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Parental COPD as a Risk Factor for the Development of COPD and Disease Severity in Offspring: A Systematic Scoping Review

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Background: There is sparse literature on parental chronic obstructive pulmonary disease (COPD) as a risk factor for the development of COPD in adult offspring, and the impact on disease severity. We aimed to map the literature reporting on the prevalence of and/or association between parental COPD and COPD in offspring, and to evaluate whether or not the literature reports on the severity of COPD or other health-related outcomes in offspring with parental COPD.

Methods: A systematic literature search in Embase and Ovid MEDLINE was performed in June 2021. Search terms revolved around COPD and predisposition.

Results: Thirteen studies were identified: 10 case–control studies, two cross-sectional studies and one cohort study. Population size varied from 44 to 2668 offspring cases; the distribution of female cases varied from 5% to 80% and mean age ranged from 27 to 65. Nine studies used an antecedents approach and evaluated the prevalence of parental COPD in patients with COPD, which ranged from 19% to 58%. Four studies used a descendants approach, by identifying patients with COPD and subsequently evaluated prevalence of COPD in their offspring, and found a prevalence of 0% to 17%. Apart from one, all the studies found an increased odds ratio for COPD in individuals with parental COPD. Four studies reported on parental smoking history and nine studies reported on smoking history in offspring. Three studies evaluated the association between parental COPD and COPD-related outcomes in patients with COPD.

Conclusion: This review indicates that parental COPD is associated with a higher risk of COPD in offspring. The literature is sparse, and we identified a knowledge gap on whether parental COPD is a risk factor for severe COPD and other health conditions in offspring.

Keywords: COPD severity, disease predisposition, familial predisposition, family history

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality worldwide, with an estimated prevalence of 10%.[1–3] Although the etiology of COPD is not yet fully understood, there seems to be consensus that several environmental and genetic factors and their interactions are involved in its development.[4] Tobacco smoking is the single most important risk factor for developing COPD, yet more than half of smokers do not develop COPD. This indicates that the susceptibility for developing COPD also depends on other environmental factors and genetic factors.[5–7] Alpha-1-antitrypsin deficiency is the only well-established hereditary defect known to cause emphysema (among smokers).[4] Several studies have investigated other possible genes that might alter the susceptibility and thereby increase the risk of developing COPD, but no consensus has been reached.

Recent research on lung function trajectories shows that low peak lung function in early adulthood increases the risk of COPD later in life and is associated with a higher prevalence of respiratory, cardiovascular, and metabolic comorbidities and premature death.[8,9] A recently published meta-analysis[10] found an association between risk of COPD in

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adulthood and early life factors, such as maternal smoking, low birth weight, childhood respiratory infections and childhood asthma.

Family history of COPD is often cited in the literature as a known risk factor for developing COPD,[11–14] and can reflect both shared environmental exposures and genetics. The definition of family history, however, differs between studies and can include all first-degree relatives (parents, children and siblings). Parental and sibling COPD are often combined as the family history exposure,[11,13] but it is important to distinguish between these. Parental and sibling COPD exposure both reflect genetics and shared environmental factors from the time of pregnancy and during childhood and adolescence, but siblingship also reflects different environmental exposures from the time siblings leave home. A systematic review from 2017[14] addressed parental COPD as a risk factor for developing COPD in adulthood and included eight studies, of which five were eligible for meta-analysis. They found a pooled prevalence of 29% for parental COPD in individuals with COPD, and an odds ratio (OR) for COPD in individuals with parental COPD of 1.57 (95% confidence interval (CI) 1.29–1.93), compared with individuals without COPD.

We hypothesize that parental COPD is a predisposing factor for the development of COPD in offspring and for more severe COPD and poor health outcome in adult offspring. Given the emerging interest in the origin of COPD and early life risk factors[15] we expected new literature had been published since the review from 2017.[14] A scoping review was found most suitable for an identification of the types of available evidence and possible knowledge gaps,[16] given that there is a lack of studies identified in the review from 2017 designed to systematically assess parental COPD as a predisposing factor for developing COPD in offspring.[14] The aim was to chart the literature on parental COPD as a predisposing factor for COPD in offspring and, secondly, to evaluate whether or not the literature reports on the severity of COPD or other health-related outcomes in offspring with parental COPD.

Methods

A research protocol was developed in accordance with the guidelines outlined in the Joanna Briggs Institute Manual for Evidence Synthesis[17] and is available upon request from the corresponding author. Reporting followed the Preferred reporting items for systematic reviews and meta-analyses extension for scoping reviews (PRISMA-ScR) guidelines.[18] The inclusion criteria for both parental and offspring COPD were broad, in order to also capture studies using definitions other than COPD. COPD was introduced in the International Classification of Diseases coding version 10 (ICD-10) in 1992, and definitions such as emphysema and chronic bronchitis (CB) were formerly used. We defined COPD as COPD, emphysema, CB, "chronic respiratory symptoms" or "chronic respiratory diseases". No criteria on how COPD was diagnosed were applied; hence, the diagnosis could be based on spirometry, self-reported information or medical records. Studies that did not specify exposure as parental, maternal or paternal were excluded (eg, studies only reporting first-degree relatives). Studies evaluating genetics as an outcome or looking at specific familiar genetics (eg, alpha-1-anti-trypsin deficiency) and studies investigating specific exposure groups (eg, occupational) were excluded. The search was not restricted by any time period, age range or geographical limitations. Studies written in languages other than English or Nordic languages were excluded. Only original reports were included.

