

## **SUPPLEMENTARY MATERIAL**

**Title: Endothelial dysfunction in chronic obstructive pulmonary disease: a systematic review and meta-analysis of studies using different functional assessment methods**

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**Supplementary Table 1.** Quality assessment of the present meta-analysis according to MOOSE checklist for observational studies (From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. JAMA. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.)

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	4-5
2	Hypothesis statement	5-6
3	Description of study outcome(s)	7-8
4	Type of exposure or intervention used	6-8
5	Type of study designs used	6-8
6	Study population	6-8
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	7
8	Search strategy, including time period included in the synthesis and key words	6-7
9	Effort to include all available studies, including contact with authors	7
10	Databases and registries searched	6-7
11	Search software used, name and version, including special features used (eg, explosion)	7-8
12	Use of hand searching (eg, reference lists of obtained articles)	6-7
13	List of citations located and those excluded, including justification	9, Supplementary Figure 1
14	Method of addressing articles published in languages other than English	6
15	Method of handling abstracts and unpublished studies	n/a
16	Description of any contact with authors	7, 10
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	7-9

18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	6-7
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	7
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	8-9
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	8-9
22	Assessment of heterogeneity	8-9
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	8-9
24	Provision of appropriate tables and graphics	Figures 1-4, Supplementary Material
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	9-12, Figures 1-3
26	Table giving descriptive information for each study included	Table 1, Supplementary Figure 4
27	Results of sensitivity testing (eg, subgroup analysis)	11-12, Figure 4, Supplementary Figures 3-5
28	Indication of statistical uncertainty of findings	n/a
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	9, Supplementary Figure 2
30	Justification for exclusion (eg, exclusion of non-English language citations)	Supplementary Figure 1
31	Assessment of quality of included studies	7, 9, Supplementary Table 3
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	14-16
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature)	14-16

	review)	
34	Guidelines for future research	16
35	Disclosure of funding source	1

**Supplementary Table 2.** Search term used for this systematic review and meta-analysis

**Pubmed** (<https://www.ncbi.nlm.nih.gov/pubmed/>)

[All Fields]

#1 COPD AND endothelial dysfunction

#2 COPD AND endothelial function

#3 COPD AND VOP

#4 COPD AND venous occlusion plethysmography

#5 COPD AND FMD

#6 COPD AND Flow mediated dilation

#7 COPD AND LDF

#8 COPD AND Laser Doppler flowmetry

#9 COPD AND glycocalyx

#10 COPD AND LSCI

#11 COPD AND Laser speckle contrast imaging

#12 COPD AND LASCA

#13 COPD AND laser speckle contrast analysis

#14 COPD AND nailfold capillaroscopy

#15 COPD AND NIRS

#16 COPD AND near-infrared spectroscopy

#17 COPD AND PAT

#18 COPD AND peripheral arterial tonometry

#19 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR  
#13 OR #14 OR #15 OR #16 OR #17 OR #18

**Scopus** (<https://www.scopus.com/home.uri>)

((COPD AND “endothelial dysfunction”) OR (COPD AND “endothelial function”) OR (COPD AND VOP) OR (COPD AND FMD) OR (COPD AND glycocalix) OR (COPD AND LASCA) OR (COPD AND RIS) OR (COPD AND PAT))

**Supplementary Table 3.** Quality evaluation of the included studies according to Newcastle-Ottawa Scale (NOS).

<b>Study</b>	<b>Selection</b>	<b>Comparability</b>	<b>Exposure</b>	<b>NOS score</b>
Barak et al., 2017	****	**	**	8
Blum et al., 2014	***	*	**	6
Costanzo et al., 2016	**	**	**	6
Eickhoff et al., 2007	****	**	***	9
Gelinas et al., 2017	****	**	***	9
Hartmann et al., 2016	****	**	**	8
Iveset et al., 2020	****	**	***	9
Keymel et al., 2016	**	**	**	6
Maclay et al., 2009	****	**	**	8
Majewski et al., 2020	****	**	**	8
Malerba et al., 2018	****	**	***	9
Marchetti et al., 2011	**	**	***	7
Moro et al., 2008	****	**	***	9
Özbenet et al., 2010	****	**	*	7
Piccari et al., 2020	***	**	***	8
Pizarro et al., 2014	****	**	***	9
Rodriguez-Miguel et al., 2018	****	**	***	9
Yang et al., 2017	****	**	**	8
Zelt et al., 2018	****	**	**	8

**Supplementary Table 4.** Study characteristics regarding presence of coronary artery disease (CAD) and cardiovascular disease (CVD) and use of common vasoactive medications.

