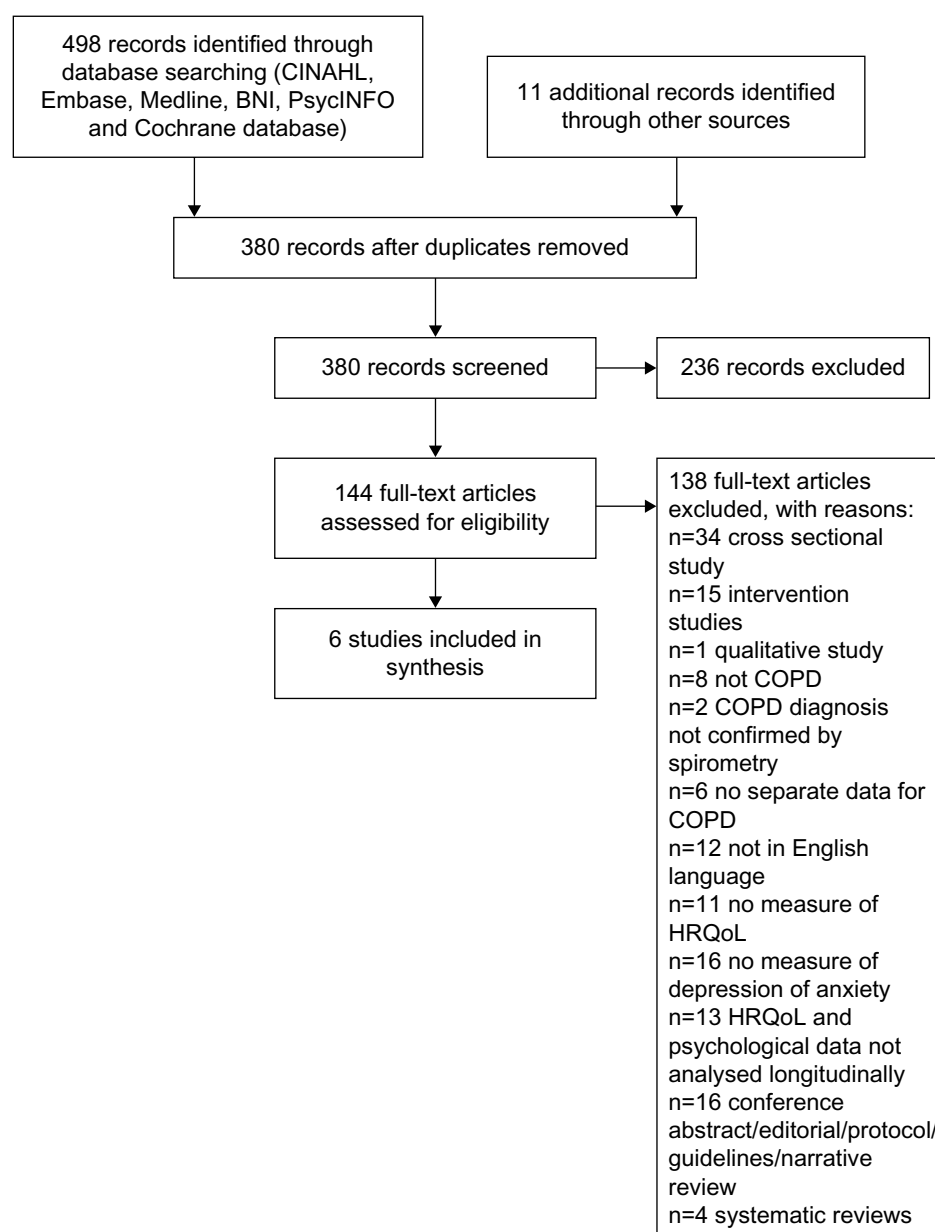
Figure 1 Search flowchart.
Abbreviations: BNI, British Nursing Index and Archive; CINAHL, Cumulative Index to Nursing and Allied Health Literature; COPD, chronic obstructive pulmonary disease; HRQoL, health-related quality of life.

exacerbation at the time they participated in the study.[44] All included studies recruited patients with a mean predicted $FEV_1 <50\%$, which indicates severe COPD.[32]

Four of the six studies[39,40,42,43] measured HRQoL using COPD-specific measures, including the SGRQ and the Chronic Respiratory Questionnaire.[46] One study[45] used the Sickness Impact Profile,[47] and another used both the Sickness Impact Profile and the SGRQ.[44] Four of the six studies[39,40,42,44] measured symptoms of depression using the Hospital Anxiety and Depression Scale (HADS).[48] One study[43] used the Hopkins Symptom Checklist,[49] and one study used the Profile of Mood States.[50] Three studies measured anxiety

symptoms using the HADS.[39,40,44] No study measured panic disorder or any other specific anxiety disorders.