An initial, limited search was conducted to identify relevant articles and extract key words related to these, to build the final search strings. A second search was then conducted, using the identified keywords and index terms. The search strategy was built up around 1) COPD and 2) predisposition, within Embase and Ovid MEDLINE, assisted by a research librarian. The final search was performed on 16 June 2021. (Tables S1 and S2 display the detailed search strategy.)

A two-stage search strategy was used to identify eligible studies. Duplicates were removed using a systematic review software program (Covidence),[19] and two authors (MGS and AKS) reviewed the title and abstracts from all studies resulting from the search. The articles eligible for full-text review were then reviewed by MGS and AKS. Disagreements were solved by discussion and, if necessary, a third author (AL) made the final decision. Finally, the reference section in each included article was searched for relevant articles.

Study characteristics and results for each study included in the review were charted in predefined tables by MGS, with input from AKS and AL. The tables were structured so that the studies using an antecedents approach (ie, evaluating parental COPD in offspring with COPD) come first and the studies using a descendants approach (ie, identifying patients

with COPD and subsequently evaluated prevalence of COPD in their offspring) come last. A crude OR was estimated in case–control studies, if OR was not presented in the study and data were available.

Results

Study Overview

After removing duplicates, 3780 studies were screened and 105 studies were found eligible for full-text review. In total, 13 studies were included in the review (Figure 1). The systematic search resulted in 11 publications; subsequently, two additional studies were included, following perusal of references. Moll et al[20] used data from the COPDGene study and then replicated the study by using data from the ECLIPSE cohort. Results from the two analyses are displayed as two separate studies in the Results section (Tables 1–3).

Table 1 displays the characteristics of the included studies. The studies were conducted in USA,[20–26] Europe,[27–29] Asia[30,31] and one was a multicentre study (ECLIPSE study).[20] Six studies were published before 2010.[21,23–25,29,30]

Three studies used cross-sectional data from the COPDGene study.[20,22,26] However, because these three studies had different aims and outcomes and, importantly, given that no synthesizing of estimates was conducted in the present scoping review, all three studies were included, as each contributes with different knowledge regarding parental COPD.

