

The dyspnoea-inactivity vicious circle in COPD: Development and external validation of a conceptual model

Maria A Ramon,^{1,2} Gerben Ter Riet,³ Anne-Elie Carsin,^{4,5,6,7} Elena Gimeno-Santos,^{2,8,9}
Alvar Agustí,^{2,8} Josep M Antó,^{4,5,6,7} David Donaire-Gonzalez,^{4,5,6} Jaume Ferrer,^{1,2,10}
Esther Rodríguez,^{1,2} Robert Rodriguez-Roisin,^{2,8} Milo A Puhon,¹¹ Judith Garcia-
Aymerich,^{4,5,6} and the PAC-COPD Study Group.

¹Department of Pneumology, Hospital Universitari Vall d'Hebron, Barcelona, Spain.

²CIBER de Enfermedades Respiratorias (CIBERES), Barcelona, Spain.

³Department of General Practice, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands.

⁴ISGlobal, Barcelona, Spain.

⁵CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain.

⁶Universitat Pompeu Fabra (UPF), Barcelona, Spain.

⁷IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain.

⁸Respiratory Institute, Hospital Clinic, Universitat de Barcelona, Barcelona, Spain.

⁹Institut d'investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

¹⁰Departament de Medicina, Universitat Autònoma de Barcelona, Barcelona, Spain.

¹¹Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland.

Corresponding author: Judith Garcia-Aymerich, ISGlobal, Centre for Research in Environmental Epidemiology (CREAL), Dr. Aiguader 88, 08003 Barcelona – Spain; Telephone +34 932147350; Fax + 34 932147302; E-mail: judith.garcia@isglobal.org

Abstract word count: 200

Text word count: 3491

“Take home” message: An externally validated model highlights exercise capacity and exacerbations as drivers of the COPD vicious circle.

ABSTRACT

The vicious circle of dyspnoea-inactivity has been proposed, but never validated empirically, to explain the clinical course of chronic obstructive pulmonary disease (COPD). We aimed to develop and validate externally a comprehensive vicious circle model.

Methods: (1)identification and validation of all published vicious circle models by a systematic literature search and fitting structural equation models (SEM) to longitudinal data from the PAC-COPD Spanish cohort (n=210, 68 years, FEV₁ 54%) testing both the hypothesised relationships between variables in the model ('paths') and model fit; and (2)development of a new model and external validation using longitudinal data of the Swiss and Dutch ICE COLD ERIC cohort (n=226, 66 years, FEV₁ 57%).

We identified nine vicious circle models for which SEMs confirmed most hypothesised paths but showed inappropriate fit. In the new model, airflow limitation, hyperinflation, dyspnoea, physical activity, exercise capacity and COPD exacerbations remained related to other variables and model fit was appropriate. Fitting it to ICE COLD ERIC all paths were replicated and model fit was appropriate.

Previously published vicious circle models do not fully explain the vicious circle concept. We developed and externally validated a new comprehensive model that gives a more relevant role to exercise capacity and COPD exacerbations.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterised by chronic airflow limitation and persistent respiratory symptoms that limit patients' activities [1, 2]. The reduction in physical activity [3] leads to patients' physical deconditioning and further impairment of respiratory symptoms [4]. This process is known as the *disease spiral* or *vicious circle* theory of dyspnoea-inactivity in COPD [5], a construct that has been helpful so far in understanding patients' concerns and generating research hypotheses [3, 6]. However, the literature contains several versions of the vicious circle, likely because they are based on expert opinion, clinical observations and on associations reported in cross-sectional studies only [5, 7–9]. Further, the vicious circle theory in COPD has never been prospectively validated.

We argue that the dyspnoea-inactivity vicious circle can be conceived as a *conceptual model*, this is a set of direct and indirect relationships among variables involved in a specific health problem usually represented by a diagram [10]. In order to build such a model, it is important to establish which are the variables and relations between variables ('paths') that play a part in the dyspnoea-inactivity vicious circle. Therefore, we aimed to establish an empirically validated a model for the dyspnoea-inactivity vicious circle in COPD through: (1) the identification and validation of all published vicious circle models using real patients' longitudinal measurements, and (2) the building and external validation of a comprehensive new vicious circle model, using repeated measurements from two European COPD cohort studies.

METHODS

Systematic literature review

We conducted a systematic literature review to identify all previously published conceptual models for the dyspnoea-inactivity vicious circle in COPD following the handbooks of the Centre for Reviews and Dissemination [11], the Cochrane Collaboration [12], and the PRISMA statement for reporting of systematic reviews [13]. All methods were specified in advance and documented in a protocol (see Online Supplement). Briefly, we searched the PubMed/Medline and SCOPUS databases from the earliest to the most recent May 2017 records (see full search strategy in the Online Supplement). Articles were included if they discussed or explained the dyspnoea-inactivity vicious circle in a diagram. No date or language restrictions were imposed. Two of the co-authors (MAR and EGS) independently reviewed the title and abstract of every citation retrieved by the database searches and a third co-author (JGA) decided upon inclusion in case of disagreement. For each study we rebuilt its vicious circle diagram in the form of a directed acyclic graph depicting the hypothesised longitudinal relationships (both direct and indirect) between involved variables. To account for the cyclic nature of relationships between variables involved in most vicious circle models, we considered most variables as time varying and included several time points (e.g., dyspnoea at $t1 \rightarrow$ physical activity at $t2 \rightarrow$ dyspnoea at $t3$). A representative of each original paper (first or corresponding author) was contacted and all (except one, who did not respond to several mail requests) agreed with our adaptation of their diagram.

Study design and participants of the European COPD cohort studies

We had access to individual patient data of two COPD multicentre cohort studies that measured longitudinally variables potentially involved in the dyspnoea-inactivity vicious circle. First, the *Phenotype and Course of COPD* (PAC-COPD) project [14] that recruited patients during their first COPD exacerbation in eight hospitals in Spain (n=342) and evaluated their characteristics during clinical stable conditions every 12-18 months, up to a maximum of 3 times. Second, the *International Collaborative Effort on Chronic Obstructive Lung Disease: Exacerbation Risk Index Cohorts* (ICE COLD ERIC) study [15] that recruited patients in primary care centres from the Netherlands and Switzerland (n=409) and evaluated them every 6 months up to 5 years; for the present study we included data from every 2 years up to 3 times, corresponding to the time span available in PAC-COPD cohort. A total of 210 and 226 patients from the PAC-COPD and the ICE COLD ERIC cohorts, respectively, had dyspnoea and physical activity data available at the 3 consecutive study time-points, and were therefore included in the present analyses (Tables S1 and S2 in the Online supplementary material). All included patients had spirometry-defined COPD (post-bronchodilator forced expiratory volume in the first second to forced vital capacity ratio [FEV₁/FVC] <0.70 during clinical stable conditions). The two cohort studies were approved by the relevant ethics committees, and written informed consent was obtained from each participant.