The prevalence of anxiety and depression varied at baseline (Table 1). The three studies that recruited patients following an admission to hospital reported that patients in their sample were experiencing symptoms of depression at baseline.[40,42,43] One study reported that 44.4% of their sample had symptoms of depression at baseline, but did not report mean HADS scores.[42] Three of the studies that recruited hospital outpatients reported that their sample had symptoms of depression that were not clinically significant at baseline.[39,44,45] However, one study of outpatients reported

Table 1 Characteristics of included studies

Reference	Country	Recruitment and sample	Mean age, years (± SD)	% Male	Mean FEV$_1$ % predicted and GOLD severity stage	HRQoL measures and mean scores	Psychological measures and mean scores	Length of follow-up
Ng et al[42]	Singapore	376 consecutive patients hospitalized for acute exacerbations between April 2002 and October 2004. FEV$_1$ <70% predicted, with or without chronic cough and sputum. Current or ex-smoker with history of ≥20 pack years	Not depressed (n=209) 71.1±8.2 Depressed (n=167) 73.5±8.5	Total 85.1 (n=320) Not depressed 85.6 (n=179) Depressed 84.4 (n=141)	Not depressed (n=209) 48.2±20.2 Depressed (n=167) 47.3±21.8 Stage III, severe COPD	SGRQ Not depressed 42.4 (SE 3.4) Depressed 52.4 (SE 3.1)	HADS 44.4% (n=167) depressed at baseline (score of ≥8 on HAD-D)	6 months and 1 year mean 313±13 days
Oga et al[39]	Japan	137 consecutive male outpatients between September 1995 and April 1997. Moderate to very severe COPD (maximal FEV$_1$/FVC ratio of <0.7 and post-bronchodilator FEV$_1$ <80% of predicted normal). Smoking history of >20 pack years	69.0±0.6	100% (n=137)	45.9 (SE 1.3) Stage III, severe COPD	SGRQ, Japanese version 36.2 (SE 1.4) CRQ, Japanese version 5.4 (SE 0.08)	HADS-Japanese version HAD-D 3.9 (SE 0.3) HAD-A 4.7 (SE 0.3)	5 years
Andenaes et al[43]	Norway	92 hospital patients diagnosed with COPD between September 1997 and February 2000	67.6±9.5	41.2 (n=21)	39.8±16.5 Stage III, severe COPD	SGRQ 65.9±10.9 WHOQOL-BREF physical 10.6±2.1 psychological 13.1±2.5 social 14.8±1.9 environmental 13.5±1.9	HSCL-25 2.1±0.5	1 month post-discharge, 6 and 9 months
Engstrom et al[44]	Sweden	68 hospital outpatients, every tenth outpatient at Department of Pulmonary Medicine.FEV$_1$ <80% predicted, 40–75 years,stratified into 3 groups: FEV$_1$ <30% (22.3%, n=21); 30%–50% (36.4%, 50%–80% 64.1±6.4 n=25); 50%–80% (60.9, n=22)	Overall 64.6±6.8 <30% 64.1±6.8 30%–50% 64.8±7.3 50%–80% 64.1±6.4	Overall 63.2 (n= 43) <30% 57.1 (n=12) 30%–50% 64.0 (n=16) 50%–80% 68.2 (n=15)	39.9±17.0 Stage III (severe COPD)	SGRQ 46.0±18.3 <30% 54.3±14.6 30%–50% 47.5±17.1 50%–80% 36.4±19.1 SIP-Swedish version 8.5±8.1 <30% 10.6±7.0 30%–50% 9.9±9.3 50%–80% 4.9±6.8	HADS-Swedish version HAD-D 5.2±4.5 HAD-A 4.4±3.8 MACL 3.0±0.6 <30% 2.9±0.5 30%–50% 3.1±0.5 50%–80% 3.1±0.8	12 months
Graydon et al[45]	Canada	143 hospital outpatients, FEV$_1$ <50% predicted (severe COPD) Data analysed for 71 patients who completed follow up	66.4 (SD not reported)	67.6 (n=48)	31.73±8.62 Stage III (severe COPD)	SIP 16.4±10.2	POMS (negative mood scales) 38.0±28.6	30 months
Coventry et al[40]	UK	79 patients admitted for acute exacerbation and referred to nurse-led early discharge service FEV$_1$ <80% predicted	65.3±9.9	44 (n=56)	42.2±18.4 Stage III (severe COPD)	SGRQ 58.8±14.6	HADS HAD-D 7.0±3.8 HAD-A 8.8±4.3 HAD total 15.8±7.0	90 days and 365 days

