Supplementary material

Inclusion and exclusion criteria for the review

The inclusion criteria for this review included English language articles containing any models predicting COPD in adults in the general population or in populations at high risk of development of COPD (smokers, asthmatics).

Studies with COPD risk prediction tools were included in this review if they met all of the following inclusion criteria:

1) the study's main aim was to develop a prediction tool for development of COPD in adults without prior diagnosis of COPD;

2) the prediction model was developed in adults in the general population, healthcare population or high risk populations (smokers, asthmatics);

3) the outcome of the prediction model was diagnosed COPD by: i) spirometry, ii) self-reported COPD, or related condition such as chronic bronchitis, emphysema, or chronic airways obstruction, not otherwise specified, or iii) COPD coded by an administrative coding system; (See Supplementary Table E7 for specific definitions)

4) development of a model based on: an *a-priori* set of predictors or predictors that were selected by statistical modelling or; updating an existing model; and

5) the study reported a formal prediction model or regression equation that has the ability to predict risk of COPD in other individuals.

We excluded studies that:

1) had a main objective to develop a predictive model for prognosis of COPD (i.e. models to predict exacerbations, hospital admissions or mortality in previously diagnosed COPD patients);

2) predicted undiagnosed COPD in a cross-sectional population;

3) used only one biomarker or one predictor in developing the model.

4) were reviews, letters, conference abstracts or expert opinion.

We assessed risk of bias and of applicability to our specific research question based on the CHARMS checklist for critical appraisal of prediction modelling studies.[15] For the risk of bias assessment, we utilised a similar approach to that used by Smit et al 2015[16] and developed similar assessment criteria for applicability concerns. Risk of bias was assessed in relation to five domains: participant selection, predictor assessment, outcome assessment, attrition and analysis. Applicability was assessed in relation to six domains: participant selection, predictor assessment, outcome assessment, analysis, results and interpretation (e-Table 3 and 4). The risk of bias or applicability was rated as high, medium or low based on criteria for each domain. If the study achieved all criteria in a specific domain, it was rated as low risk of bias or applicability concerns. If at least one of the criteria for low risk was not achieved, the study was rated as medium risk of bias or applicability concerns. If multiple criteria were not achieved or the criteria were missing or not reported, the study was rated as high risk of bias (e -Tables 3 and 4).

Table S1 Search terms used in PubMed for this review

Type of search terms	**Search terms**
Search terms related to outcomes of interest	COPD[Title] OR COAD[Title] OR "chronic obstructive airway disease"[Title] OR "chronic obstructive pulmonary disease"[Title] OR

	COPD[MeSH Terms]
Search terms related to prediction models	“risk prediction model$” OR “risk prediction” OR “predictive model$” OR “predictive equation$” OR “prediction model$” OR “risk calculator$” OR “prediction rule$” OR “risk model$” OR “Risk assessment model$” OR “Assessment tool$” OR “Prediction score$” OR “Risk Score$” OR roc curve OR c-statistic OR c statistic OR area under the curve OR

	AUC OR “Prognostic model*” OR “Prediction tool$” OR “Predictive tool$” OR “Predictive accuracy$” OR “Prognostic tool$” OR “prognostic factors” OR “predictive value$” OR “early prediction$” OR “prognostic indicator$” OR “risk prediction tool$” OR “Receiver Operating Characteristic$” “net reclassification improvement”

Table S2 Search terms used in EMBASE for this review

Number	Search term
1	COPD.m_titl.
2	COAD.m_titl.
3	chronic obstructive airway disease.m_titl.
4	chronic obstructive pulmonary disease.m_titl.
5	chronic obstructive lung disease/
6	1 or 2 or 3 or 4 or 5
7	risk prediction model$.mp.
8	risk prediction.mp.
9	predictive model$.mp.
10	predictive equation$.mp.
11	prediction model$.mp.
12	risk calculator$.mp.
13	prediction rule$.mp.
14	risk model$.mp.