Measurements

All variables involved in at least one of the vicious circle models identified in the systematic literature review had available repeated measurements in PAC-COPD cohort

and most of them in ICE COLD ERIC cohort. These included: (1) the modified medical research council (mMRC) dyspnoea scale (0 to 4) in both cohorts, which grades breathlessness during daily activities [16]; (2) physical activity by the estimated weekly energy expenditure (kcal/week) using the Yale Physical Activity Survey (YPAS) [17, 18] in the PAC-COPD cohort, and the physical activity total score from the Longitudinal Aging Study Amsterdam Physical Activity Questionnaire (LAPAQ) [19] in the ICE COLD ERIC cohort. Both YPAS and LAPAQ questionnaires ask about the frequency, intensity, and duration of a list of activities not related to dyspnoea or other respiratory symptoms, in the previous month and previous two weeks respectively. The YPAS questionnaire allows for the calculation of weekly energy expenditure in physical activity while the LAPAQ questionnaire assigns weights to each activity according to the metabolic equivalent task giving a score that ranges from 0 to 23; (3) the 6-minute walk distance (6MWD) and both the maximum ventilation during the incremental test ($V_{E\max}$) and lactic acid from a cardiopulmonary incremental exercise test with cycloergometer in the PAC-COPD study, and the number of repetitions in the 1-min sit-to-stand test in the ICE COLD ERIC study [20]; (4) handgrip force in both studies; (5) FEV₁, before and after bronchodilator, and inspiratory capacity (IC) by spirometry in both studies; total lung capacity (TLC), diffusing capacity of the lung for carbon monoxide (DLco) and arterial oxygen partial pressure (PaO₂). IC and IC/TLC were taken as indices of inspiratory constraint derived from static hyperinflation of the lung [21]; (6) Charlson index of comorbidities only available in the PAC-COPD; (7) COPD exacerbations gathered from governmental databases in the PAC-COPD and through central adjudication of both patient interviews and review of patient records in the ICE COLD ERIC; (8) health-related quality of life by the Saint George's respiratory

questionnaire [SQRQ] total score in the PAC-COPD and the Chronic Respiratory Questionnaire [CRQ] total score in the ICE COLD ERIC; and (9) the Hospital Anxiety and Depression Scale [HADS] scores in both cohorts. Detailed information about the methods, questionnaires, standardisation of the tests, and fieldwork supervision of the two studies has been previously reported [22, 23].

Statistical analysis

Sample size allowed a statistical power >99% to identify as statistically significant a better fit of our model than previously published models [24] (see power calculations in the Online Supplement).

We appraised the validity of vicious circle models obtained from the systematic review (first objective) by fitting a structural equation model (SEM) with the variables and paths depicted in each directed acyclic graph (corresponding to each identified vicious circle model) using longitudinal data from the PAC-COPD cohort and testing (1) the hypothesised relationships between variables ('paths') and (2) how well the full hypothesised model fitted the data. Briefly, a SEM is a statistical modelling technique that tests a construct of data (including variables and paths) to estimate direct and indirect relationships between the included variables [25]. First, the path coefficients estimated by the SEM informed about each hypothesised path in the model. Path coefficients were standardised ranging from -1 to +1 to facilitate comparison between paths involving different variables and can be interpreted as correlation coefficients [25]. Non-standardised coefficients were also used to better understand the strength of associations between variables in the model and to be able to compare them with

previous research. Statistically significant path coefficients in the hypothesised direction (e.g., dyspnoea negatively associated with later physical activity) supported validity of the model. Second, model fit parameters informed about how well the variables and paths included in a specific model actually represented the underlying concept (the dyspnoea-inactivity vicious circle) [26]. The three following SEM fit criteria were considered [27–31]: (1) a χ^2 relative to degrees of freedom (χ^2/df) <2.0 and a non-significant (≥ 0.05) p-value, which indicates that a non-significant amount of variance in the data remains unexplained [27,30,31], (2) a root mean square error of approximation (RMSEA) <0.07 with 90% CI between 0.05 and 0.10, which indicates that the model fits well with the population covariance matrix [28,30,31], and (3) a comparative fit index (CFI) ≥ 0.95 , which indicates that variables included in the model are well correlated among them [29,31]. A model had to fulfil all our three criteria. If not, we considered it to not appropriately explain the vicious circle theory (because e.g., the model missed some variables or paths relevant to the vicious circle).

We decided *a priori* to propose a new vicious circle model if none of the models identified in the systematic literature review proved to be valid. As this was the case (see below in Results section), we built a new vicious circle model (second objective), including as candidate variables all variables and paths involved in at least one of the previously identified vicious circles, by fitting a new SEM to PAC-COPD longitudinal data. In addition, we allowed the SEM to add any path (missing in previous models) that was statistically significant and improved fit of the model, only if it was biologically plausible (e.g., a direct path between airflow limitation and dyspnoea). In an iterative process of removing paths or variables one at a time, we removed from the SEM (1)

paths with not statistically significant path coefficients ($p \geq 0.05$), and (2) variables not related to any other variable in the model (path coefficients with $p \geq 0.05$) whose removal did not worsen the model fit. The final SEM kept variables that showed a statistically significant association with at least one of the remaining variables and/or significantly improved the model fit. As a final step, we fitted the final SEM model obtained with the PAC-COPD cohort to the ICE COLD ERIC longitudinal data. The model was considered a valid representation of the vicious circle if it met our criteria detailed above (confirmation of paths and appropriate model fit). All analyses were performed with Stata statistical software package (version 12.1; Stata Corp LP; College Station, TX, US).

RESULTS

Identification of vicious circle models in the systematic literature review

We identified 9 articles that reported the conceptual model of the dyspnoea-inactivity vicious circle as a diagram (Figure S1). There were differences in variables and paths across different models (Table 1, Figure 1). Dyspnoea was included in all models, exercise capacity in 8, physical activity in 7, and muscle strength in 6. Most of the models (6 out of 9) included dyspnoea as the starting variable of the vicious circle, whereas airflow limitation was considered the initial factor in the remaining 3 models. For each of the identified diagrams we built a directed acyclic graph (Figure 1).

Validation of the vicious circle models identified in the systematic literature review

We fitted a SEM for each of the identified 9 diagrams to the PAC-COPD longitudinal data. Patients were mostly male (93%), had mean FEV₁ of 54% of predicted and

median mMRC dyspnoea score of 2 (Table 2). Dyspnoea, physical activity and other clinical and functional variables deteriorated during follow-up (Table S3 in the online supplement).

Most paths (of the 9 models) were replicated with statistically significant path coefficients in the hypothesised direction (Figure 1). However, none of the vicious circle models showed appropriate fit, *as per* p-values (all <0.05), RMSEA values (from 0.176 to 0.352) and CIF values (from 0.347 to 0.629) (Table 3).

