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Clinical characteristics of chronic obstructive pulmonary disease in never-smokers: A systematic review

Carlota Rodríguez García [a,b,c], Alberto Ruano-Ravina [c,d,e,f,*], Mónica Pérez Ríos [c,d,e], Lucía Martín Gisbert [c,e,f], Leonor Varela-Lema [c,d,e], Cristina Candal-Pedreira [b,c], Cristina Represas-Represas [g,h], Julia Rey-Brandariz [c], Luis Valdés-Cuadrado [a,b,i], Alvar Agustí [j,k,l]

[a] Pulmonology Department, University Clinical Hospital of Santiago, Santiago de Compostela, Spain
[b] Interdisciplinary Research Group in Pulmonology, Health Research Institute of Santiago de Compostela (IDIS), Santiago de Compostela, Spain
[c] Department of Preventive Medicine and Public Health, Universidade de Santiago de Compostela, Santiago de Compostela, Spain
[d] Consortium for Biomedical Research in Epidemiology and Public Health (CIBER en Epidemiología y Salud Pública/CIBERESP), Spain
[e] Health Research Institute of Santiago de Compostela (Instituto de Investigación Sanitaria de Santiago de Compostela - IDIS), Santiago de Compostela, Spain
[f] Cross-disciplinary Research in Environmental Technologies (CRETUS), University of Santiago de Compostela, Santiago de Compostela, Spain
[g] Respiratory Medicine, Alvaro Cunqueiro University Teaching Hospital, Vigo, Spain
[h] Grupo NeumoVigo I+i, Instituto de Investigación Sanitaria Galicia Sur (IISGS), Vigo, Spain
[i] Department of Medicine, Faculty of Medicine, University of Santiago, Spain
[j] Catedra Salud Respiratoria, Universidad de Barcelona, Institut Respiratori, Clinic Barcelona, Spain
[k] Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain
[l] Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III, Madrid, Spain

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ABSTRACT

Introduction: Chronic Obstructive Pulmonary Disease (COPD) is the third cause of death worldwide. While tobacco smoking is a key risk factor, COPD also occurs in never-smokers (NS). However, available evidence on risk factors, clinical characteristics, and natural history of the disease in NS is scarce. Here, we perform a systematic review of the literature to better describe the characteristics of COPD in NS.
Methods: We searched different databases following the PRISMA guidelines with explicit inclusion and exclusion criteria. A purpose-designed quality scale was applied to the studies included in the analysis. It was not possible to pool the results due to the high heterogeneity of the studies included.
Results: A total of 17 studies that met the selection criteria were included, albeit only 2 of them studied NS exclusively. The total number of participants in these studies were 57,146 subjects, 25,047 of whom were NS and 2,655 of the latter had NS-COPD. Compared to COPD in smokers, COPD in NS is more frequent in women and older ages, and is associated with a slightly higher prevalence of comorbidities. There are not enough studies to understand if COPD progression and clinical symptoms in NS are different to that of ever-smokers.
Conclusions: There is a significant knowledge gap on COPD in NS. Given that COPD in NS account for about a third of all COPD patients in the world, particularly in low-middle income countries, and the decrease in tobacco consumption in high income countries, understanding COPD in NS constitutes a public-health priority.

1. Introduction

Although tobacco smoking is a key environmental risk factor of chronic obstructive pulmonary disease (COPD) [1–4], it is now recognized that around 30% of all COPD cases in the world occur in never-smokers (NS) [5–8]. Yet, the epidemiology, natural history and clinical characteristics of COPD in NS is quite unknown. In fact, there has been hardly any study targeting NS-COPD patients exclusively [9, 10] and available information stem from analyses of subgroups of NS-COPD patients included in large smoking-related COPD cohorts. Based on these scattered observations, it is assumed that NS-COPD is more frequent in younger women and that it is associated with milder respiratory symptoms, similar spirometric indices, though with greater obstruction of small airways and less emphysema, reduced rate of

* Corresponding author. Area of Preventive Medicine and Public Health. School of Medicine, Universidad de Santiago de Compostela, Spain.
E-mail address: alberto.ruano@usc.es (A. Ruano-Ravina).

