CAUSES, DIAGNOSIS, AND PROGRESSION OF COPD FOLLOWING WORKPLACE EXPOSURE TO VAPOURS, GASES, DUST AND FUMES

Final Report

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Abbreviations

Term	Definition
AATD	Alpha-1 antitrypsin deficiency
ACP	American College of Physicians
ACCP	American College of Chest Physicians
ATS	American Thoracic Society
BODE	Body mass index, airflow Obstruction, Dyspnea, Exercise
BMI	Body Mass Index
CAT	COPD Assessment Test
CC16	Club cell secretory protein 16
CCQ	COPD Control Questionnaire
CI	Confidence Interval
CIHI	Canadian Institute for Health Information
COPD	Chronic Obstructive Pulmonary Disease
CRP	C-reactive protein
DALY	Disability adjusted life years
ERS	European Respiratory Society
f/cc	fibers per cubic centimeter
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GOLD	Global initiative for COPD
HMOX1	Heme oxygenase 1
HMOX1 L+	HMOX1 gene with no polymorphisms, <33 GT promoter repeats
HMOX1 L-	$(GT)_n$ promoter repeat polymorphism, including ≥33 GT repeats
ICES	Institute for Clinical Evaluative Services
ILC2	Type 2 innate lymphoid cell
ILC3	Type 3 innate lymphoid cell
IQR	Interquartile range
JEM	Job exposure matrix
LLN	Lower limit of normal
LOQ	Limit of quantitation
MACRO	Macrolide Azithromycin for prevention of exacerbations of COPD
mg/m^3	Milligram/cubic meter
mg/mL	Milligram/milliliter
mMRC	modified Medical Research Council
N/A	Not applicable
N.R.	Not reported

N.S.	Not significant
OR	Odds ratio
PAF	Population attributable fraction
Pi10	Estimated square-root wall area of a single hypothetical airway with internal perimeter of 10mm
Ppm	parts per million
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRM fSAD	Parametric response mapping of functional small-airway abnormality
Ref.	Reference group
REFID	Reference identification number
RLR	Rapid Literature Review
RV	Residual volume
SCAPIS	The Swedish CArdioPulmonary BioImage Study
SEM	Standard error
SD	Standard deviation
SLR	Systematic Literature Review
SMH	St. Michael's Hospital
Tc1	Cytotoxic T cell type 1
Th1	T helper cell type 1
Th17	T helper cell type 17
Th2	T helper cell type 2
TLC	Total lung capacity
UI	Uncertainty interval
U.S.	United States of America
USPSTF	US Preventative Services Task Force
VGDF	Vapours, Gases, Dust, and Fumes
WSIB	Workplace Safety and Insurance Board
YLD	Years of life with disability
YLL	Years of life lost

1 Executive Summary

1.1 Introduction and Objectives

COPD is a chronic lung disease with a substantial global burden. As of 2019, COPD is the third leading cause of non-communicable (classified as 'Level 3') death worldwide, accounting for an estimated 3.28 million deaths in 2019, and is associated with the sixth-highest global burden of disease (disability-adjusted life years [DALYs]).[1] Smoking is recognized as one of the leading contributors of COPD, however, exposures to irritants, such as occupational exposure to vapours, gases, dust and fumes (VGDF), are also associated with COPD.[2-6] The American Thoracic Society (ATS) states that there is a substantial contribution to nonmalignant lung diseases, such as COPD, via the inhalation of workplace exposures.[7] According to the National Health and Nutrition Examination Survey III, of approximately 10,000 adults from 30-75 years of age, 19.2% of COPD cases were attributable to workplace exposure, which rose to 31.1% for non-smokers.[8,9]

The severity of COPD is multifactorial and can be impacted by the duration (e.g. time since exposure and length of exposure), concentration of exposure (e.g. pack years of smoking, mg/m^3 of VGDF), type of exposure, comorbid conditions (e.g. asthma), genetic factors and time from diagnosis.

This rapid literature review (RLR) aims to present data on the development of COPD following occupational VGDF exposure with or without smoking exposure, and identify evidence that may elucidate the difference between exposures on lung function loss/impairment.

1.1.1 Objectives

The objective of this Rapid Literature Review (RLR) was to identify and interpret evidence in the published literature regarding associations between COPD, exposure to tobacco smoke, and workplace exposures to VGDF. Specifically, this RLR addressed the following Research Questions:

1) What is COPD? Is it a single disease or group of diseases/conditions?
    a. How is COPD diagnosed? How is severity determined?
    b. What are the causes of COPD? Do different causes result in different changes (at the cellular, tissue or structural level) within the lung? Does COPD onset or progression differ according to cause?
2) Is it possible to differentiate clinically between COPD, or lung function loss/impairment, caused by cigarette smoking and that caused by workplace VGDF exposures?
3) Is COPD, or lung function loss/impairment, caused by cigarette smoking and that caused by workplace VGDF exposures separate diseases or conditions, or disease or injuring processes?
4) Do cumulative exposures (intensity x duration) to cigarette smoking and/or workplace VGDF exposures impact the amount of lung function loss/impairment? Is it possible to estimate the amount of lung function loss/impairment caused by cumulative exposures to cigarette smoking (pack-years) and that caused by workplace VGDF exposures (mg/m3-years)?
5) Are the effects of cigarette smoking and workplace VGDF exposure on lung function loss/impairment additive or multiplicative? If a person quits cigarette smoking and/or avoids workplace VGDF exposure, would that slow, stop or reverse their COPD or lung function loss/impairment?

6) Is COPD a disease or injuring process that, once triggered, follows its own course for progression of disease, similar to cancer? If yes, does this occur regardless of cause and/or continued (or discontinued) exposure?

1.2 Methodology

This study undertook a RLR of evidence published within the last five years (search strategy executed on October 1, 2020) following Cochrane methodology.[10] A search strategy for Research Question 1 was utilized to identify evidence summarized in clinical guidelines and consensus statements. Additionally, a grey literature search of select organizations was conducted. A separate search strategy was utilized to identify evidence addressing Research Questions 2-6. Studies were reviewed against separate inclusion/exclusion criteria for each search strategy, first by title/abstract, and then by full text for papers not excluded based on title/abstract. Screening was conducted using the DistillerSR® platform. Pilot screening and an artificial intelligence audit tool were used to reduce the likelihood of any studies being wrongfully excluded. Full-text papers deemed eligible for extraction, were extracted by a single reviewer.

1.3 Results

The electronic database search strategy for Research Question 1 identified 51 citations as potentially relevant. A total of 42 publications were included for full-text screening, among which seven were included for data extraction, one of which was further excluded at the data extraction phase for lack of outcomes. From the bibliography screening, one publication proceeded to data extraction, bringing the total number for inclusion to nine publications from the electronic database search. An additional six publications were identified from the targeted grey literature search of the nine selected organizations, for a total of 13 publications included for Research Question 1.

The electronic database search strategy for Research Question 2-5 identified 4,550 citations as potentially relevant. A total of 317 publications were included for full-text screening, among which 113 publications were considered for data extraction. An additional 83 publications were excluded due to a lack of data directly or inferentially supporting any of questions 2 through 6 (excluded in the PRISMA due to 'Outcomes'). A total of 20 studies had a primary focus of COPD and were included in the report. An additional 10 studies were included in the data extraction workbook as they presented supporting/inferential data related to the Research Questions but COPD was not the primary focus.

1.3.1 Research Question 1

The consensus statements from the organizations identified in this RLR vary in their definition of COPD, COPD is generally described as a chronic respiratory disease with both persistent symptoms and airflow limitation in the diagnostic criteria.

The process for diagnosing COPD includes a 1) medical history, 2) physical examination, and 3) measurement of airflow obstruction".[11] A diagnosis of COPD should be considered in any patient with a history of exposure to risk factors, including smoking and/or occupational VGDF exposure, and/or with dyspnea (progressive, on exertion, or persistent), chronic cough, or sputum production. The various guidelines (GOLD, CTS, ATS, and ERS) are consistent that patients' smoking history should be the prime focus as it remains the most important risk factor. Based on the GOLD guidelines, a COPD diagnosis requires an FEV_1/FVC ratio <70% and severity is assessed from mild to very severe based on FEV_1 levels.[8] The European Respiratory Society–American Thoracic Society task force recommend the use FEV_1/FVC < lower limit of normal (LLN) for a diagnosis of COPD.[12]

While cigarette smoking is identified as the most common risk factor for COPD, other environmental exposures and host factors also contribute such as occupational exposure, biomass fuels and α1-

antitrypsin deficiency. Moreover, the individual susceptibility to infections also a plays a significant role in COPD exacerbations.[11]

There has been a considerable amount of research conducted historically to understand the pathogenesis of COPD. Many authors have suggested the role of premature lung aging as central to the development of COPD.[12,13] Additionally, the inhalation of tobacco smoke or toxic particles such as biomass fuel smoke has been found to trigger pulmonary inflammation, which causes 1) destruction of parenchymal tissue (resulting in emphysema) and 2) the disruption of normal processes of repair and defense resulting in small airway fibrosis.[8] These pathological changes lead to gas trapping and progressive airflow limitation.[8] There is considerable evidence concerning COPD risk factors arising from cross-sectional studies that identify associations rather than causal relationships. Though cigarette smoking is well studied, some reports show the development of chronic airflow limitation among non-smokers. Non-smokers with chronic airflow limitation have fewer symptoms, milder illness and lower systemic inflammation relative to smokers with COPD.

1.3.2 Research Question 2

One study was identified that provides supporting evidence that lung function loss/impairment occurs among individuals who have experienced occupational VGDF exposure, even when controlling for smoking, providing inferential evidence of impairment due to VGDF. Paulin *et al.,* 2018 reported on the impact of VGDF exposure and cigarette smoking on computed tomographic characteristics of lung airway characteristics, including % emphysema and lung airway dimensions.[14] Significant differences were observed among individuals with VGDF exposure compared to those without VGDF exposure when looking at indicators of large-airway disease and small airway disease, when adjusting for numerous confounders including smoking. While this study provides clinical evidence of lung damage following VGDF exposure, there was no evidence of differentiating the damage by specific irritants. As such, the cause of COPD by exposure type cannot be clinically differentiated at this time.

1.3.3 Research Question 3

One study was identified in this RLR that provided inferential and/or supportive data towards differences in the etiology or pathophysiology of COPD as a disease or injuring process relative to cigarette smoking versus occupational VGDF exposure. Würtz *et al.,* 2020 investigated the impact of the HMOX1 repeat genotype on the development of COPD following exposure to either VGDF or cigarette smoke in Danish individuals aged 45-84.[15] This study observed an interaction effect between VGDF exposure and the HMOX1 L+ gene. The presence of the HMOX1 L+ genotype with VGDF exposure resulted in a significant increase in the likelihood of developing COPD, that was not observed in the absence of VGDF exposure relative to the HMOX1 L- genotype.[15] The authors were not able to repeat these results in a second cohort. While this information is informative, it does not provide any information on potential histological or biochemical differences in COPD by exposure type. At this time, it is not known if lung function loss/impairment caused by smoking and that caused by workplace VGDF exposure are separate diseases or conditions, or a disease or injuring process.

1.3.4 Research Question 4

Sixteen studies were identified in this RLR that provided evidence related to Research Question 4. Nine studies provided relevant evidence regarding the impact of cumulative exposure to various occupational VGDF, as well as duration of smoking.[16-24] Eleven studies were identified that provided evidence regarding the impact of cumulative exposure to smoking and occupational VGDF on the likelihood of developing COPD.[3,16,17,21,23,25-30] The evidence from these studies suggest that cumulative exposure, as assessed by increased intensity and/or duration, to specific occupational VGDF and/or smoking does impact the extent of lung function impairment/loss. While there is considerable variability in the degree of

impact reported, with numerous mitigating factors identified, the general trend observed from most studies was an increase in impairment or likelihood of developing COPD with greater exposure. The substantial variability across studies regarding exposure type, intensity, duration, and analysis makes it challenging to synthesize and quantify the impact, as well as generalize results to a broader population.

1.3.5 Research Question 5

Eleven studies were identified in this RLR that presented presenting data regarding additive or multiplicative effects of smoking and workplace exposure in the development of lung function/impairment and/or COPD.[16-18,21,23-28,31] The evidence captured in this RLR suggests that there may be an additive or multiplicative effect of smoking and workplace VGDF exposure on lung function loss/impairment. Similar to the other research questions in this RLR, the data captured for Research Question 5 included a wide variety of occupations, and therefore the magnitude of effect varied across studies. Six studies were identified that provided data relating to cessation of an exposure, [16,18,19,28,31,32] with a general inferential trend suggesting a positive effect of cessation on lung function or likelihood of developing COPD. Of note, only one study provided data regarding cessation of occupational exposures, while all six studies assessed cessation of smoking.

