ORIGINAL ARTICLE

The validity of health-related quality of life questionnaires in bronchiectasis: a systematic review and meta-analysis

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ABSTRACT

Background A range of questionnaires have been used to assess health-related quality of life (HRQOL) in bronchiectasis. A systematic review was conducted to evaluate their psychometric properties and assess associations between HRQOL and clinical measures.

Methods Five electronic databases were searched. Studies eligible for inclusion were those that investigated the validity of HRQOL questionnaires and/or their association with other outcomes in adults with bronchiectasis. Patients with cystic fibrosis were excluded. The identified questionnaires were assessed for convergent, discriminant and cross-cultural translation validity; missing data, floor and ceiling effects, internal consistency, responsiveness and test-retest reliability. A meta-analysis was conducted to estimate the strength of associations between HRQOL and clinical measures.

Results From 1918 studies identified, 43 studies were included in the systematic review, of which 38 were suitable for the meta-analysis. Nine HRQOL questionnaires were identified, with the most widely used being: St George's Respiratory Questionnaire, Leicester Cough Questionnaire, Quality of Life–Bronchiectasis and Short Form-36. HRQOL questionnaires had moderate to good internal consistency and good test-retest reliability. Only 8 of 18 studies that used translated HRQOL questionnaires reported or referred to the validity of the translated questionnaire. There was a stronger correlation (mean r (95% CI)) between HRQOL and subjective outcome measures, such as dyspnoea (0.55 (0.41 to 0.68)) and fatigue (0.42 (0.23 to 0.58)) compared with objective measures; exercise capacity (−0.41 (−0.54 to −0.24)), FEV_1% predicted (−0.31 (−0.40 to −0.23)) and extent of bronchiectasis on CT scan (0.35 (0.03 to 0.61)); all p<0.001.

Conclusions This review supports most HRQOL questionnaires used in bronchiectasis have good psychometric properties. There was a weak to moderate association between HRQOL and objective outcome measures. This suggests that HRQOL questionnaires assess a unique aspect of health not captured by objective measures.

Key messages

What is the key question?

- Which health-related quality of life questionnaires are used in bronchiectasis and what is the evidence for their validity?

What is the bottom line?

- Despite differences in the construct of frequently used questionnaires St George's Respiratory Questionnaire, Leicester Cough Questionnaire and Quality of Life—Bronchiectasis, there is good evidence to support their validity, internal reliability and repeatability.

Why read on?

- This article provides an in-depth review of the evidence for the validity of health-related quality of life questionnaires and their association with commonly used clinical outcome parameters; this may help investigators select the most appropriate tool for their purpose.

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INTRODUCTION

The assessment of health-related quality of life (HRQOL) is important in chronic disease as it evaluates the overall impact on health from the patient's perspective. HRQOL is defined as 'the perception of the impact of health on an individual's contentment or satisfaction with life in areas they consider important'.[1] Bronchiectasis is a persistent or progressive condition characterised by dilated thick-walled bronchi.[2] Symptoms of bronchiectasis include sputum production, cough, haemoptysis, dyspnoea and fatigue, which are worse during exacerbations. HRQOL is impaired in bronchiectasis.[3] A range of tools have been used to assess HRQOL in bronchiectasis. These include generic tools such as the Medical Outcomes Study 36-Short Form Health Survey (SF-36), organ-specific tools such as the St George's Respiratory Questionnaire (SGRQ) and Leicester Cough Questionnaire (LCQ) and the condition-specific Quality of Life-Bronchiectasis (QOL-B).[4–7] The comparative validity of HRQOL questionnaires used to assess bronchiectasis has not been investigated; such a review may inform investigators and clinicians about the choice of HRQOL questionnaires available and their validity. The aim of this

systematic literature review was to evaluate the psychometric properties of questionnaires used to assess HRQOL in bronchiectasis. This included a meta-analysis to assess the associations of HRQOL with other clinical measures.

METHODS

Study eligibility criteria

The inclusion criteria were: empirical studies of adult patients (≥18 years old) with bronchiectasis, studies reporting the psychometric properties of generic and disease-specific HRQOL questionnaires, and/or the association of HRQOL with other clinical measures. The diagnosis of bronchiectasis was established using clinical and/or radiological features. The review was limited to studies reporting in English language. Studies investigating acute exacerbations were included if they met the inclusion criteria. Studies investigating mixed populations such as adult/paediatric and non-cystic fibrosis/cystic fibrosis bronchiectasis were included if the findings reported were distinguishable by age/disease category. The exclusion criteria were: diagnosis of cystic fibrosis and review articles (used only to identify further references). Studies using cognitive interview or focus group methodology that did not include HRQOL questionnaires were also excluded.

The psychometric properties considered included convergent and discriminant validity (relationship with other clinical measures according to expectations), internal consistency (Cronbach's α coefficient: extent to which the items of a questionnaire are inter-related), test-retest reliability (repeatability during a clinically stable period), responsiveness (response to change using standardised response mean, SRM), missing data, floor (minimum score) and ceiling (maximum score) effects. The validity of translated HRQOL questionnaires was evaluated by assessing if forward/backward translation, cognitive interviews, internal consistency and reliability were reported.

Search strategy and terms

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and Scottish Intercollegiate Guidelines Network (SIGN) methodology checklist for systematic reviews and meta-analyses were used.[8 9] The search was conducted in five electronic databases: Embase (1974–2014), Pubmed, Medline (Ovid, 1946–2014), PsycINFO (1806–2014) and Cochrane Library. The keywords for search were: non cystic fibrosis bronchiectasis/bronchiectasis, quality of life/QOL/HRQOL, health status, well-being, daily living, questionnaire, validation/validity, psychology and psychometrics. The search was repeated with additional keywords that included named HRQOL questionnaires identified in the previous search. The date of search was 6 November 2014. The references from all included manuscripts were used to identify further studies. Abstracts with adequate information about study methods and results were considered for inclusion.

Study selection, data extraction and quality assessment

After duplicate references were removed, two reviewers independently assessed the studies (in abstract form) against the inclusion criteria. When there was insufficient information available in the abstract, the full text was reviewed. Discrepancies between the reviewers were resolved through discussion and consensus. Two investigators then extracted data from the selected studies including: author, year of publication, aim of the study, sample size, most common aetiology of bronchiectasis, age, gender, FEV_1% predicted, HRQOL questionnaire used and psychometric properties of HRQOL questionnaire including correlation of HRQOL with other clinical measures. Clinical measures used for convergent and discriminant validity of HRQOL included those that assessed symptoms, anxiety, depression, exercise capacity, lung function and other physiological parameters and markers of disease severity and infection/exacerbation. The quality of studies was assessed using a critical appraisal tool developed by Swigris *et al*[1] and modified for bronchiectasis (see online supplementary appendix 1). Where translated questionnaires were used, the translation procedure was assessed by evaluating the included study and related references for forward-backward translation, cognitive interviews, floor and ceiling effects, internal consistency and test-retest reliability.

The minimal clinically important difference (MCID), the smallest change in an HRQOL questionnaire score that is deemed important by patients, was identified if available for patients with bronchiectasis. Studies reporting MCID for questionnaires in other chronic respiratory disorders were presented if data was unavailable for bronchiectasis, following an additional literature search. Responsiveness of the included questionnaires was assessed from randomised-controlled trials returned in our search, by calculating the SRM when possible for the total sample population, and treatment and placebo groups individually. Clinical trials were otherwise excluded from the systematic review unless the primary purpose was to study the psychometric properties of HRQOL questionnaires.

Statistical analysis

Quantitative analysis was performed with Stata V.12.0 (StataCorp LP, Texas, USA) and MetaWin V.2.0 (Baker Hughes, Houston). Internal consistency was reported as Cronbach's α coefficient (acceptable if >0.7) and test-retest reliability as intraclass correlation coefficient (ICC) (moderate if=0.5–0.7 and good if >0.7). Meta-analysis was performed to evaluate the association between HRQOL and clinical measures when data was available from at least two studies. When multiple questionnaires were used to assess HRQOL in the same study, the most relevant questionnaire to bronchiectasis was used in the meta-analysis. When the total score was not available, the mean of the domain scores was used. When the data were repeated in multiple publications, the meta-analysis included the publication with the largest sample size that best met the inclusion criteria.

Correlation coefficients were extracted from the studies when available. The strength of association was categorised as following: weak r<0.4, moderate r=0.4–0.7 and strong r>0.7; significance p<0.05. When only p values and other metrics (t values, Cohen's d, F values, χ^2 values) were available, correlation coefficients were obtained according to formulas suggested by Rosenthal *et al*.[10] A detailed description of correlation coefficients and Fisher's Z calculations is given in online supplementary appendix 2. SRMs were calculated when data was available from mean difference in HRQOL scores (pre/post intervention)/SD of the difference (trivial effect <0.20, small effect=0.20–0.50, moderate effect=0.50–0.80 and large effect >0.80). Standard formulae for computing SD were used when values were not directly available.[11] Publication bias was assessed using funnel plots and Rosenthal's fail-safe number (Rosenthal's N),[12] online supplementary appendix 2.

RESULTS

Study characteristics

Study selection

The search retrieved 1918 publications (see online supplementary table E1). Two additional abstracts and a full manuscript were added manually from searching references.[13–15] A PRISMA flow chart illustrates the studies selection process and

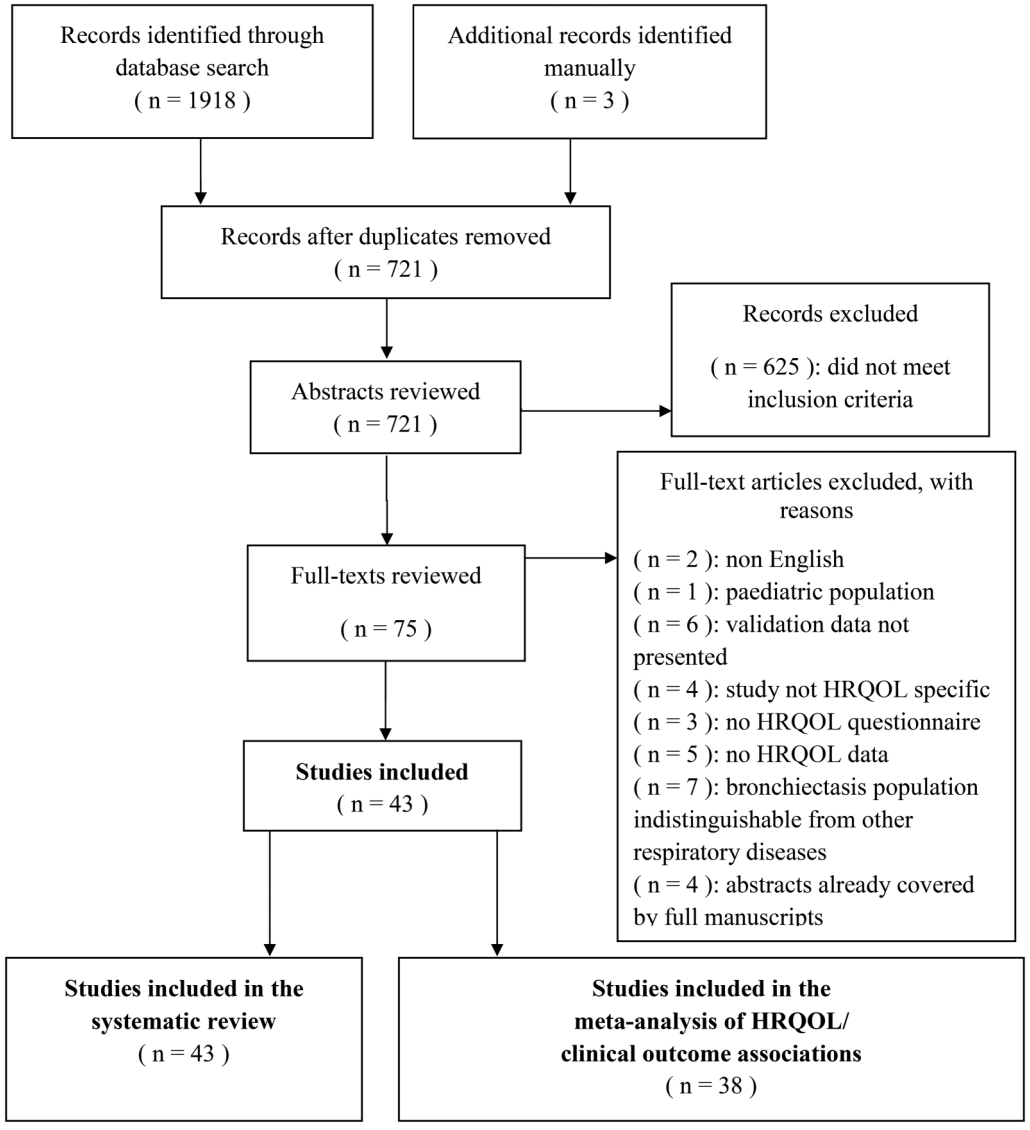

Figure 1 PRISMA flow chart of the literature review and meta-analysis selection process. HRQOL, health-related quality of life.

reasons for exclusion (figure 1). Forty-three studies met the inclusion criteria for systematic review, of which 38 were included in the meta-analysis of associations between HRQOL and other clinical measures. Studies with multiple publications were combined and considered as single publications. Five studies had subjects who overlapped with those in other publications (table 1).

Overview of included studies and study quality

The objectives of the included studies are presented in table 1. All studies were prospective. They all reported cross-sectional findings apart from one,[16] while nine studies also included longitudinal findings for the investigation of repeatability of the HRQOL questionnaires.[5–7 14 17–21] Nine studies were published in abstract form (indicated in reference list and online supplementary material). The studies met a mean (SD) of 48 (14) % of the quality criteria; range 17–78% (figure 2). No study met the criteria for all quality domains.

Characteristics of patients

Table 1 presents the clinical characteristics of patients. The studies included a total number of 3727 patients with bronchiectasis (median number of patients with bronchiectasis per study 98, range 6–608). The mean study patient age was 59 (range 43–70) years and 64 (range 37–83) % of the patients were female. Three studies also recruited participants during an exacerbation,[22–24] while all remaining studies recruited patients during a clinically stable phase. Eight studies did not report CT scan findings.[13 14 22 25–29]

HRQOL questionnaires

Overview of HRQOL questionnaires

Seven organ/disease-specific and two generic HRQOL questionnaires were identified in the selected studies (table 1). Fifteen studies administered multiple HRQOL questionnaires. Twenty-seven studies used the SGRQ, nine the LCQ, eight the SF-36, six the QOL-B V. 2.0 or V.3.0, two the Chronic Respiratory Disease Questionnaire, two the generic Euro Quality of Life and one each of the COPD assessment tool (CAT), the 20-Item Sinonasal Outcome Test and the Cough Quality of Life Questionnaire. A description of these HRQOL questionnaires is given in online supplementary appendix 3, including their length, administration and scoring. All questionnaires were originally developed in English. A summary of

Table 1 Characteristics of studies included in the literature review

Author 1st, year	HRQOL tools	Country	N	Age (year)	Female (%)	FEV_1% (pred)	Most common bronchiectasis aetiology	(%)	Relevant study objectives
Wilson, 1997a, O'Leary, 2002	SGRQ, SF-36	UK	111	52	60	66.4	Idiopathic	58	Validate SGRQ in bronchiectasis Relationship between HRQOL, anxiety and depression
Wilson, 1997b, Wilson, 1998	SGRQ, SF-36	UK	87	54	56	63.8	Idiopathic	63	Relationship between HRQOL, sputum bacteriology and systemic inflammatory markers
Chan, 2002	SGRQ, SF-36	HK	93	59	66	73.5	Idiopathic	81	Validate Hong Kong Chinese version of SGRQ
Martinez-Garcia, 2005a, 2005b	SGRQ	ES	102	70	37	60.4	Idiopathic	44	Validate SGRQ in bronchiectasis Relationship between HRQOL and clinical outcomes
Eshed, 2007	SGRQ	IL	46	63	54	72.3	NR		Relationship between SGRQ and CT scores
Tomkinson, 2009	SGRQ	UK	6	59*	83	50.5*	NR		Relationship between HRQOL and exercise capacity
Guilemany, 2009	SGRQ, SF-36, SNOT-20	ES	80	57	71	80.8	NR		Relationship between HRQOL and chronic rhinosinusitis
Lee, 2009	SGRQ, SF-36	AU	27	54	59	73.9	Postinfective	47	Relationship between HRQOL and exercise capacity
Shoemark, 2011	SGRQ	UK	53	57	71	82.1*	NR		Relationship between HRQOL and exhaled nitric oxide
Gale, 2010	SGRQ	UK	20	65*	80	67.8	NR		Relationship between HRQOL, fatigue, balance and self-reported physical activity
Batchelor, 2011	SGRQ	UK	31	59	81	NR	Postinfective	48	Relationship between HRQOL, exacerbation frequency, depression, fatigue and lung function
Chalmers, 2014	SGRQ	UK, BE, IT	608	65	60	69.3	Idiopathic and Postinfective	63	Relationship between HRQOL and Bronchiectasis Severity Index
Galindo, 2013	SGRQ	MX	19	NR	74	NR	CVID	100	Relationship between HRQOL and sex
Oliveira, 2014a, 2014b	QOL-B (V3.0), SGRQ	ES	207	57	63	68.3	Postinfective	39	Validate QOL-B (V3.0) in Spanish Relationship between HRQOL, anxiety and depression
Loebinger, 2009	SGRQ	UK	91	52	58	65.8	Idiopathic	56	Relationship between HRQOL and mortality risk
Lee, 2012	CAT, SGRQ	KR	62	61	53	67.3	NR		Validate the Korean CAT in bronchiectasis
Moreno, 2013	SGRQ	ES	70	64	69	74.0	Idiopathic	46	Relationship between HRQOL, anxiety and depression
Rowan, 2014	SGRQ	UK	60	62	70	76.5	Idiopathic	43	Relationship between HRQOL and lung clearance index
Gao, 2014	SGRQ	CN	144	46	62	67.4	Idiopathic and Postinfective	71	Relationship between HRQOL and quality of sleep
Morsi, 2014	SGRQ	EG	33	43	55	32.9	NR		Relationship between HRQOL, anxiety and depression and other clinical measures
Murray, 2009b	SGRQ	UK	32	69	63	66.5	ABPA	34	Investigate the HRQOL as an end-point for assessing treatment
Guilemany, 2006	SF-36	ES	60	52	65	81.0	NR		Relationship between HRQOL, nasal symptoms and polyposis
Jacques, 2012	SF-36	BR	70	55	69	44.9	Idiopathic	46	Relationship between HRQOL and exercise capacity
Polley, 2008	LCQ, CQLQ, EuroQOL	UK	26	58	50	73.2	NR		Relationship among different HRQOL questionnaires
Ozalp, 2012	LCQ	TR	20	44	50	62.5	NR		Relationship between HRQOL and dyspnoea, exercise capacity, fatigue
Murray, 2009a, 2009c	LCQ, SGRQ	UK	141	68	64	74.0	Postinfective	53	Relationship between HRQOL and sputum colour Validate the LCQ in bronchiectasis
Munoz, 2013	LCQ, SGRQ	ES	259	58	NR	NR	NR		Validate LCQ Spanish version in bronchiectasis
Altenburg, 2014	LCQ, SGRQ, SF-36	NL	60	67	58	82.3	Idiopathic	50	Relationship between HRQOL and lower respiratory tract infections visual analogue score
Goeminne, 2014	LCQ	BE	63	59	57	69.0	Idiopathic	27	Relationship between HRQOL, lung function and inflammatory markers
Torrego, 2006	LCQ	UK	22	59	82	82.9	NR		Relationship between HRQOL and cough reflex