Abbreviations: FEV$_1$, forced expiratory volume in 1 second; GOLD, Global initiative for chronic Obstructive Lung Disease; HRQoL, health-related quality of life; SGRQ, St George's Respiratory Questionnaire; HADS, Hospital Anxiety and Depression Scale; FVC, forced vital capacity; CRQ, Chronic Respiratory Questionnaire; HAD-A, Hospital Depression and Anxiety Scale anxiety subscale; HAD-D, Hospital Depression and Anxiety Scale depression subscale; WHOQOL-BREF, World Health Organization Quality of Life Instrument; HSCL-25, Hopkins Symptoms Checklist; MACL, Mood Adjective Checklist; SIP, Sickness Impact Profile; POMS, Profile of Mood States; SD, standard deviation; SE, standard error.

a significant increase in depressive symptoms in their sample over a 5-year study period.[39]

Three studies measured anxiety using the HADS; two were studies of hospital outpatients and neither reported clinical levels of anxiety at baseline;[39,44] one was a study of patients admitted to hospital and discharged to a nurse-led early discharge service and reported a mean HADS anxiety score of 8.8, indicating mild anxiety symptoms.[40,48]

Quality of included studies

The results of the quality review are presented in Table 2. The quality of the studies varied greatly. One study met the requirements for all three of the quality criteria,[42] two studies met two of the criteria,[40,43] and three studies did not meet any.[39,44,45] Five out of the six studies studies[39,40,42,43,45] reported attrition rates at follow-up, two of which found that those who completed the study were more likely to be younger than those who did not.[43,45] Furthermore, in one study,[39] over 40% of patients who did not complete follow-up at 5 years had died. In this study, patients who had died were found to be significantly older, more breathless, and had worse HRQoL than those who did complete follow-up.

Longitudinal association of depression with HRQoL in COPD

Six longitudinal cohort studies investigated the association between depression and HRQoL in COPD (Table 1), but only three studies could be included in the meta-analysis for depression.[39,40,43]

Ng et al[42] scored the highest score of 3 in the quality review and reported that depressed patients had significantly worse HRQoL at baseline across all subscales of the SGRQ, and this was maintained at 12-month follow-up. However, the authors did not analyze the predictive effect of depression on HRQoL across the 12-month period. Two of the studies scored 2 in the quality review.[40,43] Andenaes et al[43] studied patients who were admitted to hospital with COPD and reported a significant correlation between depression at baseline and HRQoL on follow-up at 6 and 9 months. In this study, depression was significantly correlated with the respiratory-specific SGRQ Impact subscale ($r=0.28$, n=51, $P<0.05$, 95% confidence interval [CI] not reported) and also the physical domain ($r=-0.64$, n=51, $P<0.01$, 95% CI not reported), psychological domain ($r=-0.62$, n=51, $P<0.01$, 95% CI not reported), and environmental domain ($r=-0.41$, n=51, $P<0.01$, 95% CI not reported), but not with the social domain ($r=-0.23$) of the WHOQoL-BREF (World Health Organization Quality of Life Instrument). Coventry et al[40] found that depression at baseline

Table 2 Quality of the included studies

Reference	Information on recruitment method?	Response rate	Comparison of those who did and did not respond?	Were HRQoL measures valid and reliable?	Were psychological measures valid and reliable?	Were confounding factors controlled for in analysis?	How many patients completed FU?	Comparison of those who did and did not complete FU?	Total quality score*
Ng et al[42]	No	376/503 (74.8%)	No	Yes	Yes	Yes	275/376 completed 1-year FU (73.1%)	No	3
Oga et al[39]	Consecutive male patients outpatients	No	No	Yes	Yes	No	72/137 completed 5-year FU (52.6%)	No	0
Andenaes et al[43]	No	97/107 (90.7%)	No	Yes	No – two depression questions omitted	Yes	51/92 completed 9-month FU (55.4%)	Yes	2
Engstrom et al[44]	Every tenth patient meeting inclusion criteria invited	No	No	Yes	Yes	No	Not reported	No	0
Graydon et al[45]	Invited by letter and telephone FU call	No	No	Yes	Yes	No	71/143 completed 30-month FU (49.7%)	Yes	0
Coventry et al[40]	Patients referred to early discharge services and recruited by respiratory nurse specialists	79/123 (64%)	No	Yes	Yes	Yes	62/79 completed 365-day FU (78%)	No	2