1.3.6 Research Question 6

There were no studies identified in this RLR that directly addressed or provided inferential data related to Research Question 6. Evidence identified in this RLR is largely focused on identifying risk factors associated with the development of COPD or lung function loss/impairment highlighting a substantial evidence gap regarding the progression of COPD post diagnosis.

1.4 Conclusion

The evidence from this RLR did not identify any significant changes in the understanding of COPD in regards to occupational VGDF and smoking exposure. Cumulative smoking and occupational VGDF exposure are known risk factors to lung impairment and the development of COPD, with evidence demonstrating an additive and multiplicative effect of these combined exposures. The evidence of cessation of exposure is anticipated to reduce the rate of decline of lung impairment, however there is limited novel evidence from the past five years. At present, it is not possible to distinguish between causes of COPD and there is limited pathophysiology or etiology evidence to support a greater understanding of the disease or injury process of COPD and COPD progression, in relation to potential causes. Further primary research is warranted to explore these questions further.

2 Background

Chronic Obstructive Pulmonary Disease (COPD) is a chronic, lung disease that progressively worsens over time. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), '*COPD is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar* [small air sacks of the lower lungs] *abnormalities usually caused by significant exposure to noxious particles or gases*.'[8] The global burden of COPD is substantial. As of 2019, COPD is the third leading cause of non-communicable (classified as 'Level 3') death worldwide, accounting for an estimated 3.28 million deaths in 2019, and is associated with the sixth-highest global burden of disease (disability-adjusted life years [DALYs]).[1]

Periodic exacerbations are common in COPD, ranging from mild to severe, and include symptoms such as increased dyspnoea, cough, and increased sputum production/purulence.[33] Exacerbations are associated with increased hospitalization, absenteeism, a significant decline in quality of life, and death.[33,34] In Canada, moderate to severe exacerbations in COPD have a significant impact on the public healthcare system, estimated to exceed direct costs of $646 million annually (2008 $CAD).[35]

The pathophysiology of COPD, particularly regarding the impact that various occupational exposures have on the development and or progression of the disease, is unclear. Smoking is recognized as one of the leading contributors of COPD; however, exposures to irritants, such as occupational exposure to vapours, gases, dust and fumes (VGDF), are also associated with COPD.[2-6] The American Thoracic Society (ATS) states that there is a substantial contribution to nonmalignant lung diseases, such as COPD, via the inhalation of workplace exposures.[7] Additional factors such as pre-existing conditions (e.g. asthma) are also risk factors for the development of COPD, and the presence of comorbidities leads to worsened outcomes.[36,37] The etiology and pathophysiology of COPD is complex and is further complicated by the diverse exposure types that can precipitate development of COPD.

COPD is generally diagnosed through the measurement of lung capacity via spirometry, and is scored from mild to severe based on the international GOLD guidelines.[38,39] Common clinical measurements include forced expiratory volume in 1 second (FEV_1), which is a measurement of how much air an individual exhales during a forced breath, and forced vital capacity (FVC), which is a measurement of the total amount of air expelled during the FEV test. The ratio of these two measurements is also calculated (FEV_1/FVC).[8] The GOLD guidelines state that a diagnosis of COPD in the clinical context is made following a spirometry measurement of FEV1/FVC < 0.7 post-bronchodilation.[8] However, as is noted by the ATS, using a fixed value of 0.70 for the FEV_1/FVC cutoff often leads to over estimation of lung impairment, especially in older individuals.[40] Therefore, the ATS recommends the use of the 5th percentile of the normal distribution (or lower limit of normal [LLN]) as a cut-off value for detection of COPD in clinical practice.[40] The ATS also recommends the use of vital capacity over FVC, as FVC can be altered by historical breathing patterns.[40,41] Biomarkers of inflammation (e.g. interleukin-10, C-reactive protein, tumour necrosis factor alpha) are another area of research for diagnosis/monitoring of COPD, and have been found to be elevated in individuals with COPD.[20,42,43]

The severity of COPD is multifactorial and can be impacted by the duration (e.g. time since exposure and length of exposure), concentration of exposure (e.g. pack years of smoking, mg/m^3 of VGDF), type of exposure, comorbid conditions (e.g. asthma), and genetic factors. Additionally, given that COPD increases in severity over time, time from diagnosis is an important consideration as well. Although, cigarette smoke is believed to be responsible for 80% of deaths from COPD; non-smokers exposed to VGDF are also reported to develop COPD, indicating that VGDF exposure is another important risk factor.[44-47]

According to the National Health and Nutrition Examination Survey III, of approximately 10,000 adults from 30-75 years of age, 19.2% of COPD cases were attributable to workplace exposure, which rose to

31.1% for non-smokers.[8,9] In Canada, common occupational VGDF contaminants include hazards such as dusts and gases from building materials, toxic vapours and volatile organic compounds from workplace cleansers, pesticides, gases and vapours from paints and furniture, and dusts from occupations such as farming, woodworking and mining (please see **Appendix B: Glossary of Terms** for definitions related to VGDF).[48] Other COPD risk factors include repeated lung childhood infections, genetic risk factors such as alpha-1 antitrypsin deficiency, and asthma.[49,50]

Patients with COPD report a significantly reduced quality of life, and substantial prevalence (10-42%) of depression.[51-54] Current guidelines from the Canadian Thoracic Society recommend a combination of pharmacological and nonpharmacological therapies to reduce symptoms and prevent acute exacerbations of COPD.[55] Early diagnosis is key, as early interventions include lifestyle management (including exercise, smoking cessation) and management techniques (including breathing techniques).[55] Treatment options for more moderate cases of COPD include bronchodilators to open up airways, while severe cases of COPD can be treated with combination therapy including oral pharmaceuticals (including anabolic steroids, mucolytics, and statins), oxygen, and finally as a last course, lung transplantation.[36,55]

COPD remains the sixth most burdensome disease despite the decrease in the prevalence of cigarette smoking worldwide, further underscoring the important role other factors (e.g. occupational exposure, comorbid conditions, genetic) in the development of COPD.[1] Treatment for COPD and cessation of exposures may slow progression, but there is no known cure and lung function will continue to decline over time; therefore, understanding the risk factors that lead to the development of COPD is key in prevention, thereby reducing the substantial personal and societal burden associated with this disease.[7,8,56,57]

2.1 Study Rationale

This rapid literature review (RLR) aims to present data on the development of COPD following occupational VGDF exposure with or without smoking exposure, and identify evidence that may elucidate the difference between exposures on lung function loss/impairment.

3 Study Objectives

It is well-accepted that smoking is a major contributor to COPD, however the differences between COPD as a result of smoking versus COPD as a result of occupational exposure to VGDF is not well understood including the following:

- The proportional contribution of smoking and occupational exposure to VGDF for people diagnosed with COPD who both smoke and hold an occupation subject to VGDF exposure
- Whether the cumulative effects of smoking and workplace exposure to VGDF differ with the progression of disease and whether these effects are additive or multiplicative to disease progression
- If the progression of COPD is altered when lifestyle (smoking cessation) or occupation exposure are discontinued.

Therefore, a rapid literature review was performed to identify evidence that may elucidate the difference between exposure due to smoking and occupational VGDF exposure on COPD or lung function/impairment as presented in the following research questions:

- **Question 1:** What is COPD? Is it a single disease or group of diseases/conditions?

- **Question 2:** Is it possible to differentiate clinically between COPD, or lung function loss/impairment, caused by cigarette smoking and that caused by workplace VGDF exposures?

- **Question 3:** Is COPD, or lung function loss/impairment, caused by cigarette smoking and that caused by workplace VGDF exposures separate diseases or conditions, or disease or injuring processes?

- **Question 4:** Do cumulative exposures (intensity x duration) to cigarette smoking and/or workplace VGDF exposures impact the amount of lung function loss/impairment? Is it possible to estimate the amount of lung function loss/impairment caused by cumulative exposures to cigarette smoking (pack-years) and that caused by workplace VGDF exposures (mg/m^3-years)?

- **Question 5:** Are the effects of cigarette smoking and workplace VGDF exposure on lung function loss/impairment additive or multiplicative? If a person quits cigarette smoking and/or avoids workplace VGDF exposure, would that slow, stop or reverse their COPD or lung function loss/impairment?

- **Question 6:** Is COPD a disease or injuring process that, once triggered, follows its own course for progression of disease, similar to cancer? If yes, does this occur regardless of cause and/or continued (or discontinued) exposure?

4 Research Methods

4.1 Search Strategies and Selection Criteria

The RLR methodology recommended by Cochrane was followed for this study.[10]

The RLR included two search strategies to identify relevant data to answer the research questions (Appendix A).

The search strategy for Question 1 was utilized to identify evidence summarized in clinical guidelines and consensus statements. In addition to the electronic database search, bibliographies of those publications meeting criteria for Question 1 were hand-searched for relevant publications meeting the predetermined criteria for inclusion/exclusion. Lastly, a targeted grey literature search of select organizations was conducted to supplement the available data for Question 1. The following organizations were included in the grey literature search: American Thoracic Society, National Institute for Occupational Safety and Health, Health and Safety Executive, Canadian Thoracic Society, European Respiratory Society, British Thoracic Society, Public Health Agency of Canada, the Global Initiative for Chronic Obstructive Lung Disease (GOLD)**,** and the British Medical Journal. The criteria for study selection are summarized in **Table 1**.

The search strategy for Questions 2-6 was utilized to identify evidence addressing the various objectives presented. The criteria for study selection for Questions 2-6 are summarized in **Table 2**.

Table 1: Inclusion/exclusion criteria to address Research Question 1

Criteria	Inclusion Criteria	Exclusion Criteria
Population	Adults that have been diagnosed with COPD	Adults with lung function loss/impairment not diagnosed as COPD Adults without lung function loss/impairment Adults diagnosed with both COPD and cancer Children

Exposure	• Exposure type
	  ○ Smoking
	  ○ Occupational VGDF
	  ○ Environmental (outdoor or domestic)
	  ○ Other known or suspected risk factors (e.g., childhood respiratory infection)
		None

Outcomes	• Severity of COPD
	  ○ E.g. GOLD assessment, BODE index, clinical examination
	• Age of onset
	• Duration of disease/time since diagnosis
	• Clinical examination findings
	• Tests used to measure lung function or impairment
	  ○ Spirometry
	  ○ Forced expiratory volume
	  ○ Arterial blood gas levels
	  ○ Loss of elastic recoil	

Criteria	Inclusion Criteria	Exclusion Criteria
	• Pathophysiological markers of lung function • Disability (e.g. work status, participation and activity limitations, activities of daily living, etc.) • Death	
Study design	Consensus statements Clinical guidelines	
Restrictions	Human studies	Non-English publications Non-human studies
Date of publication	Within the last 5 years (search strategy ran October 1, 2020)	
Countries/global reach	Any	None

Abbreviations: BODE: Body mass index, airflow Obstruction, Dyspnea, Exercise; COPD: Chronic Obstructive Pulmonary Disease; GOLD: Global initiative for COPD; VGDF: vapours, gases, dust, fumes

Table 2: Inclusion/exclusion criteria to address Research Questions 2–6

Criteria	Inclusion Criteria	Exclusion Criteria
Population	Adults with COPD Adults with lung function loss/impairment	Adults without lung function loss, or lung function impairment Children
Exposure	Occupational exposure to VGDF, as determined by either self-reporting or job-exposure matrices • This can include current exposure and past exposure VGDF includes vapours, gases, dusts, fumes, fibers, or mists. It refers to any of the four pollutant forms alone or combination	Environmental (outdoor or domestic) exposure (unless related to occupation, e.g., parking attendant)
Comparator	Exposure to tobacco smoke (ever, current, or ex-smokers). • This includes cigarettes, pipes, cigars This can include workplace exposure to tobacco smoke in isolation, or in addition to VGDF exposure	Environmental (outdoor or domestic) exposure to second-hand tobacco smoke (i.e., not in the workplace) Exposure to e-cigarettes Exposure to marijuana cigarettes which do not also contain tobacco

Outcomes	Lung function outcomes, including measures of severity, progression, and/or improvement:
	• Clinical examination findings
	  ○ Shortness of breath
	  ○ Chest tightness
	  ○ Chronic cough
	• Pathophysiological markers of lung function
	  ○ Elevated C reactive protein
	  ○ Plasma fibrinogen
	• Tests used to measure lung function or impairment
	  ○ Forced expiratory volume
	  ○ Arterial blood gas levels
	
	Cumulative exposure:
	• For tobacco-smoke: pack-years	

Criteria	Inclusion Criteria	Exclusion Criteria
	• For particulate exposures: mg/m^3-years, ppm, f/cc	
Study design	Primary research articles Systematic literature reviews or meta-analyses Observational studies	Case study, letters, catalogues, commentary, editorials, or essays Guidebooks or handbooks Historical article or interview News or newspaper article Notes or posters/conference abstracts Phase I, II, III, or IV clinical trials
Restrictions	Human studies only	Non-human studies Non-English publications
Date of publication	Within the last 5 years (search strategy ran October 1, 2020)	
Countries/global reach	All	None

Abbreviations: COPD: Chronic Obstructive Pulmonary Disease; f/cc: fibers per cubic centimeter; ppm: parts per million; VGDF: vapours, gases, dust, fumes

4.2 Screening

The screening was conducted in two phases:

1. Titles/abstracts were screened for relevance against the criteria provided in **Table 1** and **Table 2**. Titles/abstracts meeting the criteria, or those which could not be excluded based on the title and/or abstract alone were included as full-text papers for further review.
2. Full-text papers were screened against the eligibility criteria provided in **Table 1** and **Table 2**. Studies meeting the full criteria for inclusion were included for data extraction. In any instance in which the appropriate inclusion/exclusion decision was not able to be reasonably determined by the reviewer, the clinical content expert, Dr. Anil Adisesh, made the final decision.

