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Sexually dimorphic response to tobacco exposure in COPD: a systematic review and meta-analysis

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Abstract

Background Chronic obstructive pulmonary disease (COPD) is a heterogeneous, progressive pulmonary disorder with persistent respiratory symptoms resulting from abnormalities in the airways and/or alveoli and was prevalent globally in 10.3% of people aged 30–79 years in 2019. The prevalence of COPD has increased rapidly in women in the past decade. This may be due to increased tobacco use, but may also involve sex-specific factors.

Purpose To evaluate the prevalence of COPD in the context of sex and tobacco exposure.

Data sources and searches Comprehensive searches of MEDLINE (OVID), EMBASE and CENTRAL were conducted for articles published from inception to July 22, 2022.

Study selection We independently evaluated titles, abstracts and full-text articles in a duplicated two-staged process. Studies were included if they reported the prevalence of COPD as a primary outcome in the context of sex and tobacco exposure.

Data synthesis and analysis Pooled analysis was conducted with Review Manager 5, and heterogeneity was assessed with the I^2 statistic. For 163, 450 individuals the prevalence of COPD was 3.5–20.7% in males and 6.3–18.5% in females, and we observed a non-statistically significant difference of 1.53% [95% CI: -5.83, 8.89] ($p = 0.68$) in females compared to males with tobacco exposure ($Tau^2 = 54.02$; $Chi^2 = 53.15$; $df = 4$ ($P < 0.00001$); $I^2 = 92\%$). Females with COPD had earlier mortality, greater co-morbidities involving cardiovascular disease and others, and decreased FEV_1% predicted, as compared to males with COPD. Estrogen and androgens may protect against COPD, but smoking-induced hypogonadism may diminish these effects. Menopause could also be a contributor to worse COPD outcomes.

Limitations Included articles are limited by the quality of data on tobacco smoke exposure, primarily reported as a binary risk factor, with lack of availability on duration and intensity of exposure.

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Conclusion There was earlier mortality and reduced FEV_1 in females with COPD, as compared to males with COPD. Thus, sex-specific considerations are important in understanding the pathophysiology of COPD and should be a focus of further research.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized as a heterogeneous pulmonary disorder with persistent respiratory symptoms resulting from abnormalities in the airways and/or alveoli, leading to chronic and often progressive airflow obstruction [1]. COPD was prevalent globally in 10.3% of people aged 30–79 years in 2019 using the GOLD case definition [2]. Diagnosis is based on spirometry, which can detect COPD even in individuals who do not report symptoms. There is no cure for COPD, and pharmacological and non-pharmacological therapies (i.e., physical exercise, healhy eating) are directed toward improving symptoms and quality of life, and preventing acute disease exacerbation [3].

Tobacco smoke is the most common cause of COPD, other risk factors include environmental factors (e.g., dust, air pollution and biomass fuels) and to a lesser degree genetic susceptibility [3]. While COPD was once more prevalent in men, its prevalence and morbidity has increased more rapidly in women in the past decade. This may be attributable to increased tobacco use, but may involve other factors such as differential susceptibility to tobacco, exposure to environmental pollution and sex-specific differences [4]. Sex-specific differences in context of COPD prevalence are not well understood, and population-based studies are often expensive and difficult to conduct [5].

A study published in 2016 identified that female mice with chronic tobacco exposure developed more peripheral airway obstruction and small airway remodeling than male counterparts. However, ovariectomy and the drug tamoxifen, an estrogen receptor-a blocker, reversed this effect and a male-pattern phenotype was produced. In the female mice, chronic tobacco exposure was associated with the induction of transforming growth factor-b (TGF-b), decreased expression of antioxidants, and increased oxidative stress. The major source of reactive oxygen species was NAPDH oxidase-4, which is upregulated by TGF-b and plays a key role in airway smooth muscle proliferation and fibrosis. These observations suggest that female sex hormones may be responsible for some of these sex differences in the context of COPD prevalence [6].

COPD has a significant impact on quality of life through progressive symptoms, daily life limitations, worsening mental health, and reduced physical activity and sleep quality–its substantial social and economic impacts result in considerable humanistic burden [7, 47] . A thorough understanding of the epidemiological and comorbidity factors upon COPD is therefore warranted. Herein, a systematic review and meta-analysis of the prevalence of COPD as a primary outcome in the context of sex and tobacco exposure was conducted.

Methods

This study adhered to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [8]. An a priori protocol was published on Open Science Framework [9].

Information sources and search strategy

Comprehensive searches of MEDLINE (OVID), EMBASE and CENTRAL were conducted for articles published from inception to July 22, 2022, with the help of a medical librarian. The terms "smoking", "COPD" and "sexual dimorphism" were used. Animal studies were excluded from the searches. The search strategies can be found in the online supplementary material (Appendix S1).

Study selection

Search results were uploaded to Covidence (Veritas Health Innovation Ltd.), which is software for systematic review management. Pilots were run until the review authors reached a Cohen's kappa inter-rater reliability value of 0.8. Titles and abstracts were first screened independently for eligibility by two authors (MP, SY, SA, SS). The full texts of potentially relevant articles were then reviewed by two authors (MP, SY, SA, SS). Any reason for exclusion was documented at the full-text stage, and discrepancies were resolved through discussion and adjudication with a third reviewer (RC) if necessary. Studies were included if they reported the prevalence of COPD as a primary outcome as stratified by sex and tobacco exposure. Studies were excluded if they did not report primary data such as systematic reviews or post-hoc analyses, if they were reviews, abstracts, conference posters, comments or editorials, or if they were not published in English.

Data extraction

Data extraction was independently completed by two authors (MP, SY, SA, SS) and discrepancies were resolved through discussion with a third author (MP, SY, SA, SS) for full-text articles that met the inclusion criteria. Data on patient characteristics (sample size, age, sex, tobacco and any other substances smoking history–exposure level and pack-years, comorbidities), publication characteristics (country, journal, source of funding), diagnostic

method (spirometry, patient-reported etc.), diagnostic criteria (GOLD criteria, etc.), and cause of COPD (e.g., tobacco, non-tobacco related) was extracted.

Quality assessment

We used the Newcastle-Ottawa Scale to assess the quality of included literature [10]. The Newcastle-Ottawa Scale is a validation tool that examines literature based on eight items categorized into three groups: study group selection, group comparability, and establishment of exposure and outcomes [11].

Statistical analyses

COPD prevalence was calculated as the number of individuals diagnosed with COPD per total sample population. In studies where the standard deviation (SD) was not available, we calculated it by dividing the length of the 95% confidence interval (CI) by 3.92 and multiplying it by the square root of the sample size. Meta-analysis was performed with Review Manager software (Version 5.4.1). The heterogeneity of each meta-analysis was assessed by visual inspection of the forest plot (e.g. overlapping confidence intervals (CI) and P values), and the I^2 statistic. Previous literature recommends the following interpretation of I^2: 0–40%, might not be important; 30–60%, may represent moderate heterogeneity; 50–90%, may represent substantial heterogeneity; 75–100%, may represent considerable heterogeneity [12]. A random effects model was used to calculate the pooled prevalence.