Building a comprehensive new vicious circle model

Figure S2 in the online supplement shows all variables and paths involved in at least one of the vicious circle models identified in the systematic review. After several iterations using PAC-COPD data we obtained a final model (Figure 2a) in which (1) both airflow limitation and lung hyperinflation were directly associated with dyspnoea, (2) dyspnoea was related to future exercise capacity both directly and mediated by a reduction in physical activity, (3) both physical activity and exercise capacity were related to future dyspnoea levels, (4) COPD exacerbations, associated with prior airflow limitation, were related to future exercise capacity and dyspnoea, (5) other outcomes, such as quality of life, anxiety, depression, comorbidities, hypoxemia or muscle weakness did not contribute to the vicious circle once the abovementioned variables and paths were included in the model, and (6) model fit was good according to all parameters ($\chi^2=5.8$, $df=8$, $p=0.667$, RMSEA (90%CI)<0.001 (<0.001-0.058), and CIF>0.999). Figure S3a shows this SEM model using non-standardised coefficients.

Validation of the new vicious circle model

To validate this new model, we applied it to the ICE COLD ERIC longitudinal data. These patients (60% males, FEV₁ 57% and median mMRC 1) had in general milder COPD than those of PAC-COPD (Table 2) but their clinical and functional characteristics also deteriorated during follow-up (Table S4 in the online supplement). Figure 2b shows results of the fitted SEM which confirmed all paths with statistically significant path coefficients in the hypothesised direction and showed a good fit to the data according to all parameters ($\chi^2=14.6$, df=8, p=0.067, RMSEA (90%CI)=0.060 (<0.001-0.101), and CIF=0.984). Figure S3b shows this SEM model using non-standardised coefficients. Finally, Figure 2 shows a diagram depicting the new vicious circle conceptual model.

DISCUSSION

To our knowledge, this is the first study that developed and externally validated a model for the dyspnoea-inactivity vicious circle theory in COPD. We found that: (1) previously published conceptual models contain valid information about the vicious circle (as most paths could be replicated using longitudinal data) but do not likely explain the vicious circle concept appropriately (*as per* the low fit of the models to patients data); and (2) a new comprehensive model that gives a more relevant role to exercise capacity and COPD exacerbations was built and validated using two prospective cohorts including COPD patients with different degrees of disease severity from different geographic areas and clinical settings.

Interpretation of findings

We found that existing vicious circle models included variables and relations between variables ('paths') relevant to the vicious circle. These variables and paths describe a sequence of events from expiratory airflow limitation, increase in resting lung volumes and dynamic hyperinflation, to a shallow and rapid breathing pattern with dyspnoea worsening, decrease in physical activity, and a deterioration of exercise capacity, which further enhances dyspnoea, thus akin to the current knowledge on pathophysiology of COPD [32,33].

However, we observed that existing vicious circle models show a poor fit to real patients' longitudinal data. Our findings suggest that previous models did not fully represent the underlying theory (*i.e.*, the dyspnoea-inactivity vicious circle) because additional variables and paths should have been considered. The acquisition of good fit indices when the model built with PAC-COPD data was used on the ICE COLD ERIC data supports this assumption. Our results also suggest that any adaptation of the current vicious circle model to other chronic respiratory conditions would require real patients' data rather than simple extrapolation from COPD.

The new vicious circle model that we propose has two main differences with former ones. First, we found that COPD exacerbations, key events in the natural history of COPD and only considered in one previous model [34], are of relevance to the vicious circle, even in a primary care COPD population with infrequent exacerbations like ICE COLD ERIC. Moreover, our model supported a bi-directional role for exacerbations (both affecting future variables of the vicious circle, as previously suggested [34], and

also affected by prior variables), consistent with the current view that attributes to exacerbations a prominent role in COPD assessment, management and prognosis [1]. Second, our results show that exercise capacity has a more central role in the vicious circle than previously considered [5, 34–37], given that most of the effect of other variables (lung hyperinflation, physical activity, exacerbations) on dyspnoea are mediated by effects on exercise capacity. Again, this finding is consistent with existing knowledge on COPD [39, 40], as exercise capacity decline has been found accelerated by hyperinflation of the lung [39] and COPD exacerbations [40], and improving exercise capacity (e.g., through an exercise training programme[41]) reduces dyspnoea.

Several explanations may help to interpret why some variables included in previous vicious circle models and relevant to COPD prognosis such as skeletal muscle weakness, anxiety or depression and comorbidities did not remain in our final model [35–37, 42]. First, patients with higher prevalence of these conditions were lost to follow-up, which could have prevented us from observing variability in important variables that could contribute to the vicious circle. Second, it is possible that, once other variables and paths were specified, those variables did not provide additional information to the vicious circle. Third, the available measures of these concepts in PAC-COPD and ICE COLD ERIC cohorts could have been not sufficiently accurate. For example, our use of handgrip force instead of quadriceps force might have prevented us to find stronger associations between skeletal muscle force and other variables in the models. Fourth, variables important to COPD course, such as smoking history or body mass index, have not been included in previous vicious circle models. Their inclusion could be considered after appropriate systematic reviews of how they

affect and/or are affected by variables in the current vicious circle. Altogether, future research on this field will require repeated, most valid measurements over time of all variables potentially related to the vicious circle phenomenon.

Strengths and limitations

A strength of our study is that we followed rigorous systematic review methodology to identify all previously published models for the dyspnoea-inactivity vicious circle. Also, we used SEM to validate each of the identified models, which provides an extensive insight in the complex relationships between variables involved in the vicious circle. Finally, we used two different cohorts from different clinical settings (primary care and specialised hospital respiratory departments) including patients with a wide range of severity of their disease, which increases the external validity of our model.

Among potential limitations, first, the already mentioned lack of some relevant variables, such as quadriceps force, may have resulted in a relevant variable or path not included in our final model. Second, the present manuscript is based on a secondary analysis of two cohorts recruited with other primary research questions. As a consequence, some of the variables included in the analysis may not be the most appropriate for the study of the vicious circle concept. For example, the use of mMRC scale (instead of other measures) to assess dyspnoea could make the argument of its association with physical activity a bit circular. Third, patients lost to follow-up in both cohorts had worse clinical and functional status at baseline, which may have reduced variability in some parameters, thus limiting the ability to identify associations. However, patients who present at the clinical practice with the typical manifestations of

the vicious circle are actually those who survive to COPD without severe comorbidities, this is, those who are followed-up in research studies. Accordingly, our findings cannot be extended to COPD patients with very limited survival or severe comorbidities. Fourth, a questionnaire was used to measure physical activity in both cohorts, which could be subject to poor accuracy at the individual level of a variable key to the vicious circle. (Of note, physical activity from an accelerometer was available in the second follow-up of the PAC-COPD study but not included in this analysis in order to keep the required temporal sequence). Fifth, sample size of both cohorts was relatively small and did not allow testing any potential role of drug and non-drug treatments on the vicious circle. Sixth, although data was available for 3 different time-points (t1, t2 and t3), many variables were only available at t1 and t3 which may have hindered the identification of differences over time for some parameters. Further, the relatively short follow-up period of our cohorts (<5 years) could have limited the ability to identify novel variables relevant to the vicious circle or to estimate appropriately the contribution of relevant variables to the vicious circle. However, in both PAC-COPD and ICE COLD ERIC patients, we observed a statistically significant worsening over time in physical activity, lung function, exercise capacity and muscle force. Finally, the external validity of our new vicious circle model might not hold in the presence of large heterogeneity in COPD progression parameters.