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decline of lung function over time and a lower prevalence of comorbidities [11–13]. Biologically speaking, patients with NS-COPD seem to have fewer neutrophils and more eosinophils in sputum, as well as abnormal macrophage phagocytic function of pathogenic bacteria [1]. Some authors suggest a worse prognosis of NS-COPD because these patients experience a higher number of exacerbations [5]. These assumptions are not supported, though, by all the few available studies [14–21]. The available evidence is scarce and comes mainly from subgroup analyses where NS-COPD patients have been analyzed separately and therefore with a very low sample size.

Here, we systematically review the available literature on NS-COPD to get a better insight into the clinical characteristics and natural history of COPD in never smokers.

2. Methods

2.1. Data-sources and search strategy

We conducted a bibliographic search of PubMed (Medline) and Embase, using different combinations of the following free text; MeSH terms and boolean operators: COPD; chronic obstructive pulmonary disease; chronic airflow obstruction; chronic airflow limitation; AND non-smokers OR never-smokers. The search period was set between January 1, 2000 to December 31, 2022. We excluded editorials, monographs and communications to conferences. The **P**referred **R**eporting **I**tems for **S**ystematic Reviews and **M**eta-**A**nalyses (PRISMA) recommendations were used for literature search and synthesis of evidence [22].

2.2. Inclusion and exclusion criteria

The following inclusion criteria were used to select publications for analysis: (a) eligible study designs included cohort, case-control and cross-sectional studies; (b) the study population had to be aged 18 years or over, include both sexes, and have a minimum sample size of 100 participants, at least 20 of whom had COPD and were never-smokers; (c) studies which provided no breakdown of results for never-smokers were excluded; (d) diagnosis of COPD had to be based on clinical symptoms and objective spirometric confirmation of a post-bronchodilator values of $FEV_1/FVC < 0.70$.

We excluded studies that classified COPD patients on the basis of self-reported patient symptoms or pre-bronchodilator FEV_1/FVC ratio values, and also those published in languages other than Spanish or English.

A never-smoker was defined as anyone who met at least one of the following conditions: a person who had never smoked or had smoked (a) fewer than 100 cigarettes in his/her lifetime, or (b) less than 1 cigarette per day during less than 6 months [23]. In any case where this definition did not exist, non-smokers in the studies included had to be referred to as "never-smokers" rather than "non-smokers".

2.3. Extraction of data from selected papers

Data were extracted from selected papers using a data-extraction table specifically designed for this systematic review, which included: author(s); year of publication; study design; country of study; study population; sample size; number of never-smokers; number of NS-COPD cases; clinical characteristics analyzed; and main results.

2.4. Quality assessment

The quality of the included studies was evaluated using a scale previously used in other systematic reviews on lung cancer [24] in never-smokers [25]. It rated the following items: sample size; number of NS-COPD cases; study design; and diagnosis of COPD. Each item was scored from 0 to 2, with 0 being the minimum score and 8 the overall maximum scale score (Table 1).

3. Results

3.1. Studies included

Our initial literature search yielded 1,624 entries. After reading the titles and abstracts, 1,526 entries were discarded. Finally, 17 studies that met the inclusion/exclusion criteria discussed above were included (Fig. 1). The quality of the studies included ranged from 2 (minimum value) to 6 points (maximum value), with an average value of 3.4 points (Table 2), indicating an overall medium-low quality.

The characteristics of the 17 studies are shown in Table 2. All had a cross-sectional design, except one which was a case-control study. The total size of the sample analyzed in these 17 studies was 57,146 subjects, 25,047 of whom were NS and 2,656 of the latter had NS-COPD. In 15 of the 17 papers included, post-bronchodilator spirometry (PBD) was performed on 100% of subjects (53,959 of the total number of patients; 94% of the sample). In the other two studies, PBD was performed on 96.5% [26] and 81.9% [27] of participants, respectively.