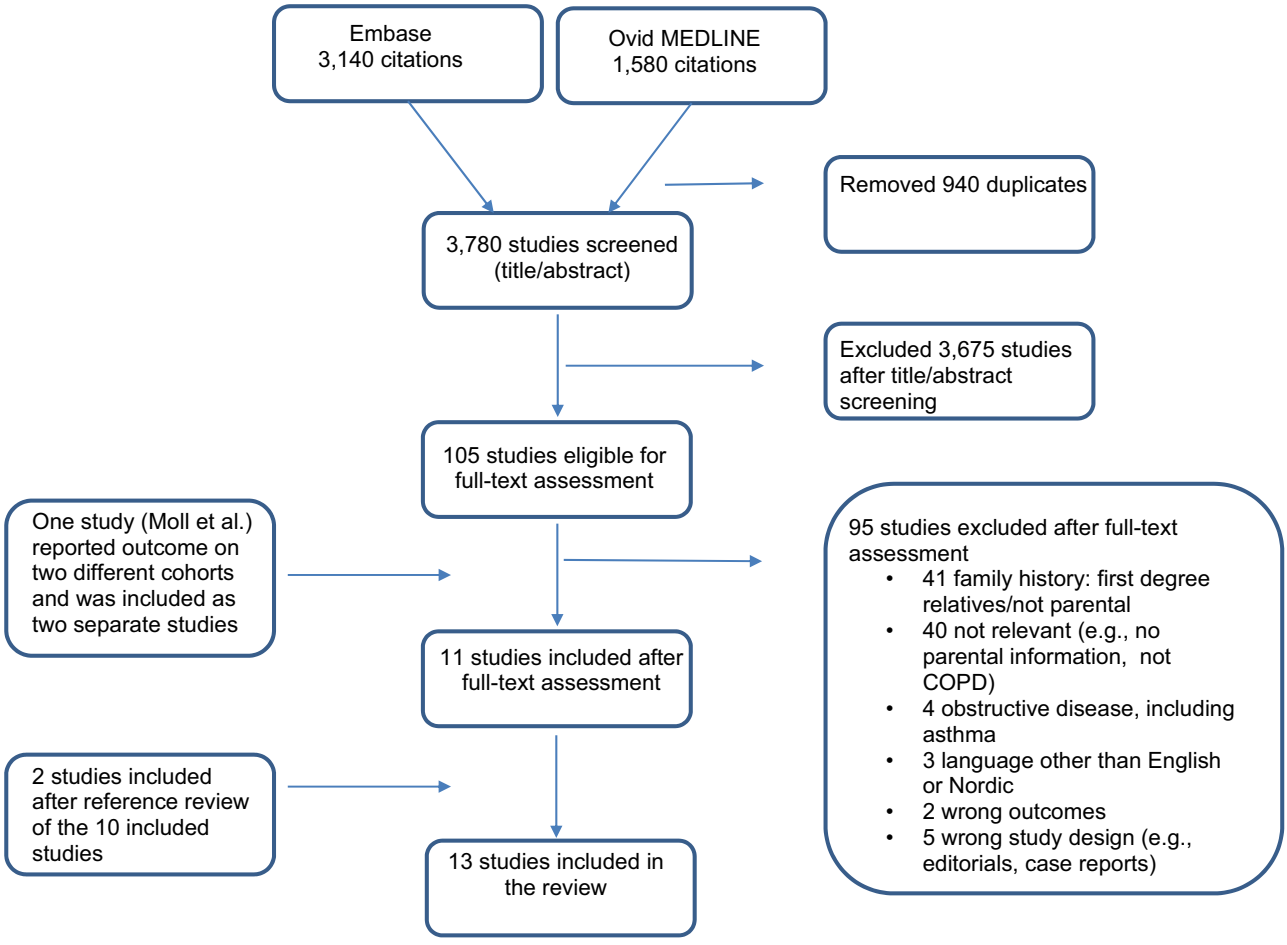

Figure 1 PRISMA flowchart of the search and inclusion process.
Notes: PRISMA figure adapted from Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. Creative Commons.[45]

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Table 1 Study Characteristics

Antecedents Approach						
Author and Publication Year	**Study Design**	**Country**	**Setting, Data Source and Study Period (Year)**	**Study Aim**	**Offspring –Diagnosis of Cases/ Controls**	**Parents – Diagnosis**
Zoller[27] 2015	Cohort study Population-based	Sweden	National registries. Adoptees born between 1932 and 2004	To examine the risk of COPD in adoptees with parental COPD in either biological or adoptive parents or in both biological and adoptive parents.	Cases: Adoptees with an ICD 7–10 code of COPD in national registries Controls: Adoptees without COPD No information on smoking history	COPD based on ICD 7–10 codes from national registries No information on smoking history
Moll[20] 2020	Case–control, Multicentre, Prognostic study	12 countries	ECLIPSE study	To assess the predictive performance of a polygenetic risk score and family history. (A replication cohort of the COPDGene cohort.)	≥10PY, 40–75 years, white Cases: FEV_1<80% and FEV_1/FVC <0,7 Controls: FEV1≥80% and FEV_1/FVC >0.7 GOLD I excluded	Reported by offspring (CB or Emphysema) No information on smoking history
Moll[20] 2020	Case–control, Cross-sectional Multicentre Prognostic study	USA	COPDGene study Questionnaire	To assess the predictive performance of a polygenetic risk score and family history.	45–80 years, ≥10PY Cases: COPD: GOLD II–IV, FEV_1<80% and FEV_1/FVC <0.7 Controls: FEV_1≥80% and FEV_1/FVC >0.7 GOLD I excluded	Maternal or paternal COPD reported by offspring (COPD, CB or Emphysema) No information on smoking history
Hersh[26] USA, 2011	Case–control, Cross-sectional Multicentre Prognostic study	USA	COPDGene study Questionnaire	To identify the effects of family history of smoking and COPD on COPD risk. Secondly, to evaluate if patients with COPD and a family history of COPD have more severe disease.	COPD: GOLD II–IV, 45–80 years ≥10PY Controls: 45–80 years, ≥10PY	Reported by offspring: (COPD, CB or emphysema) Parental history of smoking: Cases: 85.5% Controls: 82.9%
Silverman[23] 1998	Case–control, Cross-sectional	USA	Hospital (cases) Controls invited from another population-based study (controls)	Study the risk for airflow obstruction and CB in relatives of early-onset COPD cases	Cases: early onset COPD: <53 years, FEV_1<40%, No alpha-1-antitrypsine deficiency Controls: current or ex-smokers, LF unknown	Self-reported by offspring (CB, emphysema or COPD) No information on parental smoking history
Kueppers[21] 1977	Case–control, Cross-sectional	USA	12 counties in southeast Minnesota Questionnaire	Prevalence of COPD in families	45–60 years, FEV_1<0.70 and CB symptoms. Asthma and parenchymal disease excluded Matched controls with FEV_1>85	Reported by offspring, and verified by medical records, death certificates or autopsy No information on smoking history

Cosio[28] 2020	Case–control, Cross-sectional	Spain	Hospitals, Questionnaire	Describe the phenotypic characteristics of early COPD	≥10PY, 35–50 years Cases: PB-FEV_1/FVC<0.7 Controls: normal spirometry	Parental bronchitis, reported by offspring No information on smoking history
Foreman[22] 2011	Case–control, Cross-sectional Multicentre Prognostic study	USA	COPDGene study Questionnaire	To determine the effect of sex, maternal characteristics, and race on the risk for severe, early-onset COPD	Cases: Severe early-onset COPD FEV_1/FVC < 0.70 and PB-FEV_1 < 50% and < 55 years of age. Controls: Severe COPD, non-early onset. FEV_1/FVC < 0.70 and PB-FEV_1 > 50% and > 64 years	Parental COPD and parental history of smoking reported by offspring
McCloskey[29] 2001	Cross-sectional (Case–control*) * only siblings of the COPD cases have matched controls	UK	Hospital records	To quantify the risk of airflow obstruction in siblings of patients with COPD	Cases: Severe COPD FEV_1 <60% and ≤55 years OR FEV_1 <40% and 56–60 years OR FEV_1 < 20% and 61–65 years AND FEV_1/FVC < 0.6, AND Kco > 10% of the LLN AND no A1AT deficiency AND a chest radiograph compatible with COPD	COPD of living parents: self-reported by offspring or spirometry 27 (71%) parents were current or ex-smokers and 12 of them had FEV_1/FVC < 0.7
Descendent Approach						
Author and Publication Year	**Study Design**	**Country**	**Setting, Data Source and Study Period (Year)**	**Study Aim**	**Offspring -Diagnosis of Cases/ Controls**	**Parents – Diagnosis**
Amra[31] 2015	Case–control Cross-sectional,	Iran	Hospitalized patients with severe COPD 2011–2012	To evaluate pulmonary function tests and the IO in severe COPD patients' offspring.	Cases: non-smoking offspring Abnormal LF: FEV_1 or FVC<80% and FEV_1/FVC<70% Controls: Matched on sex, age and height	20 patients with severe COPD (based on GOLD) hospitalized with COPD exacerbation No information on smoking history