Continued

Table 1 Continued

Author 1st, year	HRQOL tools	Country	N	Age (year)	Female (%)	FEV_1% (pred)	Most common bronchiectasis aetiology	(%)	Relevant study objectives
Mandal, 2013	LCQ	UK	163	66	60	75.0	Idiopathic	58	Relationship between HRQOL and airway reflux
Quittner, 2010b	QOL-B	USA	35	65	57	57.1	NR		Develop and validate the QOL-B
Quittner, 2010a	QOL-B, SGRQ	USA	79	63	68	60.2	NR		Validate the QOL-B
McCullough, 2011	QOL-B	UK	71	65	69	60.0	NR		Relationship between HRQOL, clinical and demographic factors
Quittner, 2014	QOL-B, SGRQ	USA	89	64	70	60.4	NR		Develop and validate the QOL-B (V2.0 and V3.0)
Quittner, 2015	QOL-B, SGRQ, EuroQOL	USA, CA, UK, AU, FR, NL, IT, ES, BE	542	64	69	63.0	NR		Validate the QOL-B (V3.0)
Lee, 2010	CRDQ, LCQ	AU	27	64	NR	70.0	NR		Relationship between CRDQ, LCQ and exercise capacity
Courtney, 2008	CRDQ	UK	18	54*	67	58.1	Postinfective	83	Investigate the impact of physiology and inflammation in changes of HRQOL

Data presented as means unless otherwise stated. Studies presented in the same row were combined for meta-analysis.
For references see also online supplementary material.
*Median.
ABPA, allergic bronchopulmonary aspergillosis; AU, Australia; BE, Belgium; BR, Brazil; CA, Canada; CAT, COPD assessment tool; CN, China; CQLQ, Cough Quality of Life Questionnaire; CRDQ, Chronic Respiratory Questionnaire; CVID, Common Variable Immunodeficiency; EG, Egypt; ES, Spain; EuroQOL, Euro Quality of Life; FR, France; HK, Hong Kong; HRQOL, health-related quality of life; IL, Israel; IT, Italy; KR, Korea; LCQ, Leicester Cough Questionnaire; MX, Mexico; NL, Netherlands; NR, not reported; QOL-B, Quality of Life-Bronchiectasis; SF-36, Short Form 36; SGRQ, St George's Respiratory Questionnaire; SNOT-20, Sinonasal Outcome Test-20; TR, Turkey.

average HRQOL scores from studies, where available, is presented in online supplementary table E2.

Validity of translated questionnaires

Eighteen studies used a translated HRQOL questionnaire and only eight reported or referenced a validation of the translated questionnaire (see online supplementary appendix 4).

Floor/ceiling effects and missing data

Floor and ceiling effects and missing data were reported for only two HRQOL questionnaires, SGRQ and QOL-B and were relatively small for most total and domain scores (see online supplementary appendix 5).

Internal consistency

Cronbach's α coefficients for the HRQOL questionnaires ranged from moderate to high (table 2). The LCQ had the highest internal consistency (Cronbach's α coefficient 0.91–0.94).[14] QOL-B Cronbach's α coefficients ranged from 0.65 to 0.96,[6 20 21] SGRQ from 0.59 to 0.92,[5 17 30] SF-36 from 0.75 to 0.91[31] and for CAT it was 0.84.[32] The internal consistency of other questionnaires was not reported.

Test-retest reliability

Test-retest reliability data were available for SGRQ, QOL-B and LCQ. ICC was moderate to high (table 2). The SGRQ was slightly more repeatable over 2 weeks than the QOL-B (ICC range 0.89–0.97 vs 0.67–0.88, respectively).[5 6 17 20 21 33] The LCQ was highly repeatable over 6 months (ICC=0.96).[7]

MCID and responsiveness

MCID in bronchiectasis was reported only for the QOL-B questionnaire, range 7–10 units.[21 33] MCID for HRQOL questionnaires in other chronic respiratory diseases is presented in online supplementary table E3. Twenty randomised-controlled trials included sufficient data to assess responsiveness; there was a wide range of SRMs from trivial to large (see online supplementary table E4).

Discriminant ability of HRQOL questionnaires

SGRQ was able to discriminate between subjects based on the severity of dyspnoea[5 30] and wheeze,[5] sputum volume,[17 30] CT scan extent of bronchiectasis,[34] exacerbation frequency,[5 30 35] sputum colonisation by *Pseudomonas aeruginosa*,[30] history of haemoptysis in the past year[21] and the bronchiectasis severity index.[35] SGRQ total scores were able to discriminate FEV_1% categories.[30] There were conflicting data for the discriminative ability of the QOL-B based on FEV_1%. The number of QOL-B domains reported in studies as able to discriminate patients on the basis of FEV_1% ranged from one to all eight domains.[6 21 33] QOL-B was however able to discriminate between patients according to CT scan extent of bronchiectasis and sputum *Pseudomonas aeruginosa* and *Haemophilus influenza* colonisation.[21]

Associations between HRQOL and clinical measures: a meta-analysis

The associations between HRQOL and other clinical measures (convergent/discriminant validity) reported in studies were evaluated in a meta-analysis (table 3). The associations for clinical measures where only single studies were available are presented in online supplementary table E5. A wide range of associations between HRQOL and clinical measures were reported (see figures 3–6 and online supplementary figures E1–E14). The

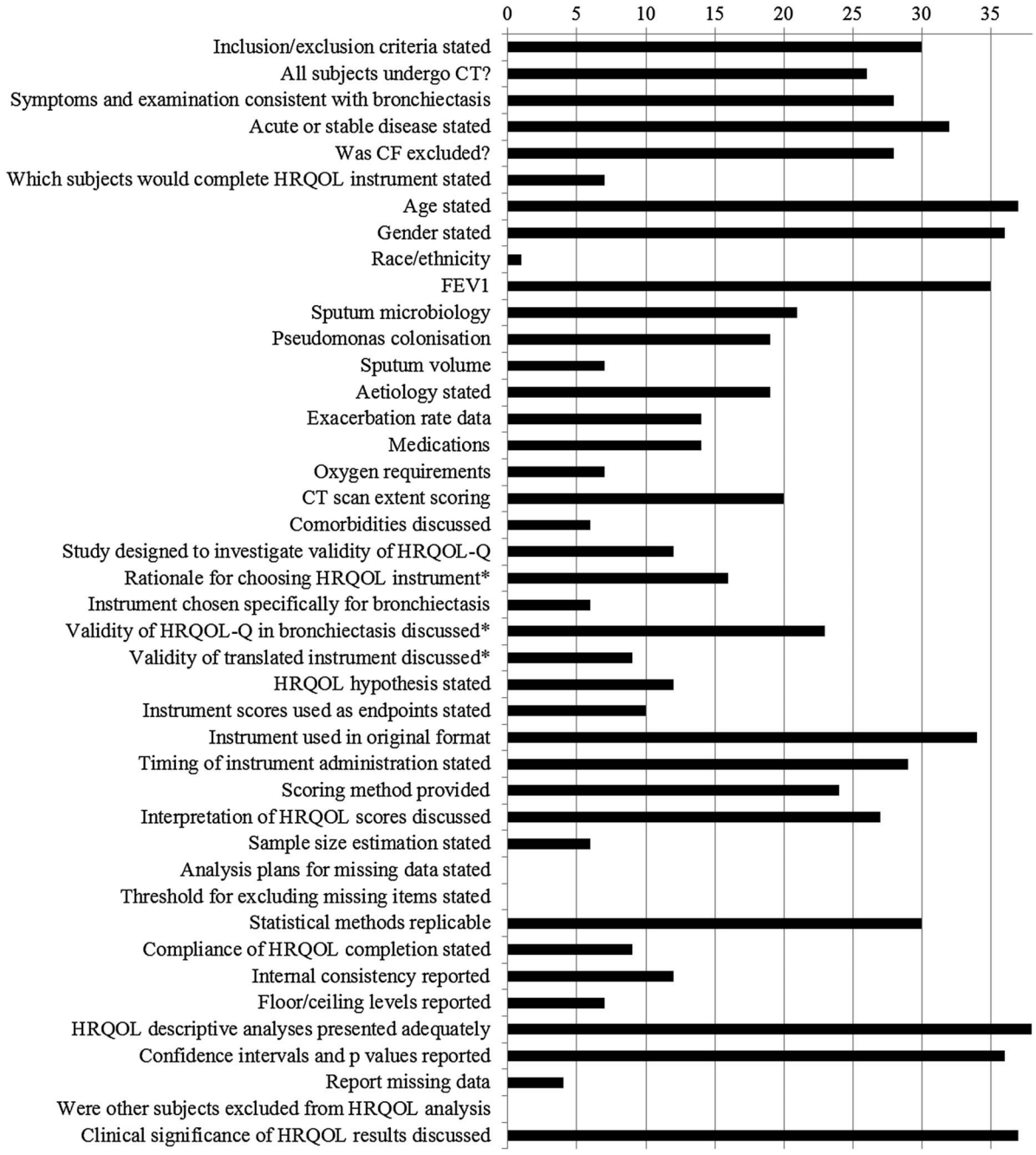

Figure 2 Estimated quality of reporting for included studies. x axis: number of studies meeting each quality criterion (total n=43), y axis: quality criterion item. Number of total evaluable studies 43 except where indicated as*. CF, cystic fibrosis; CT, computed tomography; HRQOL, health-related quality of life; HRQOL-Q, health-related quality of life questionnaire.

strongest associations of HRQOL were with dyspnoea (figure 3) and fatigue (see online supplementary figure E2) and for objective measures with exercise capacity (figure 4), where there were moderate correlations. The association with cough was r=0.56 with a p value approaching significance (p=0.06, only two studies), figure 5. There was a weak association between HRQOL and sputum volume (see online supplementary figure E4) and microbiological colonisation (see online supplementary figure E13), lung function (see figure 6 and online supplementary figure E11), exacerbation rate (see online supplementary figure E10) and extent of bronchiectasis on CT scans (see online supplementary figure E6). The association between HRQOL questionnaires ranged from weak to strong (see online supplementary appendix 6).

Analysis of publication bias and heterogeneity

Publication bias was assessed with a funnel plot for FEV_1% predicted and exercise capacity, as these were parameters with >10 studies available (see online supplementary figures E15 and E16). FEV_1% resembled a symmetric image, suggesting no publication bias. Exercise capacity funnel had slight asymmetry suggesting possibility of publication bias. However, this was not confirmed with Enger's test (p=0.189).

DISCUSSION

This is the first systematic review of the psychometric properties of HRQOL questionnaires used to assess bronchiectasis. The review included 43 studies that investigated 3727 patients

Table 2 Internal consistency and test-retest reliability of HRQOL questionnaires in non-cystic fibrosis bronchiectasis

		Internal consistency		Test-retest reliability	
Author 1st, year	**HRQOL questionnaire**	**Domain**	**Cronbach's α**	**Domain**	**ICC**
Wilson, 1997	SGRQ	Total	NR	Total	0.97
		Symptoms	0.90	Symptoms	0.93
		Activity	0.89	Activity	0.98
		Impact	0.92	Impact	0.94
Martinez-Garcia, 2005	SGRQ	Total	0.90	Total	NR
		Symptoms	0.81	Symptoms	NR
		Activity	0.87	Activity	NR
		Impact	0.81	Impact	NR
Chan, 2002	SGRQ	Total	0.92	Total	0.93
		Symptoms	0.59	Symptoms	0.94
		Activity	0.91	Activity	0.84
		Impact	0.88	Impact	0.89
Quittner, 2010b	QOL-B	8 domains	(range) 0.65–0.94	8 domains	(range) 0.72–0.88
Quittner, 2010a	QOL-B	8 domains	(range) 0.73–0.96	8 domains	NR
Quittner, 2014	QOL-B V3.0*	Physical functioning	0.94	Physical functioning	0.88
		Role functioning	0.86	Role functioning	0.84
		Vitality	0.85	Vitality	0.67
		Emotional functioning	0.72	Emotional functioning	0.82
		Social functioning	0.66	Social functioning	0.85
		Treatment burden	0.84	Treatment burden	0.76
		Health perceptions	0.77	Health perceptions	0.78
		Respiratory symptoms	0.82	Respiratory symptoms	0.80
Quittner, 2015	QOL-B V3.0	Physical functioning	0.91	Physical functioning	0.85
		Role functioning	0.84	Role functioning	0.86
		Vitality	0.73	Vitality	0.74
		Emotional functioning	0.83	Emotional functioning	0.79
		Social functioning	0.77	Social functioning	0.80
		Treatment burden	0.78	Treatment burden	0.76
		Health perceptions	0.77	Health perceptions	0.76
		Respiratory symptoms	0.81	Respiratory symptoms	0.83
Olveira, 2014	QOL-B V3.0	Physical functioning	0.91	Physical functioning	0.88
		Role functioning	0.84	Role functioning	0.86
		Vitality	0.82	Vitality	0.78
		Emotional functioning	0.84	Emotional functioning	0.86
		Social functioning	0.70	Social functioning	0.78
		Treatment burden	0.72	Treatment burden	0.68
		Health perceptions	0.71	Health perceptions	0.83
		Respiratory symptoms	0.87	Respiratory symptoms	0.83
Murray, 2009	LCQ	Total	NR	Total	0.96
		Physical	NR	Physical	NR
		Psychological	NR	Psychological	NR
		Social	NR	Social	NR
Munoz, 2013	LCQ	Total	0.91	Total	NR
		Physical	0.94	Physical	NR
		Psychological	0.93	Psychological	NR
		Social	0.93	Social	NR
Lee, 2012	CAT	Total	0.84	Total	NR
Guilemany, 2006	SF-36	8 domains	(range) 0.75–0.91		NR

*The repeatability of QOL-B V.3.0 was not reported. Table presents data from QOL-B V.2.0.[6]
Cronbach's α coefficient >0.7 is considered acceptable for HRQOL questionnaires.
For references see also online supplementary material.
CAT, COPD assessment tool; HRQOL, health-related quality of life; ICC, intraclass correlation coefficient; LCQ, Leicester Cough Questionnaire; NR, not reported; QOL-B, Quality of Life-Bronchiectasis; SF-36, Short Form 36; SGRQ, St George's Respiratory Questionnaire.

and identified nine HRQOL questionnaires. For the assessment of the questionnaires, we used criteria recommended by the Food and Drug Administration guidelines.[36] Our systematic review suggests that the identified questionnaires have generally good internal consistency, test-retest reliability and convergent validity. The SGRQ was the most widely studied questionnaire. This questionnaire was initially developed for COPD and asthma, but has subsequently been validated and used in a wide range of respiratory disorders. The next most commonly used tool was the LCQ, which was initially developed for patients with chronic cough, but has been validated in patients with bronchiectasis. The QOL-B, a recently published questionnaire, was the only questionnaire developed specifically for bronchiectasis.