In 12 of the 17 studies, the GOLD definition was used to diagnose COPD ($FEV1/FVC<0.7$)[1]. Soumagne et al. [28] applied a PBD FEV1/FVC ratio <5th percentile lower limit of normal according to the latest GLI-2012 equations. Hagstad et al. [29] used three different definitions (PBD $FEV1/FVC < 0.7$ (Swedish criterion), PBD $FEV_1/FVC < 0.7$ and PBD FEV1/FVC less than the lower limit of normal (LLN). Miratvilles et al. [30], Wang et al. [9] and Choi et al. [10] used the spirometric criteria of the European Respiratory Society (pre-bronchodilator $FEV_1/FVC < 88\%$ in men and 89%in women). Lastly, other authors [26,27,31,32] used the LLN and GOLD definitions comparatively to evaluate potentially discordant diagnoses.

3.2. Prevalence and severity

The prevalence of NS-COPD varied widely in the different studies starting from 2.15% [30] (Table 2). Albeit with important differences between studies, NS-COPD patients generally presented mild-to-moderate airflow limitation, corresponding to GOLD grades 1 and 2[1].

3.3. Sex

In 7 of the 17 studies [8,24,30,31,35,38,39], NS-COPD prevalence was higher in women compared to men. Lamprecht et al. [31] found a prevalence of NS-COPD of 48.0% in women vs. 38.2% in men for GOLD 1, and 62.5% in women vs. 32.9%in men for GOLD 2. A subsequent study confirmed these results and reported that in the moderate-to-very severe grades (GOLD 2+), prevalence of NS-COPD was higher in women

Table 1
Quality-assessment scale of the items included.

Item analyzed	Characteristics	Score
Sample size	≤100	0
	101-1000	1
	>1000	2
NS-COPD	≤20	0
	21–200	1
	>200	2
Study design	Cross-sectional	0
	Case-control	1
	Cohort	2
Diagnosis of COPD	No data on criterion used	0
	PBD FEV_1/FVC ratio <0.7	2
Total		8

COPD, chronic obstructive pulmonary disease; **NS-COPD**, chronic obstructive pulmonary disease in never-smokers; **FEV_1**, forced expiratory volume in the first second; **FVC**, forced vital capacity; **PBD**, post-bronchodilator.

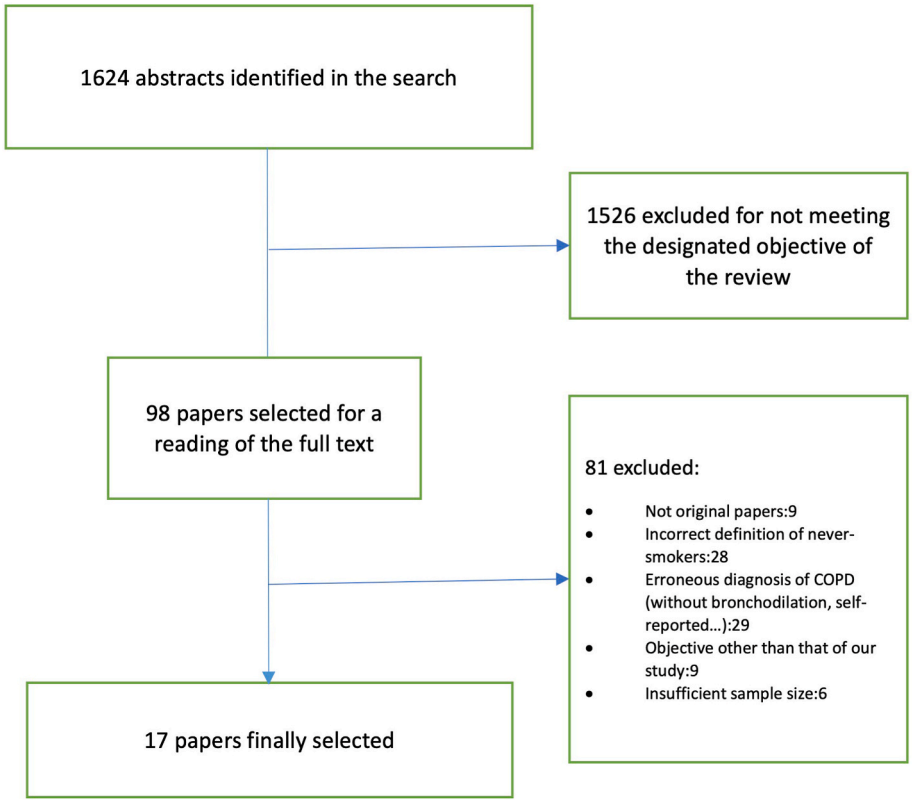

Fig. 1. Process of selection of papers included in this study (PubMed, Embase, 2000–2022).