Screening was conducted using the DistillerSR® platform and divided among four reviewers. A short pilot exercise was used to familiarize the reviewers with the inclusion/exclusion criteria. This pilot screening required all reviewers to screen the same 75 citations, and the include/exclude decisions were compared. For any instance in which there was not alignment among the four reviewers, the citation was discussed among the review team to identify and reconcile the source of conflict. When all reviewers were in agreement with respect to those 75 citations, the formal title/abstract screening process began. Reviewers worked in parallel, with each citation reviewed by one of the four reviewers. To ensure alignment among the reviewers, 10% of all citations were randomly selected for screening by a second reviewer. Cochrane recommends dual screening of 20% of citations, however, this study selected 10% for dual screening due to study timelines and because this study included a more intensive pilot review (75 articles rather than 30-50 as recommended by Cochrane) and an artificial intelligence (AI) quality check of excluded studies.[10] For these randomly selected citations, agreement between the two reviewers was required for an include/exclude decision to be final. The AI Audit tool (natural language processing technology within the DistillerSR® platform) was used to audit the screening process to identify any references which may have been wrongfully excluded during title/abstract screening. The AI Audit probability assessment calculates the likelihood that any given reference may be included based on an algorithm derived from reviewer decisions during the screening process. References identified via

DistillerAI Audit were re-screened, beginning with those most likely to be included (probability of 95% and above). Re-screening was stopped at 90% probability of inclusion as all studies with a greater than 90% probability were identified as being appropriately excluded (i.e. no studies were found to be inappropriately excluded).

In each instance involving a second reviewer (i.e., for those citations flagged via DistillerAI Audit and those randomly selected for duplicate screening), conflicting exclusion decisions between the two reviewers were flagged. If the conflict rate exceeded 10% of the citations screened in duplicate, a further 5% of the total citations were screened in duplicate. This cyclical quality assurance process was repeated twice at which point a satisfactory level of agreement (i.e., less than 10% of citations screened in duplicate) was achieved. All conflicting decisions were reconciled by a third reviewer. When conflicting decisions were not able to be reconciled, the clinical content expert, Dr. Anil Adisesh, made the final decision. WSIB was consulted regarding clarification of criteria when required.

Full-text screening identified the reason for exclusion based on the pre-defined selection criteria (**Table 1** and **Table 2**). During the full-text screening phase, the included studies were mapped/categorized with respect to which of the Research Question(s) they each addressed.

4.3 Data Extraction and Reporting

Full-text papers deemed eligible for extraction, were extracted by a single reviewer. For publications in which the relevance to any given research question was unclear, the paper was reviewed by a clinical expert in the field, Dr. Anil Adisesh, who made the final decision.

Publications that provided data directly addressing any of the respective Research Questions and those in which COPD was the primary outcome of the publication, were prioritized for data extraction and tabulation within the main body of this report.

In the instance that no evidence was found to directly answer any given Research Question, publications that presented inferential data were extracted representing the best available evidence published in the last 5-years. Publications that provided inferential data in relation to the primary interest of COPD, were tabulated and are presented throughout this report. Additionally, because COPD is a well-established disease and this RLR was limited to the most recent papers published within the last five years (2015-2020), the Global Initiative for Chronic Obstructive Lung Disease (GOLD) report was used to provide supplemental information for Research Questions 2-6. The GOLD report is a systematic literature review (SLR) that reports on the global strategy for the diagnosis and management of COPD, and is updated annually; therefore, the most recent 2020 GOLD report is used to provide a summary of the existing knowledge as it pertains to Research Questions 2-6. Lastly, Research Questions 1 and 6 were identified as having potential overlap in relevant information identified for each; therefore, the publications identified for each of Question 1 and 6 were reviewed for inclusion for both questions to supplement the evidence.

5 Results

5.1 Research Question 1

5.1.1 Database and Grey Literature Search

The electronic database search identified 51 citations as potentially relevant. Of the 51 citations,

nine were excluded following title/abstract screening, and 42 proceeded to full-text screening. Of the 42 publications included for full-text screening, seven were included for data extraction, one of which was further excluded at the data extraction phase for lack of outcomes. Five potentially relevant citations were identified via the bibliography screen of the included publications. From the bibliography screening, two publications were unavailable (guidelines that had been replaced through update), and two were excluded per screening criteria. One publication from the bibliography screen proceeded to data extraction, bringing the total number for inclusion to nine publications from the electronic database search.

An additional six publications were identified from the targeted grey literature search of the nine selected organizations. Two organizations did not offer any consensus or guideline (National Institute for Occupational Safety and Health and Health and Safety Executive), and two organizations, the American Thoracic Society and the European Respiratory Society, provided a joint consensus publication. When combined with the results from the electronic database search, a total of 13 publications were included for Research Question 1.

Finally, any relevant guidelines and/or consensus statements identified as part of the electronic search for Research Questions 2-6 were also screened for Question 1. Following screening for Research Questions 2-6, 12 publications were identified as potentially relevant for Question 1. None of the publications identified from the Question 2-6 database search met criteria for inclusion.

Figure 1 provides a detailed account of the screening process for Question 1 via a PRISMA diagram.

Figure 1: PRISMA diagram for Research Question 1

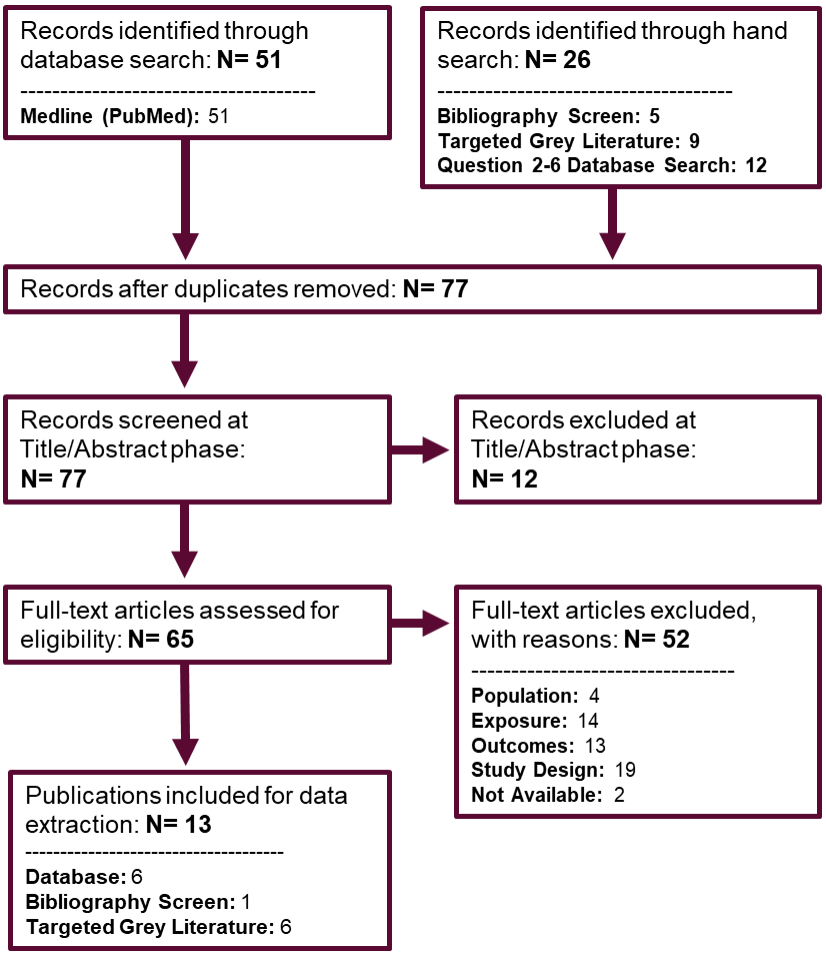


Table 3: Results of Targeted Grey Literature Search

Organization	Title	Website (Date Accessed)
Canadian Thoracic Society	Canadian Thoracic Society Clinical Practice Guideline on pharmacotherapy in patients with COPD – 2019 update of evidence	https://cts-sct.ca/guideline-library/ (Accessed: 14 Dec 2020)
American Thoracic Society	The Occupational Burden of Nonmalignant Respiratory Diseases. An Official American Thoracic Society and European Respiratory Society Statement	https://www.thoracic.org/statements/ (Accessed: 14 Dec 2020)
European Respiratory Society	Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease: A Clinical Practice Guideline Update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society	https://www.thoracic.org/statements/resources/copd/179full.pdf (Accessed: 14 Dec 2020)
British Thoracic Society	Chronic obstructive pulmonary disease in over 16s: diagnosis and management (2019)	https://www.brit-thoracic.org.uk/quality-improvement/guidelines/ (Accessed: Dec 14, 2020)
British Medical Journal	Best Practices Report for COPD (2020)	https://bestpractice.bmj.com/topics/en-us/7/management-approach (Accessed: 08 Dec 2020)
Global Initiative for Chronic Obstructive Lung Disease (GOLD)	GOLD 2021 Report	https://goldcopd.org/2021-gold-reports/ (Accessed: 02 Dec 2020)
National Institute for Occupational Safety and Health	No Results	
Health and Safety Executive	No Results	
Public Health Agency of Canada		https://www.canada.ca/en/public-health/services/publications/diseases-conditions/asthma-chronic-obstructive-pulmonary-disease-canada-2018.html#a2.2 (Accessed: Dec 14, 2020)

5.1.2 Research Question 1

Research Question 1:

a) *What is COPD? Is it a single disease or group of diseases/conditions?*

b) *How is COPD diagnosed? How is severity determined?*

c) *What are the causes of COPD? Do different causes result in different changes (at the cellular, tissue or structural level) within the lung? Does COPD onset or progression differ according to cause?*

5.1.2.1 COPD in Canada

The 2017 'Chronic Obstructive Pulmonary Disease in Ontario' report by the Institute for Clinical Evaluative Services (ICES), found the incidence of COPD was 8.8 per 1000 persons and prevalence 118 per 1000 in 2014/15.[58] The report also highlighted that the age and sex standardized incidence as well as the all-cause mortality rates declined from 1996/97 to 2014/15. However, during the same period, the prevalence rate has increased and the all-cause mortality rate among the COPD patients was 4.0%.[58]

Box 1: Key Findings Taken Directly from 2014/2015 from the Institute for Clinical Evaluation Services Report on Chronic Obstructive Pulmonary Disease in Ontario (Gershon, 2017).[58]

Individuals with COPD had 27.4 emergency department visits as well as 24.6 hospitalizations directly linked to their COPD per 1,000 person-years (where age and sex are standardized)
Similarly, the COPD- specific ambulatory care visits among the persons with COPD had around 370.4 visits per 1,000 person- years
The all-cause emergency department visits and all-cause hospitalizations among the COPD patients was found to be 774 and 182.1 respectively for every 1000 person-years
The all-cause ambulatory care visits among the COPD patients were found to be 16,154 visits per 1,000 person-years
During the period 2005/06 and 2014/15, though the rate of long-term care used declined by 20.6%, the rate of home care per 1,000 individuals with COPD increased by 15.5%
The highest rates of COPD-specific ambulatory care visits were recorded highest in Toronto Central Local Health Integration Network with 475 [95% CI: 469.9, 480] followed by the Erie St. Clair LHIN with 416 [95% CI: 411.4, 420.5