Results

Search results

We identified 3211 studies in the searches. Twenty-seven duplicates were removed, and of the remainder 3092 were excluded during title and abstract screening, leaving 92 studies for full-text screening. Sixty-four studies were excluded for not reporting primary data stratified by both sex and tobacco exposure, leaving 27 that met the a priori inclusion criteria. Of these, five had data for meta-analysis. (Fig. 1)

Twenty two studies were not incuded in the meta-analysis. Of these 22 studies, three examined populations from the USA, two examined populations from Iran, and two studies examined populations from multiple European countries. A population was studied once in Brazil, Canada, Egypt, Greece, Korea, Saudi Arabia, Spain, Sweden, Taiwan, Tanzania, Turkey, and Vietnam. Five studies collected information on race, which was reported as (n): Asian (1), Black (3), Caucasian (4), East Asian (1), Hispanic (1), American Indian (1), Multiracial (1), Native Hawaiian (1), or other (2). Furthermore, six studies reported education and five studies reported comorbidities.

Two studies reported that the prevalence of COPD among males was higher than among females. Ten studies found that tobacco smoking was associated with COPD, with a separate study finding that women had a higher likelihood of developing COPD due to tobacco smoking than men. Four studies investigated the association of occupational-related exposures with COPD, reporting an increased risk of developing COPD. Sex was associated with the prevalence of COPD according to five studies, in which three studies identified male sex as a risk factor. Four studies found that women with COPD experienced less disease severity but more comorbidities than men with COPD, including but not limited to cardiovascular disease, hypertension, dyslipidemia, anxiety, depression and rheumatoid arthritis. Two studies reported that women and men responded differently to tobacco exposure, in which one study found that women had lower FEV_1% predicted than men among those who currently or formerly smoked tobacco. Seven studies reported an association of increasing age with the prevalence of COPD.

Characteristics of included studies

Of the 27 final studies, six examined study populations from the USA, four examined populations from China, and two involved populations from Iran. A population was studied once in Brazil, Canada, Egypt, Greece, Korea, Saudi Arabia, Spain, Sweden, Taiwan, Tanzania, Turkey, and Vietnam (Table 1). Sixteen studies investigated the effect of tobacco exposure on the prevalence of COPD in both urban and rural communities, whereas 11 only examined urban populations. Moreover, only one study examined solely rural communities [23]. Seven studies collected information on race, which was reported as (n): Asian (1), [17] Black (3), [15, 17, 18] Caucasian (4), [15, 17, 25, 26] East Asian (1) [20], Hispanic (1) [17], Indian, Multiracial (1) [17], Native Hawaiian (1) [17], unknown (1) [17], or other (1) [17]. Furthermore, eight studies reported on education, and six reported on comorbidities.

Quality of screened literature

The quality of the screened literature was assessed as Good and Fair, as per the Newcastle-Ottawa Scale (Table 2). Eight studies had a rating of Good and had high methodological rigour, whereas 20 had a risk of bias rating of Fair. Scores (n articles) involving selection ranged from three (24) to four (4), indicating a low risk of bias in study participant selection. Scores (n) involving the comparability of study participants ranged from one (4) to two (24), indicating a low to moderate risk of bias in controlling for confounding variables across all studies. Scores (n) regarding bias in determining outcomes were zero (1), one (19), and two (8), indicating a high risk of bias

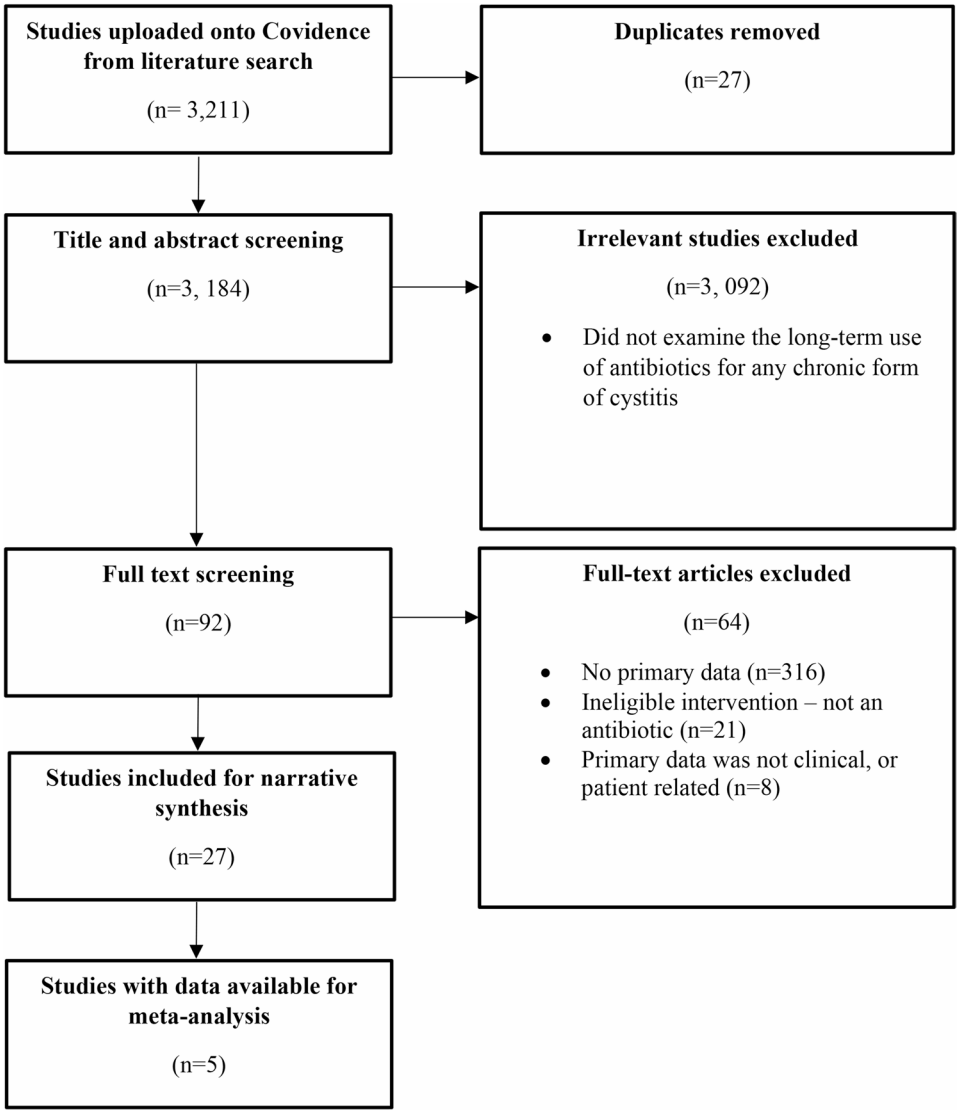

Fig. 1 Study Selection Flow Diagram. PRISMA flow diagram of included studies

in one study, which utilized self-reported patient surveys instead of secure electronic medical records, and a low risk of bias in the remaining studies.

