

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

SUPPLEMENTARY MATERIAL

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- **Sample size calculations**
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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.

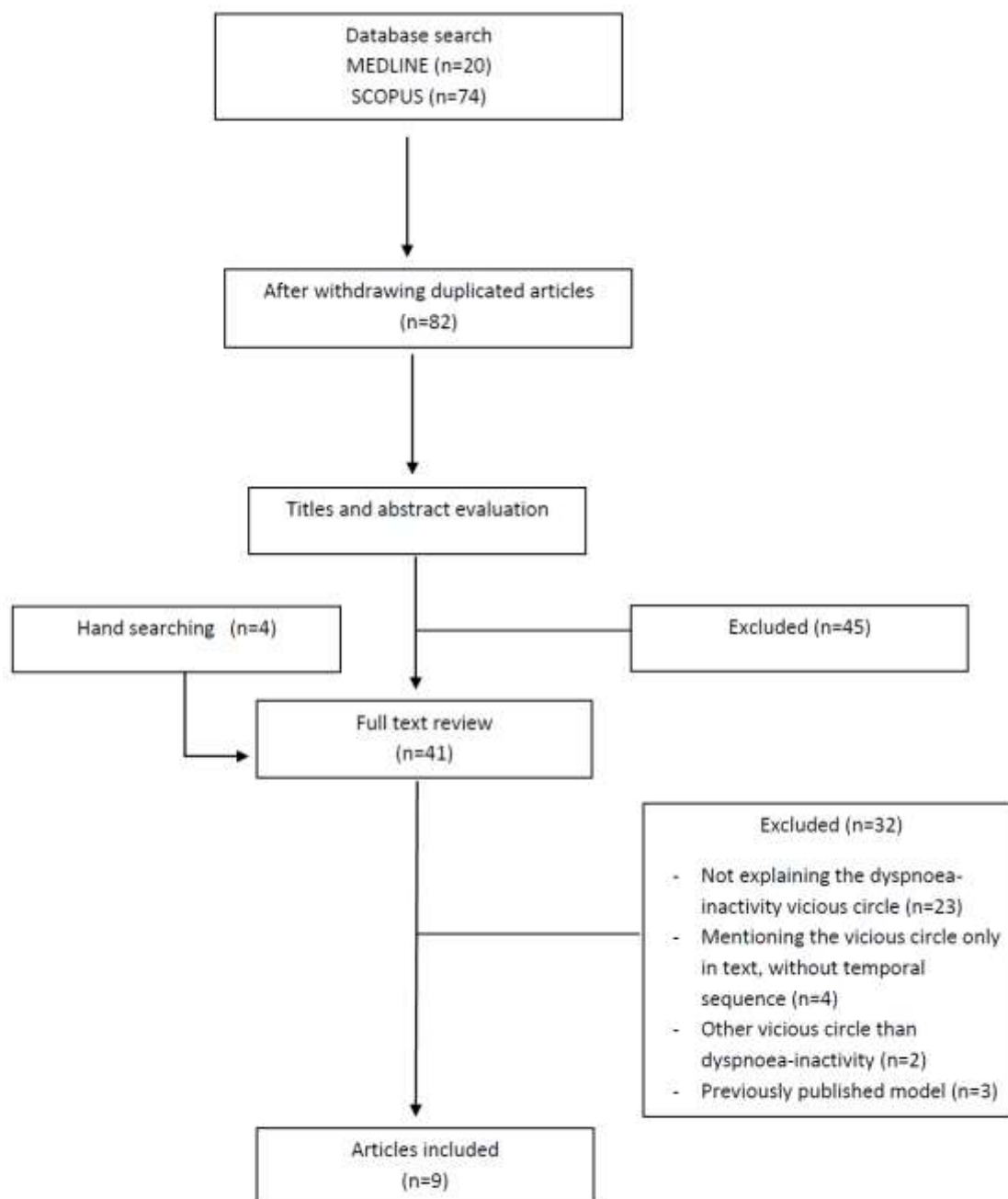


Figure S2. Comprehensive new vicious circle model, including all variables and paths involved in at least one of the previously identified vicious circles.