(70.8% vs. 37.0%). In contrast, 5 studies identified a higher prevalence of NS-COPD in men [27,28,32,33,36]. Among these latter studies, specific mention should be made of the results of Soumagne et al. series [28], in which 91% of NS-COPD cases were men, or Viet et al. series [36], in which the prevalence of NS-COPD was three times higher in men than in women (12.9% vs. 4.4%).

3.4. Age

Eight studies [8,9,26,29,31,33,35,38] considered that NS-COPD tend to be older. Lamprecht et al. showed that prevalence of NS-COPD in moderate-to-severe grades increased significantly with age ($p < 0.001$) [8]. In the moderate-to-very severe grades (GOLD 2+), NS-COPD patients were older than smoking related COPD (S-COPD) patients (66.1 years vs. 62.7, $p < 0.001$). In a Swedish series [26], a statistically significant association was observed between a higher age and prevalence of airway obstruction in never-smokers. Monserrat-Capdevila et al. [35] found a statistically significantly association between NS-COPD status and age (OR 1.03, $p < 0.01$). In other studies [10,27,34,39], however, no significant age-related differences were observed between NS-COPD and S-COPD subjects.

3.5. Symptoms

Some of the series agreed on the lower prevalence of respiratory symptoms (chronic cough, expectoration, dyspnea and wheezing) in the NS-COPD versus the S-COPD group [27,33]. The studies by Camp [37], Pérez Padilla [38] and Ojuawo [39], in contrast, reported more symptoms (dyspnea on exertion, chronic productive cough and wheezing) [39], greater limitation of physical activity, worse control of the disease, lower O_2 saturation [37], and a higher number of medical visits (OR: 1.13; 95%CI: 1.01–1.26; $p = 0.03$) and hospital admissions (OR: 2.92; 95%CI: 1.21–7.07; $p = 0.02$) [39] in the NS-COPD group than in the S-COPD group.

3.6. Comorbidities

In 9 of the studies included in this systematic review [8,10,26,27,29–31,33,35], a higher (not statistically significant) frequency of comorbidities was observed in the NS-COPD subjects versus never-smoker subjects without airway obstruction. In Hagstad et al.'s series [26], stratification of the results by GOLD severity stages showed that when GOLD 1 NS-COPD was compared to never-smokers without airflow obstruction, there were no differences in the number of comorbidities, but when GOLD 2 NS-COPD was compared to never-smokers without airflow obstruction, there were significant differences. For example, previous diagnosis of asthma (40.7% vs. 9.6%, $p < 0.001$), history of heart disease (22.2% vs. 7.8%, $p = 0.019$), and history of other lung disease (51.9% vs. 24.7%, $p = 0.003$) were higher in the GOLD 2 NS-COPD patients. In the Lee et al. study [34], no differences were found in extrapulmonary comorbidities (diabetes, cerebrovascular disease, chronic kidney disease, chronic liver disease and malignancy) or in pulmonary comorbidities (asthma, bronchiectasis) between NS-COPD subjects and never-smokers without COPD. Taking asthma as a comorbidity of COPD, 7 out of the 17 series included [8–10,26,27,31,33] coincided in reporting a higher prevalence of previous diagnosis of asthma in the group of NS-COPD subjects. The conclusion of the PLATINO study [38] was that NS-COPD subjects had a 2.6-fold higher likelihood of previous diagnosis of asthma (OR: 2.66; 95%CI: 1.28–5.50; $p = 0.01$) and 2.9-fold higher likelihood of tuberculosis (OR: 2.90; 95% CI: 1.05–7.98; $p = 0.04$) than did S-COPD subjects.

3.7. Exacerbations

Only 2 of 17 the papers included presented data on the frequency and severity of exacerbations [9,10]. The first reported current smoking habit status but not cumulative tobacco use) to be a risk factor for recurrence of exacerbations [OR: 1.84; 95%CI: 1.03–3.40; $p = 0,044$) [9]. Choi et al. did not find statistically significant differences in the

Table 2
Description of the studies included (by year of publication).