Conclusions

Previously published vicious circle models do not fully explain the vicious circle concept. We developed and externally validated a new comprehensive model that gives a more relevant role to exercise capacity and COPD exacerbations. This new model may

be of help to both clinicians and researchers to better understand the relationships among COPD characteristics involved in the dyspnoea-inactivity vicious circle, thus facilitating the design and testing of targeted therapeutic interventions.

ACKNOWLEDGMENTS

We would like to thank authors of original articles for reviewing and accepting our proposal to validate their proposed model for the dyspnoea-inactivity vicious circle: Christopher Cooper, Jean-Louis Corhay, Marc Decramer, François Maltais, Michael Polkey and Richard ZuWallack.

FUNDING

The PAC-COPD Study is funded by grants from Fondo de Investigación Sanitaria (FIS PI020541), Ministry of Health, Spain; Agència d'Avaluació de Tecnologia i Recerca Mèdiques (AATRM 035/20/02), Catalonia Government; Spanish Society of Pneumology and Thoracic Surgery (SEPAR 2002/137); Catalan Foundation of Pneumology (FUCAP 2003 Beca Marià Ravà); Red RESPIRA (RTIC C03/11); Red RCESP (RTIC C03/09), Fondo de Investigación Sanitaria (PI052486); Fondo de Investigación Sanitaria (PI052302); Fundació La Marató de TV3 (num. 041110); DURSI (2005SGR00392); and unrestricted educational grants from Novartis Farmacèutica, Spain, and AstraZeneca Farmacèutica, Spain. CIBERESP and CIBERES are funded by the Instituto de Salud Carlos III, Ministry of Health, Spain. ISGlobal is a member of the CERCA Programme, Generalitat de Catalunya. The ICE COLD ERIC COHORT study was funded by the Swiss National Science Foundation (grant # 3233B0/115216/1), Dutch Asthma Foundation (grant # 3.4.07.045) and Zurich Lung League (unrestricted grant).

No involvement of funding sources in study design; in the collection, analysis, and interpretation of data; in the writing of the report; nor in the decision to submit the article for publication. Researchers are independent from funders.

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Table 1. Reference details, type of article and list of variables of nine studies reporting the dyspnoea-inactivity vicious circle in a diagram identified through the systematic literature search.

Reference (chronological order)	Type of article	Variables involved in the dyspnoea-inactivity vicious circle
Cooper CB 2001, Med Sci Sports Exerc.[5]	Review	Dyspnoea, exercise capacity, muscle force, ventilatory requirements.
Polkey MI 2006, Clin Med.[8]	Review	Dyspnoea, muscle force, anaerobic metabolism, gas trapping, dyspnoea.
Cooper CB 2006, Am J Med. [35]	Review	Airflow limitation, gas trapping, dyspnoea, physical activity, anxiety, tachypnea, hypoxemia, exercise capacity, ventilator requirements, health related quality of live.
Reardon JZ 2006, Am J Med. [7]	Review	Dyspnoea, physical activity, exercise capacity.
Decramer M 2006, Eur Respir Rev.[34]	Review	Airflow limitation, gas trapping, dyspnoea, physical activity, exercise capacity, muscle force, COPD exacerbation, health related quality of live.
Donaldson AV 2012, Int J COPD.[36]	Review	Dyspnoea, physical activity, muscle force, anaerobic metabolism.
Maltais F 2013, Physician and sportmed.[37]	Review	Airflow limitation, gas trapping, dyspnoea, physical activity, muscle force, comorbidities, exercise capacity, health related quality of live.
Garcia-Aymerich J 2014, Clin chest med.[38]	Review	Dyspnoea, physical activity, muscle force, exercise capacity.
Corhay J 2014, Int J COPD.[42]	Review	Dyspnoea, physical activity, depression, anxiety.

Table 2. Patients' characteristics in the PAC-COPD and ICE COLD ERIC cohorts at recruitment.

	PAC-COPD n=210	ICE COLD ERIC n=226
Anthropometric and clinical data		
Males	195 (92.9)	135 (60.0)
Age (years)	67.5 (8.2)	65.7 (9.5)
Active smokers	74 (35.2)	80 (35.4)
Physical activity (YPAS scale, Kcal/week)	6056 (3345-9085)	
Physical activity (LAPAQ total score, 0-23)	-	13 (9-15)
SGRQ total score (0-100)	31.2 (22.2-44.1)	-
CRQ (mean of four domains)	-	5.2 (4.4-6.0)
HADS-anxiety	4 (2-7)	4 (2-7)
HADS-depression	3 (1-5)	3 (2-6)
Charlson index of comorbidity	2 (1-2)	-
mMRC dyspnoea score	2 (2-3)	1 (1-3)
Respiratory frequency	18 (16-20)	-
Lung function		
Post-bronchodilator FEV ₁ (% predicted)	53.5 (16.6)	56.6 (16.9)
Airflow limitation severity*		
Mild (FEV ₁ ≥ 80%)	13 (6.2)	10 (4.4)
Moderate (FEV ₁ ≥ 50%, <80%)	104 (49.5)	139 (61.5)
Severe (FEV ₁ ≥ 30%, <50%)	79 (37.6)	61 (27.0)
Very severe (FEV ₁ < 30%)	14 (6.7)	16 (7.1)
IC/TLC (%)	31.4 (0.9)	-
IC (%predicted)	69.5 (20.7)	73.9 (20.8)
PaO ₂ (mmHg)	74.8 (11.3)	-
Exercise capacity and muscle force		
6MWD (meters)	445 (84)	-
Sit to stand (numb of repetitions)	-	19.9 (9.7)
V _{E max} (L/min)	42.2 (12.7)	-
Lactic acid (mM)	4.8 (2.2)	-
Handgrip muscle force (Kg)	31.4 (8.2)	31.7 (11.6)

Data are presented as n (%), mean (SD) or median (P₂₅-P₇₅). Definition of abbreviations: YPAS: Yale physical activity survey; LAPAQ: Longitudinal Aging Study Amsterdam Physical Activity Questionnaire; SGRQ: Saint George's respiratory questionnaire; CRQ: Chronic Respiratory Questionnaire; HADS: Hospital Anxiety and Depression Scale; mMRC: modified Medical Research Council dyspnoea scale; FEV₁: forced expiratory volume in 1 second; IC/TLC: inspiratory capacity/total lung Capacity; PaO₂: arterial oxygen partial pressure; 6MWD: six minute walk distance, V_{E max}: maximum ventilation during incremental cycleergometer test.

*According to the criteria of the ATS/ERS [43].

Table 3. Validity appraisal of the nine vicious circle models identified in the systematic literature search.