(*Continued*)

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Table 1 (Continued).

Antecedents Approach						
Author and Publication Year	**Study Design**	**Country**	**Setting, Data Source and Study Period (Year)**	**Study Aim**	**Offspring –Diagnosis of Cases/ Controls**	**Parents – Diagnosis**
Lu B,[30] 2003	Case–control Cross-sectional,	China	Medical records	Evaluate the probability of familial aggregation of COPD.	Offspring invited to participate: Cases (parental COPD) Controls (no parental COPD) AO: FEV_1 < 70%	59 parents with COPD, >60 years, >20 PY FEV_1 or FVC<75% and FEV_1/FVC<70% 28 parental controls: Smokers, >60 years, no COPD
Khoury[24] 1985	Case–control Cross-sectional,	USA	Medical records and physical exterminations	Evaluate familial aggregation of COPD in first-degree relatives	Offspring invited to participate Cases: AO (FEV_1<68%) or CB. Controls: No AO or CB.	Parents: identified in medical records. 150 with COPD (FEV_1<70%) and 107 without COPD No information on prevalence of parental smoking history
Higgins[25] 1975	Cross-sectional	USA	Data from a population-based prospective cohort study Questionnaire and physical examination 1962–1965	To evaluate whether three common chronic respiratory conditions aggregate in families and whether members of families resemble one another in ventilatory lung function.	Cases: CB symptoms >16 years	Reported CB symptoms No information smoking history

Abbreviations: PY, pack-years; GOLD, global initiative for chronic obstructive lung disease; LF, lung function; Kco, carbon monoxide transfer coefficient; FEV_1, forced expiratory volume in 1 second; PB-FEV_1, post-bronchodilator FEV_1; FVC, forced vital capacity; A1AT deficiency, alpha-1 antitrypsin deficiency; LLN, lower limit of normal; CB, chronic bronchitis; COPD, chronic obstructive pulmonary disease; AO, airway obstruction, ICD-10, International Classification of Diseases.

Table 2 Study Outcomes and Results

Antecedents Approach					
Author	**Offspring Sample Size**	**Mean Age (Years, SD), Smoking History (PY) and Gender (%) of Offspring.**	**Gender % –Females**	**Prevalence of Parental COPD in Cases with COPD and Controls (If Applicable) (%)**	**OR (95% CI) of Parental COPD in Cases with COPD**
Zoller[27]	COPD cases: 1978 Controls: 78,236	Cases: Mean age: 55.9 ±13.5 Controls: NA	Cases: 57.0% Controls: 50.2%	Biological parents: 14.3% Adoptive parents: 11.7%	Biological parents: SIR = 1.98 (95% CI 1.69–2.31) OR (Crude*) = 1.40 Adoptive parents: SIR = 1.12 (95% CI 0.92–1.35) OR (crude*) = 1.21
Moll[20] (ECLIPSE)	Cases: 1713 Controls: 147	Cases: 63.6 ±7.1; 50.5 ±27.5 PY Controls: 57.3 ±9.6; 31.0 ±26.0	Cases: 32.9% Controls: 42.9%	Cases: 41.9% Controls: 34.7%	Adjusted* OR=1.33 (0.91–1.94). *age, sex and PY of cigarette smoking
Moll[20] (COPDGene)	Cases (non-Hispanic whites): 2668 Controls: 2506 Cases (African-Americans): 753 Controls: 1713	Cases (non-Hispanic whites): 64.7 ±8.1; 56.1 ±27.3 PY Controls: 59.5 ±8.7; 38.8 ±21.2 PY Cases (African-Americans): 59.3 ±8.2; 42.8 ±23.3 PY Controls 53.0 ±6.2; 36.6 ±19.7 PY	Cases (non-Hispanic whites): 44.5% Controls: 51.2% Cases (African-Americans): 45.3% Controls: 41.1%	Cases (non-Hispanic whites): 37.1% Controls: 28.3% Cases (African-Americans): 19.3% Controls: 14.4%	Adjusted* OR (non-Hispanic whites) = 1.77 (1.55 to 2.03) Adjusted* OR (African-Americans) =1.71 (1.35–2.17) *age, sex and PY of cigarette smoking
Hersh[26]	Cases: 821 Controls: 776	Cases: Age 64.2 ±8.4; 53.2 ±26.3 Controls: 58.1 ±9.0; 37.1 ±20.1	Cases: 48% Controls: 52%	Maternal: 24.6% vs 17.6% Paternal: 29.5% vs 18.3% Parental: 43% vs 31%	OR*=1.73 (1.36–2.20) Adjusted for demographic covariates, parental COPD, parental smoking, and childhood environmental tobacco smoke. OR* = 1.76 (1.40–2.23) *Adjusted for demographic covariates and parental COPD OR = 1.68 (1.32–2.13) * Adjusted for demographic covariates, parental COPD and occupational exposure

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Table 2 (Continued).