Annually, Statistics Canada compiles the data of all individuals aged over 35 years diagnosed with chronic bronchitis, emphysema or COPD by a health professional. In 2019 there were 842,600 cases of diagnosed COPD recorded in Canada.[59] Gershon *et al*., 2017 reported that in Ontario the lifetime risk of developing COPD is greater than 1 in 4 (27.6%) and higher in males (29.7%) compared to females (25.6%).[58] Though the COPD incidence varied amongst provinces and territories in Canada in 2011-2012, it was noted that Ontario is one of the four provinces with the lowest incidence rates. "The burden of COPD is known to be underestimated due to under-diagnosis, attribution of illness and death to other comorbid diseases or conditions such as pneumonia (especially among older adults), and a lack of consistent use of targeted lung function testing among at-risk populations". [2] The true burden of COPD might be considerably higher than represented in the Canadian Chronic Disease Surveillance System which is based on physician billing data and hospital records for several reasons. [2] The Canadian Institute for Health Information (CIHI) analysis for 'Trends in Income-Related Inequalities in Canada', added the Age-standardized rate of hospitalization due to COPD for patients younger than Age 75 per 100,000 as

an indicator (in Canada and at provincial level).[60] The data was analyzed from 2001- 2012 and higher rates of COPD hospitalizations are thought to reflect poorer access to appropriate and effective primary health care. Though there were some significant changes seen at National level and in some provinces, Ontario didn't show any statistically significant change between 2001 estimates and 2012 estimates.[60]

5.1.2.2 Global Burden of COPD

The latest 2019 global burden of disease statistics published in October 2020 show COPD as the sixth leading cause of death globally. However, it is ranked as the fourth leading cause among the 50-74 year group and third among the 75 years and above age group.[61] Disability Adjusted Life Years (DALYs), as defined by the World Health Organization represent, "the loss of the equivalent of one year of full health". DALYs for a disease or health condition are the sum of the years of life lost to due to premature mortality (YLLs) and the years lived with a disability (YLDs) due to prevalent cases of the disease or health condition in a population."[62]

COPD was the 11th ranked cause of DALYs at all ages in 1990 and rose to be the 6th leading cause in 2019.[61] However, between 1990 and 2019 there were large declines in age-standardized DALY rates for COPD, as shown in **Table 4** and reflecting demographic changes. Therefore, COPD represents an important public health challenge, as both a preventable and treatable chronic disease.[8] The top rankings of COPD and lung cancer in both the 50-74 years and above 75 year age groups highlight the importance of the need for tobacco control measures and reducing exposure to both indoor and outdoor air pollution. It is estimated that low and middle income countries account for nearly 62.6% of the global COPD burden and this share is likely to further increase in coming decades due to aging populations and ineffective control of tobacco and air pollution.[61]

Table 4: Comparison of COPD as the leading cause of death from the Global Burden of Disease Studies (1990 – 2019). Adapted from Vos *et al.* 2020.[61]

Year	Age	Rank	Percentage of DALYs *% (95% UI)*	Percentage change in the number of DALYs 1990-2019 *% (95% UI)*	Percentage change in age-standardized DALY rate, 1990-2019 *% (95% UI)*
1990	**All ages**	*11*	2.3 (1.9 – 2.5)	-	-
	50-74 years	*3*	6.5 (5.5 – 7.1)	-	-
	75 and older	*3*	9.9 (8.6 – 10.7)	-	-
2019	**All ages**	*6*	2.9 (2.6 – 3.2)	25.6 (15.1 – 46.0)	-39.8 (-44.9 – -30.2)
	50-74 years	*4*	4.7 (4.2 – 5.2)	12.0 (0.9 – 32.3)	-45.9 (-51.4 – -36.2)
	75 and older	*3*	8.5 (7.5 – 9.2)	63.6 (49.1 – 86.1)	-31.0 (-37.1 – -21.9)

Abbreviations: DALY: disability adjusted life year; UI: uncertainty interval.

5.1.2.3 What is COPD? Is it a single disease or group of diseases/conditions?

"COPD is a debilitating and chronic respiratory disease that imposes a significant and substantial socioeconomic burden for individuals and society", considering that both direct and indirect COPD-related costs increase with disease severity.[11] According to Dutch experts, "COPD is a complex and heterogeneous disease with pulmonary and systemic manifestations and multiple factors that affect a patients' health status as defined by four domains: physiological impairments, symptoms, functional limitations, and quality of life".[63] The Public Health Agency of Canada describes COPD as, "a chronic disease characterized by shortness of breath, cough and sputum production. While symptoms of the disease do not usually appear in people younger than age 55 years, changes to the lung begin many years earlier. COPD is an umbrella term for a number of diseases which include chronic bronchitis and emphysema. COPD progresses slowly over a period of years and increasing disease severity is associated with more frequent exacerbations, further reductions in airflow and premature death. As the disease advances, shortness of breath limits the activity levels of individuals and reduces their quality of life."[2]

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) expert committee defined COPD as, "a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and /or alveolar abnormalities usually caused by significant exposure to noxious particles or gases and influenced by host factors including abnormal lung development".[8] The current GOLD report and the previous versions do not use or emphasize the terms "emphysema" and "chronic bronchitis" in the definition of COPD. This report also emphasizes that although COPD is defined on the basis of airflow limitation, in practice the decision to seek medical help is usually determined by the impact of symptoms on a patient's functional status.[8] The Swiss National Guidelines 2018 confirm that the new GOLD definition of COPD is endorsed by both the American Thoracic Society (ATS) and the European Respiratory Society (ERS), taking into consideration the impact of respiratory symptoms and the role of lung tissue and airway abnormalities in the development of COPD.[11]

The following table (**Table 5**) highlights the critical indicators in making a COPD diagnosis, especially when the patients present with dyspnea, chronic cough or production of sputum and/or a positive history of exposure to risk factors.

Table 5: Key Indicators for considering a diagnosis of COPD. Taken directly from the GOLD 2021 report.[8]

Consider COPD and perform spirometry in an individual over 40 years if any of the following indicators are present: Spirometry is a must to establish a diagnosis of COPD.	
Dyspnea that is	Progressive over time Characteristically worse with exercise Persistent
Chronic Cough	May be intermittent and may be unproductive Recurrent wheeze
Chronic Sputum Production	Any pattern of chronic sputum production may indicate COPD
Recurrent Lower Respiratory Tract Infections	
History of Risk Factors	Host factors (such as genetic factors, congenital/developmental abnormalities, etc.)

	Tobacco smoke (including all forms and popular local preparations) Smoke from home cooking and heating fuels Occupational dusts, vapours, gases, fumes (VGDF), and other chemicals
Family History of COPD and /or Childhood Factors	History of Low birthweight, childhood respiratory infections, etc.

Abbreviations: COPD: Chronic Obstructive Pulmonary Disease

There is a growing consensus that among those who are older and with a smoking history, both the characteristics of typical asthma and COPD exist simultaneously. In one group there are severe asthma patients with smoking habits that eventually develop fixed airway obstruction, a common pattern observed in COPD. On the other hand, a positive bronchodilator test which is significant among asthma patients can also be found among COPD patients although not of the same magnitude. The term ACOS (Asthma-COPD overlap syndrome) is used to describe this group of patients who present with concomitant asthma and COPD characteristics. The prevalence of ACOS ranges between 15% - 60% indicating variations as per the age group, population sampled, and the definitions used for asthma and COPD.[64] It is critical to emphasize that in this group of patients, in spite of the clinical heterogeneity, there are two types of patients. 1) The asthmatics that develop ACOS and 2) The COPD patients presenting clinical characteristics of ACOS.[65] The consensus statements[65] for the diagnosis of ACOS recommended the following:

1. "simultaneous clinical manifestations characteristic of both asthma and COPD
2. persistent airway obstruction, defined as post-bronchodilator forced expiratory volume in 1 second (FEV_1)/ forced vital capacity (FVC) < 0.7, evaluated in a period of clinical stability
3. positive response in a bronchodilator test, defined by an increase in the value of FEV_1 of ≥200 mL and ≥12% from baseline
4. current or past history of smoking or exposure to biomass combustion"

Even though ACOS patients are usually over 40 years of age, their respiratory symptoms might have actually started in their childhood phase or during early adulthood. Supporting this, they may also give a family history of asthma or allergies, previous diagnosis of asthma made by a health professional, or a history of exposure to noxious gases or particulate matter. In these patients, airflow limitation measured by spirometry is not fully reversible to β2-mimetics, which is a major COPD feature with non-specific chest X-ray findings. However, it is now established that although the clinical meaning of this trait remains unclear, around 39% of COPD patients actually show significant reversibility in response to the bronchodilators.[64,65]

5.1.2.4 How is COPD diagnosed? How is severity determined?

The process for diagnosing COPD should be "multidimensional and include a detailed 1) medical history, 2) physical examination, and 3) measurement of airflow obstruction".[11] A diagnosis of COPD should be considered in any patient with a history of exposure to risk factors (e.g., tobacco smoking) and/or with dyspnea (progressive, on exertion, or persistent), chronic cough, or sputum production. The various guidelines (GOLD, CTS, ATS, and ERS) are consistent that patients' smoking history should be the prime focus as it remains the most important risk factor, and clinicians should be aware of an increased risk of COPD especially in individuals reporting a past medical history of asthma and/or severe childhood respiratory disease.[55]

To make a diagnosis the post-bronchodilator spirometry (FEV_1/FVC ratio <70%) is required which should be confirmed by repeated spirometry to rule out the absence or presence of airflow obstruction in patients with an FEV_1/FVC ratio between 60%- 80% (as the ratio may alter due to biological variability.[8]

The American College of Physicians (ACP), American College of Chest Physicians (ACCP), American Thoracic Society (ATS), and European Respiratory Society (ERS) recommend that "spirometry should be obtained to diagnose airflow obstruction in patients with respiratory symptoms, and spirometry should not be used to screen for airflow obstruction in individuals without respiratory symptoms".[7] Therefore, a diagnosis of COPD essentially requires spirometry in subjects with a history of exposure to known risk factors, cigarette smoking and symptoms such as dyspnea and/or chronic cough with sputum production.[12] The recent Canadian Thoracic Society's guidelines for clinicians emphasize that "spirometry is essential for the diagnosis of COPD, that is, a fixed post-bronchodilator ratio of the FEV_1/FVC of less than the lower limit of normal (LLN) ratio (i.e., less than the lower fifth percentile of the reference value from a healthy population)".[55]

Rossi *et al.,* 2017 and Volgelmeier *et al.,* 2017 emphasized that "postbronchodilator forced expiratory volume in 1 second (FEV_1)/ FVC of 0.7 or below the lower limit of normal (LLN) confirms the presence of persistent airflow limitation, the severity of which can be assessed by means of the value of FEV_1% predicted".[12,66] The GOLD criteria have categorized the severity of airflow limitations in COPD as described in **Table 6**.

Table 6: Global Initiate for Chronic Obstructive Lung Disease (GOLD) Diagnostic Criteria Taken Directly from the 2021 GOLD Report.[8]

In patients with FEV_1/FVC < 0.70		
GOLD 1	Mild	FEV_1≤ 80% predicted
GOLD 2	Moderate	50% ≤ FEV_1< 80% predicted
GOLD 3	Severe	30% ≤ FEV_1< 50% predicted
GOLD 4	Very Severe	FEV_1 < 30% predicted

Abbreviations: GOLD: Global Initiative for Chronic Obstructive Lung Disease; FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity.