We identified some relatively small differences in the psychometric properties between HRQOL questionnaires. The internal consistency was good for all questionnaires; the Cronbach's α coefficient was highest for LCQ. The test-retest reliability was high for the LCQ and SGRQ domains and variable for the QOL-B domain, ranging from moderate to good. The

Table 3 Meta-analysis: correlations reported for health-related quality of life with clinical measures

Clinical measures	K	N	Meta-analysis correlation mean r (95% CI)	Q test	I^2 (%)	Rosenthal's N
Cough	2	124	0.57 (−0.03 to 0.87); p=0.060	7.56; p=0.006	86.8*	20†
Dyspnoea	7	1216	0.55 (0.41 to 0.68); p<0.001	54.42; p<0.001	89.0*	792
Wheeze	2	213	0.42 (0.30 to 0.53); p<0.001	0.27; p=0.602	0.0	29
Fatigue	4	182	0.42 (0.23 to 0.58); p<0.001	4.72; p=0.194	36.4	40
Exercise capacity	11	1038	−0.41 (−0.54 to −0.24); p<0.001	50.81; p<0.001	80.3*	419
Depression	7	572	0.41 (0.23 to 0.55); p<0.001	27.53; p<0.001	78.2*	220
Sputum volume	3	402	0.36 (0.24 to 0.47); p<0.001	3.39; p=0.184	41.0	57
Pseudomonas presence/colonisation	2	189	0.36 (0.23 to 0.48); p<0.001	0.70; p=0.401	0.0	18†
CT bronchiectasis scores	9	1338	0.35 (0.03 to 0.61); p<0.001	253.63; p<0.001	96.8*	856
Oxygen saturation	4	324	−0.35 (−0.44 to −0.24); p<0.001	0.46; p=0.928	0.0	51
Anxiety	5	514	0.34 (0.19 to 0.47); p=0.025	11.38; p=0.023	64.9‡	97
Hospital admissions rate	2	695	0.34 (0.16 to 0.49); p<0.001	2.95; p=0.086	66.1‡	55
FEV_1%	17	2228	−0.31 (−0.40 to −0.23); p<0.001	59.32; p=0.000	73.0‡	990
Infections/exacerbations rate	8	1498	0.31 (0.24 to 0.38); p=0.001	12.99; p=0.072	46.1	380
FVC%	7	1031	−0.30 (−0.41 to −0.19); p<0.001	14.39; p=0.026	58.3‡	182
Any microbiological presence/colonisation	3	758	0.26 (0.19 to 0.33); p<0.001	0.43; p=0.805	0.0	43
Sputum colour	2	204	0.25 (0.05 to 0.43); p=0.013	1.91; p=0.167	47.6	7†
Comorbidities	2	815	0.09 (0.02 to 0.16); p=0.014	0.44; p=0.508	0.0	3†

For the purposes of comparison, higher score indicates poorer health-related quality of life.
Statistical heterogeneity among the studies was assessed using the Q test and quantified using the I^2.
I^2, Indicates the percentage of total variation across studies that is due to heterogeneity rather than chance. I^2 value of 0% was considered to indicate no observed heterogeneity.
*I^2 between 75–100% may represent considerable heterogeneity.
†Rosenthal's Number lower than $5\times k_{number\_of\_studies}+10$ indicates publication bias of the studies included in the meta-analysis.
‡I^2 between 30–60% may represent moderate heterogeneity among the studies according to Cochrane manual.
K, number of studies; N, number of overall participants; Q, Cochran's Q test, which examines the null hypothesis that all studies are evaluating the same effect; r, correlation coefficient.

convergent validity was also variable for the clinical measures studied. The association with exercise capacity was marginally better with the SGRQ and LCQ questionnaires compared with QOL-B. The association between HRQOL with FEV_1 was generally weak, irrespective of the questionnaire administered. The association with symptoms of dyspnoea was stronger with

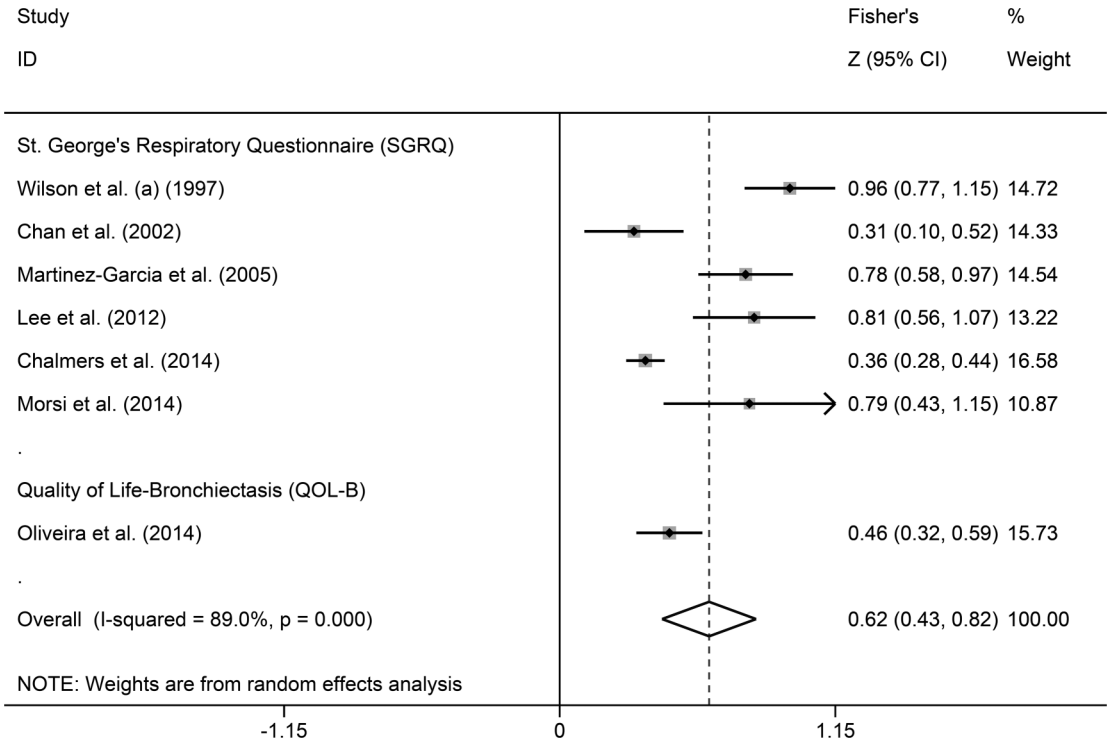

Figure 3 Forest plot for the correlation between health-related quality of life and dyspnoea. Measurements of dyspnoea used: Medical Research Council (MRC) scale (Wilson *et al*, 1997; Martinez-Garcia *et al*, 2005; Lee *et al*, 2012; Chalmers *et al*, 2014; Oliveira *et al*, 2014), 12-point Borg scale (Chan *et al*, 2002) and dyspnoea-12 (Morsi *et al*, 2014). Zero line: is illustrated to indicate the direction of association. A fisher's z value >0 indicates positive association between the two variables. A fisher's z value <0 indicates negative association between the two variables. High score = poor health-related quality of life. Dashed line: represents the overall meta-analytic mean Z. Arrow: indicates confidence interval limit. Weight was calculated using the inverse variance weight formula [weight=i/sqrt(n-3)].

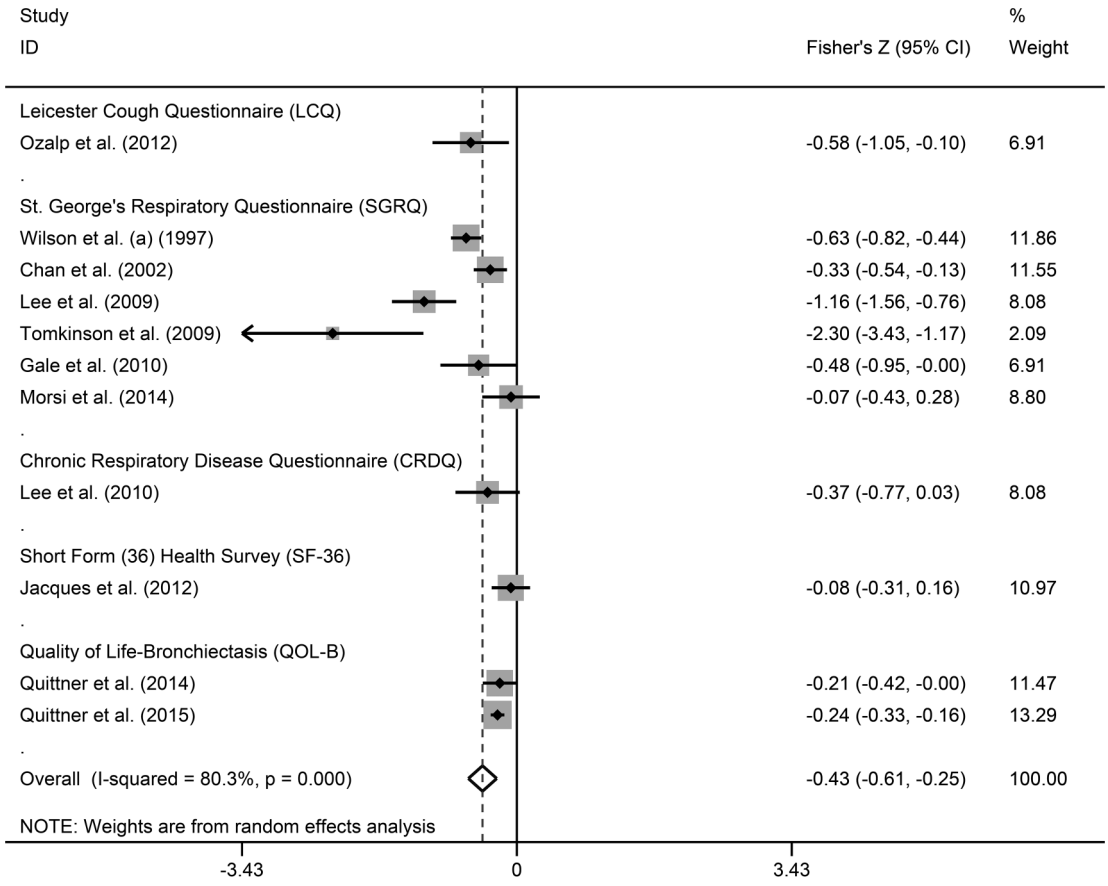

Figure 4 Forest plot for the correlation between health-related quality of life and exercise capacity. Measurements of exercise capacity used: 6-minute walk test for all studies apart from one that used incremental shuttle walk test (Wilson *et al*, 1997) and another that used both (Lee *et al*, 2010). High score = poor health-related quality of life.

SGRQ compared with QOL-B. It is possible that the differences identified in the psychometric properties of questionnaires may reflect differences in the study population, disease characteristics and study methods. Studies that directly compare HRQOL questionnaires are needed to establish similarities and differences between questionnaires with greater confidence.

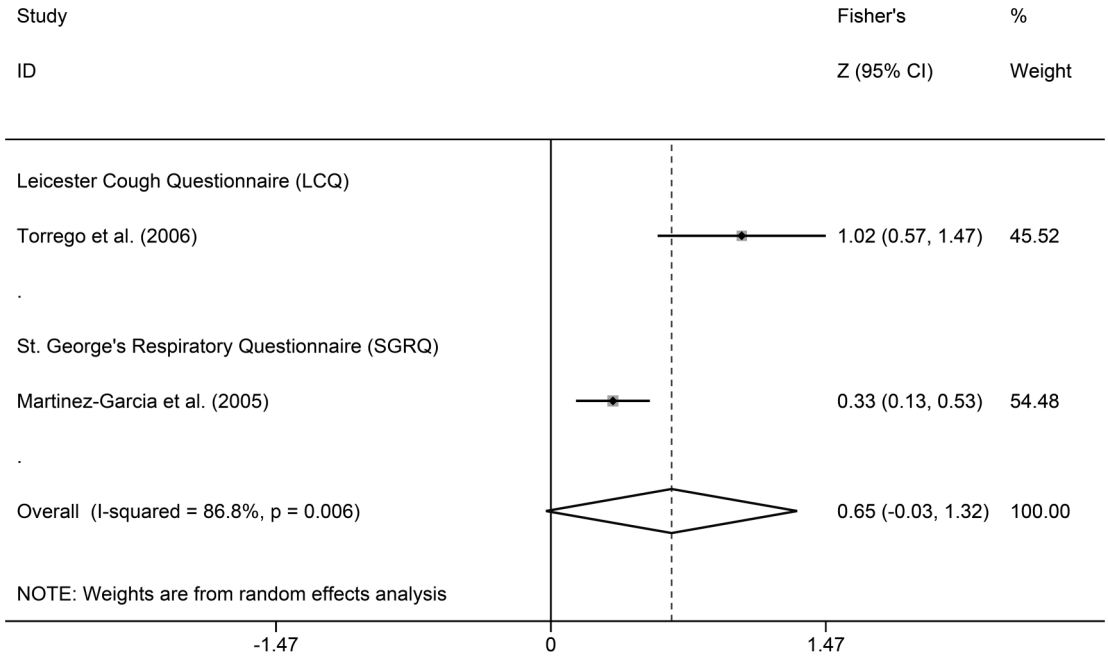

Figure 5 Forest plot for the correlation between health-related quality of life and cough. Measurements of cough used: cough reflex sensitivity to capsaicin (Torrego *et al*, 2006) and patient-reported cough frequency (Martinez-Garcia *et al*, 2005). High score = poor health-related quality of life.

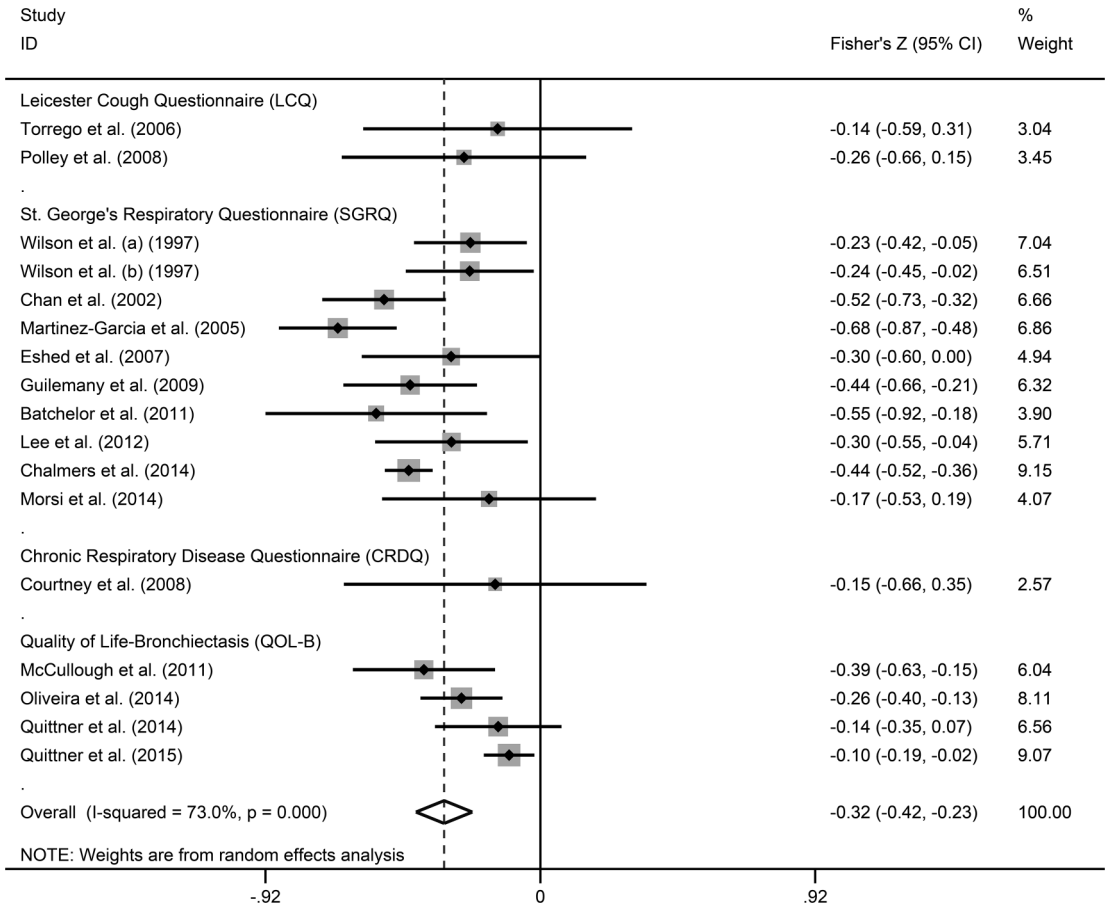

Figure 6 Forest plot for the correlation between health-related quality of life and FEV_1% predicted. High score = poor health-related quality of life.

The responsiveness, MCID and translation validity of HRQOL questionnaires were also investigated. Based on randomised controlled trials, SRMs were variable. The MCID has only been reported for one HRQOL questionnaire in patients with bronchiectasis (QOL-B);[33 37] further studies are needed to establish MCID of other widely used questionnaires. Many studies used translated HRQOL questionnaires. While there were good examples of translated HRQOL questionnaire validity in bronchiectasis, there were many studies where this procedure was either not conducted or reported. It is essential that HRQOL questionnaires are translated and validated using well recognised and standardised procedures to ensure that they are appropriately adapted to accommodate cultural differences.[38]

The assessment of convergent validity demonstrated a stronger relationship of HRQOL with subjective outcome measures compared with objective measures. The strongest association of HRQOL was with respiratory symptoms. The review also highlights a potentially important association between HRQOL and fatigue. Fatigue is a recognised symptom of bronchiectasis but its mechanism is poorly understood.[27] There was a poor association between HRQOL and frequency of acute exacerbations. This may be because most studies assessed HRQOL during a clinically stable phase. The best identified association among objective measures was with exercise capacity, such as the 6-min walk test. This is not surprising, since exercise capacity is more likely to relate to functional ability than other objective outcome measures. Our findings highlight the discordance between patient-reported outcome measures and physiological measures, such as FEV_1, and are consistent with findings for other chronic respiratory disorders, such as COPD.[39] This suggests that HRQOL questionnaires assess a unique dimension of health, which is distinct from that assessed by objective measures. HRQOL measures should ideally complement objective clinical measures in the assessment of bronchiectasis.

There are some limitations with our systematic review. Our review is susceptible to publication bias (positive findings are more likely to be published compared with negative findings) and time lag bias (inability to identify ongoing or unpublished studies), as any review article. We did not contact the study authors to retrieve unpublished data, which may lead to overinterpretation of associations between HRQOL and clinical measures; this applies particularly to studies published in abstract form. We chose to limit the review to those studies specifically evaluating the psychometric properties of HRQOL questionnaires and associations with clinical measures. For the purpose of analysis, we grouped clinical measures together. We therefore may have underestimated important associations due to the heterogeneity of clinical outcome measures. We used the average of HRQOL domain scores when total scores were not reported. Other potential sources for heterogeneity were differences in inclusion/exclusion criteria, population and disease aetiology. The quality of HRQOL data and its reporting varied between studies. We assessed the quality of studies with a modified version of a tool developed by Swigris *et al*[1] as this was the most comprehensive and relevant for our purpose. The included studies met an average 48% of the quality criteria assessed,

which is similar to a systematic review of HRQOL in idiopathic pulmonary fibrosis.[1] A greater proportion of studies met the quality criteria relating to description of patient demographics, the reporting of major clinical outcome measures of bronchiectasis and the analysis of HRQOL data. Fewer studies met the criteria for reporting details of the administration of the HRQOL questionnaires, floor/ceiling effects and missing data. It is therefore possible that the quality of studies and data-reporting may have compromised some of our findings. A greater clarity for HRQOL data-reporting is required in future studies including reporting of the rationale for choosing a particular instrument, mode of administration, details of missing data and sample size estimates. The questionnaires identified in this review have been in use for variable lengths of time. It is likely that this may have impacted on the availability of evidence.