Pooled effect of tobacco exposure on the prevalence of COPD

Five studies included information on the prevalence of COPD as stratified by both sex and tobacco exposure. The prevalence of COPD in males without exposure to tobacco ranged from 0.8 to 12.8% (Fig. 2A). The prevalence of COPD in males with exposure to tobacco ranged from 3.5 to 20.7%. Pooled analysis showed a mean difference of −6.02% [95% CI: −8.35, −3.70] ($p < 0.00001$) in males not exposed compared to those with tobacco exposure. Results for the test for heterogeneity were: $Tau^2 = 4.93$; $Chi^2 = 25.54$; df = 4 ($P < 0.0001$); and $I^2 = 84\%$. The prevalence of COPD in females without exposure to tobacco ranged from 2.1 to 7.6%. The prevalence of COPD in females with tobacco exposure ranged from 6.3 to 18.5% (Fig. 2B). Pooled analysis showed a mean difference of −6.16% [95% CI: −8.47, −3.85] ($p < 0.00001$) in females not exposed to tobacco, compared to those with tobacco exposure. Results for the test for heterogeneity were: $Tau^2 = 2.32$; $Chi^2 = 6.39$; df = 4 ($P < 0.17$); and $I^2 = 37\%$.

Prevalence of COPD vis-à-vis sexually dimorphic response to tobacco

For males not exposed to tobacco, the prevalence of COPD ranged from 0.8 to 12.8%, and for females it was 6.3–18.5% (Fig. 2C). Pooled analysis showed a non-significant trend towards reduction of 3.12% [95% CI: −0.10, 6.35] ($p = 0.06$) of COPD for females compared to males without tobacco exposure. Results for the test

Table 1 Background and Population Characteristics of Eligible Studies

Author & Year	Journal	Diagnostic Method	Country	Location	Duration	Race	Education	Mean (SD) or Range Male Age	Mean (SD) or Range Female Age		Passive Tobacco Smoke Exposure History (*n* and %)	Biomass Fuel Exposure History (*n* and %)	Mean (SD) or Range of Pack Year Smoking History	Co-morbidities	Main Findings
Badway 2016 [13]	Egyptian Journal of Chest Diseases and Tuberculosis	GOLD Criteria	Egypt	Urban/ Rural	Cross-sectional	Not reported	Not reported	40–60+	40–60+	Current smoker 1210, 50.42% Former smoker 165, 6.88% Never smoker 1025, 42.7%	Not reported	Not reported	242,10.08%	Not reported	Prevalence of COPD among males was higher than among females
Bahtouee 2018 [14]	Chronic respiratory disease	GOLD Criteria	Iran	Urban	Four years	Not reported	Primary school; secondary school; high school; university	Not reported	Not reported	Current hookah smoker 245, 50% Never smoker 245, 50%	Not reported	Not reported	Not reported	Not reported	Older age, male gender, smoking, and occupational exposure were independent predictive factors for COPD
Bang 2009 [15]	COPD	Self Reported	USA	Urban/ Rural	Seven years	White; Black; Other	Not reported	18+	18+	Not reported	Not reported	Not reported	Not reported	Not reported	Occupaction, race, sex are associated with the prevalence of COPD
Blanc 2009 [48]	The European respiratory journal	GOLD Criteria	International Europe	Urban/ Rural	Not Reported	Not reported	Not reported	48.9	48.3	61% ever-smoking	22.8	41% occupational exposure 13 years mean exposure	Not reported	Not reported	A higher COPD prevalence was associated with smoking and occupational exposures
Buist 2007 [49]	Lancet	GOLD Criteria	USA	Urban	Not Reported	Not reported	Not reported	52–58	53–60	Crude exposure data separated into never-smoker and ever-smoker	Crude exposure data of mean pack year in 12 different sub-groups	Occupational exposure, crude data	Not reported	Not reported	Although age and smoking are strong contributors to COPD, they do not fully explain variations in disease prevalence- other factors also seem to be important

Table 1 (continued)

Author & Year	Journal	Diagnostic Method	Country	Location	Duration	Race	Education	Mean (SD) or Range Male Age	Mean (SD) or Range Female Age		Passive Tobacco Smoke Exposure History (*n* and %)	Biomass Fuel Exposure History (*n* and %)	Mean (SD) or Range of Pack Year Smoking History	Co-morbidities	Main Findings
Camp 2009	Chest	GOLD Criteria	Canada	Urban	Not Reported	Not reported	Not reported	59.25 (4.82)	56.89 (5.53)	Probands: Currently smoking Females – 59 (46) & Males 49 (34) Siblings: Currently smoking Females – 123 (60) & Males 97 (46)	Probands: Women – 43.09 (18.71) & Men – 56.34 (27.22) Siblings: Women – 34.50 (19.68) & Men – 41.90 (25.97)	Not reported	Not reported	Not reported	Overall, women smokers are about 50% more likely to develop COPD than men
Carrasco-Garrido 2009 [50]	BMC pulmonary medicine	SEPAR Criteria	Spain	Urban/ Rural	Cross sectional	Not reported	Parents with no schooling; primary school; secondary school; university	67.4 (9.2)	66.1 (10.8)	Current smoker 2046, 19.1% Former smoker 6179, 57.7% Never smoker 2485, 23.2%	Not reported	Not reported	Not reported	Allergy; anxiety; depression; diabetes mellitus; heart disease; hypertension; heart disease; other	The women with COPD evaluated in this study were younger, smoked less and have more comorbidity, a poorer quality of life, and lesser disease severity than men with COPD
Chen 2000 [16]	Journal of clinical epidemiology	Survey	Canada	Urban/ Rural	1 year (1994–1995)	Not reported	Low; high; unknown	25–64	25–64	Male: Current smoker 1296, 3.5% Former smoker 155, 2.7% Never smoker 1029, 0.8% Female: Current smoker 1093, 8.2% Former smoker 276, 2.7% Never smoker 1575, 2.1% Total: Current smoker 2389, 11.7% Former smoker 431, 5.6% Never smoker 2604, 2.9%	Not pack years but cigarettes/ day Ex-Smoker Male: <20: 2.7% 20+: 3.1% Current Smoker Male: <20: 1.8% 20+: 4.3% Ex-Smoker Female: <20: 2.5% 20+: 2.9% Current Smoker Female: <20: 5.0% 20+: 10.9% Ex-Smoker Total: <20: 5.2% 20+: 6% Current Smoker Total: <20: 6.8% 20+: 15.2%	Not reported	Not reported	Not reported	Early initiation of smoking and being overweight had stronger relationships to the prevalence of COPD in women than in men