Author, year, country	Type of study	Sample size Total/NS-COPD/NS subjects/ prevalence of NS-COPD	NS-COPD Age (years)	NS-COPD Sex	NS-COPD GOLD Stages	NS-COPD Comorbidities	NS-COPD Disease progression	Quality
Miravitlles et al. (2005), Spain [30]	Cross-sectional	4035/84/NS/ 2.1%	NSp	NS-COPD subjects were most frequently women (71.4% vs. 28.6%, $p < 0.001$)	NSp	NS-COPD subjects present with an association with other respiratory diseases more frequently	Fewer respiratory symptoms compared to the S-COPD group, less expectoration in particular (4.8% vs. 60.3%, $p < 0.001$)	3
Lamprecht et al. (2008), Austria [31]	Cross-sectional	1258/141/595/ 23.7%	NS-COPD were significantly older (65.8 vs. 57.2 years, $p < 0.001$) than smokers with normal lung function	NS-COPD subjects were predominantly women (48%vs. 38.2% for GOLD I, and 62.5% vs. 32.9% for GOLD II) compared to smokers.	GOLD I: 18.2% GOLD II+: 5.5%	NS-COPD subjects report a higher number of comorbidities than healthy NS subjects: asthma ($p < 0.001$), heart disease ($p = 0.008$), AHT ($p = 0.033$), stroke ($p = 0.002$), tuberculosis ($p = 0.950$). However, they present with a lower, though not statistically significant, prevalence of DM ($p = 0.873$)	When never smoker and smoker subjects with the same degree of obstruction are compared, no differences are observed in respiratory symptoms. The symptoms increase in both groups in parallel with the severity of obstruction.	4
Zhou et al. (2009) China [33]	Cross-sectional	20,245/644/ 12,471/5.2%	Advanced age ($p < 0.001$)	Male sex ($p < 0.001$)	GOLD I: 1.4% GOLD II+: 3.7%	NS-COPD subjects had a higher likelihood of having previously received clinical diagnosis of asthma: (91 (14.1%) vs. 101 (9.9%), $p = 0.008$) with respect to S-COPD subjects	Fewer respiratory symptoms (chronic cough and expectoration) con statistical significance with respect to S-COPD subjects (36.6% vs. 48.6%, $p < 0.001$ and 29.8% vs. 46.6%, $p < 0.001$)	6
Lamprecht et al. (2011), Worldwide [8]	Cross-sectional	10,000/523/ 4291/12.2%	Prevalence of NS-COPD in moderate-to-severe grade increased with age ($P < 0.001$). In stages II + NS subjects were significantly older than S subjects (66.1 years vs. 62.7, $p < 0.001$)	Higher likelihood of being a woman (70.8% vs. 37%, $p < 0.001$)	GOLD I: 6.6% GOLD II+: 5.6%	Greater frequency of previous diagnosis of asthma, heart diseases, TB, DM, stroke and AHT with respect to healthy NS subjects	Twice the rate of respiratory symptoms compared to healthy NS subjects	5
Hagstad et al. (2012), Sweden [26]	Cross-sectional	2470/53/798/ 6.9%	Among NS a significant association ($p < 0.001$) was observed between older age and prevalence of airflow obstruction.	14.1% of men with COPD were NS versus 26.8% of women ($p = 0.001$)	GOLD II+: 3.5%	Previous diagnosis of asthma, heart disease, AHT, respiratory disease in childhood, TB, history of other statistically significant pulmonary diseases when GOLD II NS-COPD are compared to healthy NS subjects	More respiratory symptoms with respect to healthy NS subjects	3
Pérez-Padilla et al. (2012) South America [38]	Cross-sectional	5315/240/ 2278/10%	NS-COPD GOLD II+ is more frequent at advanced ages (OR: 1.04 per year; 95% CI: 1.02–1.06)	NS-COPD GOLD II+ is more frequent in women	3.5% were in GOLD II-IV stages.	NS-COPD lower number of comorbidities with respect to S-COPD subjects: asthma (0 R:2.66, 95%CI: 1.28–5.50, $p = 0.01$), tuberculosis (OR: 2.90, 95%CI: 1.05–7.98, $p = 0.04$), comorbidity index (OR: 0.72,95%CI: 0.51–1.01, $p = 0.056$)	Compared to GOLD II + S-COPD subjects, NS-COPD subjects with the same level of severity of obstruction more frequently presented with episodes of dyspnea that required medical attention (OR:1.13, 95%CI: 1.01–1.26, $p = 0.03$) or hospital admissions (exacerbations) in the previous year (OR: 2.92, 95%CI: 1.21–7.07, $p = 0.02$)	3
Camp et al. (2014) Mexico [37]	Cross-sectional	43/21/21/ 48.8%	NSp	Only women	Most of the participants were in GOLD II stage.	NSp	NS-COPD subjects presented with more symptoms, more limitation of activity and less control over their disease, measured by quality of life questionnaires, and greater desaturation at rest with respect to the S-COPD group	2