	Paths confirmation	Model fit		
	Confirmed paths* / Total hypothesised paths	Chi ² ; df; p-value	RMSEA (90%CI)	CFI
Threshold values	<i>n/n</i>	<i>Chi²/df <2.0 and p≥0.050</i>	<i><0.070 (0.050-0.100)</i>	<i>>0.950</i>
Reference (chronological order):				
Cooper CB 2001, Med Sci Sports Exerc.[5]	4/4	93.1; 6; <0.001	0.263 (0.272-0.390)	0.138
Polkey MI 2006, Clin Med.[8]	3/4	30.0; 6; <0.001	0.213 (0.141-0.292)	0.347
Cooper CB 2006, Am J Med. [35]	8/12	303.9; 52; <0.001	0.172 (0.154-0.191)	0.523
Reardon JZ 2006, Am J Med. [7]	3/3	70.3; 3; <0.001	0.327 (0.263-0.395)	0.576
Decramer M 2006, Eur Respir Rev.[34]	9/11	233.2; 42; <0.001	0.176 (0.155-0.198)	0.629
Donaldson AV 2012, Int J COPD.[36]	1/4	75.7; 6; <0.001	0.235 (0.190-0.284)	0.114
Maltais F 2013, Physician and sportmed.[37]	4/7	188.6; 21; <0.001	0.195 (0.170-0.221)	0.495
Garcia-Aymerich J 2014, Clin chest med.[38]	4/7	375.4; 21; p<0.001	0.283 (0.259-0.309)	0.098
Corhay J 2014, Int J COPD.[42]	3/5	135.0; 5; <0.001	0.352 (0.302-0.404)	0.161

Definition of abbreviations: CFI: comparative fit index; df: degrees of freedom; RMSEA: root mean square error approximation.

*Statistically significant path coefficients in the hypothesised direction / total number of tested paths. Full values in Figures S2-S10.

FIGURES

Figure 1. Directed acyclic graphs and validation* of the identified diagrams for the dyspnoea-inactivity vicious circle in COPD.

Model proposed by: **(a)** Cooper CB in 2001 (Med Sci Sports Exerc 2001; 33: S643-6); **(b)** Polkey MI et al. in 2006 (Clin Med 2006; 6: 190–196), **(c)** Cooper CB in 2006 (Am J Med 2006; 119: 21–31); **(d)** Reardon JZ et al. in 2006 (Am J Med 2006; 119: S32–S37); **(e)** Decramer M in 2006 (Eur Respir Rev 2006; 15: 51–57); **(f)** Donaldson AV et al. in 2012 (Int J COPD 2012; 7: 523–535); **(g)** Maltais F in 2013 (Phys Sportsmed 2013; 41: 66–80); **(h)** Garcia-Aymerich J et al. in 2014 (Clin Chest Med 2014; 35: 363–368); **(i)** Corhay JL et al. in 2014 (Int J Chron Obstruct Pulmon Dis 2014; 9: 27–39).

Definition of abbreviations: 6MWD: 6 minute walk distance; FEV₁: forced expiratory volume in 1s; HADS: Hospital Anxiety and Depression Scale; IC/TLC: inspiratory capacity /total lung capacity; mMRC: modified Medical Research Council dyspnoea scale; PaO₂: arterial oxygen partial pressure; SGRQ: Saint George's respiratory questionnaire (higher scores indicate more limitations); V_{E max}: maximum ventilation during incremental cycloergometer test.

* Using standardized coefficients the magnitude of the association between two variables takes values ranging from -1 to 1, where negative values indicate a negative relationship.

Figure 2. The new model of dyspnoea-inactivity vicious circle in patients with COPD: derivation (1a) and validation (1b). Relationship and standardized path coefficients* between variables in the dyspnoea-inactivity vicious circle in patients with COPD.

Definition of abbreviations: FEV₁: forced expiratory volume in 1s; IC: inspiratory capacity; TLC: total lung capacity; mMRC: modified Medical Research Council dyspnoea scale; 6MWD: six minute walk distance; LAPAQ: LASA Physical Activity Questionnaire; RMSEA: root mean square error of approximation; CFI: comparative fit index.

* Using standardized coefficients the magnitude of the association between two variables takes values ranging from -1 to 1, where negative values indicate a negative relationship.

Figure 3. Graphical representation of the new model of dyspnoea-inactivity vicious circle in patients with COPD.

The dyspnoea-inactivity vicious circle in COPD: Development and external validation of a conceptual model

SUPPLEMENTARY MATERIAL

- **Systematic literature review methods**
- **Sample size calculations**
- **Table S1.** Comparison of baseline characteristics between participant and non-participants from the PAC-COPD study.
- **Table S2.** Comparison of baseline characteristics between participant and non-participants from the ICE COLD ERIC study.
- **Table S3.** Evolution of main characteristics of COPD patients in the PAC-COPD cohort during 3 years of follow-up.
- **Table S4.** Evolution of main characteristics of COPD patients in the ICE COLD ERIC cohort during 4 years of follow-up.
- **Figure S1.** Flow diagram of study selection during the systematic review process.
- **Figure S2.** Comprehensive new vicious circle model, including all variables and paths involved in at least one of the previously identified vicious circles.
- **Figure S3.** New vicious circle model with non-standardised coefficients using (a) PAC-COPD and (b) ICE COLD ERIC data.
- **Supplementary References.**

SYSTEMATIC LITERATURE REVIEW METHODS

We conducted a systematic literature review to identify all previously published conceptual models for the dyspnoea-inactivity vicious circle in COPD following the handbooks of the Centre for Reviews and Dissemination [1], the Cochrane Collaboration [2], and the PRISMA statement for reporting of systematic reviews [3]. All methods were specified in advance and documented in a protocol.

Data source and searches

We searched the PubMed/Medline and SCOPUS databases from the earliest records to most recent May 2017. We browsed for additional data in the references of retrieved articles. The search strategy included the following terms:

(COPD OR “chronic lung disease” OR “chronic obstructive lung disease” OR “chronic bronchitis” OR emphysema)

AND

(“cycle decline” OR “vicious spiral” OR “downward spiral” OR “downward adjustment” OR “vicious cycle” OR “clinical path” OR “disease spiral” OR “circle decline” OR “vicious circle”)

AND

(dyspnea OR dyspnoea OR “shortness of breath” OR “breath shortness” OR “breath shortnesses” OR breathlessness OR breathlessnesses)

AND

(“physical activity” OR functioning OR function OR “motor activity” OR “locomotor activity” OR “chronic limitation of activity” OR “limitation of activity” OR “activity limitation” OR “sedentary lifestyle” OR “physical exertion” OR “physical effort” OR “activities of daily living” OR “daily living activities” OR “daily living activity”)

Study selection

Two of the co-authors (MAR and EGS) independently reviewed the title and abstract of every citation retrieved by the database searches. We ordered all articles that were deemed potentially eligible by at least one of them. The same two co-authors independently evaluated all retrieved full texts and made a decision on their inclusion or exclusion according to the following pre-defined selection criteria: (1) population: patients with COPD (no restriction in COPD definition); and (2) content: studies that discussed or explained the dyspnoea-inactivity vicious circle in a diagram. We did not include articles that: (1) reproduced vicious circle models previously published. Nor language restrictions neither restriction on the type of article were imposed. In case of disagreement a third co-author (JGA) decided upon with close attention to the inclusion/exclusion criteria.