Table 1 (continued)

Author & Year	Journal	Diagnostic Method	Country	Location	Duration	Race	Education	Mean (SD) or Range Male Age	Mean (SD) or Range Female Age		Passive Tobacco Smoke Exposure History (*n* and %)	Biomass Fuel Exposure History (*n* and %)	Mean (SD) or Range of Pack Year Smoking History	Co-morbidities	Main Findings
Chung 2020 [58]	BMC public health	Not Reported	Taiwan	Urban/ Rural	Three years	Not reported	Not reported	40+	40+	Smoking Status: Ever smoker Total: 10,363, 39.29% Ever smoker Male: 7065, 68.18%. Ever smoker Female: 3298, 31.82% Never smoker Total: 16,012, 60.71% Never smoker Male: 5714, 35.69% Never smoker Female: 10,298, 64.31%	Not reported	Not reported	Not reported	Coronary artery disease, stroke, hypertension	Sex, age, insured categories, residence in suburban areas, and COPD were associated with smoking in people
Cunningham 2015 [17]	COPD: Journal of Chronic Obstructive Pulmonary Disease	Not Reported	USA	Urban/ Rural	Three months	White; Black; Asian; Native Hawaiian; American Indian; Hispanic; Multiracial; Other	None; high school; technical school; graduated high school or technical school	10+	18+	In Study Total: Current smoker 60,446, 14.9% Former smoker 126,784, 31.2% Never smoker 218,356, 53.9% Among Those with COPD: Current smoker 59,600, 16.0% Former smoker 100,574, 27.0% Never smoker 212,324, 57.0% Among those without COPD: Current smoker 33,088, 36.7% Former smoker 12,143, 39.2% Never smoker 12,970, 24.1%	Not reported	Not reported	Not reported	Arthritis; asthma; cancer; coronary heart disease; depression; diabetes; high cholesterol; hypertension; kidney disease; stroke	Current and former cigarette smokers were more likely than never smokers to have COPD and most of the other chronic diseases examined

Table 1 (continued)

Author & Year	Journal	Diagnostic Method	Country	Location	Duration	Race	Education	Mean (SD) or Range Male Age	Mean (SD) or Range Female Age		Passive Tobacco Smoke Exposure History (*n* and %)	Biomass Fuel Exposure History (*n* and %)	Mean (SD) or Range of Pack Year Smoking History	Co-morbidities	Main Findings
deMarco 2011 [51]	American journal of respiratory and critical care medicine	GOLD Criteria	10 European countries	Urban	Multiple time periods	Not reported	Not reported	20–44	20–44	Not reported, incidence rate ratio is but hard to reverse calculate without base rates	Not reported	Not reported	Not reported	Not reported	Airway hyper-responsiveness, a family history of asthma, and respiratory infections in childhood are important determinants of COPD
Fang 2018 [52]	The Lancet Respiratory Medicine	GOLD Criteria	China	Urban/ Rural	1 year	Not reported	Primary and lower; secondary; high school and higher	54.7 (10.9)	55.0 (11.3)	Never smoker 40 070/66 567 (59·8%) Former smoker 6438/66 567 (8·8%) Current smoker 20 059/66 567 (31·4%)	None to less than ten 5801/24 775 (23·4%) Ten to less than 25 6593/24 775 (26·6%) 25 to less than 50 8610/24 775 (34·8%) 50 or more 3771/24 775 (15·2%)	Exposure to dust or chemicals in the workplace29 808/66 722 (46·6%)	8 914/66 686 (40·7%)	Not reported	The prevalence of COPD differed significantly between men and women, mainly because of a significant difference in smoking status between men and women
Foreman 2011 [18]	American journal of respiratory and critical care medicine	ATS Criteria	USA	Urban	Not Reported	White; Black	Not reported	45–80	45–80	Subject with Early-Onset COPD: Current smoker: 39, 56% Older Subjects with COPD: Current smoker: 52, 17% Total subjects: Current smoker: 91, 24%	Subject with Early-Onset COPD: Current smoker: 42 (24) Older Subjects with COPD: Current smoker: 61 (30)	Subjects with Early-Onset COPD: Maternal Smoking: 49 & 70% Paternal Smoking: 55 & 78% Older Subjects with COPD: Maternal Smoking: 135 & 44% Paternal Smoking: 236 & 77% Total subjects: Maternal Smoking: 184 & 49% Paternal Smoking: 291 & 77%	Not reported	Not reported	Severe, early-onset COPD is prevalent in females and is influenced by maternal factors

Table 1 (continued)

Author & Year	Journal	Diagnostic Method	Country	Location	Duration	Race	Education	Mean (SD) or Range Male Age	Mean (SD) or Range Female Age		Passive Tobacco Smoke Exposure History (*n* and %)	Biomass Fuel Exposure History (*n* and %)	Mean (SD) or Range of Pack Year Smoking History	Co-morbidities	Main Findings
Grahn 2021 [19]	Environmental research	GOLD Criteria	Sweden	Urban	Not Reported	Not reported	Pre-secondary; secondary; post-secondary	25–70	25–70	COPD: - Never Smoker: 339, 15.9% - Ever Smoker: 1792, 84.1% Non-COPD: Never Smoker: 20,317, 48.9% Ever Smoker: 21,229, 51.1%	All in Median Unexposed to Biomass/Fuel COPD: - Male: 23.0 - Female: 20.0 Non-COPD: - Male: 15.0 - Female: 12.0 Exposed to Biomass/Fuel COPD: - Male: 26.0 - Female: 21.0 Non-COPD: - Male: 18.3 - Female: 13.8	Not reported	COPD: Never Smoker: - Male: 50, 14% - Female: 29, 18% Ever Smoker: - Male: 296, 86% - Female: 129, 82% Non-COPD: Never Smoker: - Male: 2437, 43% - Female: 1204, 52% Ever Smoker: - Male: 3169, 57% - Female: 1118, 48%	Not reported	A positive exposure-response relationship was found for RCS, gypsum and insulation, diesel exhaust, and welding fumes. Also, exposure to high levels of asphalt/bitumen and various organic particles was associated with a higher risk for COPD.
Gunen 2008 [53]	European Journal of Internal Medicine	BOLD, ERS/ATS	Turkey	Urban/ Rural	Not Reported	Not reported	Not reported	19–70	19–70	Only for current smokers All Patients: 477, 41.1% Male: 327, 57.2% Female: 150, 25.5	Not reported	Not reported	All Patients: 393, 33.9% Male: 194, 33.9% Female: 199, 33.8%	Not reported	Smoking leads to COPD more frequently than previously known, and it has an increasing trend with age