According to the GOLD guidance, "adoption of the LLN values, as recommended by the European Respiratory Society–American Thoracic Society task force on lung-function tests, would be even more "imperfect" due to biases caused by age, height, and sex differences". However, prospective analysis of both spirometric criteria and an expert-based diagnosis of COPD suggested that the presence of COPD in elderly subjects was overestimated and underestimated by the fixed ratio and the LLN respectively. It was recommended to incorporate FEV_1 and residual volume (RV)/total lung capacity (TLC) in the COPD definition.[12] The US Preventive Services Task Force (USPSTF) recognizes that there may be under-reporting among patients who have mild COPD symptoms. The USPSTF urges all the clinicians to provide patients who are actively smoking with smoking cessation interventions and to seek active case-finding for COPD in patients with risk factors (e.g. exposure to cigarette/ tobacco smoke or heating fuels, occupational exposure to dusts or chemicals, or a family history of alpha (α)1-antitrypsin deficiency).[67]

To assess the impact of respiratory symptoms on a patient's life, it is encouraged to use both a modified Medical Research Council (mMRC) questionnaire and the COPD Assessment Test (CAT) or the COPD Control Questionnaire (CCQ). The mMRC dyspnea scale should be used to grade the breathlessness according to the level of exertion required to elicit it and the scale also relates well to other measures of health status and predicts future mortality risk.[8] The CAT and CCQ are simple scoring methods that have a broader coverage of the impact of COPD on the patient's daily life and well-being. The CAT is "a standard and validated assessment tool containing eight items for the evaluation of the impact of COPD on health status; each response is graded 0-5 with a higher score indicating worse health status".[11] Moreover, patients with more advanced or more complex COPD and/or asthma might benefit from a more

structured approach towards assessment of all four domains of health status, namely physiological impairments, symptoms, functional limitations, and quality of life.[63] The other factors in addition to FEV_1 that predict prognosis are weight (very low weight is a negative prognostic factor), distance walked in 6 minutes, and the degree of shortness of breath with activities. These factors are known as the Body mass index, airflow Obstruction, Dyspnea, and Exercise (BODE) index and can be used to provide information on the prognosis for 1-year, 2-year, and 4-year survival. Moreover, in patients with stable COPD, the elevation of adrenomedullin, arginine vasopressin, atrial natriuretic peptide, and C-reactive protein is associated with an increased risk of death.[68]

Recently there has been more interest on comorbidities and prior exacerbations as the predictor of COPD course. In predicting the prognosis for patients with COPD, the CODEX index (comorbidities, obstruction, dyspnea, and previous severe exacerbations) has proved to be superior to the BODE index.[68]

5.1.2.5 What are the causes of COPD?

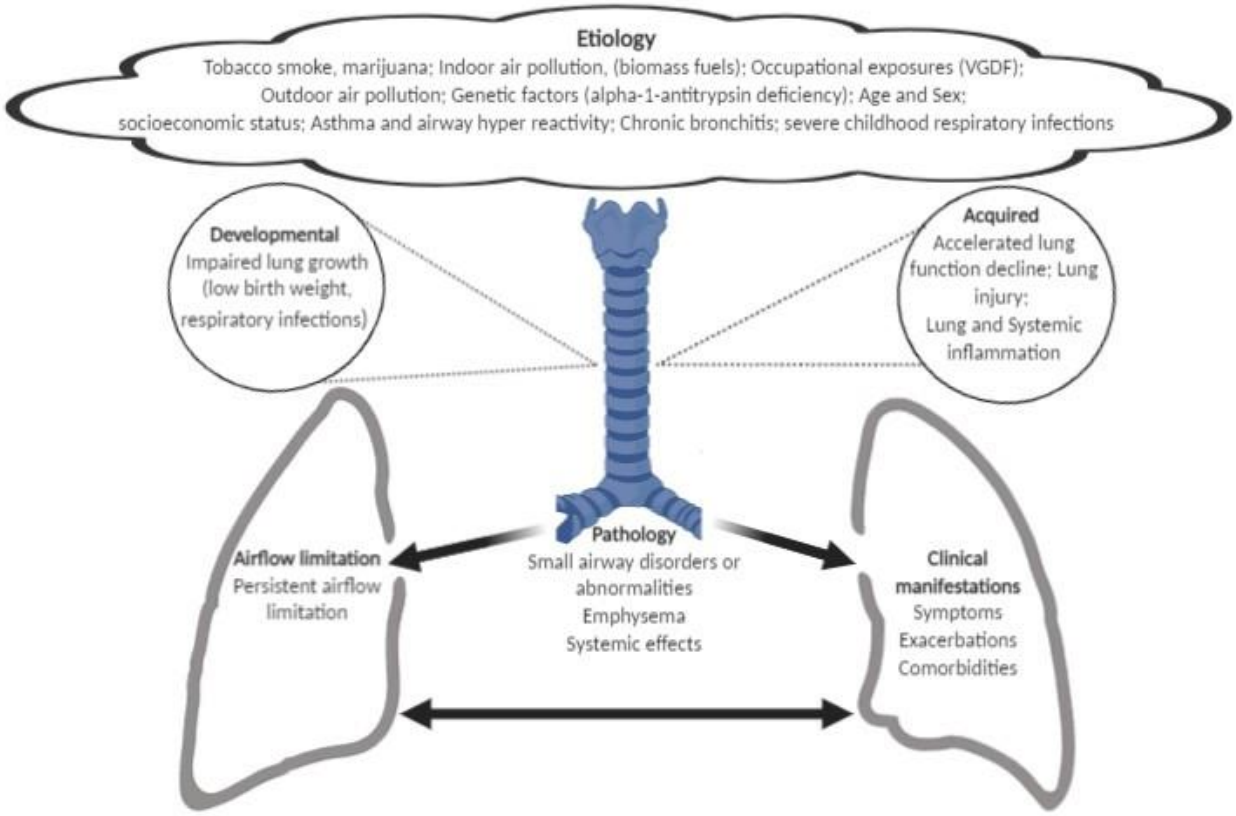
Even though cigarette smoking is identified as the most common risk factor for COPD, there are other environmental exposures and host factors that also contribute such as occupational exposure, biomass fuels and α1-antitrypsin deficiency. Moreover, the individual susceptibility to infections also a plays a significant role in COPD exacerbations.[11] As highlighted in the GOLD 2021 report, other types of tobacco (used in pipe, cigar, water pipe), marijuana and passive exposures to cigarette smoke (environmental tobacco smoke) also contributes to COPD.[8] Inhalation of vapours, gases, dusts, or fumes (VGDF) in the workplace is common worldwide, with occupation being an important global contributor to the burden of respiratory disease. The contribution of workplace exposures for Asthma and COPD has been a particular focus of attention in the policy statements of the American Thoracic Society.[7] The causes of COPD (**Figure 2**Figure 2: Etiology, Pathobiology and Pathology of COPD resulting in airflow limitation and clinical manifestations. Based on from GOLD 2021.) and their underlying mechanisms are summarized in **Table 7** below.

Table 7: Summary of the causes of COPD and their underlying mechanisms. Based on from BMJ Best Practice COPD 2020.[68]

Risk factor	Strong/ Weak	Underlying mechanism/ cause
Behavioral- Cigarette smoking	Strong	Most important risk factor (causes 40%-70%) Stimulates an inflammatory response thereby causing cilia dysfunction and oxidative injury.
Genetic factors	Strong	Alpha-1 antitrypsin deficiency (a genetic disorder, among people of northern European ancestry causing panacinar emphysema in lower lobes)
Unmodifiable- Age	Strong	The effect of age may be related to a longer period of cigarette smoking as well as the normal age-related loss of FEV_1
Sex differences	Weak	More common in men, likely due to more smokers being male. However, women may be more susceptible than men to the effects of tobacco smoke
Race/ White ancestry	Weak	More common in white people than black and South Asian people, after adjusting for factors such as smoking, age, sex, and socioeconomic status
Developmental- Lung growth and development	Weak	Frequent childhood infection may cause scarring of lungs, decrease elasticity, and increase the risk for COPD.
Environmental exposure to Air pollution	Weak	the risk of COPD increases with chronic exposure to dust, fumes from the traffic exhaust, and sulfur dioxide
Exposure to burning solid or biomass fuel	Weak	The household exposure to burning coal or exposure to biomass fuel increases the risk of COPD
Occupational exposure to dusts, chemicals, vapour, fumes, or gases	Weak	Around 14% of COPD cases are attributable to occupational exposure
Socioeconomic factors	Weak	The risk of developing COPD is high among people with lower socioeconomic status. However, this may also reflect exposure to cigarette smoke, pollutants and other factors

Risk factor	Strong/ Weak	Underlying mechanism/ cause
Medical conditions		
Rheumatoid arthritis	Weak	Epidemiologic studies indicate an association between the risk of COPD and a history of rheumatoid arthritis
Chronic bronchitis	Strong	There is an association between mucus hypersecretion and increased FEV_1 decline and in young adults who smoke, chronic bronchitis has been associated with an increased likelihood of developing COPD
Asthma and airway hyper-reactivity	Strong	A longitudinal cohort study (Tucson) found a 12 times higher risk of acquiring COPD compared to non-asthmatics In a European respiratory health survey, airway hyper-responsiveness was identified as the second leading cause of COPD after cigarette smoking
Infections	Weak-Strong	*Severe respiratory* infections during childhood are associated with reduced lung function and increased respiratory symptoms in adulthood. Moreover, susceptibility to infections also play a key role in the exacerbations of COPD *HIV positives* are more at risk of COPD than HIV negative controls *Tuberculosis* is a recognized risk factor for COPD.

Figure 2: Etiology, Pathobiology and Pathology of COPD resulting in airflow limitation and clinical manifestations. Based on from GOLD 2021.[8]



5.1.2.6 Do different causes result in different changes (at the cellular, tissue, or structural level) within the lung?

In COPD there is a consensus that inflammation in the small airways is related to cigarette smoking as the main risk factor. Many authors have suggested the role of premature lung aging as central to the pathogenesis of COPD, where the essential equilibrium senescence and antisenescence factors is disrupted toward senescence in the COPD lungs. In COPD lungs, telomere attrition is predicted, and this view is further supported by the prevalence of other comorbidities such as weight loss, cardiovascular diseases, osteoporosis and depression where abnormalities of premature senescence and telomere length abnormalities have been identified. These senescence-related markers in COPD are demonstrable mainly in the mesenchymal cells (fibroblasts and endothelial cells).[12] The goal of the Macrolide Azithromycin for Prevention of Exacerbations of COPD (MACRO) study was to investigate the relationship between peripheral blood leukocyte telomere length and clinical outcomes including general health status, degree of exacerbation and the risk of mortality in people with COPD. The study concluded that shorter telomere lengths of leukocytes may be a clinically translatable biomarker to classify people at increased risk of poor clinical outcomes in COPD.[13]

The inhalation of tobacco smoke or toxic particles such as biomass fuel smoke triggers pulmonary inflammation, which causes 1) destruction of parenchymal tissue (resulting in emphysema) and 2) the disruption of normal processes of repair and defense resulting in small airway fibrosis (**Figure 2**). These pathological changes lead to gas trapping and progressive airflow limitation. The pathological changes in COPD include recurrent inflammation with an elevated number of inflammatory cells such as

macrophages and neutrophils in different areas of the lung and structural changes arising from repetitive injuries and repairs.[8]

The GOLD 2021 report states that the inflammation observed in COPD patients' respiratory tract appears to be a modification of the normal inflammatory response of the respiratory tract to chronic irritants such as cigarette smoke.[8] The mechanisms are not yet known for this form of inflammation but may be genetically determined in part. Some patients develop COPD without smoking, but the existence of the inflammatory response of these patients is unknown to date. The lung inflammation continues even after smoking cessation through unknown mechanisms, although some autoantigens and perturbations in the lung microbiome may play some role.[8]

The consensus statements of various respiratory societies and GOLD also highlight the role of oxidative stress as an amplifying mechanism in COPD as the biomarkers such as hydrogen peroxide and 8-isoprostane are increased in exhaled breath condensate, sputum, and systemic circulation. The oxidative stress is further increased during exacerbations and the oxidants are also produced mostly by the cigarette smoke and other inhaled particles.[8,69]

In peripheral airways, lung parenchyma, and pulmonary vessels there are increased numbers of inflammatory cells (macrophages) together with activated neutrophils and lymphocytes, which include Tc1, Th1, Th17, and ILC3 cells in COPD. There may also be a rise in eosinophils, Th2 or ILC2 in some patients. Multiple inflammatory mediators are released by these inflammatory cells along with epithelial and structural cells. These mediators attract circulating inflammatory cells (chemotactic factors), amplify the inflammatory cycle (proinflammatory cytokines), and trigger structural changes (growth factors).[8] Another pathologic change in COPD patients and asymptomatic smokers is peribronchiolar and interstitial fibrosis. In smokers and those with prior airway inflammation who have COPD, excessive production of growth factors can be found. It was also established that Club cell secretory protein-16 (CC16) is the major secreted product of airway club cells (formerly Clara cells). Exposure to cigarette smoke decreases airway levels of anti-inflammatory CC16 thereby leading to the genesis of COPD.[70] Inflammation may precede the fibrosis development, or repetitive damage to the airway walls itself may lead to excessive production of muscle and fibrous tissue, which may contribute to the development of small airway limitation. This process eventually leads to the obliteration which may precede the development of emphysema.[8]

Peripheral airway inflammation and narrowing contributes to a decrease in FEV_1. The parenchymal damage caused by emphysema also contributes to the restriction of airflow and leads to a reduction in gas transfer. The extent of inflammation, fibrosis, and luminal exudates in small airways is correlated with the reduction in FEV_1 and FEV_1/FVC ratios and the accelerated decline in FEV_1 is characteristic of COPD.[8]

The restriction of the peripheral airway gradually traps gas during expiration, resulting in hyperinflation. Static hyperinflation decreases inspiratory capacity and is usually associated with dynamic hyperinflation during exercise, resulting in increased dyspnea and decrease in exercise capacity. These factors lead to the impairment of the respiratory muscles' intrinsic contractile properties. Gas exchange abnormalities lead to hypoxemia and hypercapnia through various mechanisms in COPD. As the disease progresses, the gas transfer between oxygen and carbon dioxide worsens. There is also mucus hypersecretion in some COPD patients due to an elevated number of goblet cells and enlarged submucosal glands caused by cigarette smoke and other noxious agents by chronic airway irritation.[8]