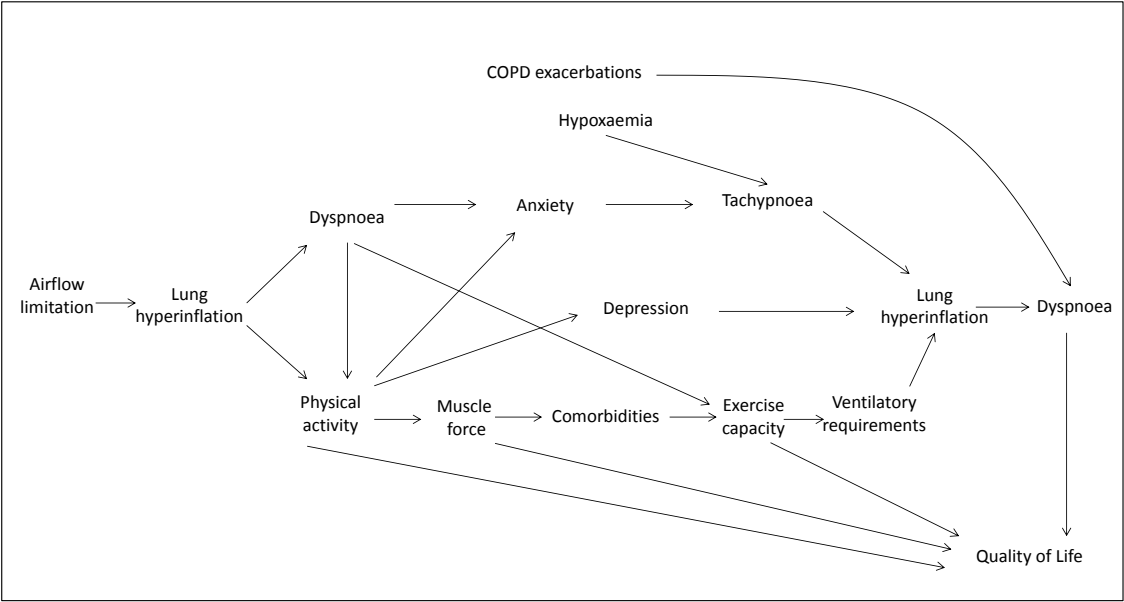
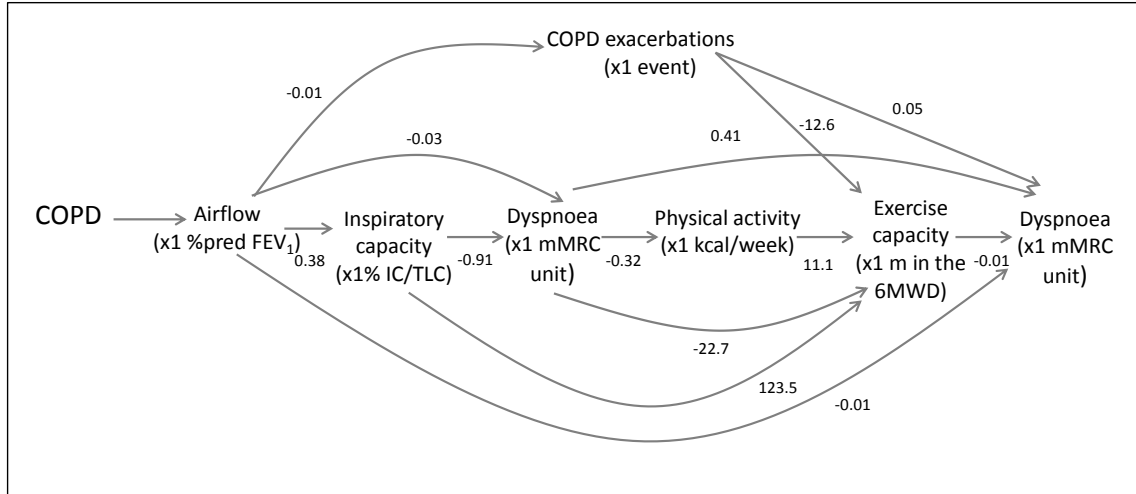
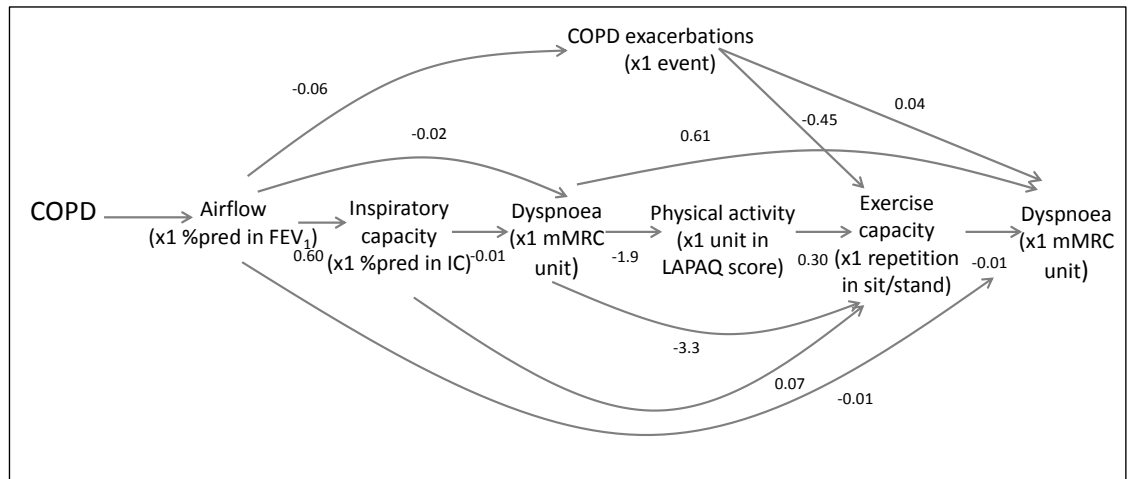


Figure S3. New vicious circle model with non-standardised coefficients using (a) PAC-COPD and (b) ICE COLD ERIC data.

(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.

SUPPLEMENTARY REFERENCES

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