Table 1 (continued)

Author & Year	Journal	Diagnostic Method	Country	Location	Duration	Race	Education	Mean (SD) or Range Male Age	Mean (SD) or Range Female Age		Passive Tobacco Smoke Exposure History (*n* and %)	Biomass Fuel Exposure History (*n* and %)	Mean (SD) or Range of Pack Year Smoking History	Co-morbidities	Main Findings
Kiani 2021 [54]	BMC pulmonary medicine	GOLD and LLN criteria	Iran	Urban/ Rural	Not Reported	Not reported	Illiterate; <5 years; 6–8 years; 9–12 years; >12 years	35–70	35–70	Total Current smoker: 1288, 16.1% Former smoker: 612, 7.7% Never smoker: 6078, 76.2% Male: Current smoker: 1272, 33.3% Former smoker: 596, 15.6% Never smoker: 1956, 51.2% Female: Current smoker: 16, 0.4% Former smoker: 16, 0.4% Never smoker: 4122,99.2%	Total 1–10: 974 & 12.2% 10–20: 583 & 7.3% >20: 343 & 4.3% Male 1–10: 777 & 20.3% 10–20: 712 & 18.6% >20: 379 & 9.9% Female 1–10: 32 & 0.8% 10–20: 0 & 0% >20: 0 & 0%	Not reported	Total Gas: 5198, 65.2% Oil/gasoline: 1801, 22.6% Wood/ firewood/ animal dung: 979, 12.3% Male Gas: 2519, 65.9% Oil/ gasoline: 868, 22.7% Wood/ firewood/ animal dung: 437, 11.4% Female Gas: 2679, 64.5% Oil/ gasoline: 933, 22.5% Wood/ firewood/ animal dung: 542, 13%	Cardiovascular disease; chronic lung diseases; hypertension; diabetes mellitus; dyslipidemia; metabolic syndrome; anxiety and depression; musculoskeletal disorders; rheumatoid arthritis; osteoporosis; fatty liver	Age, fewer years of schooling, a smoking history of 10 or more pack years were associated with COPD

Table 1 (continued)

Author & Year	Journal	Diagnostic Method	Country	Location	Duration	Race	Education	Mean (SD) or Range Male Age	Mean (SD) or Range Female Age		Passive Tobacco Smoke Exposure History (*n* and %)	Biomass Fuel Exposure History (*n* and %)	Mean (SD) or Range of Pack Year Smoking History	Co-morbidities	Main Findings
Lam 2014 [20]	COPD	GOLD	Vietnam	Urban/ Rural	One year	East Asian	Not reported	50–60	50–60	Age < 50 Male: Current smoker: 99, 63.5% Former smoker: 21, 13.5% Never Smoker: 35, 22.6% Female: Current smoker: 2, 1.1% Former smoker: 0, 0% Never Smoker: 188, 98.9% Age > 50 Male: Current smoker: 61, 59.8% Former smoker: 27, 26.5% Never Smoker: 14, 13.7% Female: Current smoker: 0, 0% Former smoker: 1, 0.8% Never Smoker: 11, 99.2%	Not reported	Not reported	Not reported	Not reported	Age, smoking and sex are associated with the prevalence of COPD
Li 2018 [21]	The Journal of international medical research	GOLD criteria	China	Urban	Two years	Not reported	Not reported	59.9 (4.6)	59.2 (5.6)	Male: Current Smoker: 119, 45% Former Smoker: 56, 21.2% Never Smoker: 89, 33.8% Female: Current Smoker: 10, 10.5% Former Smoker: 10, 10.5% Never Smoker: 75, 78.9%	Male: 38.4 (16.7) Female: 29.1 (10.7)	Not reported	Not reported	Not reported	FEV1% pred was significantly lower in women than men in the smoking and smoking cessation groups. Sex-related differences may partially explain why smoking women experience more severe pulmonary function impairment than men among patients with COPD

Table 1 (continued)

Author & Year	Journal	Diagnostic Method	Country	Location	Duration	Race	Education	Mean (SD) or Range Male Age	Mean (SD) or Range Female Age		Passive Tobacco Smoke Exposure History (*n* and %)	Biomass Fuel Exposure History (*n* and %)	Mean (SD) or Range of Pack Year Smoking History	Co-morbidities	Main Findings
Machado 2006 [22]	American Journal of Respiratory and Critical Care Medicine	GOLD Criteria	Brazil	Urban/ Rural	Seven years	Not reported	Not reported	69.3 (7.2)	62.9 (6.5)	Not reported	Total: 69.6 (30.1) Male: 72.5 (30.1) Female: 65.7 (29.8)	Not reported	Not reported	Charlson Comorbidity Index	After accounting for potential confounders (age, pack-years smoked, PaO2), among patients with COPD on long term O2 therapy, women were more likely to die than men.
Magitta 2018 [23]	The European respiratory journal	GOLD criteria	Tanzania	Rural	Not Reported	Not reported	Not reported	30+	30+	COPD smoker: 33, 37.9% No COPD smoker: 92, 22.5% All Subjects: Current Smoker: 371, 74.8% Former Smoker: 98, 19.8% Current Smoker: 27, 5.4%	Of the 496 pts, 27 were analyzed for Fagerstrom-based nicotine dependency and 12 pts provided data on pack-years: Low-to-moderate dependency: 11.69 (11.84) Significant dependency: 8.54 (4.88)	Not reported	Not reported	Not reported	Tuberculosis, smoking and male sex are important risk factors for COPD
Papaioannou 2014 [24]	International journal of chronic obstructive pulmonary disease	GOLD Criteria	Greece	Urban	Cross-sectional	Not reported	Not reported	69	64	Male: Current Smoker: 1982, 46% Former Smoker: 2061, 47.9% Never Smoker: 262, 6.1% Female: Current Smoker: 887, 52.4% Former Smoker: 458, 27.3% Never Smoker: 349, 20.6%	Mean (interquartile range) Male: 52 (36–75) Female: 35 (22–50)	Not reported	Not reported	Not reported	Female patients were characterized by milder forms of the disease, but comorbidities were more prevalent in men

Table 1 (continued)