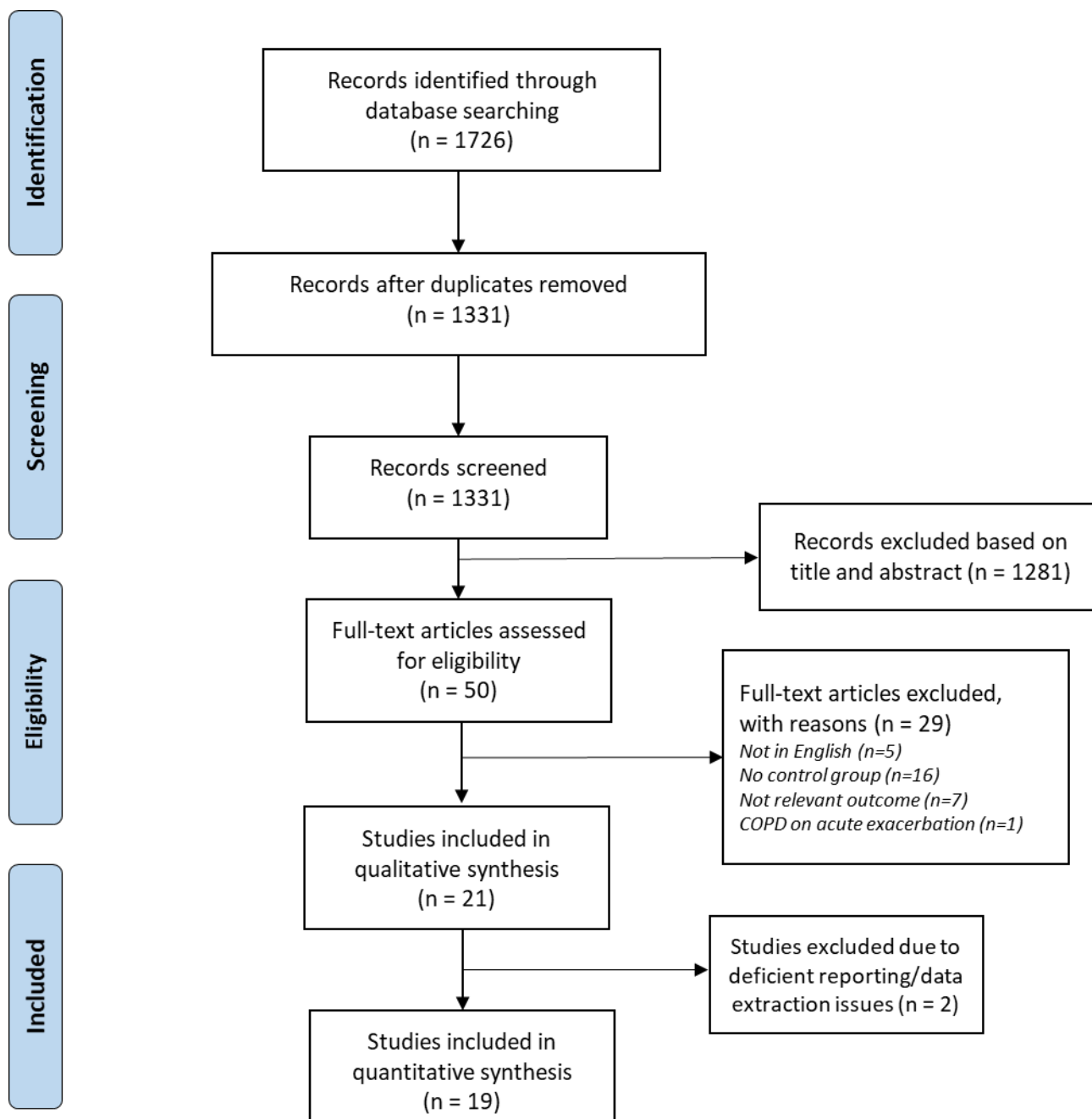
Study	CVD/CAD definition	Inclusion/exclusion criteria	Patients with CVD	b-blocker	RAAS inhibitors	CCBs	Nitrate
Barak et al., 2017	No clear definition	-	CAD: COPD 5.9%, Controls 0% PAD: COPD 11.8%, Controls 0%, no information about stroke	COPD 23.5%, Controls 10%	COPD 47.1%, Controls 10%	COPD 17.6%, Controls 0%	n/a
Blum et al., 2014	No clear definition	-	CAD: COPD: 26%, Controls 0%, no information about PAD, stroke	n/a	n/a	n/a	n/a
Costanzo et al., 2016	CVD defined as: history of ischemic heart disease, heart failure, severe valvular heart disease, cardiomyopathy, arrhythmias	CVD was an exclusion criterion	CAD: 0%, no information about PAD or stroke	COPD 15% Controls 11%	COPD 54% Controls 60%	n/a	n/a
Eickhoff et al., 2008	CVD defined as: cerebrovascular disease, chest pain on exertion, congestive heart failure, coronary heart disease, peripheral artery occlusive disease, acute pulmonary embolism or revascularization within the past 24 months	CVD was an exclusion criterion	0%	n/a	0%	n/a	n/a
Gelinas et al., 2017	CVD defined as: myocardial infarction, stroke, heart failure	CVD was an exclusion criterion	0%	n/a	COPD 54.2%, Controls 6.0%,	n/a	n/a
Hartmann et al., 2016	CVD defined as: cerebrovascular disease, myocardial infarction, angina, arrhythmia, valvular heart disease, chronic heart failure, peripheral arterial disease	CVD was an exclusion criterion	0%	n/a	n/a	n/a	n/a
Ives et al., 2020	CAD from patients' history	-	CAD: COPD: 6.7% Controls 3.3%, no information about PAD, stroke	COPD: 6.7% Controls 13.3%	COPD: 40.0% Controls 10.0%	COPD: 30.0% Controls 6.7%	n/a
Keymel et al., 2016	CAD was diagnosed by coronary angiography	CAD was an inclusion criterion	100%	n/a	n/a	n/a	n/a
Maclay et al., 2009	CVD defined as: cardiovascular, cerebrovascular, and peripheral vascular disease	CVD was an exclusion criterion	0%	0%	0%	n/a	n/a
Majewski et al., 2020	No clear definition	-	CAD: COPD: 7.7% Controls 0%, no information	n/a	n/a	n/a	n/a