Antecedents Approach					
Author	**Offspring Sample Size**	**Mean Age (Years, SD), Smoking History (PY) and Gender (%) of Offspring.**	**Gender % –Females**	**Prevalence of Parental COPD in Cases with COPD and Controls (If Applicable) (%)**	**OR (95% CI) of Parental COPD in Cases with COPD**
Silverman[23]	Cases: 44 Controls: 20	Cases: 47.2 ±5.6; 38.8 ± 22.5 PY Controls: 49.3 ±6.8; 24.6 ±16.7 PY	Cases: 80% Controls: 75%	Cases: 58% Controls: NA	OR = 7.9 (95% CI 2.0–30.9)* *no adjustment for smoking
Kueppers[21]	Cases: 227 Controls: 227	NA	NA	Maternal: 9.6% vs 5.3% (No statistical difference) Paternal: 16.8% vs 14.2% (No statistical difference)	Maternal: OR (crude*) = (11/103)/(6/108) = 1.9 Paternal: OR (crude*) = (23/4719/94)/(16/97) = 1.2
Cosio[28]	Cases: 91 Controls: 107[a]	Cases: 45.8 ±3.5; 31.6 ±116.3 PY Controls: 43.3 ±4.4; 24.8 ±13.7 PY	Cases 35% Controls: 50%	Case: Maternal: 16% Paternal: 46% Controls: Maternal: 8% Paternal: 27%	Maternal: OR (crude*) = (15/76)/(8,6/98,4) = 2,3 Paternal: OR (crude*) = (42/49)/(29/78)= 2,3
Foreman[22]	Cases:70 Controls: 306	Cases: 51 ±3; 42 ±24PY Controls: 71 ±4; 61 ±30PY	Cases: 66% Controls: 43%	Maternal: 23% vs 12%; P=0.03 Paternal: 21% vs 13%; P=0.2	Maternal: OR*= 4.7 (1.3–17); P = 0.02. *multivariable logistic regression (incl. own and maternal smoking history) Paternal: OR (crude*) = (15/55)/(40/266)= 1.8
McCloskey[29]	Cases: 150	Females: 51.5 ±6.8; 37.4 ±18.1 PY Males: 52.9 ±7.0; 46.8 ± 26.4 PY	Cases: 46%	Female cases: Maternal COPD = 29%; Paternal COPD =33% Male cases: Maternal COPD=32% Paternal COPD=37%	Not possible to calculate

Descendent Approach					
Author	**Offspring Sample Size**	**Mean Age (Years, SD) and Smoking History (PY)**	**Gender % –Females**	**Prevalence COPD in Offspring with Parental COPD (%)**	**OR of COPD in Cases with Parental COPD**
Amra[31]	Cases: 54 Matched controls: 54	Non-smoking offspring: 34.3 Controls: 34.2	Cases: 31% Controls: 33%	0%	Not possible to calculate
Lu B,[30]	Cases: 117 Controls: 55	Offspring: 40.9 ±5.8; 19.2 ±12.9 PY Controls: 39.6 ±6.0; 12.9 ±9.4 PY	Cases: 5% Controls: 8%	0%	OR (adjusted)=2.0 (OR: the odds of offspring having a FEV_1/FVC <0.70)
Khoury[24]	Case: 134 Control: 102	Offspring: 27.4 Controls: 27.3 Smoking history NA	Cases: 55% Controls: 50%	Cases: AO: 6% and CB: 14.9% Controls: 1.0% and 7.8%	AO: OR (crude)=6.4; P<0.05 CB: OR (crude)=2.1; P<0.05
Higgins[25]	Cases[b]: 16–39 years: M: 152/ F: 53 40+ years: M: 32/F: 17	NA	Cases: 38%	Prevalence by age group and gender: 16–39 years: 17.3% (M)/6.6% (F) 40+ years: 16.7% (M)/8.3% (F)	Not applicable

Notes: Crude*: calculated odds ratio based on available data; [a]1 case and 90 controls excluded; no reason stated; [b]estimated based on Table 1.

Abbreviations: COPD, chronic obstructive pulmonary disease; M, male; F, female; AO, airway obstruction; CB, chronic bronchitis; PY, pack years; FEV_1, forced expiratory volume in 1 second; SIR, standardized incidence rate; SD, standard deviation; NA, not available; OR, odds ratio.