Our review highlights the questionnaire options available. SGRQ is a good choice for a research study if extensive experience of use of an HRQOL questionnaire is important. SGRQ also has good psychometric validity and the strongest association with dyspnoea. Its disadvantage is that it is a long questionnaire and potentially may not be as responsive to change as disease-specific tools; this requires further study. LCQ is brief, well validated in bronchiectasis and may be particularly advantageous if cough is the symptom of primary focus. QOL-B is the only disease-specific questionnaire and has good psychometric properties. The disadvantage of QOL-B is that it is relatively long and does not have a total score that would simplify interpretation of data. SF-36 may be useful in comparative studies that include non-pulmonary disorders, as it is a generic tool. It is however a relatively long questionnaire and is not as extensively validated in bronchiectasis as some of the alternatives. There is a need for briefer tools with simplified scoring (ideally inclusive of a total score) for use in the clinical and research settings. The bronchiectasis severity index is one such example, although not a measure of HRQOL.[3 5]

In conclusion, HRQOL questionnaires used in bronchiectasis have generally good psychometric properties. There are some differences between questionnaires in their association with clinical measures. Investigators should select questionnaires for their study based on the ease of administration and the questionnaire's correlation with the primary health domain under investigation. More research is needed to investigate longitudinal changes in HRQOL and establish MCID of instruments.

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ONLINE SUPPLEMENTS

Figure E8. Forest plot for the correlation between health-related quality of life and anxiety.

Figure E9. Forest plot for the correlation between health-related quality of life and rate of hospital admissions.

Figure E10. Forest plot for the correlation between health-related quality of life and rate of infections/exacerbations.

Figure E11. Forest plot for the correlation between health-related quality of life and forced vital capacity (FVC).

Figure E12. Forest plot for the correlation between health-related quality of life and sputum colour.

Figure E13. Forest plot for the correlation between health-related quality of life and positive bacterial sputum culture.

Figure E14. Forest plot for the correlation between health-related quality of life and comorbidities.

Figure E15. Funnel plot of FEV_1% assessing the publication bias for the relevant meta-analysis studies.

Figure E16. Funnel plot of exercise capacity assessing the publication bias for the relevant meta-analysis studies.

References. References of supplementary material and additional references of the main paper.

ONLINE APPENDIX 1

QUALITY CRITERIA USED TO ASSESS ARTICLES INCLUDED IN THE REVIEW

A. Bronchiectasis Case Definition and HRQOL Study Subject Assembly

1. Were the inclusion and exclusion criteria reported?
2. Did all bronchiectasis subjects undergo CT or bronchography?
3. Inclusion criteria included symptoms and physical examination consistent with a diagnosis of bronchiectasis?
4. Did the authors state if acute or stable disease and definition of it?
5. Was cystic fibrosis excluded for bronchiectasis?
6. Did the authors state which subjects would complete the HRQOL instrument?

B. Clinical Characteristics of Bronchiectasis Subjects

7. For the subjects with bronchiectasis, is the age distribution given?
8. For the subjects with bronchiectasis, is the gender distribution given?
9. For the subjects with bronchiectasis, is the race/ethnicity distribution given?
10. For the subjects with bronchiectasis, are there data for FEV_1?
11. For the subjects with bronchiectasis, are there data for sputum microbiology?
12. For the subjects with bronchiectasis, are there data for pseudomonas chronic colonisation or intermittent infection?
13. For the subjects with bronchiectasis, are there data for sputum volume?
14. For the subjects with bronchiectasis, are there data for aetiology?
15. For the subjects with bronchiectasis, are there data for exacerbation rate?
16. For the subjects with bronchiectasis, are there data for medications?
17. For the subjects with bronchiectasis, are there data for oxygen requirements?
18. For the subjects with bronchiectasis, is there an objective measure (e.g. a CT scoring scale) for the degree of abnormality on CT?
19. Were potentially relevant comorbidities discussed?

C. HRQOL Instrument Selection

20. *****Was this study designed to evaluate, validate or develop a HRQOL questionnaire in bronchiectasis?
21. If this study is not designed to "validate" an instrument, did the authors provide a rationale for choosing the HRQOL instrument(s) studied?
22. Was the instrument(s) chosen for this study specifically designed to assess HRQOL in bronchiectasis patients?
23. If this study is not a study designed to "validate" an instrument, did the authors discuss (or reference) previously published data that supports the reliability (e.g. test-retest and internal consistency) of the chosen instrument(s) in bronchiectasis patients?
24. If a translated instrument was used, did the authors discuss (or reference) data that verifies the cultural validity of the translated instrument?

D. HRQOL Endpoints and Instrument Administration

25. *****Was the hypothesis regarding HRQOL stated?
26. Did the authors state which instrument scores (e.g. the total instrument score or specific domain scores) were specified as endpoints?
27. Was the instrument(s) administered in the format (e.g. self- or interviewer-administered) that the instrument developers intended?
28. Did the authors adequately describe the timing of instrument(s) administration (as applicable) in the context of a single administration, an individual study visit, and throughout the course of the study?
29. Did the authors provide details of the scoring methods used?
30. Did the authors provide information on how to interpret scores (e.g. do higher scores indicate better or worse HRQOL)?

E. Methods of Statistical Analysis

31. Did the authors provide documentation of sample size estimation?
32. Did the authors describe how missing data (e.g. items missing responses and data from drop-outs) would be accounted for (e.g. by using imputation methods)?
33. Did the authors define what would deem a subject's HRQOL data inadequate (or did they define what constitutes adequate data) for analysis?
34. Were the statistical methods used to assess (and if applicable, to compare) HRQOL described in enough detail that other researchers could repeat the analysis if the full data were made available?

F. Reporting Results

35. Was compliance (% of patients who were asked to complete the instrument and actually completed it) data for each administration given?
36. *****Did the investigators calculate Internal Consistency Reliability (i.e. Cronbach's alpha) for the instrument (and/or its subscales in this study's population?
37. *****Were the floor and ceiling effect levels reported?
38. Were the results of the primary and secondary HRQOL analyses presented adequately (e.g. mean or median scores) to support the conclusions drawn?
39. Were confidence intervals or p-values reported for the results of the hypothesized HRQOL endpoints?
40. Did the authors adequately report missing data (e.g. due to item non-response, due to non-completion of the instrument)?
41. Were subjects excluded from the HRQOL analysis?
    a. If "Yes" did the investigators describe the circumstances surrounding subjects excluded from the analysis?
42. Was the clinical significance of the HRQOL results addressed?

***Not applicable for the studies included in the meta-analysis of HRQOL correlations only.**

ONLINE APPENDIX 2

SUPPLEMENTAL ANALYSIS

The correlation coefficients were converted to Fisher's Z using $z = 2^{-1} \cdot l \{(1+r)/(1-r)\}$ and subjected to meta-analytic models (Borenstein et al. 2011). For the final interpretation of the findings, a mean r correlation coefficient for associations was calculated from Fisher's Z as per $r = \frac{\exp(2z) - 1}{\exp(2z) + 1} = \tanh(z),$. A random effects model was used to produce a pooled estimate of the correlation coefficients. Statistical heterogeneity was assessed using Cochran's Q test, which examines the null hypothesis that all studies are evaluating the same effect (Higgins et al. 2003). Statistical significance for heterogeneity was set as $p \leq 0.10$. Heterogeneity was quantified using the I^2 statistic, indicating the percentage of total variation across studies that is due to heterogeneity rather than chance (Higgins et al. 2003). I^2 value of 0% was considered to indicate no observed heterogeneity whilst a value >50% substantial heterogeneity (Higgins et al. 2002).

A funnel plot was created for the clinical measures with ≥10 studies (Cochrane Group). This is a scatter plot of the effect estimates from individual studies against a measurement of the study's sample size or precision. Resemblance of a symmetrical inverted funnel supports that findings are due to sampling variation alone; thus absence of bias (Sterne et al. 2011). For the funnel plots indicating publication bias, an Engel's test was performed (null hypothesis: studies are no subject to publication bias, significance $p<0.05$). Rosenthal's N expresses the number of un-retrieved or negative studies that are needed to overturn the results of the meta-analysis and create a non-significant meta-analytic result.

References in online supplement.

ONLINE APPENDIX 3

HEALTH-RELATED QUALITY OF LIFE QUESTIONNAIRES

Saint George's Respiratory Questionnaire (SGRQ): was originally developed to measure HRQOL of patients with Chronic Obstructive Pulmonary Disease (COPD) and asthma. It has 50 items (76 weighted responses) categorised into 3 domains: symptoms (8 items), activity (16 items) and impact (26 items). The total score ranges from 0 to 100, with 0 indicating no HRQOL impairment (Jones et al. 1992).

Leicester Cough Questionnaire (LCQ): is a cough-specific questionnaire, which assesses the impact of cough on HRQOL and was developed for adults with chronic cough. LCQ has 19 items with 7-point Likert response scales. LCQ is divided into 3 domains: physical (8 items), psychological (7 items) and social (4 items). The total score is calculated using the sum of the domain scores and ranges from 3 to 21, with lower scores indicating greater HRQOL impairment (Birring et al. 2003).

Chronic Obstructive Pulmonary Disease Assessment Tool (CAT): was developed for patients with COPD, using Rasch Analysis (a quantitative method of eliminating the instrument's items to create a linear scale). It consists of 8 items with 0-5 response scales. The total score ranges from 0 to 40, where 0 indicates no HRQOL impairment (Jones et al. 2009).

Chronic Respiratory Disease Questionnaire (CRDQ): is an interviewer-administered questionnaire measuring physical and emotional aspects of respiratory disease. It has 20 items categorised into the domains of dyspnoea, fatigue, emotional function and mastery. The higher score indicates no HRQOL impairment (Guyatt et al. 1987).

Quality of Life - Bronchiectasis (QOL-B): was developed specifically for assessing HRQOL in bronchiectasis. QOL-B Version 3.1 has 37 items in 8 domains: respiratory symptoms, physical functioning, vitality, role functioning, health perceptions, emotional functioning, social functioning and treatment burden Domain scores range from 0 to 100, with higher scores indicating better HRQOL, and no total score is calculated (Quittner et al. 2014).

Medical Outcomes Study 36-item Short-Form Health Survey (SF-36): is a generic HRQOL questionnaire that has 8 subscales: bodily pain, general health, mental health, physical functioning, role emotional, role physical, social functioning and vitality. These scales are grouped into either SF-36 Physical and SF-36 Mental Component scores that range from 0 to 100, with 0 indicating greater HRQOL impairment (Ware and Sherbourne 1992).

Cough Quality of Life Questionnaire (CQLQ): is a questionnaire specific to cough. It consists of 28 items and a 4-point Likert response scale and has 6 domains: physical complaints, psychosocial issues, functional abilities, emotional well-being, extreme physical complaints and personal safety fears. Higher scores indicate greater HRQOL impairment. Maximum score is 112 (French et al. 2002).

EuroQOL: is a generic health-related quality of life questionnaire consisting of 2 parts. The first is the EuroQOL 5 dimension component (EQ-5D) for mobility, self-care, usual activities, pain/discomfort and anxiety/depression, which has a 3-category response scale. Its scoring has a total of 243 possible health states defined in a 5 digit code, where each state is referred to in its place on the code (eg. 11111 indicates no problem in any domain). The second part is a 100 mm vertical scale, the EuroQOL visual analogue scale (EQ-VAS), where

100 indicates the best state you can imagine and 0 the worst state you can imagine. A single index can be generated (Brooks 1996).

20-Item Sino-Nasal Outcome Test (SNOT-20): is a health-related quality of life questionnaire developed for patients with rhinosinusitis. This is a modification of the 31-item Rhinosinusitis Outcome Measure, and contains 20 nose, sinus and general items. Greater score indicates poorer quality of life (Piccirillo et al. 2002).

References in online supplement.

ONLINE APPENDIX 4

THE VALIDATION OF TRANSLATED HEALTH-RELATED QUALITY OF LIFE QUESTIONNAIRES

Eighteen studies used a translated HRQOL questionnaire. Translated SGRQ was used in Spain (Chalmers et al. 2014, Guilemany et al. 2009, Giron Moreno et al. 2013), Italy (Chalmers et al. 2014), France (Chalmers et al. 2014), Belgium (Chalmers et al. 2014), Korea (Lee et al. 2012), Netherlands (Altenburg et al. 2014), Mexico (Galindo-Pacheco et al. 2013), Egypt (Morsi et al. 2014), China (Gao et al. 2014), Hong Kong (Chan et al. 2002) and Israel (Eshed et al. 2007); QOL-B in Italy, Belgium, Spain, France and Netherlands (Quittner et al. 2015); LCQ in Spain (Casilda Olveira et al. 2014), Belgium (Chalmers et al. 2014), Netherlands (Altenburg et al. 2014) and Turkey (Ozalp et al. 2012); SF-36 in Spain (Guilemany et al. 2006, Guilemany et al. 2009), Netherlands (Altenburg et al. 2014) and Brazil (Jacques et al. 2012b); and CAT in Korea (Lee et al. 2012). Eight out of 18 studies reported or referenced a validation of the translated questionnaire. The validation of translated HRQOL questionnaires has been reported for: SGRQ in Mexican (Galindo-Pacheco et al. 2013), Hong Kong Chinese (Chan et al. 2002), Chinese (Gao et al. 2014) and Korean (Lee et al. 2012), LCQ in Spanish (Giron Moreno et al. 2013), Dutch (Huisman et al. 2007) and Turkish (Kalpaklioglu et al. 2005), QOL-B in all aforementioned languages (Quittner et al. 2015); and SF-36 in Spanish (Guilemany et al. 2006, Guilemany et al. 2009) and Portuguese Brazilian (Jacques et al. 2012a). These studies validated the translated questionnaires in patients with bronchiectasis, with only exceptions being the Korean SGRQ (range of chronic respiratory diseases) (Lee et al. 2012); Dutch and Turkish LCQ (chronic cough) (Huisman et al. 2007, Kalpaklioglu et al. 2005) and the Brazilian SF-36 (COPD and rheumatoid arthritis) (Jacques et al. 2012a). One study used factor analysis to demonstrate

that the structure of the translated Spanish questionnaire was similar to the original SGRQ (Martinez Garcia et al. 2005).

References in online supplement.

ONLINE APPENDIX 5

FLOOR/CEILING EFFECTS AND MISSING DATA

Floor and ceiling effects and missing data were reported for only 2 HRQOL questionnaires, SGRQ and QOL-B. The floor and ceiling effects for SGRQ in English and Spanish versions were small for all domains (<3%) (Wilson et al. 1997a, Martinez Garcia et al. 2005). The floor effect for SGRQ Hong-Kong Chinese was <6.4% (activity domain 11.7%) and ceiling effect <1.1% (Chan et al. 2002). English and Spanish QOL-B floor effects were ≤5%, with the exception of 3 domains: vitality (7%), physical (6%) and social functioning (6%). The QOL-B ceiling effects were highest in 3 out of 8 domains: treatment burden 17%, social functioning 22%, role functioning 22%, and emotional functioning 24% (all other domains <14%) (Quittner et al. 2014, Quittner et al. 2015, Casilda Olveira et al. 2014). Martinez-Garcia et al and Chan et al reported missing data for SGRQ domains with a range 2.0-7.9% and 1.3-7.2% respectively (Martinez Garcia et al. 2005, Chan et al. 2002). Quittner et al also reported minimal missing data for QOL-B for all domains with the exception of treatment burden (up to 8.7%) (Quittner et al. 2014, Quittner et al. 2015).

References in online supplement.

ONLINE APPENDIX 6

ASSOCIATIONS BETWEEN HEALTH-RELATED QUALITY OF LIFE QUESTIONNAIRES

Several studies reported the strength of association between HRQOL questionnaires. The correlation coefficients ranged from weak to strong. The SGRQ total score correlated with CAT (Chalmers et al. 2014), SNOT-20 and LCQ (Murray et al. 2009, Munoz et al. 2013) ($r=0.72$, $r=0.72$ and $\rho=-0.70$ respectively, all $p<0.01$). SGRQ total correlated weakly to moderately with SF-36 Physical (range $r=-0.35$ to -0.68, $p<0.01$) (Wilson et al. 1997a, Chan et al. 2002) and QOL-B V2.0/V3.0 (range $r=-0.34$ to -0.81, $p<0.01$) (Quittner et al. 2010, Casilda Olveira et al. 2014, Quittner et al. 2014). The LCQ correlated strongly with SGRQ ($\rho=-0.70$, $p<0.01$) and CQLQ ($r=-0.88$, $p<0.001$) (Lee et al. 2010) and moderately with CRDQ total ($r=0.51$, $p<0.01$) (Lee et al. 2010) and EuroQOL ($r=0.52$ to 0.67, $p<0.001$) (Polley et al. 2008). The correlation between QOL-B domains and EuroQOL was weak to moderate ($r=0.29$ to 0.66, $p<0.001$) (Quittner et al. 2015).

References in online supplement.

ONLINE SUPPLEMENT Table E1. Systematic review search terms and number of retrieved studies for each database.