Data extraction

The following information was extracted from included studies: (1) first author's name; (2) publication year; (3) aim of the article; (4) type of article; and (5) diagram depicting the conceptual model of interest and list of variables involved in the dyspnoea-inactivity vicious circle.

Data synthesis

For each study we rebuilt the vicious circle diagram in the form of a directed acyclic graph depicting the hypothesised longitudinal relationships (both direct and indirect) between involved variables. To account for the cyclic nature of relationships between variables involved in most vicious circle models, we considered most variables as time

varying and included several time points (e.g., dyspnoea at $t1 \rightarrow$ physical activity at $t2 \rightarrow$ dyspnoea at $t3$). A representative of each original paper (first or corresponding author) was contacted and all (except one, who did not respond several email requests) agreed with our adaptation of their diagram.

SAMPLE SIZE CALCULATIONS

The sample size was fixed by the primary scientific objectives of the PAC-COPD and ICE COLD ERIC studies. Before any analysis, we calculated whether the number of available patients (210 patients in the PAC-COPD and 226 in the ICE COLD ERIC cohort) would provide enough statistical power for the implementation of structural equations modelling (SEM) techniques. To our knowledge, there are no sample size calculation formulas for SEM. However, our sample was greater than the proposed 10 cases per variable's rule-of-thumb conventionally used to guide sample size selection in SEM [4]. Using the approach proposed by MacCallum RC, et al. [5] after conducting the analysis, our sample allowed a statistical power >99% to identify, with statistical significance level of 10%, a better fit of our model than previously published models.

Table S1. Comparison of baseline characteristics between participant and non-participants from the PAC-COPD study.

	Participants (n=210)	Non-participants (n=132)	p-value
Anthropometric and clinical data			
Males, n (%)	195 (92.9)	123 (93.2)	0.909
Age (years)	67.5 (8.2)	68.6 (9.1)	0.259
Active smokers, n (%)	74 (35.2)	46 (34.9)	0.945
YPAS, Kcal/week	6056 (3345-9085)	4980 (2310-8664)	0.095
SGRQ total score (0-100)	31.2 (22.2-44.1)	37.8 (25.3-53.4)	0.007
HADS-anxiety	4 (2-7)	5 (2-9)	0.390
HADS-depression	3 (1-5)	4 (2-7)	0.003
Charlson index of comorbidity	2 (1-2)	2 (1-3)	0.003
mMRC dyspnoea score	2 (2-3)	2 (2-3)	0.189
Respiratory frequency	20 (16-22)	20 (16-22)	0.628
Lung function			
Post-bronchodilator FEV ₁ (% predicted)	53.5 (16.6)	50.7 (15.5)	0.123
IC/TLC (%)	31.4 (0.9)	30.9 (0.9)	0.638
PaO ₂ (mmHg)	74.8 (11.3)	73.5 (9.4)	0.253
Exercise capacity and muscle force			
6MWD (meters)	445 (84)	415 (101)	0.077
V _{E max} (L/min)	42.2 (12.7)	44.9 (15.5)	0.192
Lactic acid (mM)	4.8 (2.2)	4.8 (1.9)	0.843
Handgrip muscle force (Kg)	31.4 (8.2)	29.0 (8.3)	0.013

Data are presented as n (%), mean (SD) or median (P₂₅-P₇₅). Definition of abbreviations: YPAS: Yale physical activity survey; SGRQ: Saint George's respiratory questionnaire; HADS: Hospital Anxiety and Depression Scale; mMRC: modified Medical Research Council dyspnoea scale; FEV₁: forced expiratory volume in 1 second; IC/TLC: inspiratory capacity/total lung Capacity; PaO₂: arterial oxygen partial pressure; 6MWD: six minute walk distance, V_{E max}: maximum ventilation during incremental cycloergometer test.

Table S2. Comparison of baseline characteristics between participant and non-participants from the ICE COLD ERIC study.

	Participants (n=226)	Non- participants (n=183)	p-value
Anthropometric and clinical data			
Males, n (%)	135 (60.0)	98 (53.6)	0.209
Age (years)	65.7 (9.5)	69.3 (10.2)	<0.001
Active smokers, n (%)	80 (35.4)	76 (41.5)	0.310
LAPAQ total score (0-23)	13 (9-15)	9 (5-13)	<0.001
CRQ (mean of four domains)	5.2 (4.4-6.0)	4.8 (3.8-5.6)	0.002
HADS-anxiety	4 (2-7)	4 (2-8)	0.428
HADS-depression	3 (2-6)	5 (2-8)	0.001
mMRC dyspnoea score	1 (1-3)	2 (1-4)	0.002
Lung function			
Post-bronchodilator FEV ₁ (% predicted)	56.6 (16.9)	54.1 (16.2)	0.135
IC (% predicted)	73.9 (20.8)	69.1 (19.4)	0.023
Exercise capacity and muscle force			
Sit to stand (num of repetitions)	19.9 (9.7)	14.3 (9.2)	<0.001
Handgrip muscle force (Kg)	31.7 (11.6)	27.2 (10.8)	<0.001

Data are presented as n (%), mean (SD) or median (P₂₅-P₇₅). Definition of abbreviations: YPAS: Yale physical activity survey; CRQ: Chronic Respiratory Questionnaire; HADS: Hospital Anxiety and Depression Scale; mMRC: modified Medical Research Council dyspnoea scale; FEV₁: forced expiratory volume in 1 second; IC: inspiratory capacity.

Table S3. Evolution of main characteristics of COPD patients in the PAC-COPD cohort during 3 years of follow-up.

	Visit 1 (baseline)	Visit 2 (9-12 months follow-up)	Visit 3 (18-24 months follow-up)	p-value (visit 1 vs. visit 3)
Anthropometric and clinical data				
Males, n (%)	195 (92.9)	-	-	
Age (years)	67.5 (8.2)	-	-	
Active smokers, n (%)	74 (35.2)	-	77 (36.7)	0.365
YPAS, Kcal/week	6056 (3345-9085)	5123 (2982-8280)	5010 (3368-7358)	0.006
SGRQ total score (0-100)	31.2 (22.2-44.1)	-	27.3 (16.0-44.7)	<0.001
HADS-anxiety	4 (2-7)	-	-	
HADS-depression	3 (1-5)	-	-	
Charlson index of comorbidity	2 (1-2)	-	2 (1-3)	<0.001
mMRC dyspnoea score	2 (2-3)	2 (2-3)	2 (3-4)	0.221
COPD exacerbations rate*	-	-	0.3 (0.7)	
Respiratory frequency	20 (16-22)	-	18 (16-20)	0.318
Lung function				
Post-bronchodilator FEV ₁ (% predicted)	53.5 (16.6)	-	50.8 (15.8)	<0.001
IC/TLC (%)	31.4 (0.9)	-	29.8 (0.9)	0.010
PaO ₂ (mmHg)	74.8 (11.3)	-	73.7 (10.0)	0.029
Exercise capacity and muscle force				
6MWD (meters)	445 (84)	-	412 (93)	<0.001
V _{E max} (L/min)	42.2 (12.7)	-	-	
Lactic acid (mM)	4.8 (2.2)	-	-	
Handgrip muscle force (Kg)	31.4 (8.2)	-	28.5 (9.1)	<0.001