			about PAD, stroke				
Malerba et al., 2018	CVD defined as history of any cardiovascular disease (except hypertension)	CVD was an exclusion criterion	0%	COPD: 25.0% Controls: 37.5%	COPD: 50.0% Controls: 62.5%	COPD: 13.3% Controls: 37.5%	n/a
Marchetti et al., 2011	No clear definition. (PAD, CAD, stroke reported as distinct conditions)	PAD was an exclusion criterion	0%	0%	COPD: 25% Controls 0%	COPD: 12.5% Controls 0%	n/a
Moro et al., 2008	No clear definition	-	CAD: COPD: 22.9%, Controls: 15.9% PAD: COPD 10.4% Controls 22.7% Cerebrovascular: COPD 20.8% Controls 36.4%	COPD: 22.9%, Controls: 11.4%	COPD: 75.0%, Controls: 58.1%	COPD: 16.7%, Controls: 15.9%	COPD: 10.4%, Controls: 18.2%
Özben et al., 2010	No clear definition	-	No information about stroke/PAD	n/a	n/a	n/a	n/a
Piccari et al., 2020	n/a	-	n/a	n/a	n/a	n/a	n/a
Pizarro et al., 2014	CVD was defined as: established cardiovascular or cerebral-vascular disease	CVD was an exclusion criterion	0%	n/a	n/a	0%	0%
Rodriguez-Miguel et al., 2018	No clear definition (CVD only referred as not clinical diagnosis of overt CVD)	CVD was an exclusion criterion	0%	n/a	COPD 5.8%, Controls 6.7%	COPD 23.5%, Controls 0%	0%
Yang et al., 2017	n/a	-	n/a	n/a	n/a	n/a	n/a
Zelt et al., 2018	No clear definition	-	CAD: COPD: 12.5% Controls 6.3%, no information about PAD, stroke	n/a	n/a	n/a	n/a