Keywords	Pubmed	Embase	Medline	Cochrane	PsycINFO
bronchiectasis AND quality of life	241	71[#]	207	11	7
bronchiectasis AND QOL	28	50	15	1	4
bronchiectasis AND health status	94	93	59	2	2
bronchiectasis AND psychometrics	2	0	1	0	1
bronchiectasis AND well being	86[#]	18	7	5	0
bronchiectasis AND psychology	39	12	2	1	0
bronchiectasis AND daily living	57	10	12	1	0
bronchiectasis AND HRQOL	8	22	8	2	0
bronchiectasis AND questionnaire	160	268	118	2	7
bronchiectasis AND validation	34	61	27	5	1
bronchiectasis AND validity	15	29	11	0	1

[#]: The search was conducted using the keyword "non-cystic fibrosis bronchiectasis" instead of "bronchiectasis". This more specific search was used to limit the number of studies obtained using "bronchiectasis" (the number of retrieved results using "bronchiectasis" was 1,303 and 542 for Pubmed and Embase respectively).

ONLINE SUPPLEMENT Table E2. Average health-related quality of life scores for Leicester Cough Questionnaire, St George's Respiratory Questionnaire and Quality of Life - Bronchiectasis.

Table E2-a. Leicester Cough Questionnaire (LCQ).

Author 1st, year	n	LCQ Total
Polley, 2008	26	14.1
Ozalp, 2012	20	14.7
Murray, 2009a	120	16.9
Munoz, 2013	259	15.1
Altenburg, 2014	30	17.2
Goeminne, 2014	63	15.3
Mandal, 2013	163	17.3
Total/Mean	681	15.8

Table E2-b. St George's Respiratory Questionnaire (SGRQ).

Author 1st, year	n	SGRQ Total
Wilson, 1997 & O'Leary, 2002	111	44.4
Wilson, 1997 & Wilson, 1998	87	44.4
Martinez-Garcia, 2005	102	45.8
Eshed, 2007	46	41.7
Guilemany, 2009	80	34.2
Batchelor, 2011	608	42.6
Chalmers, 2014	19	19.1
Oliveira, 2014a & 2014b	91	45.9
Loebinger, 2009	62	31.5
Lee, 2012	70	32.5
Moreno, 2013	60	38.2
Rowan, 2014	144	32.3
Ozalp, 2012	32	45.7
Murray, 2009b	141	35.4
Munoz, 2013	30	27.1
Total/Mean	1683	37.4

Table E2-c. Quality of Life - Bronchiectasis (QOL-B).

Author 1st, year	**n**	**QOL-B**							
		Physical Functioning	Vitality	Health Perceptions	Social Functioning	Role Functioning	Respiratory Symptoms	Treatment Burden	Emotional Functioning
McCullough, 2011	71	31.0	37.0	39.0	42.0	46.0	53.0	56.0	73.0
Quittner, 2014	89	44.7	46.7	42.1	47.8	58.4	49.5	66.2	79.8
Quittner, 2015	542	51.2	49.9	44.7	54.0	63.0	56.0	65.6	77.8
Oliveira, 2014a & 2014b	207	57.5	57.6	46.5	72.4	70.4	70.7	67.1	71.0
Total/Mean	909	46.1	47.8	43.1	54.1	59.5	57.3	63.7	75.4

Mean scores unless otherwise stated.
HRQOL scores not available from the included studies in the systematic review are not listed in this table.

For references see main paper and online supplement.

ONLINE SUPPLEMENT Table E3. Minimal clinically important difference (MCID) of health-related quality of life questionnaires utilized in bronchiectasis studies.

Questionnaire	MCID study disease population	MCID (units)	Studies
QOL-B	Bronchiectasis	0 to 13.3 (domains)	(Quittner et al. 2015, Casilda Olveira et al. 2014)
SGRQ	COPD	4.0	(Jones 2005)
	COPD	5.8	(Schunemann et al. 2003)
	IPF	7.0	(Swigris et al. 2005)
LCQ	Chronic cough	1.3	(Raj et al. 2009)
CQLQ	IPF	5.0 to 5.7	(Lechtzin et al. 2013)
	Chronic cough	10.6	(Fletcher et al. 2010)
CAT	COPD	1.2 to 3.8	(Kon et al. 2013)
SF-36	IPF	2.0 to 4.0	(Swigris et al. 2005)
EuroQOL (EQ-5D VAS)	COPD	8.0	(Zanini et al. 2015)
CRDQ	COPD	0.5	(Jaeschke et al. 1989)

COPD: chronic obstructive pulmonary disease, IPF: idiopathic pulmonary fibrosis, SGRQ: St George's Respiratory Questionnaire, LCQ: Leicester Cough Questionnaire, CQLQ: Cough Quality of Life Questionnaire, CAT: COPD Assessment Tool, SF-36: Short Form-36, CRDQ: Chronic Respiratory Disease Questionnaire.

References in online supplement.

ONLINE SUPPLEMENT Table E4. Standardised response mean for the included questionnaires, based on randomised-control trials identified in original study search.

Study	Quest.	Interv. (n)	Control (n)	Intervention	Age (yr)	FEV	Fm (%)	Total Sample SRM (95% CI)			Intervention Group SRM (95% CI)			Control Group SRM (95% CI)		
(Bilton et al. 2013)	SGRQ	231	112	Mannitol	62	74.7	65	-1.21	(-1.40,	-1.05)	-3.34	(-3.62,	-3.10)	-0.53	(-0.80,	-0.30)
(Bilton et al. 2014)	SGRQ	233	228	Mannitol	60	62.2	63	-0.69	(-0.80,	-0.56)	-0.78	(-0.97,	-0.60)	-0.60	(-0.80,	-0.40)
(Diego et al. 2013)	SGRQ	16	14	Azithromycin	59	62.0	53	-0.67	(-1.20,	-0.14)	-2.55	(-3.53,	-1.60)	1.08	(0.25,	1.91)
(Drobnic et al. 2005)	SGRQ	20	20	Tobramycin	65	51.8	NR	-0.15	(-0.60,	0.29)	-0.23	(-0.87,	0.41)	-0.12	(-0.80,	0.52)
(Haworth et al. 2014)	SGRQ	73	71	Colistin	59	56.7	58	-0.10	(-0.30,	0.13)	-0.13	(-0.46,	0.20)	-0.06	(-0.40,	0.27)
(Hernando et al. 2012)	SGRQ	37	33	Budesonide	67	64.6	51	-0.35	(-0.70,	-0.01)	-0.07	(-0.53,	0.39)	-1.60	(-2.20,	-1.00)
(Lavery et al. 2011)	SGRQ	32	32	S-management	60	61.0	55	-0.20	(-0.60,	0.15)	-0.46	(-0.96,	0.05)	0.06	(-0.40,	0.56)
(Liaw et al. 2011)	SGRQ	13	13	IMT	60	67.4	85	-0.62	(-1.20,	-0.05)	-0.51	(-1.32,	0.30)	-0.72	(-1.50,	0.11)
(Maa et al. 2007)	SGRQ	11	13	Acupressure	59	NR	40	-0.19	(-0.80,	0.39)	-0.32	(-1.20,	0.57)	-0.09	(-0.90,	0.71)
(Mandal et al. 2012)	SGRQ	12	15	Exercise	65	74.0	47	-0.81	(-1.40,	-0.25)	-1.23	(-2.15,	-0.30)	-0.33	(-1.10,	-0.41)
(Martínez-García et al. 2006)	SGRQ	29	28	Fluticasone propionate	69	61.0	29	-0.18	(-0.50,	0.19)	-0.24	(-0.76,	0.29)	-0.10	(-0.60,	0.44)
(Newall et al, 2005)	SGRQ	12	9	Exercise	60	67.5	91				-0.64	(-1.50,	0.22)			
(Nicolson et al. 2012)	SGRQ	20	20	HTS	57	82.6	63	-0.47	(-0.90,	-0.02)	-0.58	(-1.23,	0.07)	-0.34	(-1.00,	0.30)
(Serisier et al. 2013a)	SGRQ	22	20	Ciprofloxacin	65	56.9	55	-0.46	(-0.90,	-0.02)	-0.18	(-0.79,	0.42)	-0.70	(-1.40,	0)
(Serisier et al. 2013b)	SGRQ	59	58	Erythromycin	62	71.0	61	-0.28	(-0.50,	-0.02)	-0.45	(-0.82,	-0.10)	-0.17	(-0.50,	0.20)
(Stockley et al. 2013)	SGRQ	22	16	NEI	62	NR	55	-0.31	(-0.80,	0.15)	-0.43	(-1.04,	0.19)	-0.12	(-0.80,	0.60)
(Bilton et al. 2013)	LCQ	231	112	Mannitol	62	74.7	65	0.22	(0.07,	0.37)	0.28	(0.09,	0.46)	0.09	(-0.20,	0.35)
(Lee et al. 2014)	LCQ	43	42	Exercise	64	73.5	72	0.23	(-0.10,	0.54)	0.11	(-0.31,	0.54)	0.35	(-0.10,	0.78)
(Nicolson et al. 2012)	LCQ	20	20	HTS	57	82.6	63	2.48	(1.89,	3.08)	2.99	(2.05,	3.93)	2.10	(1.30,	2.90)
(Mandal et al. 2012)	LCQ	12	15	Exercise	65	74.0	47	0.68	(0.12,	1.24)	1.13	(0.22,	2.04)	0.14	(-0.60,	0.88)
(Mandal et al. 2014)	LCQ	30	30	Atorvastatin	60	76.1	52	0.11	(-0.20,	0.47)	0.35	(-0.17,	0.87)	-0.16	(-0.70,	0.36)
(Serisier et al. 2013b)	LCQ	59	58	Erythromycin	62	71.0	61	0.31	(0.05,	0.57)	0.39	(0.02,	0.76)	0.23	(-0.10,	0.60)

Study	Quest.	Interv. (n)	Control (n)	Intervention	Age (yr)	FEV	Fm (%)	Total Sample SRM (95% CI)			Intervention Group SRM (95% CI)			Control Group SRM (95% CI)		
(Quittner et al. 2015)-AIR-BX1	QOL-B	134	132	Aztreonam	65	62.5	68									
	Resp. S.							0.32	(0.15,	0.49)	0.29	(0.05,	0.53)	0.38	(0.13,	0.62)
	Phys. F.							-0.03	(-0.20,	0.14)	-0.08	(-0.32,	0.16)	0.05	(-0.20,	0.29)
	Vitality							0.05	(-0.10,	0.22)	0.02	(-0.22,	0.26)	0.10	(-0.10,	0.34)
	Role F.							0.02	(-0.20,	0.19)	-0.07	(-0.32,	0.17)	0.16	(-0.10,	0.41)
	Heal. P.							-0.01	(-0.20,	0.16)	0.03	(-0.21,	0.27)	-0.05	(-0.30,	0.19)
	Emot. F.							0.00	(-0.20,	0.17)	0.01	(-0.23,	0.25)	0.00	(-0.20,	0.24)
	Soc. F.							0.09	(-0.10,	0.26)	0.07	(-0.17,	0.31)	0.12	(-0.10,	0.37)
	Treat. B.							-0.18	(-0.30,	-0.01)	-0.12	(-0.37,	0.12)	-0.22	(-0.50,	0.02)
(Quittner et al. 2015)-AIR-BX2	QOL-B	136	138	Aztreonam	63	63.6	69									
	Resp. S.							0.37	(0.20,	0.54)	0.47	(0.22,	0.71)	0.27	(0.03,	0.50)
	Phys. F.							-0.01	(-0.20,	0.16)	-0.06	(-0.30,	0.17)	0.07	(-0.20,	0.30)
	Vitality							0.03	(-0.10,	0.20)	-0.03	(-0.27,	0.21)	0.10	(-0.10,	0.34)
	Role F.							-0.08	(-0.30,	0.09)	-0.11	(-0.35,	0.13)	-0.05	(-0.30,	0.19)
	Heal. P.							0.08	(-0.10,	0.25)	0.05	(-0.19,	0.29)	0.11	(-0.10,	0.35)
	Emot. F.							0.16	(0,	0.33)	0.10	(-0.14,	0.34)	0.23	(0 ,	0.47)
	Soc. F.							0.09	(-0.10,	0.25)	0.03	(-0.21,	0.26)	0.15	(-0.10,	0.39)
	Treat. B.							-0.29	(-0.50,	-0.12)	-0.24	(-0.48,	0)	-0.33	(-0.60,	-0.10)
(Quittner et al. 2015)-AIR-BX1	EQ-5D	134	132	Aztreonam	65	62.5	68	0.10	(-0.10,	0.27)	0.17	(-0.07,	0.41)	0.01	(-0.20,	0.25)
(Quittner et al. 2015)-AIR-BX2	EQ-5D	136	138	Aztreonam	63	63.6	69	0.04	(-0.10,	0.21)	0.13	(-0.10,	0.37)	-0.05	(-0.30,	0.19)

Data presented as means, unless otherwise stated.

Quest.: Questionnaire, Interv.: Intervention, Emot. F.: Emotional functioning, Fm: Female, FB: formoterol-budesonide combined, FEV: Forced Expiratory Volume in the first second % predicted, Heal. P.: Health perceptions, HTS: hypertonic saline, IMT: inspiratory muscle training, NEI: neutrophil elastase inhibitor, NR: Not reported, Phys. F.: Physical functioning, PR: pulmonary rehabilitation, Resp. S: Respiratory symptoms, Role F.: Role functioning, S-management: self-management, Soc. F.: Social functioning, Treat. B.: Treatment burden.

Data presented from Quittner et al, 2015 also include relevant data by Baker et al, 2014.

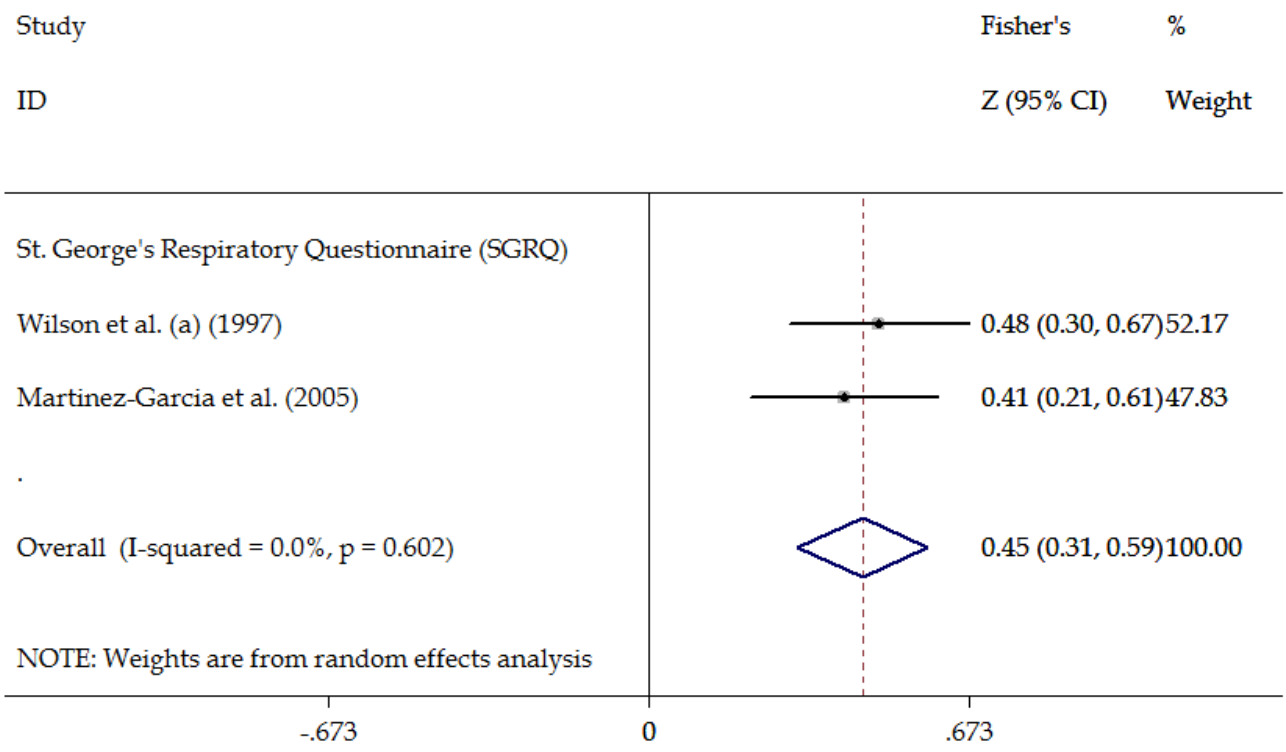
References in online supplement.

ONLINE SUPPLEMENT Table E5. Correlations of health-related quality of life with other clinical measures reported in single studies (not included in the meta-analysis).