15	Risk assessment model$.mp.
16	Assessment tool$.mp.
17	Prediction score$.mp.
18	Risk Score$.mp.
19	roc curve.mp.
20	c-statistic.mp.
21	c statistic.mp.
22	area under the curve.mp.
23	AUC.mp.
24	Prognostic model*.mp.
25	Prediction tool$.mp.
26	Predictive tool$.mp.
27	Predictive accuracy$.mp.
28	Prognostic tool$.mp.
29	prognostic factors.mp.
30	predictive value$.mp.

31	early prediction$.mp.
32	prognostic indicator$.mp.
33	risk prediction tool$.mp.
34	Receiver Operating Characteristic$.mp.
35	net reclassification improvement.mp.

Table S3 Criteria for scoring of risk of bias based on the CHARMS checklist

Potential bias	**Items to be considered for potential bias**	**Guo et al., 2015[21]**	**Kotz et al., 2014[22]**	**Himes et al., 2009[23]**	**Higgins et al., 1982[24]**
Participant selection					
	Low risk of bias if:		✓	✓	✓
	- selection bias was unlikely	×	✓	✓	✓
	- study avoided inappropriate inclusions or exclusions	✓	✓	✓	✓
	- in- and exclusion criteria were adequately described	✓	✓	✓	✓
	- participants were enrolled at a similar presentation of their disease	✓	✓	✓	✓
	Moderate risk of bias if:				
	- not satisfying one of the above or	✓			
	- no adequate description of recruitment of study sample				
	- no adequate description of the sample for key predictors				
	High risk of bias if : - both items were not adequately described				

Predictor assessment					
	Low risk of bias if:		✓		✓
	- predictor definitions were the same for all participants,	✓	✓	✓	✓
	- predictor measurement was blinded to outcome data	✓	✓	✓	✓
	- all predictors were available at the time the model is intended to be used	✓	✓	✓	✓
	- predictors were measured with valid and reproducible methods such that misclassification was limited	×	✓	✓	
	- sufficient sample size to number of predictor	✓	✓	×	✓
	- predictors were assessed in a similar way for all study participants	✓	✓	✓	✓
	Moderate risk of bias if one of the criteria was not satisfied	✓		✓	
	High risk of bias if predictor assessment was not adequately described				
Outcome assessment					
	Low risk of bias if:		✓	✓	✓
	- outcome was pre-specified	✓	✓	✓	✓

	- measured with sufficient validity and reproducibility	✓	✓	✓	✓
	- measured in a similar way for all study participants	✓	✓	✓	✓
	- if the outcome was assessed independent from assessment of predictors.	✗	✓	✓	✓
	Moderate risk of bias if : - method for assessment of outcome was not adequately described	✓			
	High risk of bias if method for assessment of outcome was not adequately described				
Attrition					
	Low risk of bias if				
	there was no loss-to-follow-up				
	there were no important differences on key characteristics between included participants and those who were lost-to-follow-up or missing				
	Moderate risk of bias if				
	1. - loss-to-follow-up was lower than 20% and there were no important differences on key characteristics between included participants and those who were lost-to-follow-up or missing OR:				
	2. - loss-to-follow-up was higher than 20% but missing data and loss-to-follow-up were imputed				

	adequately or there were no important differences on key characteristics between included participants and those who were lost-to-follow- up or missing				
	High risk of bias if	✓	✓	✓	✓
	loss-to-follow-up was higher than 20% and/or	-	-	-	✓
	there were important differences on key characteristics between included participants and those who were lost-to-follow-up or missing	-	-	-	✓
	loss-to-follow-up was not described	×	×	×	×
Analysis^					
	Low risk of bias if - relevant aspects of analysis were described allowing to judge the quality of the analysis to be adequate				
	- # outcome events per candidate predictor reasonable	×	✓	×	✓
	- missing data handled appropriately or no differences	×	✓	×	×
	- predictors included independent of p-value	✓	✓	✓	✓
	- over-fitting and optimism accounted for	×	×	×	×
	- weights assigned according to regression coefficient	✓	✓	✓	✓