(*continued on next page*)

Table 2 (*continued*)

Author, year, country	Type of study	Sample size Total/NS-COPD/NS subjects/ prevalence of NS-COPD	NS-COPD Age (years)	NS-COPD Sex	NS-COPD GOLD Stages	NS-COPD Comorbidities	NS-COPD Disease progression	Quality
Hagstad et al. (2015) Sweden [29]	Nested cohort cross-sectional	1839/74/967/ 7.7%	NS-COPD GOLD II+: 0.6% at ages <40 years, 1.6% at ages 40–60 years, 4.2% at ages >60 years (p = 0.002)	GOLD I NS-COPD tends to be more common among women non-smokers and GOLD II + NS-COPD more common in male non-smokers; sex-related differences were statistically significant.	Prevalence of GOLD II+ in NS-COPD: 2% Prevalence of GOLD II+ in S-COPD: 8.2% (p < 0.001)	Although comorbidities (heart disease, ischaemic heart disease, DM, stroke) are more frequent in GOLD II + NS-COPD than in non-COPD subjects, AHT was the only statistically significant comorbidity (47% vs. 20%, p = 0.008)	Chronic or intermittent respiratory symptoms were reported in 63% of NS-COPDII + patients compared to 37% (p = 0.028) of healthy NS subjects. Only wheezing and production de sputum showed statistically significant differences between NS-COPDII+ and healthy NS subjects	3
Viet et al. (2015), Vietnam and Indonesia [36]	Cross-sectional	1506/117/ 1506/6.9%	NSp	NS-COPD was three times higher in men than in women: 12.9% (95%CI: 9.1–18.0) vs. 4.4% (95%CI: 3.0–6.5)	NSp	NSp	NSp	4
Denguezli et al. (2016), Tunisia [27]	Cross-sectional	717/23/807/ 4.7%	NS-COPD II subjects have approximately the same age as smokers.	NS-COPD was significantly higher in men than in women (GOLD I: 1.3% vs. 0.3% and GOLD II: 4.5% vs. 1.1%; p < 0.05)	GOLD I: 1% GOLD II+: 3.7%	GOLD I + NS-COPD have a higher number of comorbidities than S-COPD patients and healthy NS subjects (p < 0.05): asthma, heart disease, AHT, DM.	Less production of sputum, cough, wheezing, dyspnea and use of medication for respiratory disease (p < 0.05) than S-COPD subjects	2
Cushen et al. (2016) Ireland [32]	Cross-sectional	372/29/227/ 12.8%	NSp	76% of NS-COPD cases are men versus 24% of women.	GOLD I: 69% GOLD II: 31%	NSp	Greater proportion of lower respiratory tract symptoms and significant increase in wheezing	2
Lee et al. (2018), South Korea [34]	Cross-sectional	400/77/131/ 58.8%	No differences in age (73 vs. 74, p = 0.314) between NS-COPD and S-COPD.	No differences by sex (women: 38 vs. 57, p = 0.793)	Mild: 59.7% Moderate: 39% Severe: 1.3%	No statistically significant differences in extrapulmonary comorbidities or in pulmonary comorbidities between NS-COPD and healthy NS subjects	No differences with respect to MRC dyspnea scale (p = 0.536) or CAT (p = 0.830) between NS-COPD and healthy NS subjects	2
Montserrat-Capdevila et al. (2019), Spain [35]	Cross-sectional	512/170/170/ NS	Age was a factor associated very significantly with NS-COPD status (OR 1.03 p < 0.001)	Female gender was a factor associated very significantly with NS-COPD status (OR 12.4; p < 0.001)	Mild: 35.3% Moderate: 51.8% Severe: 11.8% Very severe: 1.2%	NS-COPD subjects presented with a lower prevalence of DM and lower Charlson index with respect to smokers/ex-smokers, but higher prevalence of dyslipidaemia and AHT	NS-COPD subjects without previous severe exacerbations (OR 0.39, 95% CI: 0.23–0.65, p < 0.001)	3
Ojuawo et al. (2019) Nigeria [39]	Retrospective	135/38/71/ 57.6%	The mean age of subjects who had at some time been smokers was older than that of never smokers (68.4 ± 11.0 vs. 64.5 ± 11.7), though the differences were not statistically significant	47.4% men 52.6% women	GOLD I: 50% GOLD II: 7.9% GOLD III: 18.4% GOLD IV: 23.7%	AHT: 36.8% Cor Pulmonale: 13.2% Cancer: 10.5%	Chronic cough: 89.5% Dyspnea on exertion: 89.5% Chronic productive cough: 78.9% Wheezing: 28.9%	4
Soumagne et al. (2020) NS [28]	Case-control	4788/22/44/ 50%	NSp	91% of NS-COPD are men	NSp	No significant differences for comorbidities such as AHT, DM, osteoporosis, OSA and GORD between NS-COPD and S-COPD subjects	NS-COPD and S-COPD have the same impact on symptoms (dyspnea measured by MRC, chronic cough, production of sputum) but S-COPD subjects had BDI and CAT more than did never-smokers.	4
Wang et al. (2022) China [9]	Retrospective	1034/200/200/ 100%	Older in NS-COPD (75 vs. 70.5, p < 0.001)	Fewer men (70.0 vs. 97.6%, p < 0.001)	NSp	Higher risk of AHT in NS with respect to S subjects.	S-COPD more susceptible to recurrence of exacerbations than NS-COPD subjects.	4
Choi et al. (2022)	Prospective	2477/200/200/ 100%	No significant differences between NS-COPD and S-COPD	Higher proportion of women (57.5% vs. 3.3%)	NSp	NS-COPD present with more AHT, osteoporosis, GORD, bronchiectasis,	No significant differences were observed in symptoms, exercise	4