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Table 3 COPD-Related Outcomes in Offspring

Study	Predictive Models of Association Between Family History of COPD and Outcomes
Moll[20]	ECLIPSE data SGRQ: OR=3.6 (95% CI 1.4–5.8) (P = 0.0008) No association: Frequent exacerbations, 6MWD and BODE Emphysema: NA
Moll[20]	COPDGene data Non-Hispanic whites: Frequent exacerbations: OR= 1.65 (95% CI 1.26 to 2.16) 6MWD: −27m (95% CI −49 to −5.4) (P = 0.016) SGRQ: OR= 0.27 (95% CI 0.21–0.33) (P < 0.001) Paraseptal emphysema: OR= 1.57 (95% CI 1.17 −2.11) (P =0.0029) BODE: OR=0.43 (95% CI 0.3–0.56) (P < 0.001) African-Americans: SGRQ: OR=0.39 (95% CI 0.26 to 0.52) (P < 0.001) BODE: OR=0.61 (95% CI 0.39 to 0.83) (P < 0.001) Paraseptal emphysema: OR=1.68 (95% CI 1.04 to 2.7) (P = 0.034) No association: Frequent exacerbations and 6MWD
Study	COPD-related outcomes in COPD offspring with parental COPD exposure vs no parental COPD exposure
Hersh[26]	FEV_1 (%-predicted): 47.7±18.4 vs 50.5±18.3 (P = 0.0004) Dyspnea (mMRC): 2.4±21.3 vs 2.0±1.5 (P = 0.0001) BODE: 3.4±2.1 vs 2.9±2.1 (P = 0.0003) Number of severe exacerbations in the past year: 95 (26.9%) vs 88 (18.8%) (P = 0.0057) SGRQ score: 43.4±20.5 vs 36.2±21.2 (P < 0.0001) No association: 6MWD, emphysema

Notes: No association: P-value > 0.05.

Abbreviations: BODE index, body mass index, obstruction, dyspnoea and exercise capacity; SGRQ, total St. George's Respiratory Questionnaire score; mMRC, modified Medical Research Council; FEV_1, forced expiratory volume in 1 second; m, meters; 6MWD, 6-minute walking test; NA, not available; COPD, chronic obstructive pulmonary disease.

Study Methodology

All studies included in the review were observational (Table 1). The majority of studies used a case–control study design with cross-sectional data and only one cohort study[27] and two cross-sectional studies[25,29] were found. Assessing parental COPD as a predisposing factor for developing COPD in offspring was part of the aim in five studies.[21–23,26,27] Nine studies used an antecedents approach and evaluated parental COPD in patients with COPD. Four studies used a descendant approach, in which the index-person was individuals with COPD (ie, parents with COPD) and cases were defined as offspring of the index-persons.[24,25,30,31]

COPD Diagnostic Criteria

We included studies with a broad range of COPD definitions (Table 1). Spirometry was included as part of the COPD diagnosis in offspring (cases) in all studies using the antecedents approach, aside from the cohort study. Parental COPD was identified by offspring reporting, and this was verified by, eg, spirometry or medical records in a few studies.[21,29] The cohort study used ICD 7–10 coding in the national databases for both cases and parents.[27]

The case–control studies using a descendant approach firstly identified patients who were either hospitalized with COPD or identified in medical records, and then identified their offspring. Offspring were then invited to participate. Three studies[24,30,31] used spirometry to identify offspring with abnormal lung function. The cross-sectional study used data from a cohort study where family members were interviewed regarding symptoms of CB.[25]

Population Characteristics

Study sizes varied considerably between studies (Table 2). The largest study was Moll et al,[20] which included 2668 non-Hispanic white cases and 2506 non-Hispanic white controls from the COPDGene study. The smallest sample size was Silverman et al, with 44 cases and 20 controls.[23] Mean age of cases were >45 years in all the studies using an antecedents approach (age not available in one study[21]) and 27–41 years in the studies using a descendant approach. The distribution of genders also varied greatly between studies; Lu et al[30] included 95% male cases, whereas Silverman et al[23] included 80% female cases (Table 2).

Parental COPD – Prevalence, Incidence and OR

Except for one,[20] all studies with a reported or calculated OR found an increased risk of COPD in individuals with parental COPD (Table 2). The prevalence in case–control studies using the antecedents approach ranged from 19.3% to 58%. Three studies found highest prevalence among cases with paternal exposure,[21,26,28] and one study among cases with maternal exposure.[22] The prevalence in studies using the descendant approach ranged from 0% to 17%.

One study found a higher prevalence of parental COPD among non-Hispanic white cases (37.1%) compared to African-American cases (19.3%), but the ORs did not differ substantially; adjusted OR (non-Hispanic white) = 1.77 (1.55 to 2.03) and adjusted OR (African-American) = 1.71 (1.35–2.17).[20] Two studies reported on the prevalence of parental COPD in cases with early-onset COPD, of which Foreman et al[22] found almost the same prevalence in cases with maternal exposure (23%) and paternal exposure (21%). Cosio et al,[28] however, found the highest prevalence among cases with paternal exposure (46%), compared to maternal exposure (21%).

One study reported a standard incidence ratio (SIR) of COPD in offspring with parental COPD in biological and adoptive parents, using data from the Swedish national registries.[27] They found a higher SIR of COPD in offspring with parental COPD in biological parents (SIR = 1.98; 95% CI 1.69–2.31) than in offspring with parental COPD in adoptive parents (SIR = 1.12; 95% CI 0.92–1.35), with the latter SIR being statistically insignificant.