Clinical Measures	**N**	**Correlation coefficient**
Chronic rhinosinusitis	80	0.96*
Nasal symptoms	80	0.67*
Maximum expiratory pressure	20	-0.51*
Short-acting β_2-agonist	86	0.49*
Oral steroids cycles	86	0.41*
Respiratory failure	86	0.36*
Cough reflex sensitivity	86	0.32
Karnofsky performance scale (functional impairment)	93	-0.30*
Long-acting β_2-agonist	86	0.27*
Number of lobes affected by bronchiectasis	46	0.25*
Fibrogen	86	0.24
Timed up and go (mobility and balance test)	20	-0.15

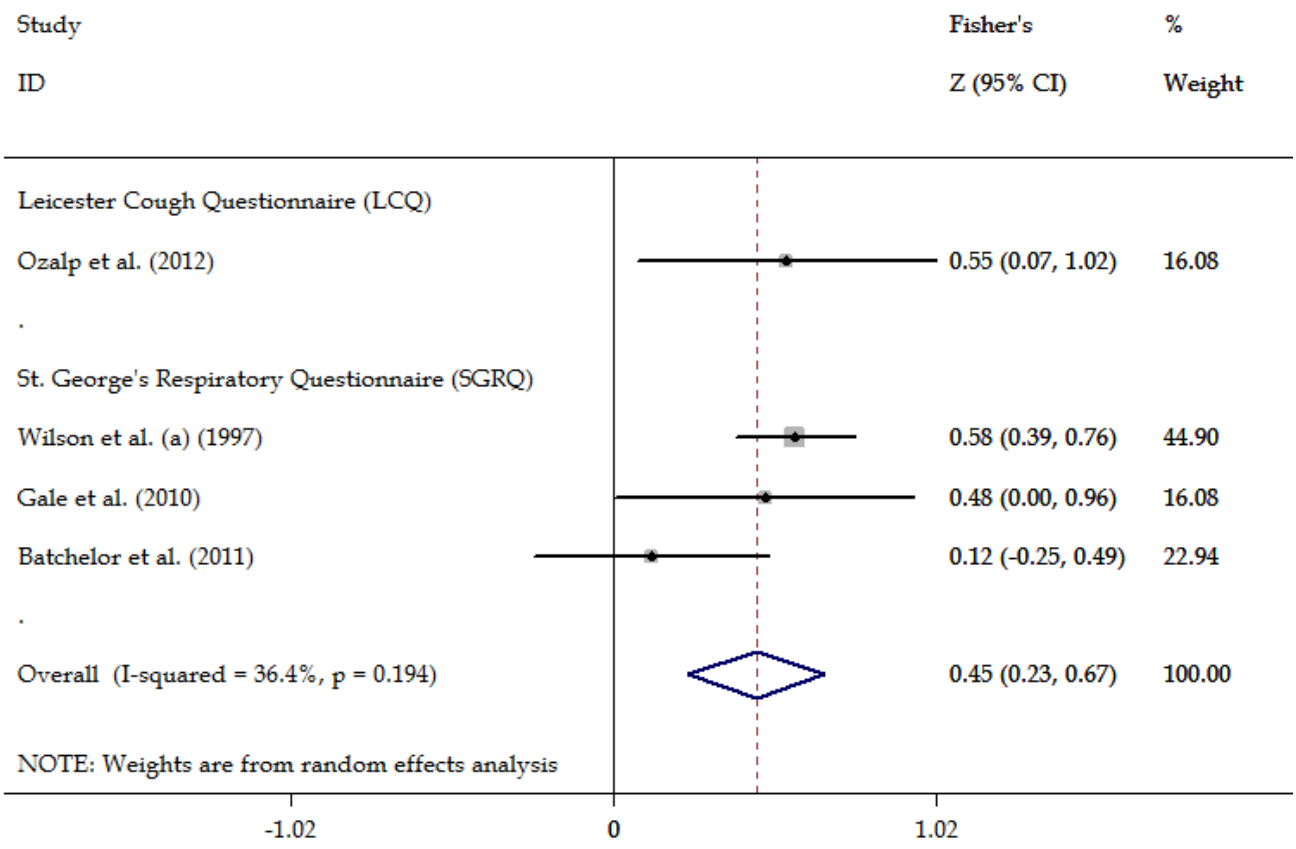
N: number of study subjects; * $p<0.05$

ONLINE SUPPLEMENT Figure E1. Forest plot for the correlation between health-related quality of life and wheeze.



For references see main paper and online supplement.

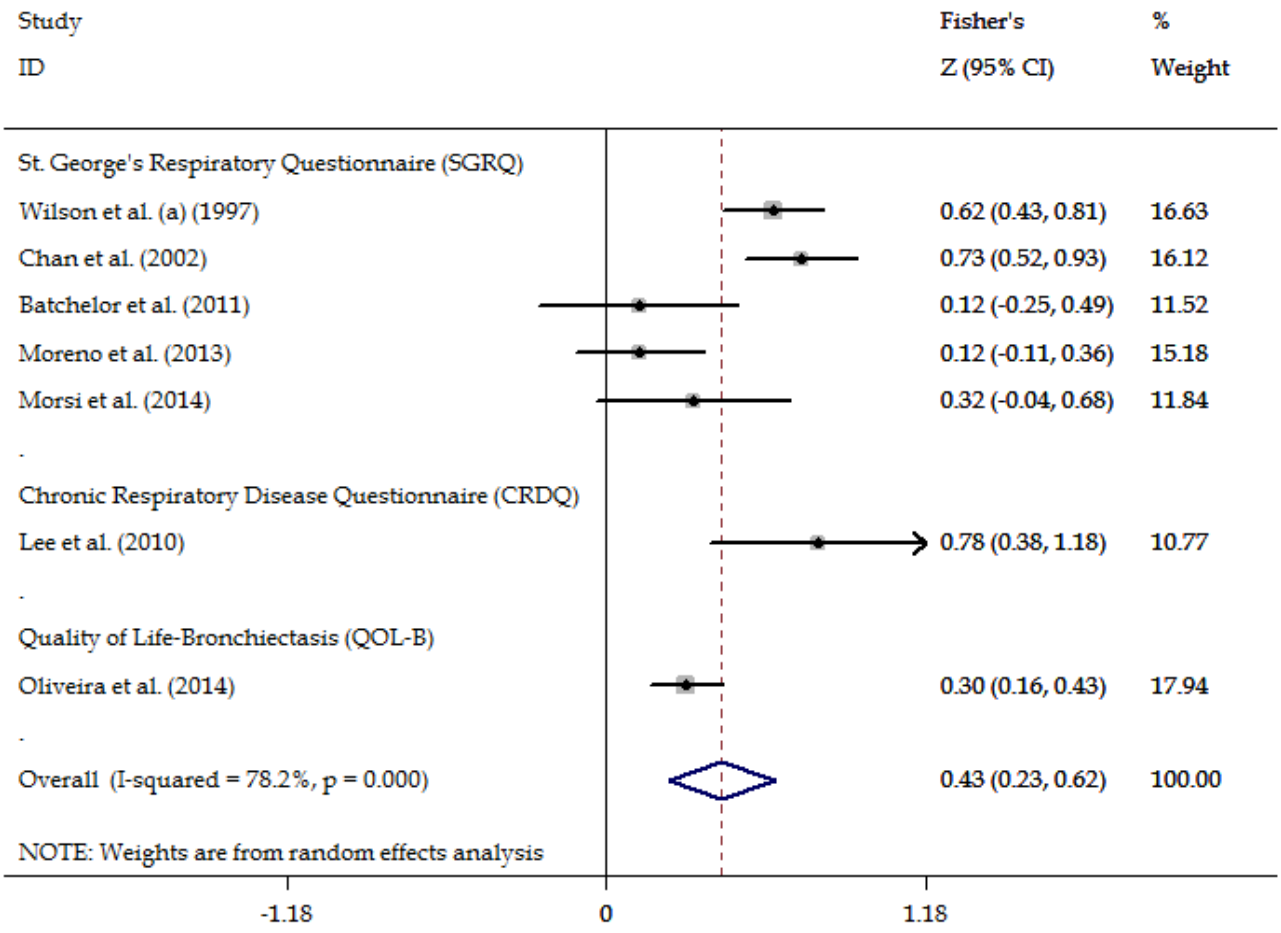
ONLINE SUPPLEMENT Figure E2. Forest plot for the correlation between health-related quality of life and fatigue.



Measurements of fatigue used: 14-point fatigue scale (Wilson et al. 1997a), fatigue severity scale (Ozalp et al. 2012), multidimensional fatigue inventory (Gale et al. 2010) and functional assessment of chronic illness therapy - fatigue questionnaire (Batchelor et al. 2011).

For references see main paper and online supplement.

ONLINE SUPPLEMENT Figure E3. Forest plot for the correlation between health-related quality of life and depression.

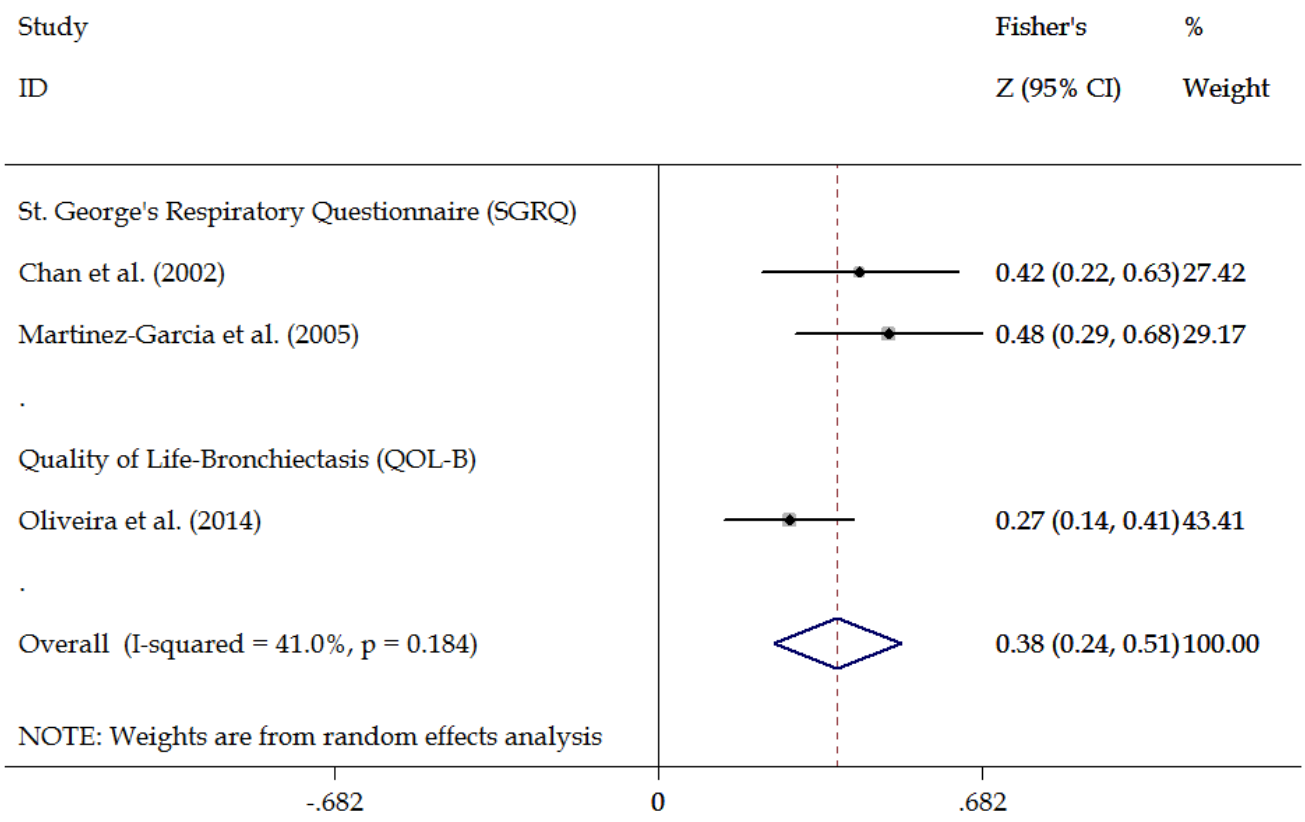


Arrow indicates that the confidence intervals extent the limits of the current graph.

Measurements of depression used: hospital and anxiety scale (Wilson et al. 1997a, Chan et al. 2002, Lee et al. 2010, C. Olveira et al. 2014), centre for epidemiologic studies depression scale (Batchelor et al. 2011), state-trait anxiety inventory (Giron Moreno et al. 2013), Hamilton depression rating scale (Morsi et al. 2014).

For references see main paper and online supplement.

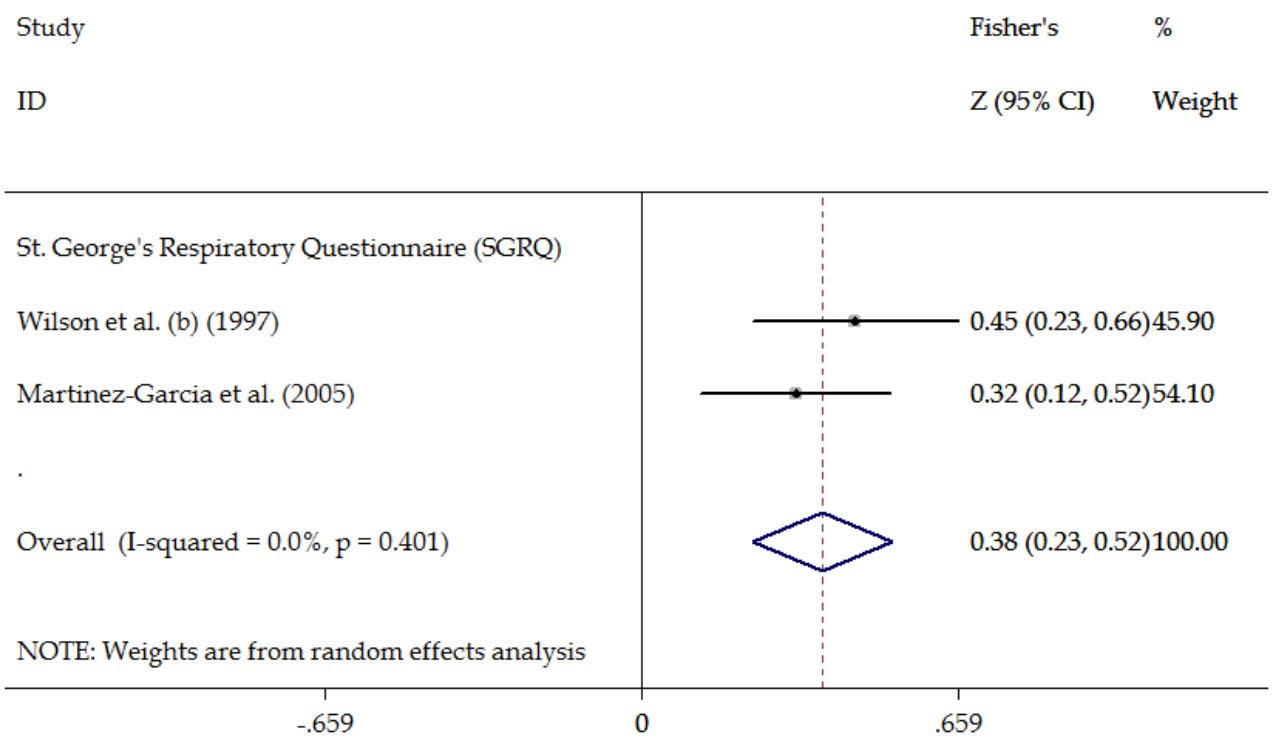
ONLINE SUPPLEMENT Figure E4. Forest plot for the correlation between health-related quality of life and sputum volume.



Measurements of sputum volume used for all studies: mean volume of sputum collected every 24 hours on three successive days.

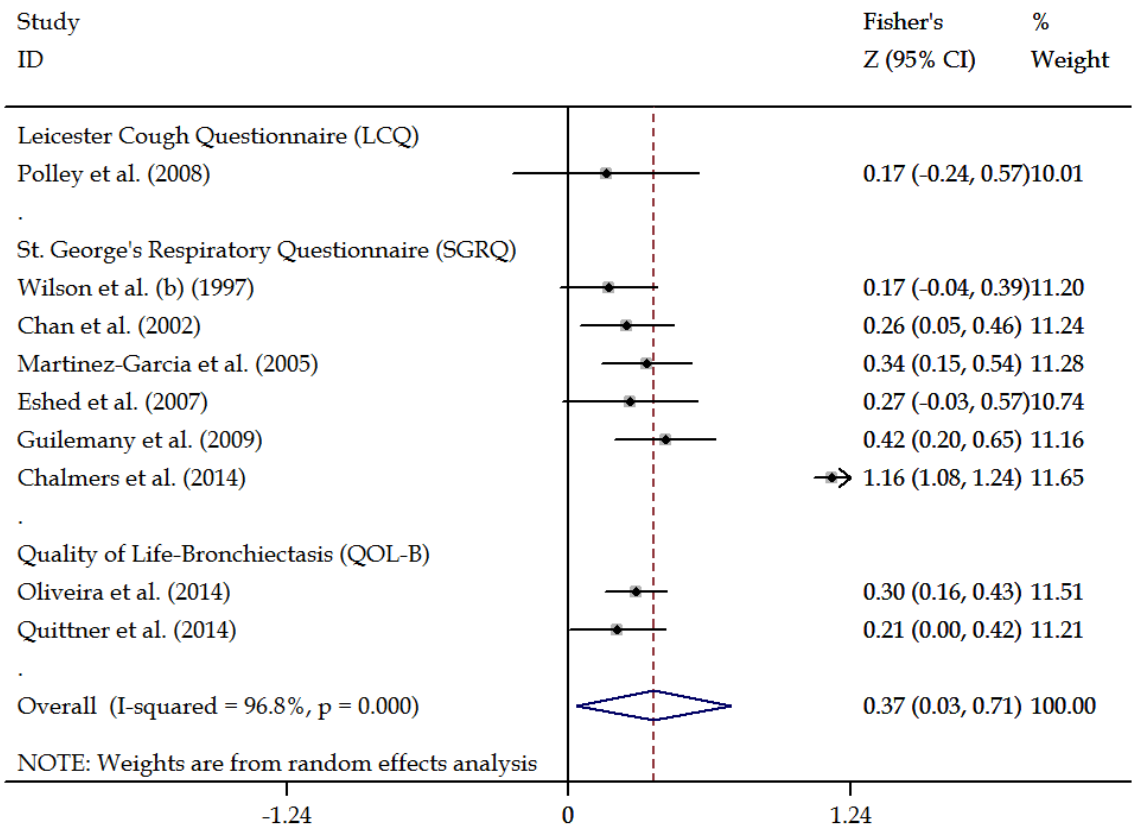
For references see main paper and online supplement.

ONLINE SUPPLEMENT Figure E5. Forest plot for the correlation between health-related quality of life and presence/colonisation with pseudomonas aeruginosa.



For references see main paper and online supplement.