	- calibration and discrimination assessed	×	✓	×	×
	- recalibrated or described that it was not needed	×	✓	×	×
	Moderate risk of bias if:				
	-relevant aspects of analysis were described allowing to judge the quality of the analysis to be adequate and part or none of the model evaluation items were reported	✓	✓	✓	✓
	High risk of bias if : - not satisfying any of the aspects under low risk of bias				

Table S4 Criteria for scoring of Applicability or Generalisability to answer the specific research question posed by this review based on the CHARMS checklist

Applicability concerns	**Items to be considered for applicability concerns**	Guo et al., 2015[21]	Kotz et al., 2014[22]	Himes et al., 2009[23]	Higgins et al., 1982[24]
Participant selection	**Low risk of applicability concerns** if:		✓		
	- selection bias was unlikely	×	✓		
	- in- and ex-clusion criteria were adequately described and appropriate	×	✓	✓	✓
	- participant description adequate and population appropriate for RQ	×	✓	×	✓
	- study dates provided and relevant	✓	✓	✓	×
	Moderate risk of applicability concerns if:	✓		✓	✓
	- not satisfying one of the above or				
	- no adequate description of recruitment of study sample				
	- no adequate description of the key predictors				
	High risk of applicability concerns if: - no adequate description of study sample				
Outcome	**Low risk of applicability concerns** if:	✓	✓	✓	×

	- outcome definition appropriate and measured with sufficient validity and reproducibility appropriate for the RQ				
	- measured in a similar way for all study participants				✓
	- if the outcome was assessed independent from assessment of predictors.				✓
	Moderate risk of applicability concerns if: - one of the criteria was not satisfied				✓
	High risk of applicability concerns if: - not satisfying any of the aspects under low risk of bias				
Predictor	**Low risk of applicability concerns** if: - predictor definition appropriate and measured with sufficient validity and reproducibility	✗	✓	✓	✓
	- measured in a similar way for all study participants	✓	✓	✓	✓
	- measured at an appropriate time (e.g., at patient presentation, at diagnosis, at treatment initiation)	✓	✓	✓	✓
	Moderate risk of applicability concerns if: - one of the criteria was not satisfied	✓			
	High risk of applicability concerns if:				

	- not satisfying any of the aspects under low risk of bias				
Analysis	**Low risk of applicability concerns** if: - shrinkage of predictor weights or regression to improve applicability and avoid over-fitting and optimism	×	×	×	×
	- calibration and discrimination assessed	×	✓	×	×
	- recalibrated or described that it was not needed	×	×	×	×
	Moderate risk of applicability concerns if: -relevant aspects of analysis were described allowing the quality of the analysis to be judged as adequate and part or none of the model evaluation items were reported		✓		
	High risk of applicability concerns if: - not satisfying any of the aspects under low risk of bias	✓		✓	✓
Results	**Low risk of applicability concerns** if: -Final and other multivariable models (e.g., basic, extended, simplified) presented, including predictor weights or regression coefficients, intercept, baseline survival, model performance measures (with standard errors or confidence intervals)	✓	✓		✓

	- Any alternative presentation of the final prediction models, e.g., sum score, nomogram, score chart, predictions for specific risk subgroups with performance	✓	✓	✗	✓
	Moderate risk of applicability concerns if: - one of the criteria was not satisfied			✓	
	High risk of applicability concerns if: - not satisfying any of the aspects under low risk of bias				
Interpretation and Discussion	**Low risk of applicability concerns** if:		✓		
	-Interpretation of presented models (confirmatory, i.e., model useful for practice versus exploratory, i.e., more research needed)	✗	✓	✓	✓
	-Comparison with other studies, discussion of generalizability, strengths and limitations.	✓	✓	✗	✗
	Moderate risk of applicability concerns if: - one of the criteria was not satisfied	✓		✓	✓
	High risk of applicability concerns if: - not satisfying any of the aspects under low risk of bias				

Table S5 Definitions of predictors included in the presented final prediction models