Author & Year	Journal	Diagnostic Method	Country	Location	Duration	Race	Education	Mean (SD) or Range Male Age	Mean (SD) or Range Female Age		Passive Tobacco Smoke Exposure History (*n* and %)	Biomass Fuel Exposure History (*n* and %)	Mean (SD) or Range of Pack Year Smoking History	Co-morbidities	Main Findings
Sverzellati 2009 [25]	The European respiratory journal	GOLD criteria	Italy	Urban	Two years	White	Not reported	58.1 (5.9)	57.56 (5.9)	Male: Current Smoker: 414, 67.4% Former Smoker: 198, 32.2% Female: Current Smoker: 266, 77.5% Former Smoker: 75, 21.8%	Male: 46.30 (22.1) Female: 38.35 (17.8)	Not reported	Not reported	Not reported	Males and females respond differently to the type and location of lung damage due to tobacco exposure
Thompson 2010 [26]	Respiratory care	ICD-9 diagnostic codes	USA	Urban	Cross-sectional	White; Unknown; Other	Not reported	50+	50+	Total: Current Smoker: 8149, 38.9% Former Smoker: 279, 0.1% Never Smoker: 12,478 & 59.7% Male: Current Smoker: 7730, 94.8% Former Smoker: 268, 96.1% Never Smoker: 11,724, 94.0% Female: Current Smoker: 419, 5.2% Former Smoker: 11, 3.9% Never Smoker: 754, 6%	Not reported	Not reported	Not reported	Not reported	Smomking, age and male sex were significant risk factors for COPD
Wali 2014 [55]	Saudi medical journal	GOLD Criteria	Saudi Arabia	Urban/ Rural	Cross sectional	Not reported	Not reported	40–60+	40–60+	Total: 2138, 22.3% Male: 1994, 31.9% Female: 144, 0.4%	Male: 25.4 (23.7) Female: 17.9 (22.0)	Not reported	Not reported	Not reported	Male, age, and smoking were the main risk factors for COPD

Table 1 (continued)

Author & Year	Journal	Diagnostic Method	Country	Location	Duration	Race	Education	Mean (SD) or Range Male Age	Mean (SD) or Range Female Age		Passive Tobacco Smoke Exposure History (*n* and %)	Biomass Fuel Exposure History (*n* and %)	Mean (SD) or Range of Pack Year Smoking History	Co-morbidities	Main Findings
Wang 2018 [27]	Lancet	GOLD Criteria	China	Urban/ Rural	Three years	Not reported	Primary school or less; middle and high school; college and higher	20+	20+	Male: Current Smoker: 10,978,9.8% Former Smoker: 2626, 9.7% Never Smoker: 7842, 40.6% Female: Current Smoker: 746, 2.2% Former Smoker: 212, 0.6% Never Smoker: 28,587, 97.2%	Male: 0 pack-years: 7842 & 43.6% 1–9 pack-years: 3018 & 18.2% 10–19 pack-years: 2635 & 14.1% >20 packyears: 6578 & 24.1% Female: 0 pack-years: 28,587 & 97.5% 1–9 pack-years: 361 & 1.0% 10–19 pack-years: 164 & 0.5% >20 packyears: 285 & 1.0%	Male: 6881 & 35.2% Female: 16,342 & 56.5%	Male: 5866, 26.4% Female: 16,342, 56.5%	Pneumonia or bronchitis in childhood; tuberculosis	Cigarette smoking, ambient air pollution, underweight, childhood chronic cough, parental history of respiratory diseases, and low education are major risk factors for COPD
Yoo 2011 [56]	Respirology	GOLD Criteria	Korea	Urban/ Rural	Cross-sectional	Not reported	Elementary school or lower; middle school; high school; college or higher	19+	19+		Not reported	Not reported	Not reported	Not reported	The prevalence of COPD was significantly higher in men than in women and increased with age

Table 1 (continued)

Author & Year	Journal	Diagnostic Method	Country	Location	Duration	Race	Education	Mean (SD) or Range Male Age	Mean (SD) or Range Female Age		Passive Tobacco Smoke Exposure History (*n* and %)	Biomass Fuel Exposure History (*n* and %)	Mean (SD) or Range of Pack Year Smoking History	Co-morbidities	Main Findings
Zha 2019 [57]	BMC Pulmonary Medicine	GOLD Criteria	China	Urban/ Rural	Cross sectional	Not reported	Primary school or lower; secondary school; higher	53.6	53.9	Total Current smoker: 780, 28.5% Former smoker: 231, 7.7% Never smoker: 1758, 55.0% Male: Current smoker: 756, 51.5% Former smoker: 219, 15.2% Never smoker: 386, 17.7% Female: Current smoker: 24, 1.8% Former smoker: 12, 0.8% Never smoker: 1372, 97.4%	Total =0 pack-years: 1754 & 64.9% 0–15 pack-years: 269 & 11.2% 15–30 pack-years: 297 & 10.7% 30 + packyears: 398 & 13.1% Male: =0 pack-years: 385 & 28.4% 0–15 pack-years: 251 & 14.4% 15–30 pack-years: 292 & 22.5% 30 + packyears: 389 & 27.0% Female: =0 pack-years: 1369 & 97.8% 0–15 pack-years: 18 & 1.4% 15–30 pack-years: 5 & 0.2% 30 + pack years: 9 & 0.6%	Not reported	Total: 961, 40.8% Male: 489, 37.5% Female: 472, 43.9%	Not reported	Tobacco smoking and indoor air pollution (exposure to coal for cooking or heating) are major preventable risk factors for the disease in Anhui

Table 2 Quality assessment using the Newcastle-Ottawa scale of eligible cohort studies

Study, year	Selection	Comparability	Outcome	Quality
Badway 2016 [13]	3	2	1	Fair
Bahtouee 2018 [14]	3	1	1	Fair
Bang 2009 [15]	3	2	1	Fair
Blanc 2009	3	2	1	Fair
Buist 2007	3	2	1	Fair
Camp 2009	3	2	1	Fair
Carrasco-Garrido 2009	3	2	1	Fair
Chen 2000 [16]	4	2	1	Fair
Chung 2020	3	2	2	Good
Cunningham 2015 [17]	3	1	0	Fair
deMarco 2011	3	2	2	Good
Fang 2018	4	2	1	Fair
Foreman 2011 [18]	3	2	2	Good
Grahn 2021 [19]	3	2	1	Fair
Gunen 2008	3	2	2	Good
Kiani 2021	3	2	2	Good
Lam 2014 [20]	3	2	1	Fair
Li 2018 [21]	3	2	1	Fair
Machado 2006 [22]	3	2	1	Fair
Magitta 2018 [23]	3	2	1	Fair
Papaioannou 2014 [24]	3	2	2	Good
Sverzellati 2009 [25]	3	2	2	Good
Thompson 2010 [26]	3	2	1	Fair
Wali 2014	3	1	1	Fair
Wang 2018 [27]	4	2	2	Good
Yoo 2011	3	2	1	Fair
Zha 2019	4	2	1	Good

Scores involving selection ranging from three to four indicate a low risk of bias in study participant selection. Scores involving the comparability of study participants ranging from one to two indicate a low to moderate risk of bias in controlling for confounding variables across all studies

for heterogeneity were Tau = 12.48; $Chi^2 = 107.22$; df = 4 ($P < 0.00001$); and $I^2 = 96\%$. In males exposed to tobacco, the prevalence of COPD ranged from 3.5 to 20.7%, and in females it was 6.3–18.5% (Fig. 2D). Pooled analysis showed a reduction of 1.53% [95% CI: −5.83, 8.89] ($p = 0.68$) in females compared to males with tobacco exposure. Results for the test for heterogeneity were: $Tau^2 = 54.02$; $Chi^2 = 53.15$; df = 4 ($P < 0.00001$); and $I^2 = 92\%$.