(*continued on next page*)

Table 2 (*continued*)

Author, year, country	Type of study	Sample size Total/NS-COPD/NS subjects/prevalence of NS-COPD	NS-COPD Age (years)	NS-COPD Sex	NS-COPD GOLD Stages	NS-COPD Comorbidities	NS-COPD Disease progression	Quality
South Korea [10]						asthma, TB, respiratory infections and higher BMI	capacity and 6MWT and MRC, SGQLQ and CAT score between NS-COPD and S-COPD subjects.	

OSA, obstructive sleep apnea; **BDI**, Beck Depression Inventory; **CAT**, COPD Assessment Test; **DM**, diabetes mellitus; **GORD**, gastro-oesophageal reflux disease; **AHT**, arterial hypertension; **MRC**, medical research council; **NSp**, not specified; **NS**, never-smoker; **S**, smokers; **SGQLQ**, Saint George quality of life questionnaire; **6MWT**, 6-min walking test. **OR**: odds ratio; **95%CI**, 95% confidence interval.

number of moderate-to-severe exacerbations across one year of follow-up, when NS-COPD were compared to S-COPD subjects [10].

3.8. Mortality

None of the papers included discussed mortality or medium/long-term disease course in the NS-COPD group of patients.

4. Discussion

The main observation of this systematic review is the noteworthy lack of studies focused exclusively on NS-COPD patients since only 2 out of the 17 studies analyzed [9,37] focused on NS-COPD. With this caveat in mind, several observations deserve specific discussion.