Note: *The total quality score is calculated by awarding 1 point for each of the following criteria: 1) response rate >70% at baseline, 2) confounding factors controlled for in the analysis, and 3) response rate of >70% at FU.
Abbreviations: FU, follow-up; HRQoL, health-related quality of life.

was significantly correlated with respiratory-specific HRQoL at 3 months (r=0.52, P<0.001) and 1-year follow-up (r=0.64, P<0.001) in patients discharged from hospital under the care of early discharge services (Table 3). Three studies did not meet any of the key quality criteria.[39,44,45] Firstly, Oga et al[39] reported that depression measured at baseline was significantly correlated with respiratory-specific HRQoL at 1-year follow-up (r=0.47, P<0.001); this association remained after 5 years (r=0.47, P<0.001) in the sample of outpatients with severe COPD.[39] Secondly, Engstrom et al found that depression as measured by the Hospital Depression and Anxiety Scale depression subscale (b=0.39, P<0.001), 6-minute walk distance (b=0.05, P<0.05), and vital capacity (b=0.15, P<0.001) were the best predictors of HRQoL, explaining 59% of the variance in multiple regression analyses when SGRQ scores were excluded.[44] Finally, Graydon et al found that negative mood, as measured by the Profile of Mood States at baseline, was significantly correlated with HRQoL after 12 months (r=0.49, P<0.0001, 95% CI not reported).[45] However, they did not include depression as a predictor variable in their multiple regression analyses.

Meta-analysis of longitudinal association between depression and HRQoL in COPD

Three studies were eligible for inclusion in meta-analysis for depression.[39,40,43] Random effects meta-analysis of the three studies (Figure 2) found a large positive correlation between depression at baseline and HRQoL measured at follow-up (r=0.48, 95% CI 0.37–0.57, P<0.001). A moderate to high degree of heterogeneity was found across the studies (Q=6.60 df=2, P=0.037, I^2=69.7%).[41]

Longitudinal association of anxiety with HRQoL in COPD

Two cohort studies report the longitudinal association between anxiety and HRQoL in COPD (Table 4).[39,40] The study by Coventry et al met two of the key quality criteria for this review and found that anxiety at baseline was significantly correlated with respiratory-specific HRQoL at 3 months (r=0.40, P=0.002) but this did not remain significant at 1-year follow-up (r=0.26, P=0.052).[40] The second study did not meet any of the key quality criteria but reported that anxiety was correlated with respiratory-specific HRQoL at 1-year (r=0.41, P<0.001) and 5-year follow-up (r=0.51, P<0.001).[39]

Meta-analysis of longitudinal association between anxiety and HRQoL in COPD

Two studies were eligible for inclusion in the meta-analysis.[39,40] The random effects meta-analysis of the two studies (Figure 3) found that anxiety at baseline was associated with a moderate and significant positive correlation with HRQoL at follow-up (r=0.36, 95% CI 0.23–0.48, P<0.001). A low degree of heterogeneity was found across the studies (Q=1.22, df=1, P=0.269, I^2=18.3%).

Discussion

We conducted a systematic review and meta-analysis of longitudinal cohort studies to assess the temporal association between depression and anxiety and HRQoL in COPD. We identified six studies in total, of which three met the criteria for inclusion in the meta-analysis. Results indicated that both depression and anxiety predict future HRQoL. The association was stronger for depression than for anxiety.