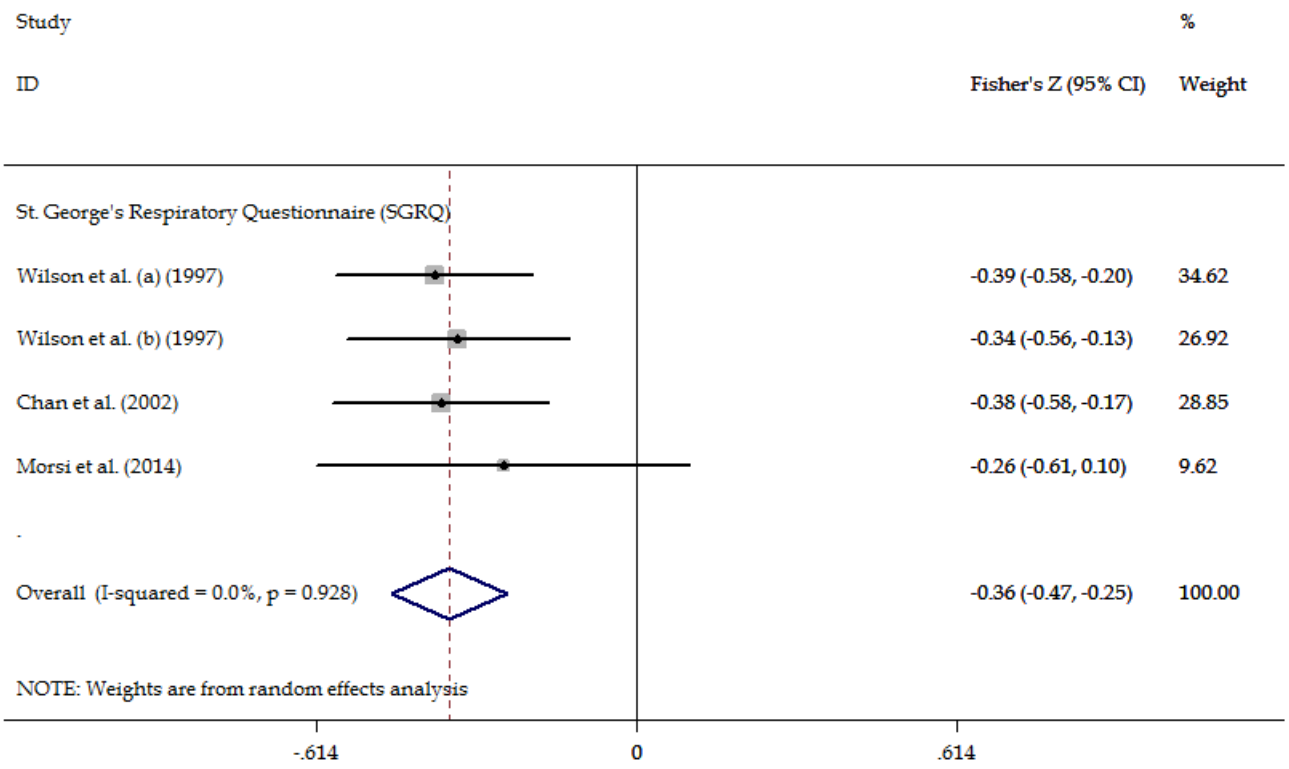
ONLINE SUPPLEMENT Figure E6. Forest plot for the correlation between health-related quality of life and extent of bronchiectasis on computed tomography scan.



Measurements of extent of bronchiectasis used: Bhalla score (Eshed et al. 2007, Polley et al. 2008, Martinez Garcia et al. 2005, Casilda Olveira et al. 2014), Reiff score (Wilson et al. 1997b, Chalmers et al. 2014), other specified scores (Guilemany et al. 2009, Quittner et al. 2014) and number of bronchiectatic lobes (Chan et al. 2002).

For references see main paper and online supplement.

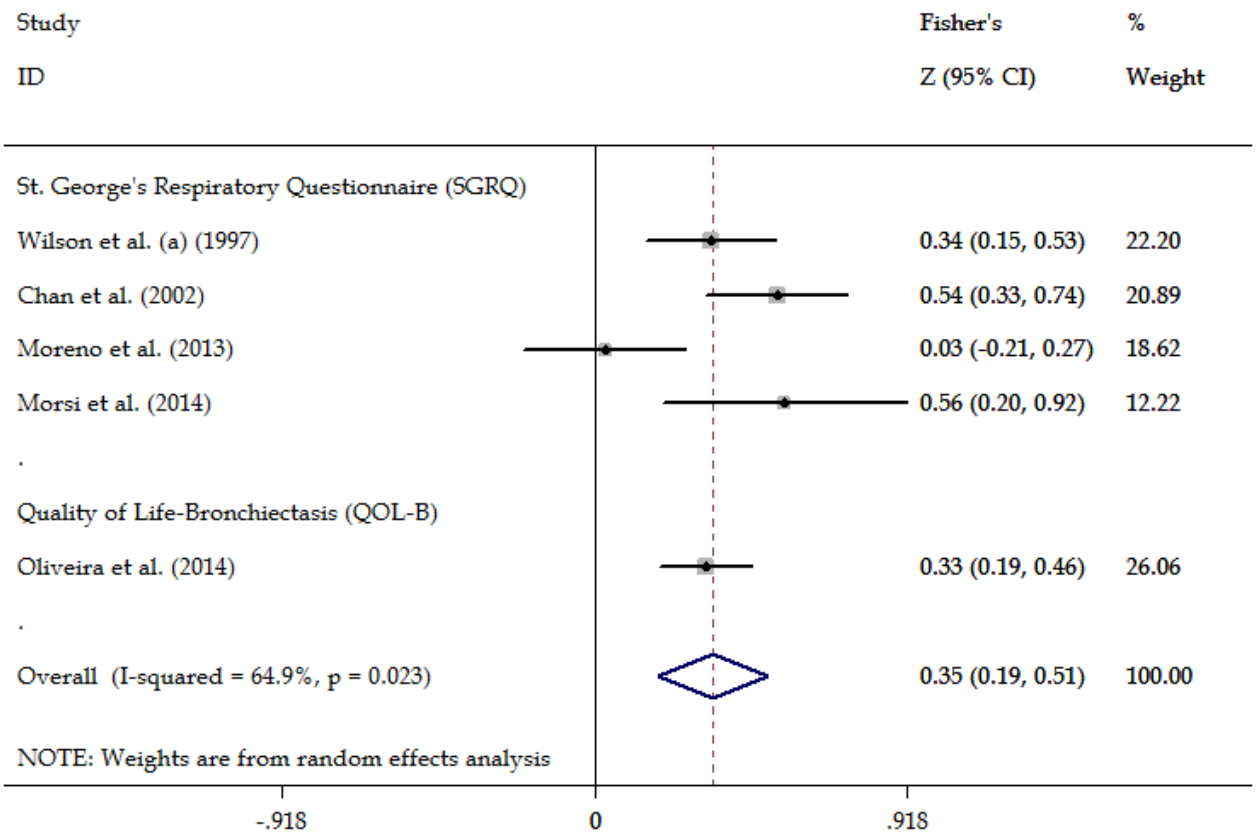
ONLINE SUPPLEMENT Figure E7. Forest plot for the correlation between health-related quality of life and oxygen saturation.



Measurements of oxygen saturation used: earlobe sampling (Wilson et al. 1997a, Wilson et al. 1997b) and pulse oximetry (Chan et al. 2002, Morsi et al. 2014) .

For references see main paper and online supplement.

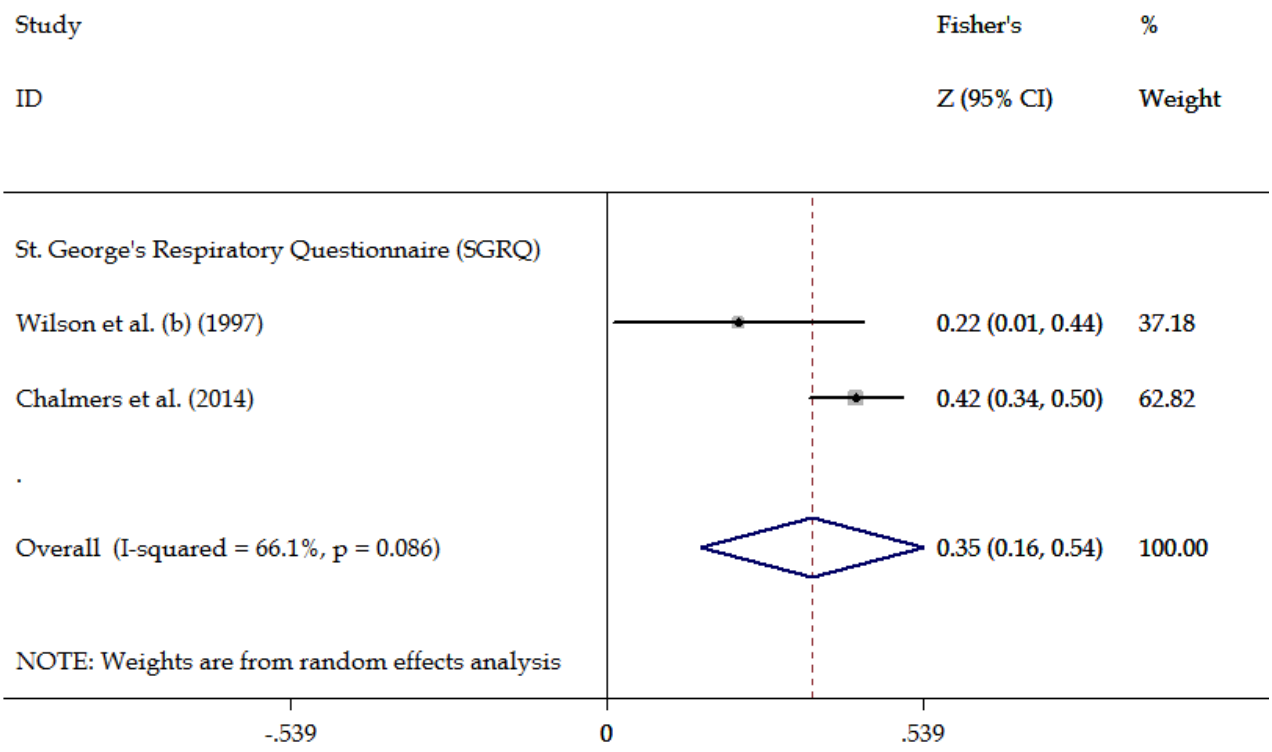
ONLINE SUPPLEMENT Figure E8. Forest plot for the correlation between health-related quality of life and anxiety.



Measurements of anxiety used: hospital anxiety and depression scale (Chan et al. 2002, Wilson et al. 1997a, C. Olveira et al. 2014), Hamilton anxiety rating scale (Morsi et al. 2014) and state trait anxiety inventory (Giron Moreno et al. 2013) .

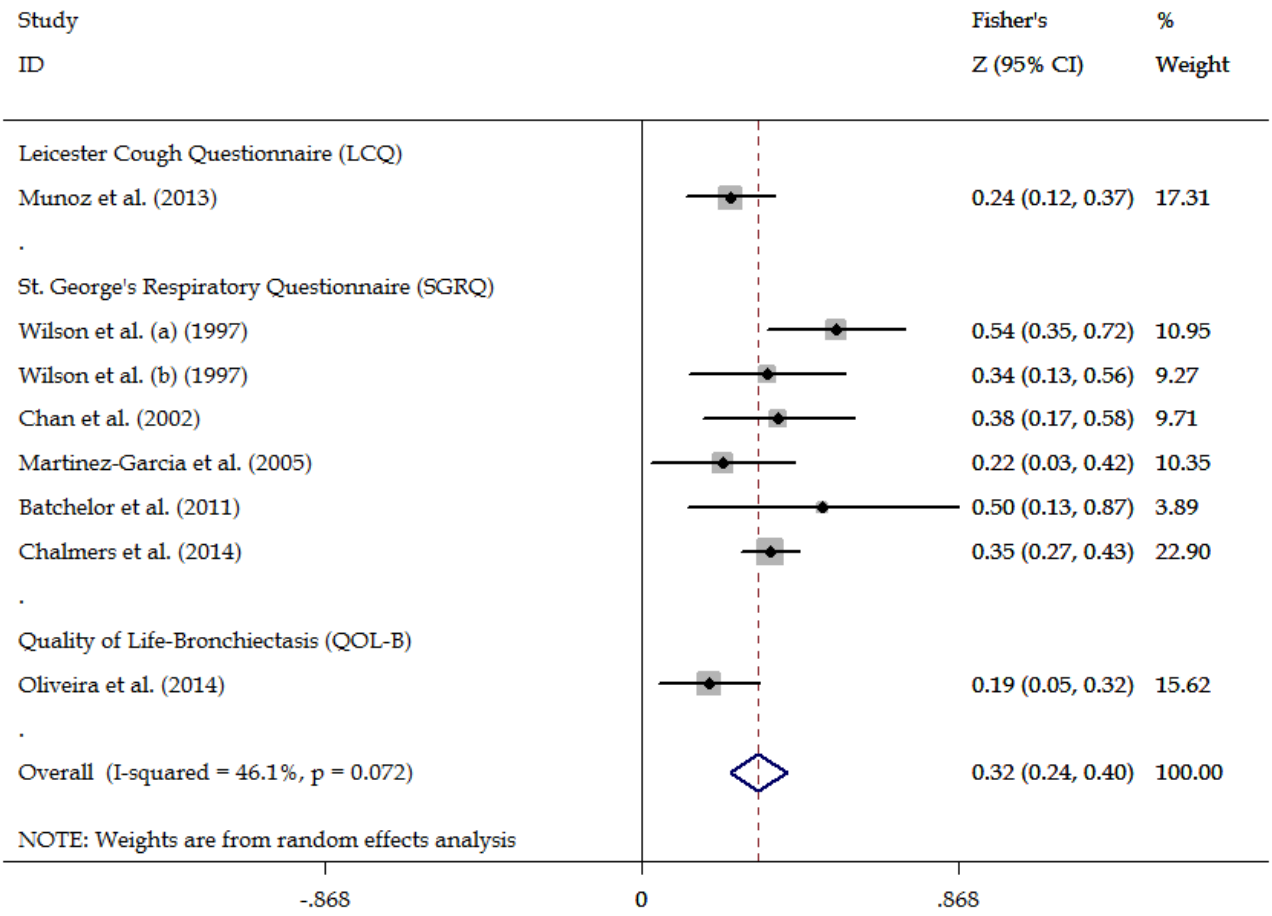
For references see main paper and online supplement.

ONLINE SUPPLEMENT Figure E9. Forest plot for the correlation between health-related quality of life and rate of hospital admissions.



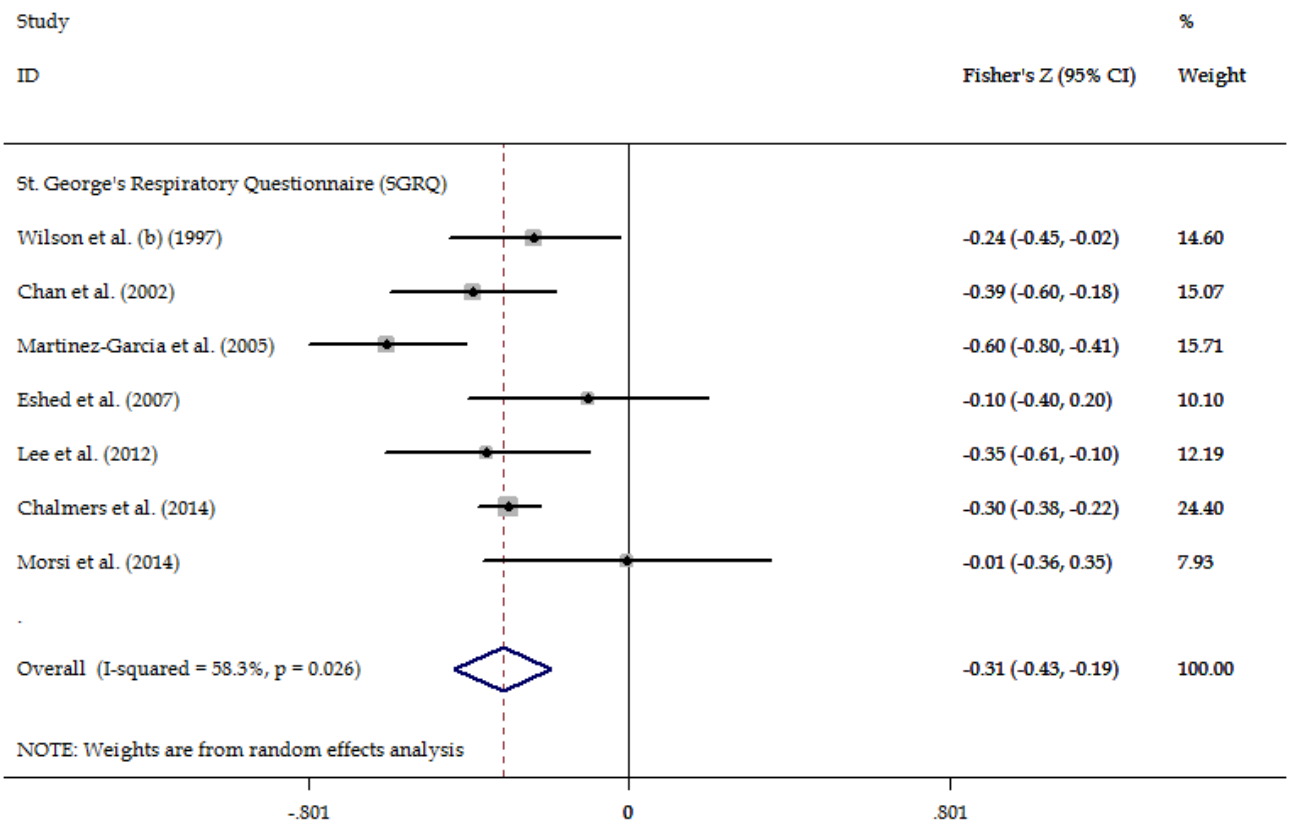
For references see main paper and online supplement.

ONLINE SUPPLEMENT Figure E10. Forest plot for the correlation between health-related quality of life and rate of infections/exacerbations.