Ref	Age	Sex	Smoking	Asthma		Race		SES	Other
Guo et al., 2015[21]	_	Male and female	Smoking history (presence of smoking history = 1, no smoking history = 0)	_		_		_	Respiratory infection in early life; low birth weight (<2,500 g) and six genetic variables (rs2070600, rs10947233, rs10947233, rs1800629, rs2241712 and rs1205)
Kotz et al., 2014[22]	Categorised into 35–39, 40–44, 45–49, 50–54, 55–59,	Developed two models for males and females	Ever-smokers (patients recorded as 'smoker' or 'ex-smoker' at any time) and never-smokers (patients recorded as 'non-smoker' at any time and no coding	Asthma diagnosis (Identified as a risk factor if recorded prior to the patient's		_		Measured using the Carstairs Index of Deprivation (coded 1 = least deprived	_

	60–64 and 65+ years	separately	as ‘smoker’ or ‘ex-smoker’ at any other time in electronic medical database).	entry date into the cohort)				to 5 = most deprived)	
Himes et al., 2009[23]	Categorised into 18–44, 45–64, 65–74, and 75+ years	Male and female	Smoking history (“Negative” if the smoking status was determined to be “never smoker” or“Positive” otherwise)	_		“White,” “Black,” “Hispanic,” and “Asian.”		_	Eight comorbidities: Acute upper respiratory infections; acute bronchitis and bronchiolitits; pneumonia, organism unspecified; shortness of breath; heart failure; respiratory distress or insufficiency; and diabetes mellitus

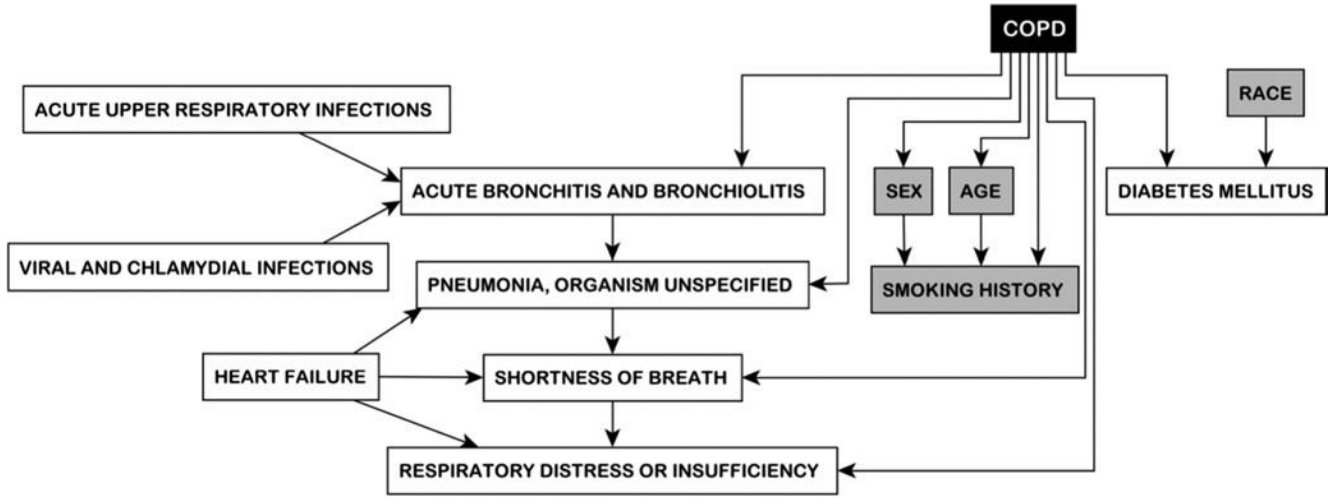
Higgins et al., 1982[24] ^	Age in years 20, 25, 30, 35, 40, 45, 50, 55, 60, 65	Developed two models for males and females separately	Cigarettes/Day 0, 4, 9, 13, 18, 22, 27, 31, 35 Change in Cigarettes/Day -37, -28, -19, -9, 0, 9, 19, 28, 37	_		_		_	%FEV1 (only in females) and %Vmax50