Table 3 Longitudinal correlations between depression and HRQoL in chronic obstructive pulmonary disease

Reference	Depression measure	HRQoL measure	Length of follow-up	Sample size	Correlation (r)	P-value
Andenaes et al[43]	HSCL-25	SGRQ symptoms	9 months	51	−0.079	NS
	HSCL-25	SGRQ impact	9 months	51	0.279	<0.05
	HSCL-25	SGRQ activities	9 months	51	−0.138	NS
	HSCL-25	WHOQOL physical	9 months	51	−0.638	<0.001
	HSCL-25	WHOQOL psychiatric	9 months	51	−0.622	<0.001
	HSCL-25	WHOQOL social	9 months	51	−0.225	NS
	HSCL-25	WHOQOL environment	9 months	51	−0.405	<0.01
Oga et al[39]	HAD-D	SGRQ total	1 year	128	0.471	<0.001
	HAD-D	CRQ total	1 year	128	−0.581	<0.001
	HAD-D	SGRQ total	5 years	72	0.473	<0.001
	HAD-D	CRQ total	5 years	72	−0.549	<0.001
Coventry et al[40]	HAD-D	SGRQ total	3 months	79	0.517	<0.001
	HAD-D	SGRQ total	1 year	62	0.636	<0.001

Abbreviations: HSCL-25, Hopkins Symptoms Checklist; SGRQ, St George's Respiratory Questionnaire; CRQ, Chronic Respiratory Questionnaire; HAD-D, Hospital Anxiety and Depression Scale depression subscale; HRQoL, health-related quality of life; NS, not significant; WHOQOL-BREF, World Health Organization Quality of Life Instrument.

Table 4 Longitudinal correlations between anxiety and HRQoL in chronic obstructive pulmonary disease

Reference	Anxiety measure	HRQoL measure	Length of follow-up	Sample size	Correlation (*r*)	*P*-value
Oga et al[39]	HAD-A	SGRQ total	1 year	128	0.412	<0.001
	HAD-A	CRQ total	1 year	128	−0.534	<0.001
	HAD-A	SGRQ total	5 years	72	0.505	<0.001
	HAD-A	CRQ total	5 years	72	−0.641	<0.001
Coventry et al[40]	HAD-A	SGRQ total	3 months	79	0.369	0.002
	HAD-A	SGRQ total	1 year	62	0.258	0.052

Abbreviations: HAD-A, Hospital Anxiety and Depression Scale anxiety subscale; HRQoL, health-related quality of life; SGRQ, St George's Respiratory Questionnaire; CRQ, Chronic Respiratory Questionnaire.
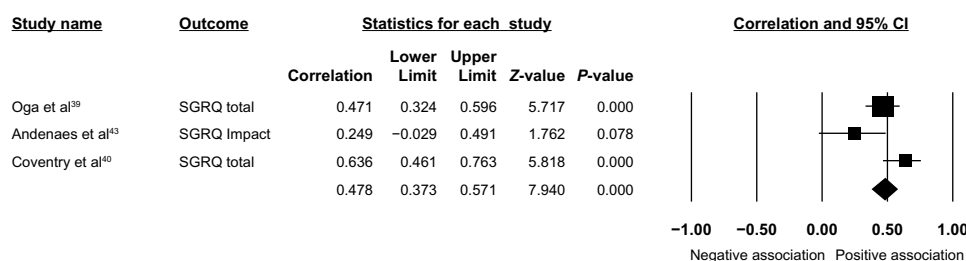
Strengths and limitations

This review has several strengths. Firstly, the search was designed to take a broad approach to the identification of papers that included depression and anxiety. Terms to identify both clinically significant and subclinical depression and anxiety symptoms were included. Secondly, the search strategy for this review was designed to find cohort studies that had investigated the strength of the longitudinal association between depression, anxiety or panic disorder, and HRQoL in COPD which has not been done before. The decision to exclude studies where samples had been exposed to any intervention was made to ensure that any prospective change in HRQoL would be unconfounded with treatment effects. Furthermore, cohort studies are often easier to recruit into than randomized controlled trials, and therefore the samples may be less open to threats to their external validity.[51] The search resulted in identification of 380 studies, a relatively small number for a systematic review. Therefore, it is possible that inclusion of methodological terms to locate only prospective studies may have reduced the sensitivity of the search. However, we are confident that our search identified all potentially eligible relevant studies and we believe we have identified at least two studies[40,45] not included in a recent meta-analysis of studies that measured factors influencing HRQoL in COPD.[25] Finally, the detection of between-study variance can be interpreted as a positive finding since the very likely present heterogeneity has been identified and appropriately accounted for using a random effects model.[52]

This review has some weaknesses. Firstly, we used a quality scoring system that presents an overall quality score which rates methodological weaknesses equally. There is a lack of empirical support for the assumption that all methodological weaknesses have equal weight. Therefore, we present details of the performance of each study on each methodological criterion and also highlight the three criteria deemed to be most important for longitudinal studies.[34] The quality review highlighted several methodological issues with the studies eligible for inclusion in this review. One of the studies that was rated as the highest quality[42] was not eligible for inclusion in the meta-analysis because data on the longitudinal association between baseline depression or anxiety and HRQoL at follow-up were not available. The three studies that did report this data were of varying quality, with two meeting two of the specified quality requirements,[40,43] and one failing to meet any.[39] Only one study[40] provided information on sampling and recruitment procedures and recruitment response rates.