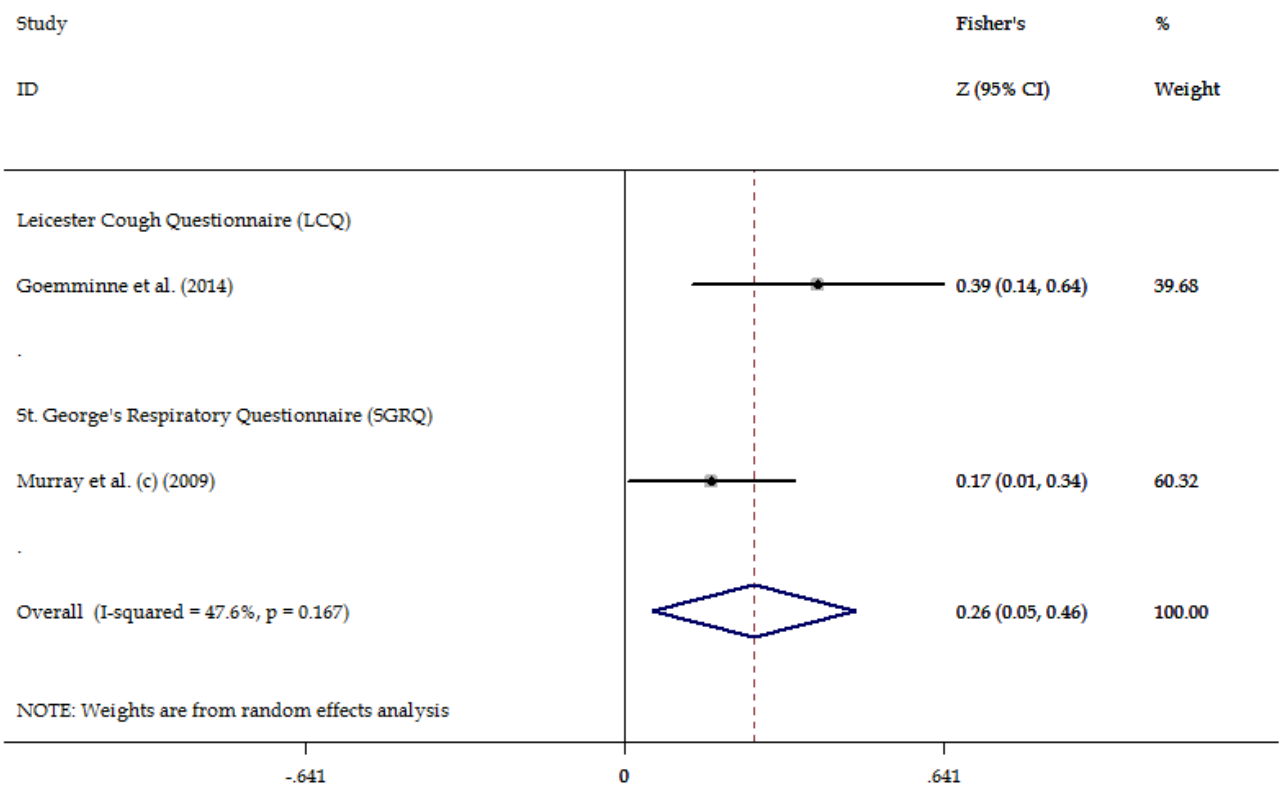
For references see main paper and online supplement.

ONLINE SUPPLEMENT Figure E11. Forest plot for the correlation between health-related quality of life and forced vital capacity (FVC).



For references see main paper and online supplement.

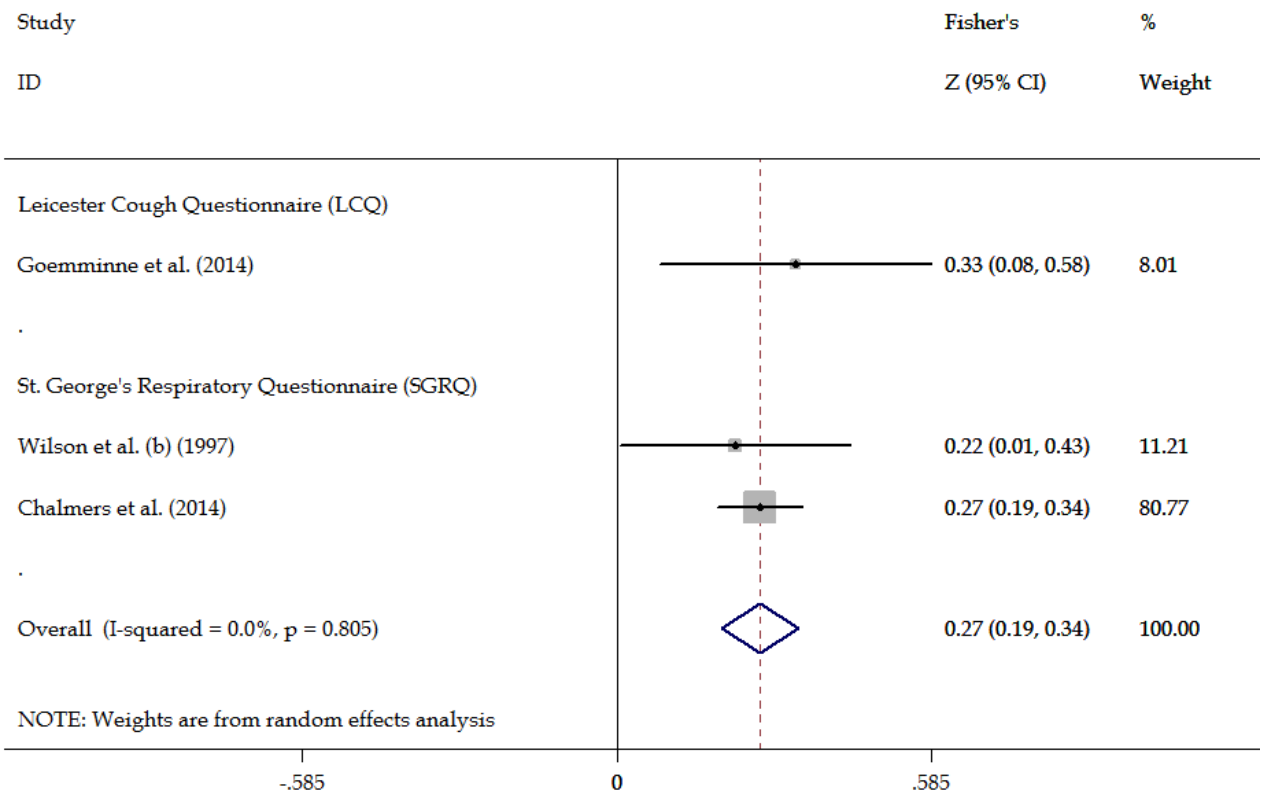
ONLINE SUPPLEMENT Figure E12. Forest plot for the correlation between health-related quality of life and sputum colour.



Measurements of sputum colour used for both studies: sputum colour chart.

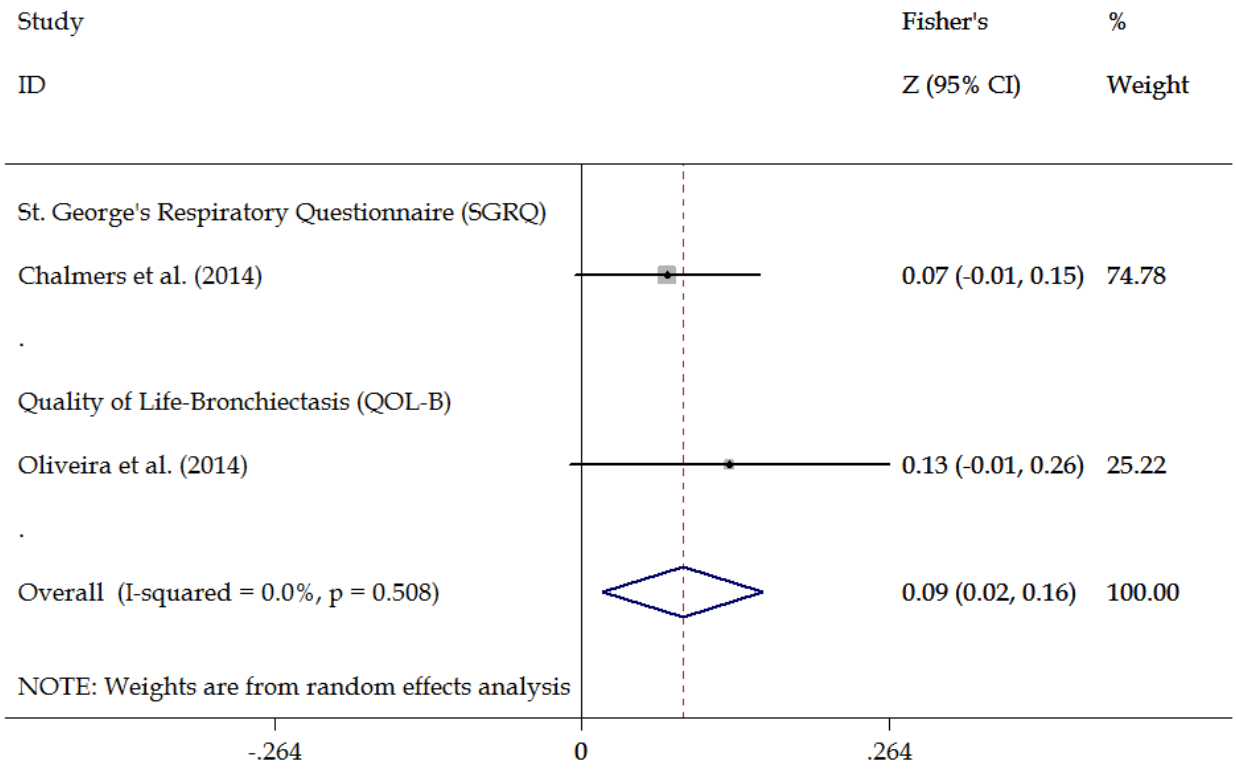
For references see main paper and online supplement

ONLINE SUPPLEMENT Figure E13. Forest plot for the correlation between health-related quality of life and positive bacterial sputum culture.



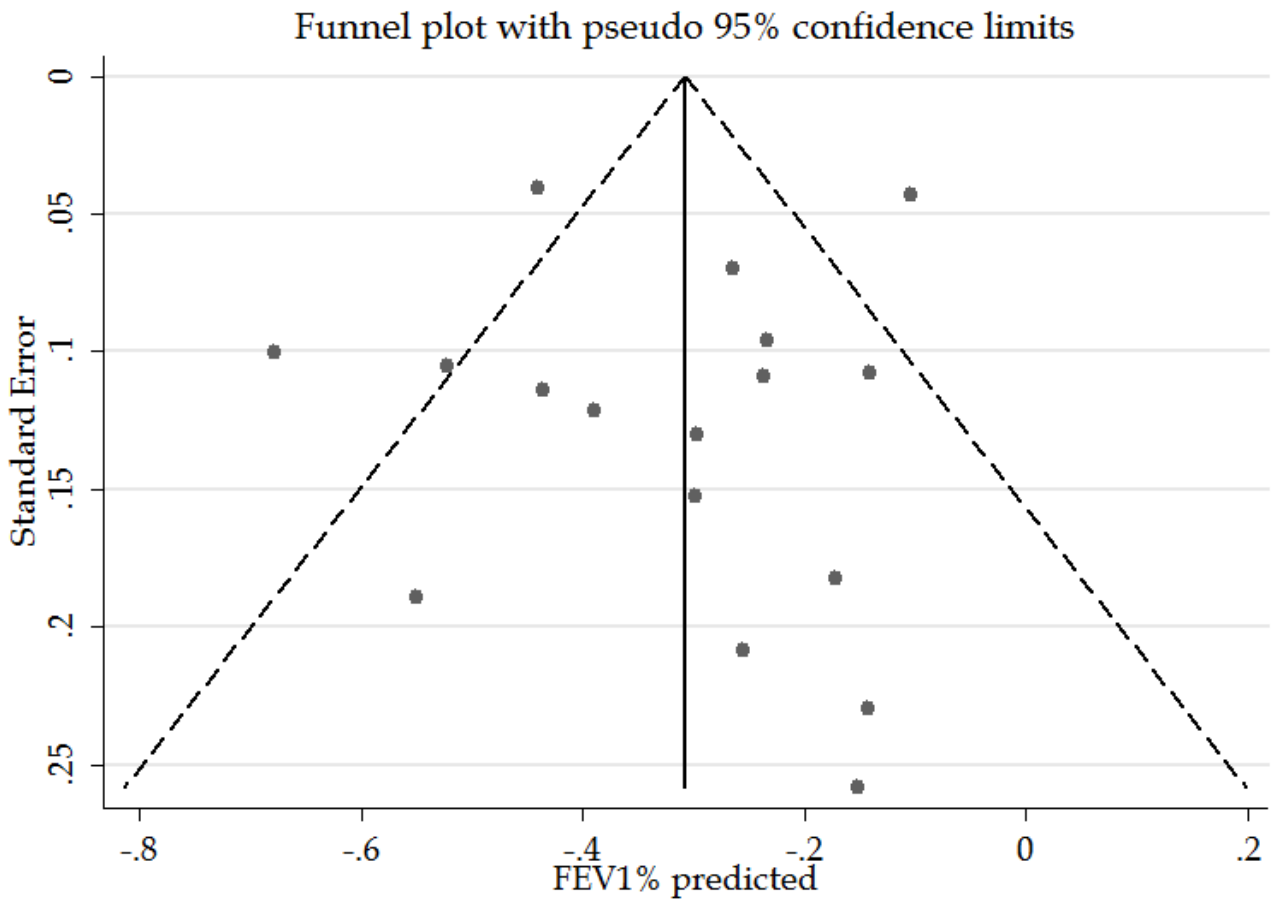
For references see main paper and online supplement.

ONLINE SUPPLEMENT Figure E14. Forest plot for the correlation between health-related quality of life and comorbidities.



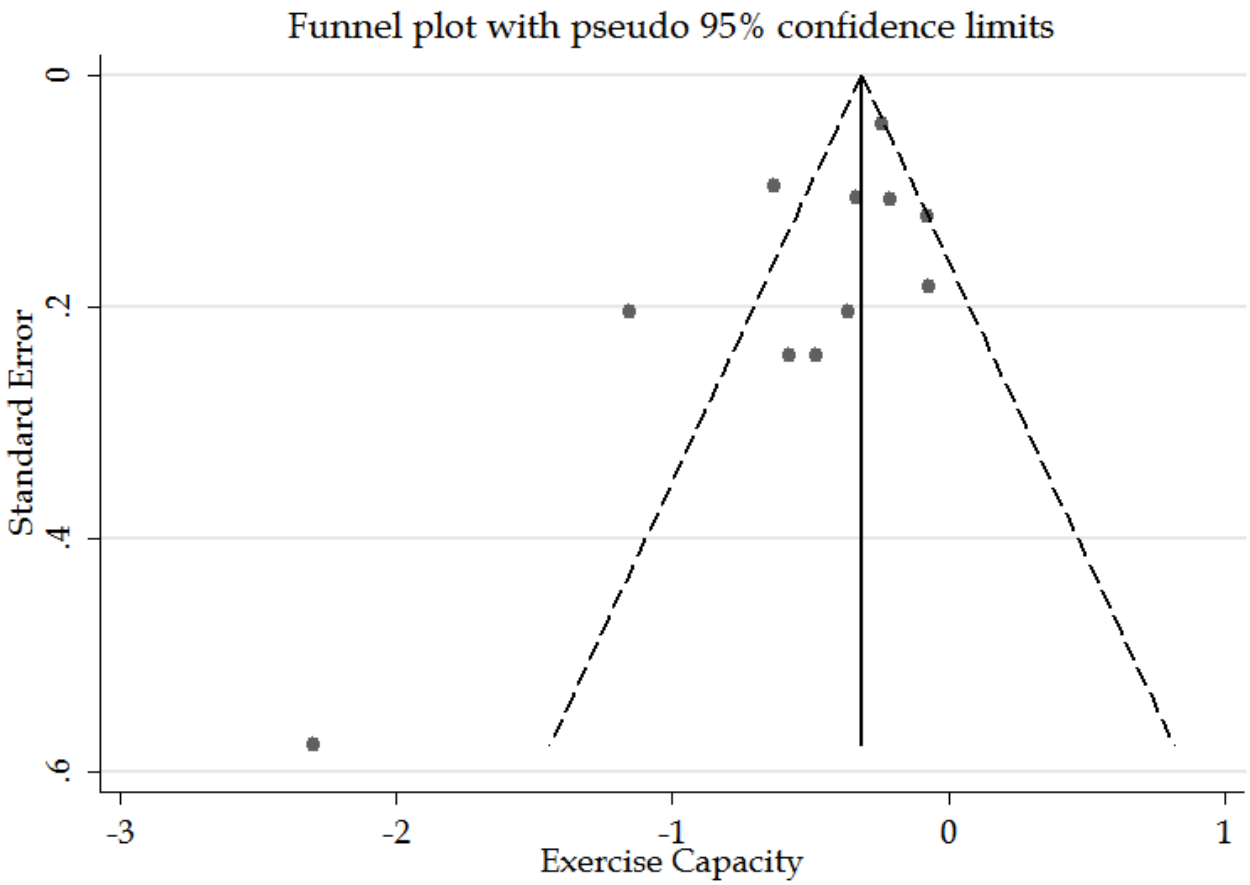
For references see main paper and online supplement.

ONLINE SUPPLEMENT Figure E15. Funnel plot of FEV_1% assessing the publication bias for the relevant meta-analysis studies.



Each study is illustrated as a dot. Symmetric image of the funnel plot studies distribution indicates no publication bias.

ONLINE SUPPLEMENT Figure E16. Funnel plot of exercise capacity assessing the publication bias for the relevant meta-analysis studies.



Each study is illustrated as a dot. Asymmetric image of the funnel plot studies distribution indicates possibility of publication bias.

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