4.1. Interpretation of observations

NS-COPD seems to be more prevalent among women. In developed countries the prevalence of smoking related COPD is similar in men and women [1]. This is different in low-middle income countries (LMIC) where exposure to other indoor and outdoor pollutants is higher in women [5]. Therefore, it is important to consider the country where the study took place in order to estimate the prevalence of NS-COPD. It seems that the least wealthy is the country, the highest is the NS-COPD prevalence, due perhaps to higher exposures to indoor contaminants (i.e. cooking fumes and biomass exposure). It is also important to mention that some LMIC countries have a lower prevalence of tobacco consumption and the percentage of never smoking population is higher than in developed countries [5]. In our review, 7 of the studies analyzed have been carried out in LMIC countries [9,27,33,36–39].

NS-COPD appear to be diagnosed at an older age than smoking related COPD. This may be explained by either the need of a longer exposure period, the mildness of associated symptoms and severity of airflow obstruction and/or under-recognition and under-diagnosis [8,26,29]. Primary care physicians also use to think on COPD in ever-smokers but when a never smoking patient presents with symptoms compatible with COPD, such symptoms may be associated with other clinical conditions apart from COPD.

By contrast, comorbidities seem more prevalent in patients with NS-COPD than in smoking related COPD. Since comorbidities are generally related to ageing, this may be related to the older age of patients at diagnosis. Alternatively, the mechanisms causing NS-COPD can also favor the occurrence of comorbid diseases. In this respect, it is of note that abnormal development of lung function in infancy and adolescence, is associated to a higher prevalence and earlier incidence of COPD [40].

Finally, it is important to consider that there is heterogeneity in the definition of COPD in the studies reviewed here. While many studies used the GOLD diagnostic criteria [1], others used the LLN proposed by of the European Respiratory Society/American Thoracic Society (ERS/ATS) [41] or used slow spirometry (Swedish criterion) [29]. Likewise, all studies so-far are cross-sectional with a single spirometric measurement not repeated over time.

4.2. Strengths and potential limitations

To our knowledge, this is the first systematic review which analyzes the clinical characteristics of NS-COPD at diagnosis and its progression. Among the strengths of our study, the fact that we followed PRISMA recommendations and used a quality scale purposedly designed for this analysis enabled the objective assessment of the quality of the studies included [25]. We acknowledge, however, some potential limitations. These include the possibility that some studies may have been excluded because they were published in languages other than those considered and the fact that sample size of NS-COPD patients was generally small because they were part of a larger cohort of COPD patients. Finally, as per quality of the studies, the main limitation is not having case-control

studies specifically designed to define the etiology or characteristics of smokers versus never-smokers and also the lack of follow-up studies aiming to observe if there are differences on exacerbations or other clinical outcomes comparing COPD ever-smokers versus never-smokers.

5. Conclusions

There is a significant lack of knowledge on NS-COPD. Due to the high heterogeneity of the different studies included in this systematic review, there is an urgent need for studies well-designed to investigate their clinical characteristics and natural history of this disease. This is of particular importance given the trends on the decline of smoking prevalence in developed many countries. It might be useful to analyze inflammatory biomarkers, in order to ascertain whether these patients have a molecular pattern different to that presented by smoking related-COPD. The multicentre RADEPOCNS case-control study, which is a multicentric study conducted in Spain, has already included close to 300 patients with COPD and never-smokers, and might be able to provide answers to these questions.

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Data sharing

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Authorship contributions

Alberto Ruano-Ravina, Luis Valdés-Cuadrado and Alvar Agustí; conceived the idea. Carlota Rodríguez-García, Mónica Pérez-Ríos, Leonor Varela-Lema and Cristina Represas-Represas conducted the literature search. Carlota Rodríguez-García, Mónica Pérez-Ríos, Leonor Varela-Lema, Cristina Candal-Pedreira, Julia Rey-Brandariz and Lucía Martín-Gisbert extracted the data. Carlota Rodríguez-García, Alberto Ruano-Ravina and Mónica Pérez-Ríos analyzed the data. Carlota Rodríguez-García wrote the first draft of the manuscript. All authors critically reviewed successive versions of the manuscript and made intellectual contributions to it. All authors gave their final approval to the final version to be published. All authors are responsible for all aspects of this work.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Alberto Ruano-Ravina reports financial support was provided by Carlos III Health Institute. Alvar Agusti reports a relationship with Gold that includes: board membership.

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