Therefore, it was not possible to evaluate whether the sampling method was open to selection bias in the included studies of lower quality. Furthermore, none of the studies provide any comparison between those who were and those who were not recruited, making evaluation of possible response bias impossible. The inconsistent reporting of response and attrition bias throughout the studies has implications for the

Study name	Outcome	Statistics for each study					Correlation and 95% CI
		Correlation	Lower Limit	Upper Limit	Z-value	*P*-value	
Oga et al[39]	SGRQ total	0.471	0.324	0.596	5.717	0.000	
Andenaes et al[43]	SGRQ Impact	0.249	−0.029	0.491	1.762	0.078	
Coventry et al[40]	SGRQ total	0.636	0.461	0.763	5.818	0.000	
		0.478	0.373	0.571	7.940	0.000	

−1.00   −0.50   0.00   0.50   1.00
Negative association   Positive association

Figure 2 Forest plot of the longitudinal effect of depression on health-related quality of life in COPD.
Notes: Heterogeneity χ^2=6.60 (*df*=2); *P*=0.037; I^2=69.7%.
Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; SGRQ, St George's Respiratory Questionnaire.
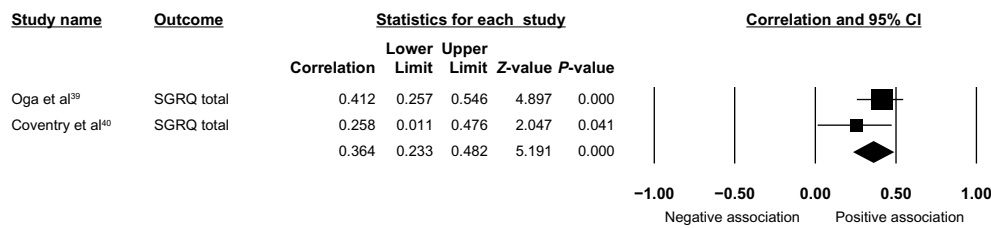
Figure 3 Forest plot of the longitudinal effect of anxiety on health-related quality of life in COPD.
Notes: Heterogeneity $\chi^2=1.22$ (df=1); $P=0.269$; $I^2=18.3\%$.
Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; SGRQ, St George's Respiratory Questionnaire; HAD-A, Hospital Anxiety and Depression Scale anxiety subscale.

inferences that can be drawn from this review. It may be that the results cannot be generalized to older COPD patients because they were less likely to complete follow-up in two studies,[42,44] although these studies were not eligible for inclusion in the meta-analysis. All of the included studies used validated measures of quality of life and psychological factors. However, one study[43] that used the Hopkins Symptom Checklist (HSCL-25) modified the measure, removing two of the items relating to suicidal ideation and loss of libido, which are symptoms commonly associated with depression. This reduces the validity of the measure and may have resulted in an underestimate of the prevalence of depressive symptoms in this sample. Unpublished studies were not included in this review, which may have introduced publication bias into this review because studies that report higher effect sizes are more likely to be published.[53] Where total scores for HRQoL measures were not available for meta-analysis, the most appropriate subscale was chosen. In the case of one paper,[43] the SGRQ impact subscale was chosen because it provides a measure of social functioning and psychological disturbance that would maximize any observed association between depression and HRQoL. We did not formally test for publication bias in this review due to the small number of studies eligible for inclusion.[54] Finally, one of the assumptions made in random effects meta-analysis is that study effects should be normally distributed. This is not always easy to confirm when the number of studies included in the model is small. However, methods have been found to be relatively robust even under extreme distributional scenarios.[55]