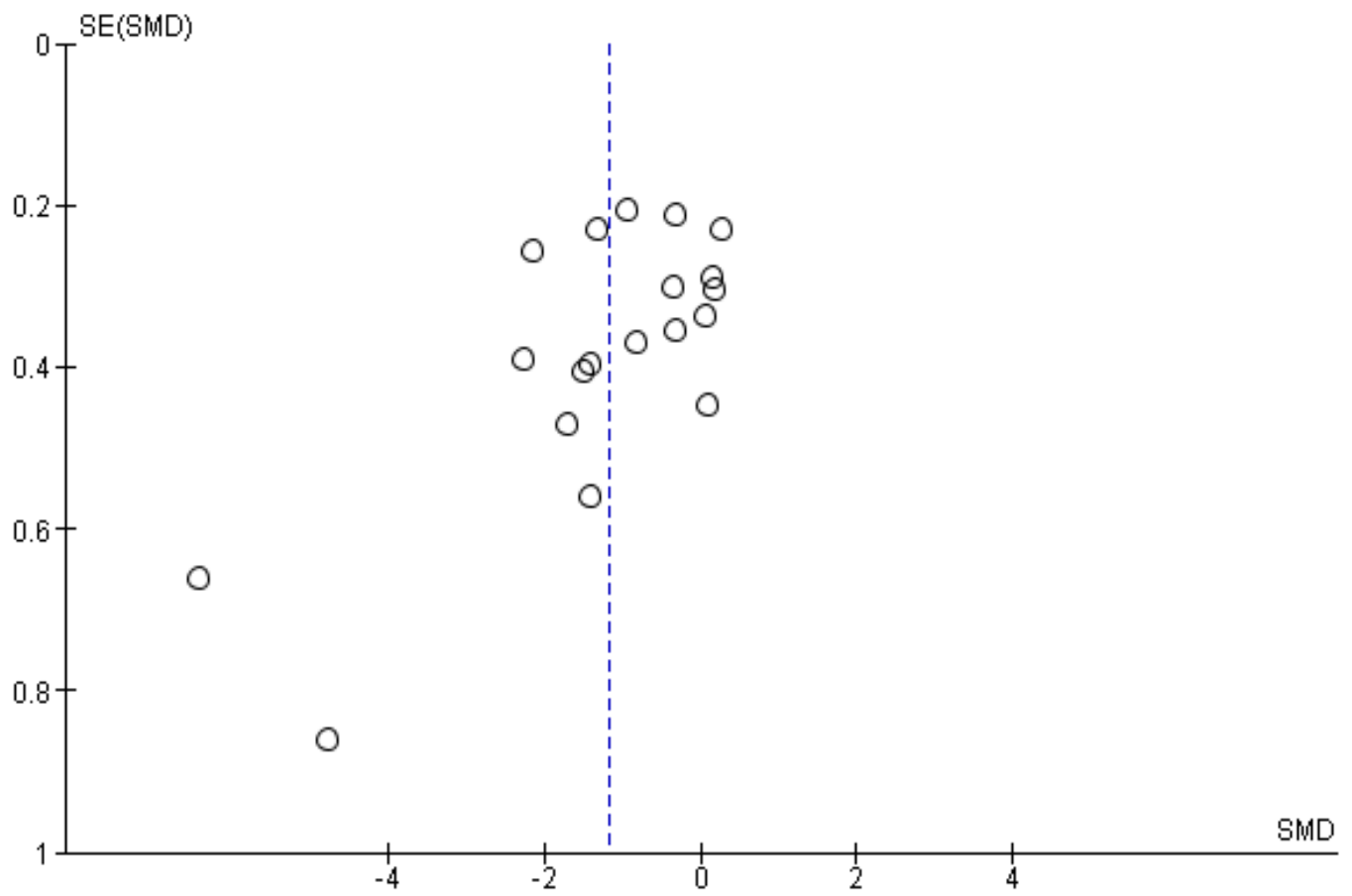
Abbreviations: CAD, coronary artery disease, CCB, calcium channel blocker; COPD ,chronic obstructive pulmonary disease; CVD, cardiovascular disease; n/a, not applied; PAD, peripheral arterial disease; RAAS, renin-angiotensin aldosterone system