5.1.2.7 Does COPD onset or progression differ according to cause?

There is considerable evidence concerning COPD risk factors arising from cross-sectional studies that identify associations rather than causal relationships. Though cigarette smoking is well studied, some

reports show the development of chronic airflow limitation among non-smokers. Non-smokers with chronic airflow limitation have fewer symptoms, milder illness and lower systemic inflammation relative to smokers with COPD. Additionally, there does not seem to be an elevated risk of lung cancer or cardiovascular comorbidities among never smokers with versus those without chronic airflow limitation.[8]

"COPD results from complex interactions between genes and the environment. Though cigarette smoking is the leading cause as an environmental risk factor for COPD, fewer than 50% of heavy smokers develop COPD during their lifetime. A genetic risk factor that is best documented, is a severe hereditary deficiency of alpha-1 antitrypsin (AATD), a major circulating inhibitor of serine proteases. A systematic review of 20 studies in European populations found AATD PiZZ genotypes in 0.12% of COPD patients (range 0.08-0.24%) and a prevalence ranging from 1 in 408 in Northern Europe to 1 in 1,274 in Eastern Europe. Occupational exposures to organic and inorganic dusts, chemical agents, and fumes are under-appreciated risk factors for COPD, and studies have shown that self-reported exposure to dust and fumes in the workplace is not only associated with increased restriction of airflow and respiratory symptoms, but also with more emphysema and gas trapping evaluated by computed tomography scan in both males and females. The American Thoracic Society concluded that occupational exposures account for 10-20 percent of all symptoms and functional impairments associated with COPD. There is increasing evidence that exposure to indoor biomass during cooking may predispose women to developing COPD in many developing countries. High levels of urban air pollution are harmful to individuals with existing heart or lung disease, but its role as a risk factor for COPD is unclear and is small in adults compared to cigarette smoking."[8]

A study from the UK by Darby et al. in Sheffield, an industrialized area looked at people with COPD, emphysema or chronic bronchitis, with or without concomitant asthma, there was an OR 32.04 (CI 95, 15.92-64.47) with both high smoking and exposure to VGDF, and OR 5.63 (2.60-12.20) for never smoking and exposure to VGDF.[71] Another nested case control study by Blanc et al found that self-reported occupational exposure to VGDF was associated with an increased risk of developing COPD (OR 2.11; 95% CI 1.59-2.82) and a population attributable fraction (PAF) of 31%.[72] In support of these findings a Burden of Obstructive Lung Disease (BOLD) study reported from Latin America and European countries among the participants with COPD GOLD stage II and above, a 0.8% increase in COPD prevalence for each 10% increase in exposure prevalence.[73] Further work by Blanc reported on a US case referent study with a physician diagnosis of chronic bronchitis OR 2.5 (CI95, 1.9 to 3.4) and a PAF 32% (21 to 41%) for self-reported VGDF.[4]

5.2 Research Questions 2-6

5.2.1 Database and Hand Search

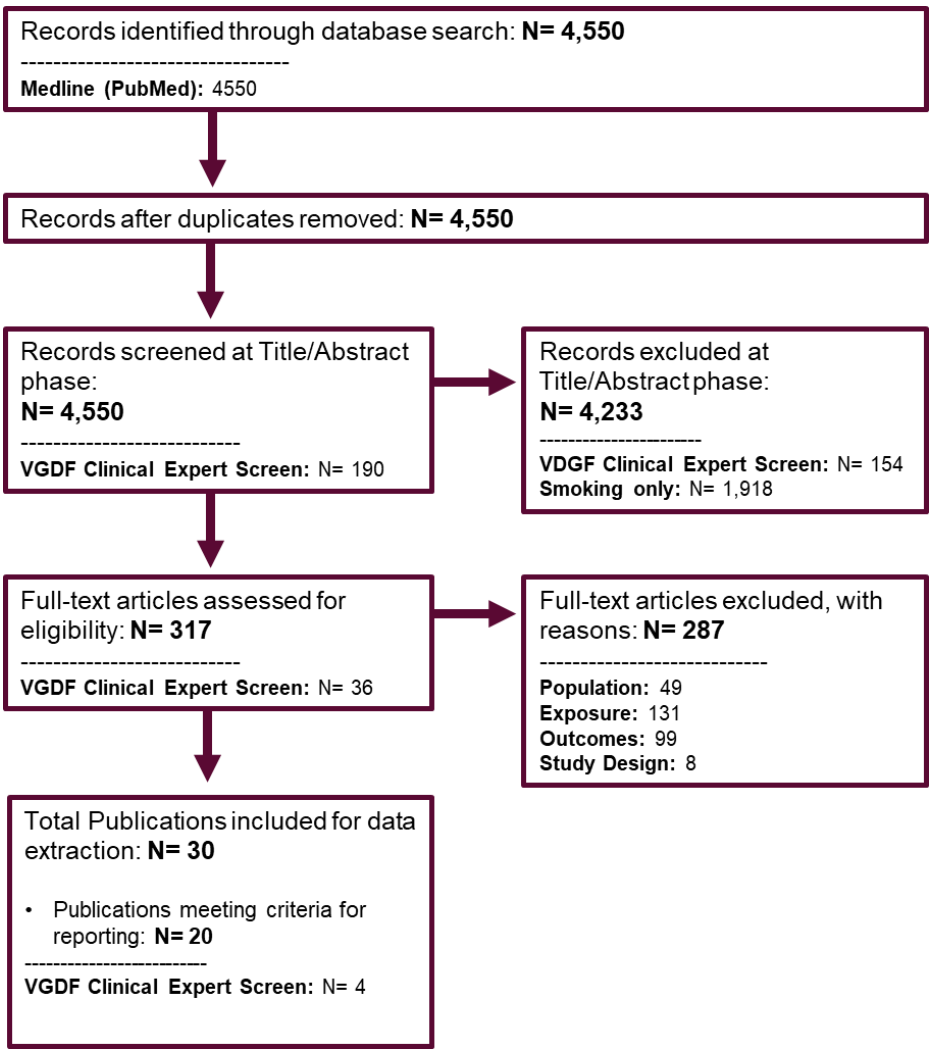
The electronic database search identified 4,550 citations as potentially relevant. Of the 4,550 citations, 4,233 were excluded following title/abstract screening, and 317 proceeded to full-text screening. Of the 317 publications included for full-text screening, 204 were excluded, and the remaining 113 publications were considered for data extraction. During the data extraction phase an additional 113 publications were further excluded due to a lack of data either directly, or inferentially, supporting any of Research Questions 2 through 6 (excluded in the PRISMA largely due to 'Outcomes').

During the title/abstract screening phase, 190 publications were identified that reported data for occupational VGDF exposure only, without addressing cigarette smoking exposure in either the title or the abstract. Due to the comparative nature of Questions 2-6 (occupational VGDF exposure vs. cigarette smoking exposure in relation to COPD), the 109 titles and abstracts were identified as not eligible in the title/abstract phase. However, due to the possibility of these studies potentially controlling for smoking status within their analyses, the 109 publications were screened separately by a clinical content expert, Dr. Anil Adisesh, for relevance. Of the 109 title/abstracts reviewed, 36 publications were identified as eligible for full-text review. Following full-text review, four publications were included for data extraction.

Altogether, a total of 30 publications were included for data extraction for Questions 2-6 in this review. It is important to note, that although publications may have been included for data extraction, only those for which COPD was the primary focus (n=20), are presented in the main body of the report. **Figure 3** provides a detailed account of the screening process via PRISMA diagram.

Quality assessment for the 20 studies included within this report was performed via the National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. The results of the quality assessment can be found in **Appendix D: Quality Appraisal .**

Figure 3: PRISMA diagram for Research Questions 2-6



5.2.2 Research Question 2

Research Question 2: Is it possible to differentiate clinically between COPD, or lung function loss/impairment, caused by cigarette smoking and that caused by workplace VGDF exposures?

5.2.2.1 Results

There were no studies identified in the last five years as a part of this RLR that directly addressed Question 2. One study was identified that provides supporting evidence that lung function loss/impairment occurs among individuals who have experienced occupational VGDF exposure, even when controlling for smoking, providing inferential evidence of impairment due to VGDF. Additionally, supplemental information has been included to provide contextual reference as to the clinical measurements and manifestations related to COPD.[8]

5.2.2.2 Supplemental Information

The GOLD report highlights that although cigarette smoking is the most commonly studied risk factor for COPD, that epidemiological evidence shows that non-smokers may also develop chronic airflow limitation, as the inhalation of cigarette smoke and other particulates can both cause inflammation in the lungs.[8]

The GOLD 2021 report states that lung function is typically measured by spirometry since it is the most commonly available, objective and the most reproducible measure of airflow limitation.[8] This test measures the volume of air that is forcibly exhaled (FEV) after a full inhalation (FVC), as well as the volume of air exhaled during the first second of this breath (FEV_1). The ratio of these two measurements is also calculated (FEV_1/FVC).[8] A decrease in both FEV_1 and FVC is typically noted in COPD patients.[8] The criteria for airflow limitation is cited as a fixed ratio of $FEV_1/FVC < .70$ in the GOLD 2021 report.[8] However, the ATS recommends the use of the LLN as a cut-off value for detection of COPD in clinical practice.[40]

Although narrowing of peripheral airways lends to a decrease in FEV_1, the GOLD 2021 report cautions that FEV_1 alone is not a reliable marker of the severity of COPD symptomology (i.e., breathlessness, exercise limitation, health status impairment), and that substantial heterogeneity exists in the rate of decline measured across individuals potentially due to complex genetic predispositions and environmental exposures.[8] The GOLD report does not present any evidence regarding clinical comparisons in the development of COPD between smoking and VGDF exposures, or the ability to differentiate between the two exposures using clinical measurements.

The ATS assessed the contribution of occupational exposures to COPD by estimating the pooled population attributable fraction (PAF) from 26 studies. They estimated the pooled PAF to be 14%, and this rose to 31% when considering non-smokers only (pooled data from 6 studies). However, this is based on an estimate of the excess risk of developing COPD with occupational exposures, not based on clinical differentiation of the causes of disease.

In terms of pathophysiology, the disease process of COPD can lead to the following characteristic symptoms and abnormalities often observed clinically in patients.[8]

- Airflow limitation: inflammation in airways is correlated with a reduction in the FEV_1 and FEV_1/FVC ratio. This limitation can trap gas during expiration, which can result in hyperinflation (overinflation of the lungs preventing exhalation of air in the lungs).[8]
- Gas exchange abnormalities: generally gas transfer of oxygen and carbon dioxide worsens as COPD progresses. Gas exchange issues can result in hypoxemia (low levels of oxygen in the blood) and hypercapnia (elevated levels of carbon dioxide in the blood).[8]

- Mucus hypersecretion: when present in COPD patients, mucus hypersecretion may be due to an increased number of goblet cells and submucosal glands (due to chronic airways irritation from smoking or exposure to other agents).[8]
- Pulmonary hypertension: this may develop in later stages of COPD and is thought to be due to hypoxic vasoconstriction (narrowing of the small pulmonary arteries).[8,74]
- Exacerbations: infections, pollutants or unknown factors could cause exacerbations of respiratory symptoms.[8]
- Systemic features: many individuals with COPD also experience other chronic diseases (potentially due to airflow limitation and inflammatory mediators).[8]

5.2.2.3 Supporting Evidence for the Differentiation of COPD Caused by Cigarette Smoking versus Occupational VGDF exposure via the Clinical Measurement of Lung Function Loss/Impairment.

5.2.2.3.1 Study Characteristics

Although no comparative evidence was identified to directly answer Research Question 2, one study was identified in this RLR that provided supportive data demonstrating the clinical impact of occupational VGDF exposure on lung function. Study characteristics of this included study is presented in **Table 8.**

Paulin *et al.,* 2018 reported on the impact of VGDF exposure and cigarette smoking on computed tomographic characteristics of lung airway characteristics, including % emphysema and lung airway dimensions.[14] This study was conducted in the United States (U.S.) on individuals exposed to organic dusts following occupational exposure as dairy farmers.[14]

Studies in which COPD is not the primary focus that present supporting/inferential data regarding a variety of conditions related to lung function loss/impairment are included in the Data Extraction Workbook that accompanies this report.[20,75-78]

Table 8: Study Characteristics of Publications Providing Supportive Evidence for Question 2

Study Name Author, Year	Occupation(s)	Main Exposure of Interest	Method of Exposure Measurement	Stratified by Smoking Status *(Yes/No)*	Primary Outcome of Interest	Method of Outcome Assessment	Study Dates (year-year)	Country
Observational Studies – Cross-Sectional								
Paulin 2018 [14] REFID: 3053	N.R.	VGDF	Questionnaire	Yes	Airway Obstruction COPD	Spirometry	-	United States

Abbreviations: COPD: Chronic obstructive pulmonary disease; N.R.: not reported.