Implications for research and practice

The results of the meta-analysis show that depression and anxiety predict future HRQoL. These findings are consistent with the results of a recently published systematic review and meta-analysis that assessed the association between psychological and symptom-based factors and HRQoL in COPD patients.[25] Tsiligianni et al found that depression, anxiety, exercise, and dyspnea were more highly correlated with HRQoL in COPD than FEV_1,[25] but this finding was based only on cross-sectional studies and therefore did not include several studies which were eligible to be included for meta-analysis in our review.[39,40,43] Our review, which is the first to only include longitudinal studies, has further advanced our knowledge of the association between depression and anxiety and HRQoL in COPD by showing that depression and anxiety are correlated with prospective HRQoL. Unfortunately, we were not able to compare the association between depression and anxiety and HRQoL with that of FEV_1 because the necessary data were not reported in the published papers. Two authors were contacted[39,40] and invited to provide the correlations between FEV_1 and HRQoL. However, only one author responded, so the analysis could not be completed. This should be a priority for future longitudinal research in this area.

Future studies would be improved by including other common mental health problems that are prevalent in COPD. Panic disorder has a prevalence in COPD estimated to be ten times that of the prevalence in the general population.[56,57] Panic disorder is known to have a significant negative impact on quality of life in the general population[58,59] and in patients with long-term conditions such as heart failure[60] and diabetes.[61] However, no studies were identified in this review that had considered the impact of panic attacks or panic disorder in COPD. Panic attacks and panic disorder comorbid with COPD have been found to cause greater levels of distress relating to physical health,[62] and to predict worse health outcomes, including increased hospital admissions[63] and poorer functional status.[64] Therefore, it is important to investigate if panic disorder is a significant driver of HRQoL in COPD because it may be a more important predictor than depression or generalized anxiety.

The findings of this review highlight the importance of regularly assessing patient-centered outcomes such as HRQoL in people with COPD, regardless of their disease severity as measured by lung function. HRQoL is an important marker of functioning, and is potentially mediated by extrapulmonary

features of COPD such as anxiety and depression. Whereas self-management and education have had limited impact on the psychological health of COPD patients,[65–67] case management that draws on integrated and collaborative approaches has been shown to reduce depression and improve physical health in people with diabetes and coronary heart disease,[68] although their effectiveness and safety in COPD is unknown.[69] As well as scope for testing the acceptability and effectiveness of collaborative care models in COPD, there is also a need to test mediational models proposing that psychological processes and improvements in psychological health predict improvements in HRQoL and possibly improve physical health outcomes and responses to rehabilitation.[70]

Conclusion

The findings of this review confirm that there is an association between depression, anxiety, and HRQoL that endures over time. However, this longitudinal analysis does not show cause and effect between depression and anxiety and future HRQoL. Future studies should identify psychological predictors of poor HRQoL in well designed prospective cohorts with a view to isolating the mediating role played by anxiety disorders and depression.

Acknowledgments

Author contributions

AB: planned and designed this systematic review and meta-analysis, the inclusion and exclusion criteria, and search strategies; conducted the search, identified eligible papers, extracted the data, and performed the meta-analysis; interpreted findings and wrote the drafts of the paper for submission; coordinated with coauthors to collate comments; and wrote the final draft of the paper. CD: supervised the planning and design of this review and meta-analysis; assisted in the development of inclusion and exclusion criteria,

development of search strategies, meta-analysis, interpretation of findings, and drafting of the paper; and approved the final version of the paper. EG: supervised the planning and design of this review and meta-analysis; assisted in the development of inclusion and exclusion criteria, development of search strategies, meta-analysis, interpretation of findings, and drafting of the paper; and approved the final version of the paper. PB: supervised the planning and design of this review and meta-analysis; assisted in the development of inclusion and exclusion criteria, development of search strategies, meta-analysis, interpretation of findings, and drafting of the paper; and approved the final version of the paper. EK: supervised the planning and design of this review and meta-analysis; assisted in the development of inclusion and exclusion criteria, development of search strategies, meta-analysis, interpretation of findings, and drafting of the paper; and approved the final version of the paper. CA: Made a substantial contribution to the acquisition and interpretation of data by assisting in data extraction, reviewing the quality of included papers, drafting of the paper, making critical revisions to the final draft and approved the final version of the paper. PAC: supervised the planning and design of this review and meta-analysis, assisted in the development of inclusion and exclusion criteria, development of search strategies, meta-analysis, interpretation of findings, drafting of the paper; and approved the final version of the paper.

Disclosure

None of the authors had competing interests to declare.

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