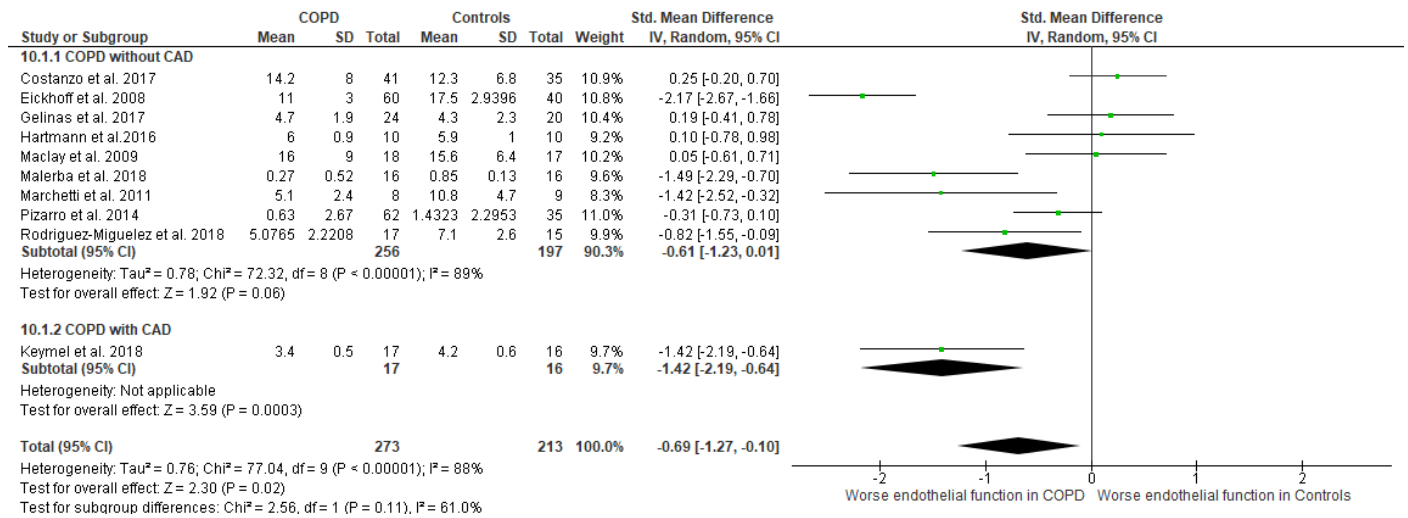
**Supplementary Figure 1.** Flow diagram of study selection process



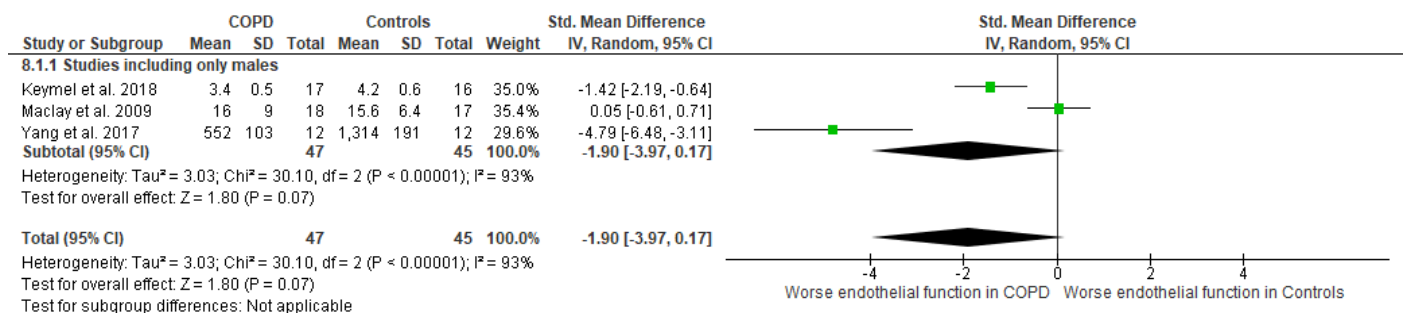
**Supplementary Figure 2.** Funnel plot assessing publication bias for the total of the studies.



**Supplementary Figure 3.** Subgroup analysis comparing endothelial function between patients with COPD and with/without coronary artery disease (CAD) and controls



**Supplementary Figure 4.** Forest plot of the difference in endothelial function among male patients with COPD and non-COPD controls.



**Supplementary Figure 5.** Sensitivity analysis (included studies with NOS score ≥7): Forest plot of the difference in endothelial function among patients with COPD and non-COPD controls