Four studies reported on parental smoking history[22,26,29,30] and nine studies reported on smoking history in offspring.[20,22,23,26,28–31] In most of these studies, cases were older and had more cumulative smoking exposure pack-years than controls. Hersh et al compared smoking COPD cases with smoking non-COPD controls and found parental COPD to be a significant risk factor for COPD in offspring (OR = 1.73; 95% CI 1.36–2.20) when adjusting for demographic variables, parental COPD, parental smoking, and childhood environmental tobacco smoke. They found an OR = 1.76 (95% CI 1.40–2.23) when only adjusting for demographic variables and parental COPD.

Severity of COPD and Other Health Outcomes in Offspring with Parental COPD

Three studies evaluated the association between parental COPD and COPD-related outcomes in patients with COPD. Table 3 summarizes the most assessed COPD-related outcomes between the three studies. Hersh et al[26] found that cases with parental COPD had lower forced expiratory volume (FEV_1), more dyspnea (mMRC), lower quality of life – based on St. George's Respiratory Questionnaire (SGRQ) score, and higher number of severe exacerbations than COPD cases without parental COPD. Moll et al[20] assessed the association of parental COPD with various COPD-related outcomes in offspring with COPD, using a prediction regression model. An association between the total SGRQ score and parental COPD (OR=3.6; 95% CI 1.4–5.8) was found in the ECLIPSE data. The COPDGene data showed an association between frequent exacerbations, decreased 6-minute walking distance (6MWD), increased SGRQ score, the body mass index, obstruction, dyspnoea, exercise capacity index (BODE index), and paraseptal emphysema and parental COPD in non-white Hispanic cases, whereas an association was only seen for SGRQ score, BODE and paraseptal emphysema in the African-American cases (Table 3).

No other studies evaluated the impact of parental COPD on COPD severity or other health outcomes. The studies using a descendant approach were not suitable to an assessment of the impact of parental COPD on COPD severity and health-related outcomes, because none of the controls had COPD or because information on parental status was missing.

Discussion

We conducted a systematic scoping review that included 13 studies assessing parental COPD exposure in adults with COPD. We found parental COPD to be associated with developing COPD in adulthood. Two studies found the association for early-onset COPD. Zoller et al, who used the Swedish national registries, found an association between COPD in adopted offspring and their biological parents, whereas no association was found between COPD in adopted offspring and their adoptee parents. This suggests that genetics and/or in utero exposures play an important role in the susceptibility for developing COPD in adulthood. Only one study, based on the ECLIPSE data, did not find an association between parental COPD and COPD in adulthood. This may be explained by the imbalance of controls (n = 147) compared with cases (n = 1713); however, sensitivity analyses did not alter the lack of association.[20]

We used a broad definition of COPD in order to map any studies that included parental COPD history. This resulted in heterogeneous studies with vast differences in the definition of COPD and obstructive airways. The methodologies, and particularly the characteristics of cases and controls, such as age, gender distribution and smoking history, varied greatly between studies.

We identified six studies that were not included in the review from 2017.[14] Three of the studies were published later than the search conducted in 2015 by Li et al[20,28] and three studies were published prior to 2015.[21,22,30] The inclusion of the latter three studies in our review is likely due to broader inclusion criteria. One study published in 1988 was not included in our review because of Russian language.[32] Li et al included one study evaluating early onset COPD.[23] The study found parental COPD to be highly associated with early onset COPD. The present review adds to this knowledge by including two more studies that found increased risk of early onset COPD in offspring with parental COPD.[22,28]

Although smoking is the most common environmental exposure leading to COPD, adjustment for parental and own smoking history was absent in most studies assessing measures of association. One study adjusted for both parental smoking and childhood environmental tobacco smoke, and found significantly higher OR for parental COPD in smoking offspring with COPD compared to smoking offspring without COPD. These findings suggest an increased risk of COPD in offspring with parental COPD, independent of parental and personal smoking history, which supports genetic susceptibility as an important factor.[26]

All studies using an antecedent approach, apart from one,[27] identified parental COPD history by offspring reporting and only one study used spirometry to confirm the diagnosis.[29] Research shows that knowledge about COPD is limited in patients with COPD, and in particular in individuals without COPD.[33] Therefore, the risk of recall bias and misclassification of parental COPD status by offspring reporting is highly likely. It is also likely that cases with COPD are more aware of whether their parents suffered the same disease as themselves in contrast to controls without COPD. This would lead to underreporting of exposure in the control group. Because COPD is vastly underdiagnosed worldwide and parents are not assessed with spirometry, it is also likely that a significant share of parents have undiagnosed COPD, which will contribute to an underestimation of parental COPD.[34–36]

Assessing Family History

COPD develops gradually and is often diagnosed late, when lung function impairment is substantial and damage to the lungs irreversible. Individuals with undiagnosed COPD have increased mortality and worse prognosis than individuals with normal lung function.[34,37] The identification of high-risk populations and early diagnosis are imperative in order to prevent the development and progression of COPD.

Physicians seldom take into account family history of COPD when assessing individuals at risk of developing COPD. Our present review highlights a scarcity of longitudinal follow-up studies assessing parental COPD as a predisposing factor for developing COPD. We did not include other cohort studies, apart from Zoller et al, who evaluated the incidence rate of adult COPD using biological and adoptee parents as the exposure.