Data are presented as n (%), mean (SD) or median (P₂₅-P₇₅). Definition of abbreviations: YPAS: Yale physical activity survey; SGRQ: Saint George's respiratory questionnaire; HADS: Hospital Anxiety and Depression Scale; mMRC: modified Medical Research Council dyspnoea scale; FEV₁: forced expiratory volume in 1 second; IC/TLC: inspiratory capacity/total lung Capacity; PaO₂: arterial oxygen partial pressure; 6MWD: six minute walk distance, V_{E max}: maximum ventilation during incremental cycleergometer test.

*COPD exacerbations requiring hospitalization between visit 1 and 3

Table S4. Evolution of main characteristics of COPD patients in the ICE COLD ERIC cohort during 4 years of follow-up.

	Visit 1 (baseline)	Visit 2 (2 years follow-up)	Visit 3 (4 years follow-up)	p-value (visit 1 vs. visit 3)
Anthropometric and clinical data				
Males, n (%)	135 (60.0)	-	-	
Age (years)	65.7 (9.5)	-	-	
Active smokers, n (%)	80 (35.4)	80 (35.4)	66 (29.2)	0.006
LAPAQ total score (0-23)	13 (9-15)	11 (9-15)	11 (7-15)	<0.001
CRQ (mean of four domains)	5.2 (4.4-6.0)	5.2 (4.3-5.9)	5.1 (4.1-5.9)	0.071
HADS-anxiety	4 (2-7)	4 (1-7)	4 (1-8)	0.876
HADS-depression	3 (2-6)	4 (2-7)	4 (2-7)	<0.001
mMRC dyspnoea score	1 (1-3)	1 (1-2)	2 (1-3)	0.007
COPD exacerbations *	-	-	1(0-3)	
Respiratory frequency	-	-	-	
C-reactive protein (mg/dl)	2.7 (1.2-6)	-	-	
Lung function				
Post-bronchodilator FEV ₁ (% pred)	56.6 (16.9)	57.9 (18.9)	55.8 (19.3)	0.030
IC (% pred)	73.9 (20.8)	71.1 (21.8)	69.9 (25.0)	0.001
Exercise capacity and muscle force				
Sit to stand (num of repetitions)	19.9 (9.7)	20.7 (8.9)	18.9 (10.3)	0.012
Handgrip muscle force (Kg)	31.7 (11.6)	29.9 (10.9)	27.9 (10.0)	<0.001

Data are presented as n (%), mean (SD) or median (P₂₅-P₇₅). Definition of abbreviations: LAPAQ: Longitudinal Aging Study Amsterdam Physical Activity Questionnaire; CRQ: Chronic Respiratory Questionnaire; HADS: Hospital Anxiety and Depression Scale; mMRC: modified Medical Research Council dyspnoea scale; FEV₁: forced expiratory volume in 1 second; IC: inspiratory capacity

*COPD exacerbations between visit 1 and 3

Figure S1. Flow diagram of study selection during the systematic review process.

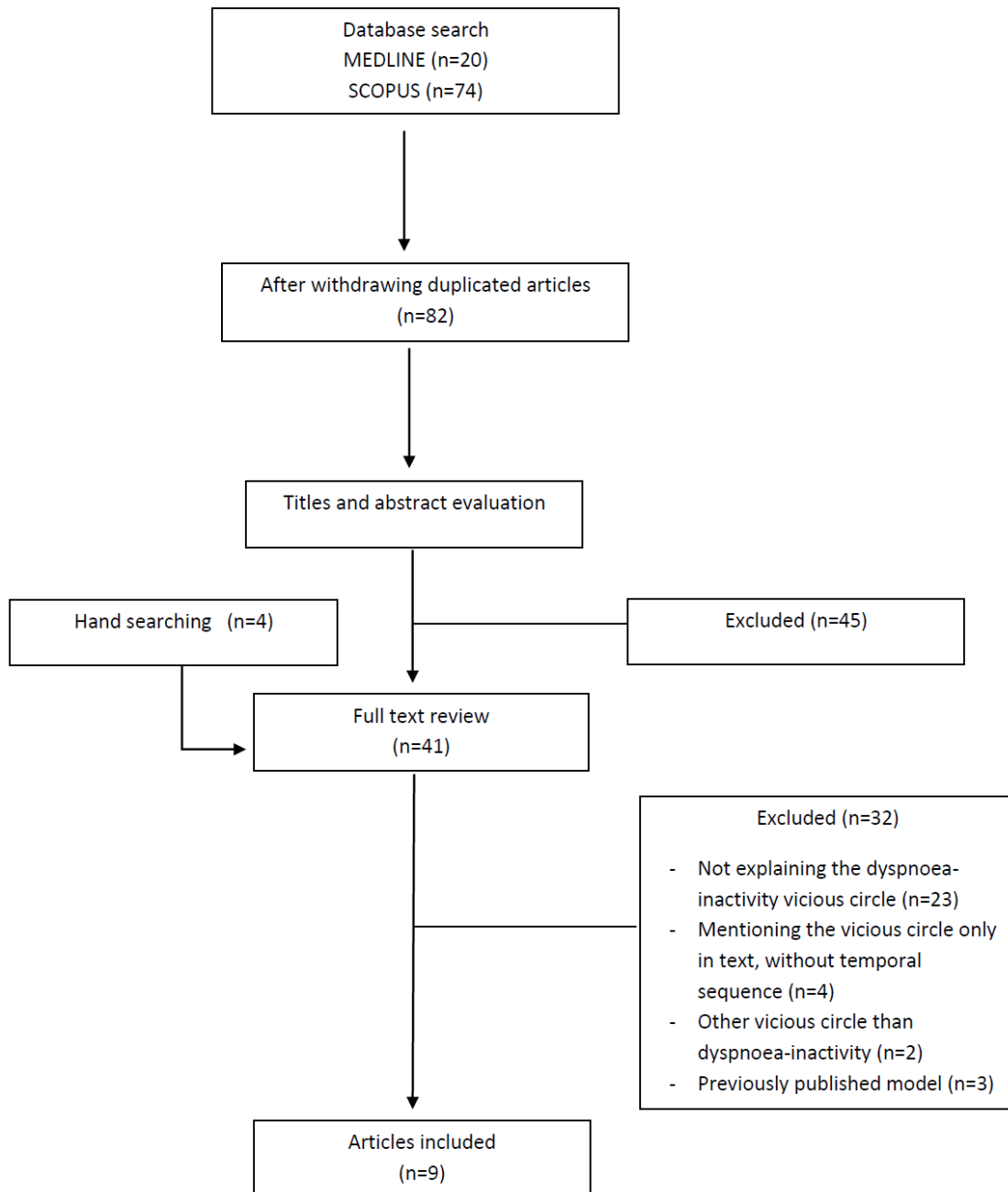


Figure S2. Comprehensive new vicious circle model, including all variables and paths involved in at least one of the previously identified vicious circles.