Discussion

We evaluated the association between sex, tobacco smoking status, and developing COPD by performing a meta-analysis of COPD prevalence in 163,450 individuals across five cohorts and identified differences in prevalence according to sex and smoking status [16, 26–29]. Our findings showed no statistically significant trend towards reduced COPD in women at baseline with no tobacco exposure compared to men, as well as a trend towards reduced prevalence with tobacco exposure. However, evidence regarding sex, COPD, and tobacco exposure was diverse, and more research on the prevalence of COPD and sex-specific risk factors is needed. Although the prevalence of COPD was not statistically significant, women have different clinical outcomes to tobacco [24, 25]. There is an obvious sexually dimorphic response in the development of COPD in both populations when exposed to tobacco compared to no exposure [13–15].

The role of tobacco

Tobacco exposure is overwhelmingly responsible for the development of COPD [17]. Risk factors for tobacco exposure and dependence have been previously identified and include age, sex, genetics, depression, substance use,

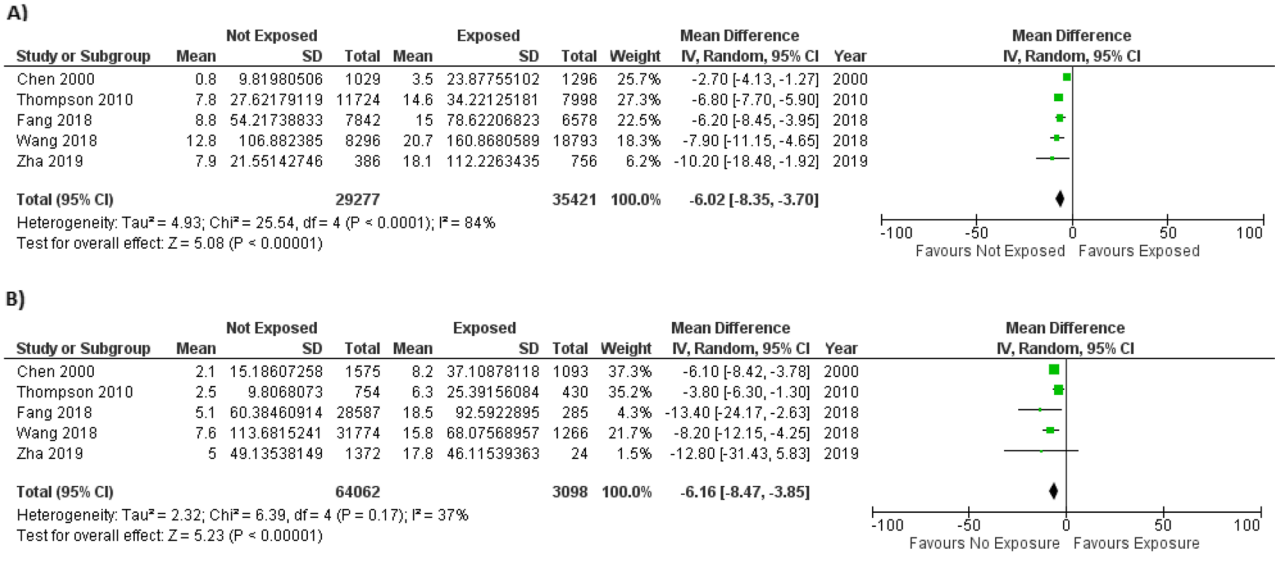

Fig. 2 Effect of tobacco exposure on COPD prevalence in (**A**) males and (**B**) females

education, income, race, and geographic location [16, 17, 28, 30]. It is imperative to examine the relationship between sex and COPD having corrected for tobacco exposure and other moderating variables, as females were found to have greater tobacco-related co-morbidities such as airway hyper-responsiveness, asthma, respiratory infections in childhood, cardiovascular disease, anxiety, depression, and rheumatoid arthritis [19, 27, 29, 31]. A previous study found that predicted forced expiratory volume in 1 s (FEV_1%) was significantly lower in women than men in both groups, who did and did not stop tobacco smoking [21]. On the other hand, women had significantly higher predicted FEV_1% in the group without active tobacco smoking history, as compared to males who did not smoke tobacco. Therefore, women experience a greater detrimental response to tobacco exposure than their male counterparts [21]. A study from Greece found that women had milder forms of disease and men had more comorbidities [24]. In contrast, a study from Brazil, found that after correcting for potential confounders including age, smoking pack-years, and the partial pressure of oxygen in the blood, women were more likely to die than men [22]. Overall, studies from different geographic regions have heterogenous findings.

Tobacco and Estrogen

Estrogens have long been known to be active inflammatory mediators in asthma pathogenesis [32]. Although their role in COPD pathogenesis is not clear, estrogens are inflammatory response modulators in COPD., In COPD, cytotoxic lymphocytes in the airways are markedly elevated with higher levels of estrogen playing a protective role [23]. A study measuring the impact of hormone-replacement therapy on FEV_1% predicted in post-menopausal women found that those using hormone-replacement therapy (HRT) had a higher FEV_1% predicted and less obstruction, compared to those not using HRT [17]. Early menopause is associated with a higher risk of COPD-related hospitalizations and death [33]. Furthermore, oral contraceptives are associated with lower risks of COPD-related hospitalizations, death, and a higher FEV_1 and forced vital capacity [33].

Tobacco and testosterone

Androgens protect against asthma symptoms and exacerbations in men, with childhood asthma disappearing during adolescence and reappearing in the fifth decade of life – this closely follows the ebb and flow of androgen production across a lifetime. Higher levels of testosterone and dehydroepiandrosterone in men are associated with greater lung capacity and airway calibre, suggesting a protective role in other inflammatory lung pathologies including COPD [34]. A 2019 study investigated the role of testosterone replacement therapy (TRT) in men with COPD, and found that TRT decreased the rate of COPD-related hospitalizations and slowed the progression of the disease [35]. Total and free testosterone levels are elevated in males who smoke tobacco compared to males who do not smoke. Testosterone levels are similar in those who never smoked or formerly smoked, indicating a dose-dependent effect of cigarette smoking on testosterone production [36]. More than half of the participants in a 2012 study of COPD had a testosterone level of less than 2.8ng/ml. When comparing serum testosterone with the severity of COPD, the lower the testosterone the more severe the COPD [37, 38].