In contrast to COPD, family history assessment is an essential element in preventing other common chronic diseases, such as asthma, diabetes, heart disease and cancer, can aid identification of high-risk individuals and early diagnosis, and can motivate behavioral change.[38–40] Life-course studies of common preventable chronic diseases, such as diabetes and cardiovascular disease, have for instance found that, in addition to preventable risk factors (eg, obesity and smoking),

heredity is a significant factor in the development of disease. For that reason, heredity is an important element in the detection of individuals in high risk of diabetes and heart disease.[41–43]

Parental COPD and Early Signs of COPD in Offspring

The four studies using a descendent approach were not designed to identify an association between parental COPD and COPD in offspring, but rather familial aggregation of COPD. The studies identified offspring with a low mean age, and they were therefore not likely to have developed spirometry-identifiable airway obstruction, defined as FEV_1/FVC <68–70% in the three studies using spirometry. Hence, two studies (of which one only included non-smoking offspring) found no airway obstruction in offspring. An older study (Khoury, 1985) did, however, find indications of a familial clustering of CB (OR >2.1) and airway obstruction (OR=6.4) among offspring with parental CB. These cross-sectional studies did not evaluate the development of lung function over time. This has been done in a 27-year follow-up study in individuals with a mean age of 41 and FEV_1/FVC of 70–75%.[44] Cases received more respiratory medicine and had higher rate of hospitalization for lung diseases, more contacts to general practice and lower income than individuals with FEV_1/FVC >75%. This study suggests that preventative measures in young adults with early signs of obstructive airways may reduce respiratory morbidity later in life.[44]

COPD Severity and Other Health Conditions

Low peak lung function in early adulthood increases the risk of COPD later in life and is associated with a higher prevalence of respiratory, cardiovascular, and metabolic comorbidities[8,9] Therefore, we hypothesized that parental COPD is a prognostic factor for a worse course of COPD and poor general health outcomes in adult offspring with COPD. However, the review revealed a vast knowledge gap on this topic. Only three studies evaluated COPD-related outcomes in offspring and no studies reported on other health-related outcomes. Hersh et al was the only study with the aim of assessing the impact of parental COPD on the severity of COPD in offspring. That study found parental COPD to be associated with lower lung function, greater dyspnea, higher share of severe exacerbations and lower quality of life at baseline. Moll et al evaluated the predictive performance of a prognostic model and likewise found parental COPD to be associated with several COPD-related outcomes. However, cross-sectional studies cannot assess how disease burden and other health-care outcomes (eg, comorbidities) vary from the time of diagnosis and onwards. Thus, it is still unclear whether assessing parental COPD history can be used to identify individuals in risk of worse course of COPD and generally worse health outcomes.

Strengths and Limitations

This scoping review has several strengths. The search strategy was assisted by an academic librarian, the reviewing process was conducted independently by two authors, and the reference review included extra studies that were not captured by the search. There are some limitations: the search was restricted to English and Nordic languages, and some articles in other languages may have been missed. This was a scoping review and no quality assessment of the studies was performed.[16,17] Therefore, the results on prevalence and OR drawn from this scoping review must be interpreted carefully. We excluded studies that combined sibling and parental COPD or solely evaluated sibling COPD as the exposure; thus, the results do not provide information on the share of siblings with COPD, which would be valuable information when assessing the impact of parental COPD on offspring.

Conclusion

The literature on the association between parental COPD and COPD in offspring is sparse. The studies vary vastly in design and population characteristics, which makes comparison of results difficult. We do not currently find grounds for a systematic review and meta-analysis based on this scoping review. Only eight studies would be eligible (ie, studies using an antecedents approach), and three of these studies use COPDGene data with overlapping cases, which makes a synthesis of the data problematic.

We identified a lack of follow-up studies, and in particular follow-up studies that assess whether parental COPD is a risk factor for worse course of COPD and other health-related outcomes.

More recent publications with spirometry confirmed diagnosis, more uniform definitions of COPD and elaboration on environmental exposures are lacking. Population-based studies designed to evaluate parental COPD as a risk factor for COPD in adulthood are called for, and, importantly, follow-up studies evaluating the health-related consequences of parental COPD.

Nevertheless, the studies included in this scoping review indicate that parental COPD is associated with a higher risk of COPD in offspring. Thus, based on the current literature, evaluating parental COPD history may aid in early detection of individuals in high risk of COPD.

Abbreviations

A1AT deficiency, alpha-1 antitrypsin deficiency; AO, airway obstruction; BODE index, body mass index, obstruction, dyspnoea and exercise capacity; CB, chronic bronchitis; CI, confidence intervals; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, global initiative for chronic obstructive lung disease; Kco, carbon monoxide transfer coefficient; LF, lung function; LLN, lower limit of normal; mMRC, modified Medical Research Council; NA, not available; OR, odds ratio; PB-FEV_1, post-bronchodilator FEV_1; PY, pack-years SGRQ, total St. George's Respiratory Questionnaire score; SIR, standardized incidence rate; 6MWD, 6-minute walking test.

Ethical Approval

The study did not involve human participants, and ethical approval was not required.

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Author Contributions

MGS is the guarantor of the work. MGS, AL, AK and OH contributed with the conception of the study. MGS extracted data, summarized the articles, prepared the first draft of the manuscript, and created the tables and figure. MGS and AK conducted the systematic search and literature review. AK, AL and OH critically revised the manuscript. All authors revised the manuscript and accepted the final version and agreed to publish the article and have agreed on the journal to which the article has been submitted. All authors take responsibility and are accountable for the integrity of the work as a whole, from inception to published article.

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