5.2.2.3.2 Findings

Paulin *et al.,* 2018 reports that current and former smokers with VGDF exposure in the longest held job had significantly greater % emphysema than individuals without VGDF exposure in the longest held job compared with non-smoking controls (**Table 9**). It is important to note that conditions such as emphysema and chronic bronchitis have been used in previous definitions of COPD, however, the GOLD 2021 report asserts that these terms are not used in the current GOLD definition.[8]

Individuals with VGDF exposure in the longest held job also had greater wall area percentage in the segmental and subsegmental airways, and greater Pi10 (estimated square-root wall area of a single hypothetical airway with internal perimeter of 10mm, measure of wall area) compared to individuals without VGDF exposure in the longest held job, which is indicative of large-airway disease (**Table 9**).

No statistical significance was found between VGDF exposure groups for the measures of gas trapping and PRM fSAD (parametric response mapping of functional small-airway abnormality), which are measures of small-airway disease (**Table 9**).[14]

Bivariate analysis on former and current smokers found that VGDF exposure was associated with increased wall area percentage in the segmental and subsegmental airways and increased segmental wall area (**Table 10**). Importantly, following adjustment for age, sex, race, current smoking status, pack-years of smoking, body mass index (BMI), and study site, the association between VGDF exposure and wall area percentage (both segmental and subsegmental) remained significant for segmental wall area percentage (***β: 1.19*** 95% CI, 1.07 – 1.32), and for subsegmental wall area percentage (***β: 1.11*** 95% CI, 1.01 – 1.22). Following adjustment, VGDF exposure was also significantly associated with gas trapping, segmental lumen area, and percent emphysema. VGDF exposure was associated with a 1.34-fold increased odds ratio for percent emphysema (95% CI, 1.12 – 1.60) greater than 95% of the non-smoking controls.[14]

When looking at individuals with a confirmed COPD diagnosis (n=1,809), VGDF exposure was only significantly associated with wall area percentage, after adjustment for the previously mentioned confounders.

Paulin *et al.,* 2018 also identified a trend towards increased lung impairment in males within the longest held job compared to women after adjustment for age, sex, race, current smoking status, pack-years of smoking, BMI, and study site. Both measures of wall area percentage (segmental and subsegmental), segmental airway wall area and percent air trapping all showed significant associations with the longest held job in males but not in females.[14]

Table 9: Study Outcomes of Publication Providing Supporting Evidence for Question 2

Study Name Author, Year	Occupation/ Group	Smoking Status	COPD *n (%)*	Quantitative Computed Tomographic Characteristics					
				% Emphysema	**Pi10**	**Wall area % †Segmental ‡Subsegmental**	**Airway lumen area †Segmental ‡Subsegmental**	**Airway wall area †Segmental ‡Subsegmental**	**Small airway †% gas trapping ‡% PRM fSAD**
Observational Studies – Cross-Sectional									
				Median (IQR), 95th percentile	***Mean (SD), 95th percentile***	***Mean (SD; 95th percentile), p-value***	***Median (IQR), p-value mm²***	***Mean (SD), p-value mm²***	***Median (IQR), 95th percentile***
Paulin 2018 [14] REFID: 3053	Controls	Non-smoking (n=202)	0	1.0 (1.4), 4.5	3.67 (0.08), 3.80	†57.5 (4.1; 65.0) ‡61.4 (3.8; 68.5)	†24.5 (10.8) ‡14.5 (6.4)	†37.8 (8.9) ‡26.1 (8.4)	†3.4 (7.1), 21.6 ‡3.8 (8.0), 24.4
	Combined VGDF exposure groups	Current and former smokers (n=2,736)	1,809 (66.1)	3.2 (9.8)	3.71 (0.08)	†60.6 (4.7) ‡64.1 (4.6)	†20.4 (11.6) ‡11.1 (7.9)	†32.8 (9.9) ‡21.7 (9.1)	†18.3 (33.2) ‡18.1 (25.0)
	No VGDF Exposure in Longest Held Job	Current and former smokers (n=1,390)	895 (64.4)	2.9 (8.7)*	3.71 (0.08)*	**†60.4 (4.8), <0.005** ‡64.0 (4.8)	**†20.0 (11.4), <0.005 ‡11.0 (7.8), <0.005**	**†32.1 (9.6), <0.005 ‡21.4 (9.3), <0.005**	†17.9 (31.9) ‡17.6 (24.8)
	VGDF Exposure in Longest Held Job	Current and former smokers (n=1,346)	914 (67.9)	3.5 (11.2)*	3.72 (0.08)*	**†60.8 (4.7), <0.005** ‡64.1 (4.5)	**†20.7 (11.6), <0.005 ‡11.3 (8.1), <0.005**	**†33.6 (10.1), <0.005 ‡22.0 (8.8), <0.005**	†18.7 (34.8) ‡18.3 (25.1)
				β (95% CI), p value	***β (95% CI), p value***	***β (95% CI), p value***	***β (95% CI), p value***	***β (95% CI), p value***	***β (95% CI), p value***
	Longest Job Exposure* - individuals	Adjusted for in model	1,809 (66.1)	**1.17 (0.44 – 1.89), 0.002**	0.008 (0.002 – 0.014), 0.01	**†0.487 (0.320 – 0.654), <0.001 ‡0.400 (0.275 – 0.527), <0.001**	**†-0.652 (-1.060 – -0.244), 0.002** ‡-0.846 (-1.521 – -0.170), 0.01	†-0.156 (-0.481 – 0.169), 0.35 ‡-0.297 (-0.549 – -0.045), 0.02	**†2.6 (1.11 – 4.09), 0.001** ‡1.45 (0.31 – 2.60), 0.01

Study Name Author, Year	Occupation/ Group	Smoking Status	COPD *n (%)*	Quantitative Computed Tomographic Characteristics					
				% Emphysema	**Pi10**	**Wall area % †Segmental ‡Subsegmental**	**Airway lumen area †Segmental ‡Subsegmental**	**Airway wall area †Segmental ‡Subsegmental**	**Small airway †% gas trapping ‡% PRM fSAD**
	Longest Job Exposure* - individuals with COPD confirmed	Adjusted for in model	1,809 (100%)	0.76 (-0.21 – 1.74), 0.12	0.003 (-0.005 – 0.011), 0.43	**†0.302 (0.098 – 0.506), 0.004 ‡0.321 (0.164 – 0.479), <0.001**	†-0.379 (-0.875 – 0.118), 0.14 ‡-1.025 (-2.087 – 0.037), 0.06	†-0.062 (-0.409 – 0.397), 0.98 ‡-0.371 (-0.704 – -0.038), 0.03	†2.05 (0.23 – 3.87), 0.03 ‡1.32 (0.02 – 2.67), 0.05

Abbreviations: BMI: Body Mass Index; CI: Confidence Interval; COPD: Chronic Obstructive Pulmonary Disease; IQR: interquartile range; Pi10: estimated square-root wall area of a single hypothetical airway with internal perimeter of 10mm; PRM fSAD: parametric response mapping of functional small-airway abnormality; SD: standard deviation; VGDF: Vapour, dust, gas, fume.

* Adjusted for Age, Sex, Race, Current Smoking Status, Pack-Years of Smoking, BMI, Study Site

Bolded values indicate a significant difference was detected

5.2.2.4 Limitations

There are inherent limitations that lend considerable difficultly to answering the question at hand. The initial premise of the question assumes that the cause of COPD can be determined between cigarette smoking and occupational exposure to VGDF, and that clinical measures are sensitive enough to differentiate the cause of COPD between the two exposures. According to the GOLD 2021 report, spirometry measures are required for the diagnosis of COPD.[8] However, spirometry values vary and may be an unreliable marker at the individual patient level without adherence to quality standards. In monitoring the occupational populations at risk of COPD spirometry may not be a sensitive enough tool to detect the early onset of accelerated lung function decline prior to the development of COPD. Neither can it differentiate the cause or contribution of different exposures in COPD.[8,79-81] The average within-person variation can range between 4-6% with good and variable quality spirometry, respectively.[79] Other clinical indicators such as dyspnea, chronic cough (also a symptom of other diseases [e.g. asthma, gastroesophageal reflux], chronic sputum production, and recurrent lower respiratory tract infections are all symptoms of COPD likely lacking sensitivity to differentiate a cause.[8]

Of note, other clinical measurement tools utilized in the diagnosis of COPD include: chest x-rays, lung volumes and diffusing capacity, oximetry and arterial blood gas measurement, exercise testing and assessment of physical activity, and to a limited extent biomarkers.[8] The GOLD 2021 report does not discuss the ability of these tools to determine the cause or contribution of various exposures to COPD, and there were no studies identified in the RLR that reported using these tools to clinically distinguish causes of COPD.

Another major limiting factor to answering this research question is the lack of study designs identified in this RLR that supports the required comparison. Study designs within occupational exposure literature may report the proportional distribution of smoking status as a part of group characteristics, however results are often reported for the combined group and not stratified by smoking. For those studies that stratify results by smoking status, the presence of an isolated smoking group (no occupational exposure), is often lacking, preventing an assessment of the clinical development of COPD due to occupational VGDF exposure.

Paulin *et al.* 2018 provides evidence of lung damage following VGDF exposure, which persisted when smoking status and pack-years was controlled for in the analysis..[14] Individuals with COPD were specifically analyzed in multivariate analysis, controlling for smoking, and found fewer measures of lung impairment to be significantly associated with VGDF exposure. The authors do not offer a potential explanation for this observation.

5.2.2.4.1 Evidence Gaps

The supplemental information in combination with the lack of supporting evidence identified in this review (past 5 years) suggest that the ability to clinically differentiate cigarette smoking versus occupational exposure as the cause of COPD is not available at this time. The lack of sensitivity of the current clinical tools utilized for diagnosis, in addition to the inherent complexities of isolating occupational exposure (controlling for cigarette smoking), and cigarette smoking alone, present notable challenges in answering this question. To address the risk of COPD associated with occupational exposures to VGDF, future studies must be designed to control for smoking and occupational exposure, and present comparative data stratified by these groups.

5.2.2.5 Conclusion

The evidence identified in this RLR, as well as the evidence presented by both the GOLD and ATS reports, do not provide information regarding factors that may differentiate as to whether the pathology that leads to the development of COPD is distinguishable between those who smoke compared to those who have occupational VGDF exposure. The ability to capture a clinically measurable difference in COPD

caused by smoking or VGDF is thereby limited by the lack of a distinguishable difference in the pathological cause for COPD at this time.

5.2.2.6 Clinical Comment

The most useful information that may help to distinguish between causes is an objective and accurate assessment of tobacco smoke exposure (i.e. pack year smoking history) versus years of at risk of exposure in the workplace. Occupational COPD is most clearly defined when there is no or a minimal (<10 pack year) history of smoking. However the combination carries more risk than either alone. Therefore the occupational contribution should be considered in smokers. Ruling out additional causes of obstructive lung disease (both occupational and non-occupational) are also important.

Patients with biomass smoke related COPD when compared to cigarette smoke related COPD usually have less emphysema and more of the chronic bronchitis phenotype. However, the study by Paulin (2018) would suggest the same association does not hold true when considering occupational COPD vs smoking related COPD. Thus, this study reinforces the notion that it is difficult to distinguish between occupational COPD and smoking related COPD.

There are no other measures that would be readily available to distinguish different causes of COPD.

5.2.3 Research Question 3

Research Question 3: Is COPD, or lung function loss/impairment, caused by cigarette smoking and that caused by workplace VGDF exposures separate diseases or conditions, or disease or injuring processes?

5.2.3.1 Results

There were no studies identified in the last five years as a part of this RLR that directly addressed Question 3. However, one study was identified in this RLR that provided inferential and/or supportive data towards differences in the etiology or pathophysiology of COPD as a disease or injuring process relative to cigarette smoking versus occupational VGDF exposure. Additionally, supplemental information from the GOLD 2021 report has been included to provide contextual reference as to the pathophysiology and etiology of COPD.