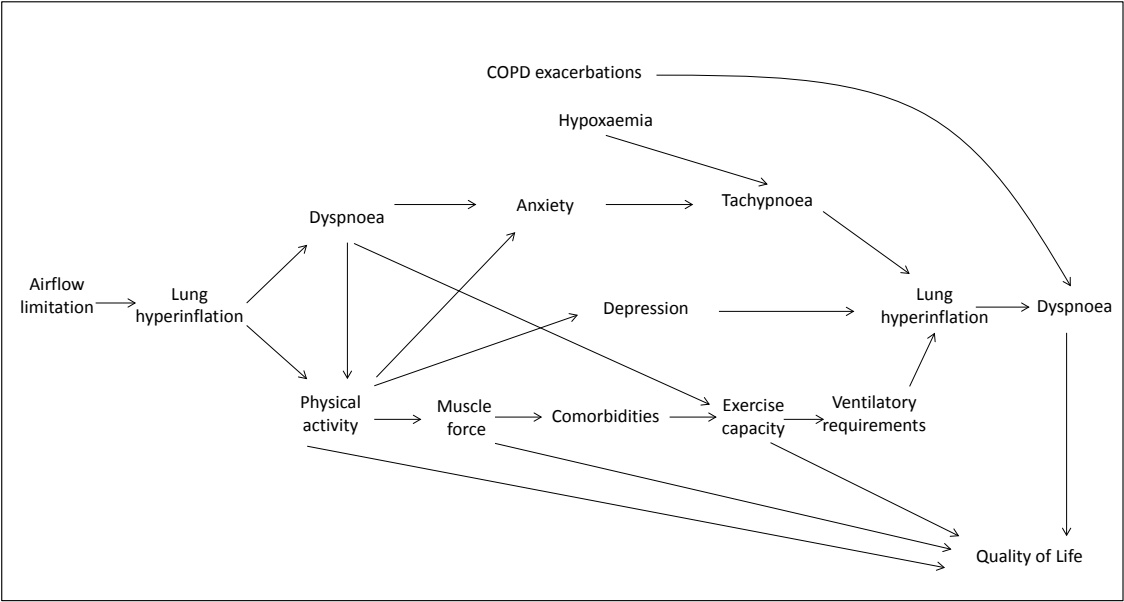
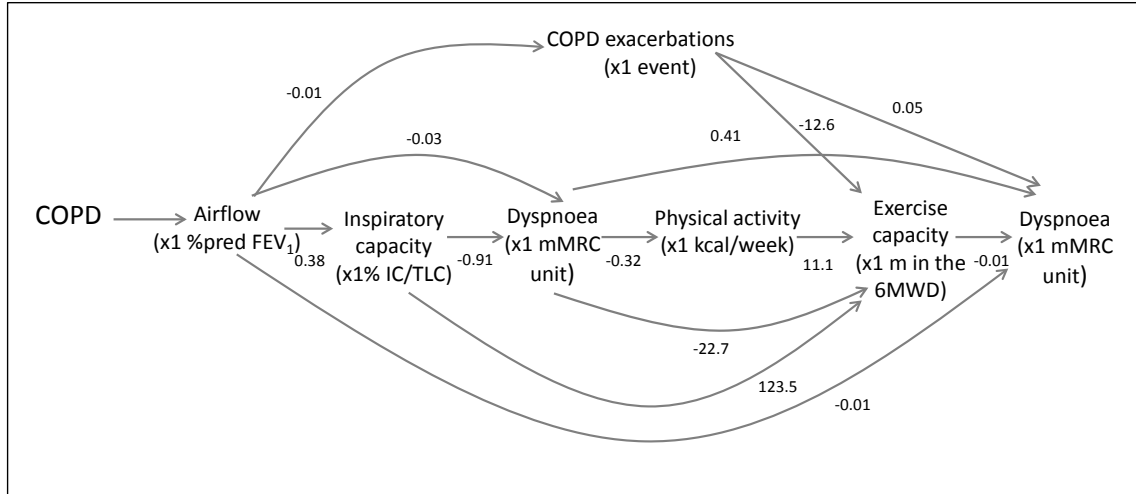
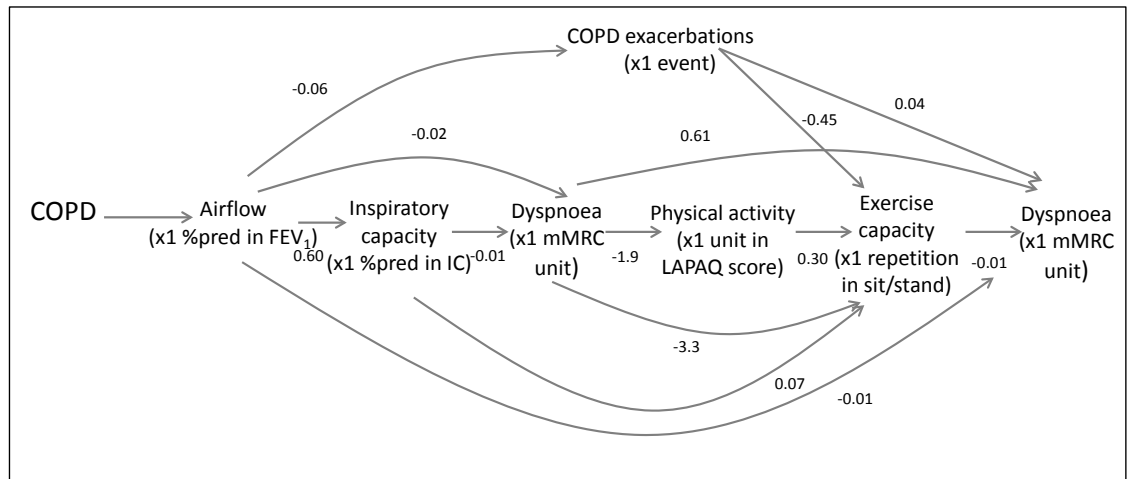


Figure S3. New vicious circle model with non-standardised coefficients using (a) PAC-COPD and (b) ICE COLD ERIC data.

(a)



(b)



Definition of abbreviations: FEV₁: forced expiratory volume in 1s; IC: inspiratory capacity; TLC: total lung capacity; mMRC: modified Medical Research Council dyspnoea scale; 6MWD: six minute walk distance; LAPAQ: LASA Physical Activity Questionnaire; RMSEA: root mean square error of approximation; CFI: comparative fit index.

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