^Definitions given for the predictors included in best predictive models for males and females

Table S6 Prediction models presentation format

Ref	Prediction model as presented in paper			
Guo et al., 2015[21]	COPD = 1/[1 + exp (−2.4933−1.2197 gender + 1.1842 respiratory infection in early life + 2.4350 low birth weight + 1.8524 smoking − 1.1978 rs2070600 + 2.0270 rs10947233 + 1.1913 rs10947233 + 0.6468 rs1800629 + 0.5272 rs2241712 + 0.4024 rs1205)] For example, if the value calculated using the formula is >0.5 for an individual, it can be speculated that the patient is more likely to develop COPD prior to becoming symptomatic.			
Kotz et al., 2014[22]			**Males**	**Females**
	Age category	35-39	0.0000	0.0000
		40-44	0.7226	0.7195
		45-49	1.3540	1.3113
		50-54	1.7945	1.7030
		55-59	2.2681	2.0982
		60-64	2.6401	2.3529

		65+	3.4623	3.2485
	Ever smoker	Ever smoker	1.9057	2.2623
		Never smoker	0.0000	0.0000
	Level of deprivation (Carstairs)	1st quintile (least deprived)	0.0000	0.0000
		2nd quintile	0.3073	0.2233
		3rd quintile	0.4686	0.4989
		4th quintile	0.6470	0.6666
		5th quintile (most deprived)	0.9262	0.9485
	History of asthma	yes	1.2148	1.0250
		no	0.0000	0.0000
		Minimum PI* score:	0.0000	0.0000

	Maximum PI* score: 7.5090 7.4843 PI = prognostic index
Himes et al., 2009[23]	Predictive network of Chronic Obstructive Pulmonary Disease (COPD). 

Higgins et al., 1982[24] ^	Points 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 Age 20 25 30 35 40 45 50 55 60 65 Cigarettes/Day 0 9 19 28 37 46 59 Change in Cigarettes/ Day -62 -46 - 31 -15 0 15 31 46 62

	FEV_1 % Predicted	144	140	136	131	127	123	119	114	110	106	102	98	93	89	85	81	76	72	68

Calculation of Probability	Total Points	Probability
	<19	Low Risk
_____ Age	19	.01
+ _____ Cigarettes/Day	20	.02
+ _____ Change in Cigarettes/ Day	21	.03
+ _____ FEV_1 % Predicted	22	.04
= _____ Total Points → Probability	23	.06
	24	.10
	25	.14
	26	.21
	≥27	High risk

Table S7: Definitions of COPD in the selected prediction models

Reference	Definition of COPD	Incidence of COPD reported in derivation cohort
Guo et al., 2015[21]	COPD was diagnosed according to the criteria established by the National Heart, Lung and Blood Institute/World Health Organization Global Initiative for COPD (GOLD): post BD FEV1/FVC ratio, 0.70 cut-off.	Case-control study
Kotz et al., 2014[22]	The definition of COPD was based on codes from the Read Clinical Classification System, which was produced for clinicians in primary care and is used by the majority of primary care electronic patient record systems (read codes H3, H31 and below (excluding H3101, H31y0, H3122), H32 and below, and H36 to H3z).	5.53 per 1,000 patient-years (5.46-5.60)
Himes et al., 2009[23]	Cases are those subjects who had COPD, determined by having a value of "1" in International Classification of Diseases, Ninth Revision (ICD-9) codes corresponding to at least one of the following: "Chronic Bronchitis," "Emphysema," or "Chronic Airways Obstruction, not otherwise specified."	COPD 9.02% (843/9349)
Higgins et al., 1982[24]	COPD was defined as obstructive airways disease manifested by a FEV1 less than 65% of the predicted value in combination with an FEV1/FVC ratio less than 80%.	Males 65/1225 – 5.3%

	Values of FEV1 in the range of 65 to 69% of predicted were considered to be borderline abnormal.	Females 43/1405 – 3.1%

References

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