Tobacco and prolactin

Increased plasma nicotine directly correlates with increased prolactin levels and acutely raises prolactin in a dose-dependent manner [38]. Also, increased serum prolactin decreases the secretion of gonadotropin-releasing hormone (GnRH) [39, 40]. With GnRH chronically suppressed, less estrogen and testosterone are produced. This hormonal pathway may partially explain the difference in pathophysiology and predisposition for COPD of men compared to women. In both sexes, testosterone and estrogen may play a protective role, but women may experience worse COPD outcomes than men due to more significant decreases of estrogen with age.

Proteomic, Genetic, and epigenetic consequences of tobacco smoking

Cigarette smoking results in a distinct and long-lasting epigenetic signature caused by DNA methylation. This prominent consequence has the potential to elucidate how cigarette smoking predisposes individuals to multiple disorders including those of a respiratory nature [41]. Quantifying epigenetic age acceleration is possible thanks to measures such as GrimAge acceleration (GrimAA), which relies on analyzing these DNA methylations to create an inferred age. Those who were smoking currently displayed an almost 5-year increase in GrimAA compared to their chronological age. When stratifying by sex, females who smoke showed a 3.85-year increase and males showed a 7.37-year increase in GrimAA compared to their chronological age, indicating a sexually dimorphic response to cigarette smoking [42]. This study provides further evidence for a protective effect of estrogen in cigarette smoking-related pathologies.

Cigarette smoking alters the proteome of the respiratory tract. However, a recent study showed that levels of 81 out of 203 total proteins detected in the respiratory tract are significantly altered in people who currently smoke. When comparing women to men, the proteomic differences are markedly increased in women, particularly when investigating proteins of the complement pathway [43]. This sex-related difference may also shed

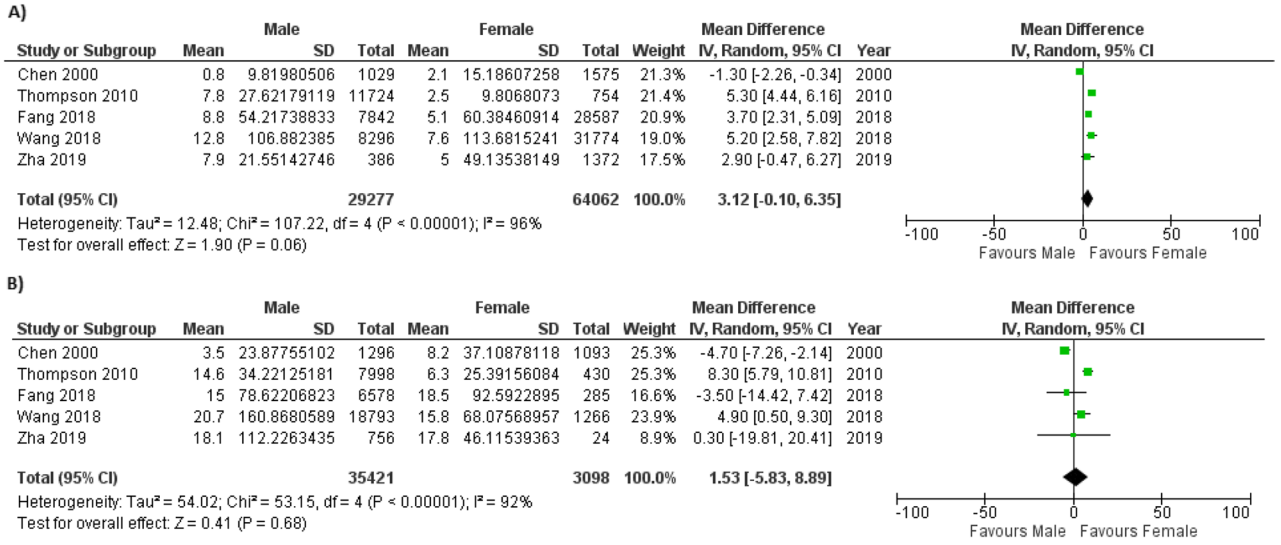

Fig. 3 Effect of sex on COPD prevalence in those with (**A**) tobacco exposure and those (**B**) without tobacco exposure

light on the differing predispositions of women and men to COPD. While considering the consequences of genetic expression in cigarette smoking, a 2014 study found that 175 genes were differentially expressed in males who smoke compared to those who do not smoke, and 237 genes were differentially expressed in females who smoke compared to those who do not smoke [44].

Limitations

A limitation of the studies that we examined was that the authors of included articles herein did not control for the potential of second-hand smoke exposure in populations that were not actively exposed to tobacco. This would bias the results towards the null, whereby a difference in COPD prevalence would be more difficult to detect. There is also limited quality of data reporting tobacco smoke exposure, as it is primarily reported as a binary risk factor with no further details. Furthermore, there is a lack of data reporting duration and intensity of tobacco smoke exposure. Rates of COPD also differed between countries, potentially due to environmental, cultural, genetic, geographical, socioeconomic, political, and structural factors or other reasons that could not be controlled.

Conclusions

Our meta-analysis of 163,450 individuals across five cohorts conducted showed that women have no statistically significant lower prevalence of COPD compared to men. Narrative synthesis showed that women have worse outcomes, such as earlier mortality and decreased FEV_1% predicted. Tobacco exposure is overwhelmingly responsible for the development of COPD, and as such, tobacco dependence management is the mainstay of non-pharmacologic COPD treatment [45]. Estrogen and androgens may have protective effects against COPD, but smoking-induced hypogonadism may diminish this effect. Menopause could also be a large contributor to worse COPD outcomes in women. Cigarette smoking also has a long-lasting epigenetic signature through DNA methylation, which may contribute to the predisposition toward respiratory disorders in those who smoke tobacco. Overall, this study highlights the importance of sex-specific considerations in understanding the pathophysiology and development of COPD, in addition to environmental, cultural, genetic, geographical, socioeconomic, political, and structural factors and underlines the need for further research into this topic, as many other reviews have emphasized [46] (Fig. 3).

Supplementary Information

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Supplementary Material 1.

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Authors contributions

RC: conceptualization and original draft; MP: investigation; MC: original draft; JW: invsetigation; RG: investigation; SY: investigation; DLN: investigation; SAA: investigation; SS: investigation; AX: investigation; PA: invsetigation; RF: investigation; RS: investigation; SP: conceptualization and original draft.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

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