5.2.3.2 Supplemental Information

The GOLD report highlights that the etiology of COPD is the result of complex interactions of long-term exposure (no specified parameters to define long-term exposure) to noxious gases and particles that include lifestyle choices (e.g. smoking), environmental/occupational pollutants, genetics, and pathobiological factors associated with lung development and reactivity.[8] While the report does not directly discuss the etiology of COPD, it does state that inhalation of cigarette smoke and other particulates causes inflammation in the lungs.[8] A chronic inflammatory response is noted in patients who develop COPD which in turn may induce parenchymal tissue disruption (or emphysema) and disruption of normal repair and defense mechanisms in the lungs.[8] These changes can result in progressive airflow limitation.[8]

The GOLD 2021 report summarizes the genesis of several pathological changes that take place in the lungs of people with COPD. Pathological changes in the lungs could include chronic inflammation (increased quantity of inflammatory cells observed in various parts of the lung), and structural changes (e.g. airway and/or alveolar abnormalities, narrowing of small airways, destruction of the lung parenchyma and loss of alveolar attachment to small airway, and/or decreased lung elastic recoil).[8]

Several contributing factors related to the pathophysiology of COPD have been identified including, oxidative stress, protease-antiprotease imbalance, inflammatory cells, inflammatory mediators, and peribronchiolar and interstitial fibrosis. The structural lung changes that take place with COPD are largely attributed to the cyclic process of injury and repair, mediated by sustained inflammation, in response to chronic exposure of the respiratory track to irritants,[8] While there is evidence of differences in inflammation (composition of inflammatory cells) between COPD and asthma,[8,82], as mentioned in Research Question 2, the GOLD report does not provide information regarding factors that may differentiate as to whether the pathology that leads to the development of COPD is distinguishable based on differing irritants.

The ATS pooled PAF analysis discussed previously[7] provides evidence that additional risk factors outside of smoking and occupational exposure are also involved in the pathophysiology of COPD, adding further complexity to the question of COPD etiology.

5.2.3.3 Supporting Evidence for the Classification of COPD as a Disease or Injury Processes

5.2.3.3.1 Study Characteristics

Although, no comparative evidence was identified to directly answer Research Question 3, one observational, cross-sectional study addressed lung function loss/impairment through identification of biomarkers. Würtz *et al.,* 2020 investigated the impact of the HMOX1 repeat genotype on the

development of COPD following exposure to either VGDF or cigarette smoke in Danish individuals aged 45-84.[15]

Study characteristics of the included study are presented in **Table 10**. Studies in which COPD is not the primary focus but present supporting/inferential data regarding a variety of conditions related to lung function loss/impairment, are included in the Data Extraction Workbook that accompanies this report.[83]

Table 10: Study Characteristics of Publications Providing Supporting Evidence for Question 3

Study Name Author, Year	Occupation(s)	Main Exposure of Interest	Method of Exposure Measurement	Stratified by Smoking Status *(Yes/No)*	Primary Outcome of Interest	Method of Outcome Assessment	Study Dates (year-year)	Country
Observational Studies – Cross-Sectional								
Würtz 2020 [15] REFID: 4320	Various occupations[a]	VGDF	Years exposed	No	COPD	Spirometry	2004-2006	Denmark

Abbreviations: COPD : Chronic Obstructive Pulmonary Disease; VGDF: Vapours, Gases, Dusts, Fumes.

[a]The authors clarified in the supplemental material that 72 specialist jobs were identified via DISCO-88 (Danish adaptation of The International Standard Classification of Occupations, revision 1988) codes due to known occupational exposures to VGDF.[15] See Appendix C for more detail.

5.2.3.3.2 Findings

Würtz *et al.,* 2020 reported that the HMOX1 L+ genotype is significantly associated with the likelihood of having COPD (OR: 1.75 95%: 1.18-2.60; **Table 11**).[15] Of interest, there was an observed interaction effect between VGDF exposure and the HMOX1 L+ gene. The presence of the HMOX1 L+ genotype without VGDF exposure did not result in a significant increase in the likelihood of developing COPD (OR: 1.06 95% CI: 0.55-2.06) relative to the HMOX1 L- genotype without exposure. However, with exposure, the likelihood was 3.07-fold higher among those with HMOX1 L+ (OR:3.07 95%CI: 1.81-5.20) and was not significantly higher among those with HMOX1 L- (OR: 1.21 95% CI: 0.87-1.69), both relative to individuals with MHOX1 L- with no VGDF exposure. Increased smoking pack-years was also observed to significantly increase the likelihood of having COPD among individuals with the HMOX L+ gene, when adjusting for sex, age, VGDF exposure and general practitioner practice. However, it should be noted that the authors were not able to replicate these results in a second cohort.[15]

Table 11: Supporting Evidence for Question 3: Associations between COPD and Heme oxygenase 1 (HMOX1) polymorphism with and without VGDF exposure.

Study Name Author, Year	Group	Smoking		VGDF Exposure	HMOX1	OR for development of COPD *OR (95% CI), p-value*[a]
		Status	Amount *pack-years*	Status	Status	
Würtz 2020 [15] REFID: 4320	HMOX1 L+ (Reference group: HMOX1 L-)	Mixed	Controlled	Controlled	L+	**1.75 (1.18-2.60), <0.05**
		Mixed with VGDF interaction			L+	1.06 (0.55-2.06)
		Never			L+	2.41 (0.75-7.78)
	VGDF exposed (Reference group: no exposure)	Mixed	Controlled	Ever exposed	L+	**1.38 (1.39-3.91), <0.05**
		Mixed with VGDF interaction		Ever exposed	L+	1.21 (0.87-1.69)
		Never		Ever exposed	L+	**5.12 (1.70-15.46), <0.05**
	HMOX1 L+ and VGDF exposure interaction (Reference group: no exposure/L-)	Mixed with VGDF interaction	-	Controlled	L+	**2.38 (1.04-5.46), <0.05**
		Never			L+	N/A
	Pack-years of smoking (Reference group: <10)	Mixed	10-20	Controlled	L+	**2.69 (1.57-4.60), <0.05**
		Mixed with VGDF interaction	10-20		L+	**2.70 (1.58-4.61), <0.05**
		Mixed	>20		L+	**7.64 (5.13-11.39), <0.05**

		Mixed with VGDF interaction	>20		L+	**7.67 (5.15-11.42), <0.05**
	HMOX1 and VGDF exposure (Reference: HMOX L-, no exposure)	Mixed	Controlled	Never	L+	1.06 (0.55-2.06)
		Mixed	Controlled	Ever exposed	L-	1.21 (0.87-1.69)
		Mixed	Controlled	Ever exposed	L+	3.07 (1.81-5.20)

Abbreviations: CI: confidence interval; COPD: Chronic Obstructive Pulmonary Disease; HMOX1: Heme Oxygenase 1; L-: no polymorphisms, <33 GT promoter repeats; L+: $(GT)_n$ promoter repeat polymorphism, including ≥33 GT repeats; N/A: not available, too few observations: OR: odds ratio.

Bolded values indicate a significant difference was detected

[a] Mixed random effect logistic regression model adjusted for pack-years of smoking, sex, age, VGDF exposure (fixed effects) and general practitioner practice (random effect)

5.2.3.4 Limitations

The major limiting factors to determining whether COPD (or lung function loss/impairment) caused by cigarette smoking and that caused by occupational exposure to VGDF is a disease or injuring process, are two-fold. The initial premise of the question assumes that the cause of COPD can be determined between cigarette smoking and occupational exposure to VGDF. According to the GOLD 2021 report, cigarette smoking is a substantial factor in the development of COPD, however, the report also states that exposure to organic/inorganic dusts, chemical agents and fumes is an underappreciated risk factor for COPD.[8,84,85] Additionally, the study identified as being relevant for Research Question 3, as well as many other studies identified in this RLR, is a cross-sectional epidemiological study.[15] Epidemiological studies that utilize a cross-sectional design identify the exposure and the outcome at the same time and can only provide information regarding potential factors are that are associated with a disease; therefore, they cannot determine causality. Thus the cause of COPD, and the ability to differentiate causes of COPD between patients, is not realized at this time.

Additionally, the only study identified as being relevant for Research Question 3 assessed the association between the HMOX1 gene and COPD, looking at the interaction of VGDF, which is informative, but does not provide any information on potential histological or biochemical differences in COPD by exposure type. Caution should be used when interpreting results from Würtz *et al.*, 2020 due to the lack of reproducibility using another cohort with an age range of 20-44 (n=1168). Therefore, these results may not be generalizable to a broader population.[15] The authors attributed differences between these two cohorts to a smaller sample size and lower VGDF exposure in the second cohort study. However, a healthy worker bias may also be involved, as responders included more young women and fewer individuals in older groups.[15] Lastly, additional genetic factors that may account for the association between VGDF and HMOX1 interaction were not accounted for within the analysis.[15]

Finally, the GOLD 2021 report cautioned that much of the data regarding pathology of COPD comes from studies in smokers, suggesting that there may be a population bias.[8] It is unclear if the pathological changes identified in smokers are generalizable to different exposure populations independent of smoking. Additionally, the GOLD report highlights asthma as a significant contributing factor for the development of COPD. Future studies evaluating the pathological differences in the development of COPD between smoking and occupational exposure for VGDF will need to control for individuals with asthma.

5.2.3.5 Evidence Gaps

The historical evidence presented by the GOLD 2021 report, and the lack of rigorous supporting evidence identified in this review, suggest that the ability to differentiate whether the pathogenesis of COPD caused by cigarette smoking versus occupational exposure is a disease or injuring process, is not known at this time. The inherent complexities of isolating various exposures (behavioral factors [i.e., cigarette smoking]; geographical/environmental exposure [i.e., proximity to environmentally or industrially produced VGDF, governmental regulations of pollutants]; home exposure [e.g., biomass and/or second hand smoke]), and potential genetic predispositions and/or conditions related to lung function impairment (e.g., asthma), presents substantial challenges in clearly understanding nuances in the pathogenesis of COPD.

Chronic inflammation is recognized as the chief architect of the pathological structural changes that take place in the lung with prolonged exposure to irritants. Chronic inflammation is also recognized as a complex process that may vary between individuals. Therefore, chronic inflammation presents another layer of substantial difficulty for studies to isolate any given component to compare differences between people with COPD who smoke and those who have occupational exposure to VGDF.

Future studies will need to isolate components of the inflammatory response for comparison to identify and/or quantify any differences that may exist in the development of COPD by different exposure types.

5.2.3.6 Conclusion

Based on the evidence identified in this RLR, it is not possible to determine if lung function loss/impairment caused by smoking and that caused by workplace VGD exposure are as separate diseases or conditions or to understand if it is a disease or injuring process. Different study designs and clinical assessments from what is currently observed in the literature over the last five years are required to provide further evidence addressing this research question.

5.2.3.7 Clinical Comment

From a clinical perspective, COPD whether caused or contributed to by cigarette smoking or occupational exposure is managed and treated the same – with the exception that in occupational COPD, there would be consideration of advising removal of the patient from ongoing exposure (just as smoking cessation would be recommended), there would also be reporting to WSIB for compensation purposes.

The findings of Wurtz (2020) are consistent with clinical expectations in that some individuals become ill (with VGDF exposure or cigarette smoke) whilst others do not, so there must be some genetic or personal predisposition to disease that is not fully elucidated. Alpha1 antitrypsin deficiency would be the classic example of a genetic predisposition to COPD.

5.2.4 Research Question 4

Research Question 4: Do cumulative exposures (intensity x duration) to cigarette smoking and/or workplace VGDF exposures impact the amount of lung function loss/impairment? Is it possible to estimate the amount of lung function loss/impairment caused by cumulative exposures to cigarette smoking (pack-years) and that caused by workplace VGDF exposures (mg/m3-years)?

5.2.4.1 Results

This RLR identified a total of 16 studies within the past five years providing evidence related to Research Question 4. Nine studies provided relevant evidence that together demonstrate that cumulative exposure to various occupational VGDF, as well as duration of smoking, impact the amount of lung function loss/impairment.[16-24] Additionally, 12 studies were identified that together demonstrate that cumulative exposure to smoking and occupational VGDF increase the likelihood of developing COPD, with a dose response relationship demonstrated by many studies.[3,16,17,21,23,25-31] Not all studies found significant associations, and some studies even reported trends of reduced risk with some longer exposure durations relative to shorter durations. While it may be possible to estimate the amount of lung function loss/impairment attributable to cumulative exposure to either smoking or occupational VGDF at the individual study level, the data identified in this RLR demonstrate that numerous risk factors are involved (rather than a singular cause) and the heterogenous nature of the data would make a potential meta-analysis of the data challenging. Supplemental information from the GOLD 2021 report has also been included to provide contextual reference to established information pertaining to cumulative exposures and COPD.

5.2.4.2 Supplemental Information

The GOLD 2021 report did not directly provide any evidence on how continuous or cumulative exposure history may impact lung impairment over time. However, the report did state that smokers have a higher prevalence of lung abnormalities, respiratory symptoms, greater annual rates of decline in FEV_1, and greater mortality rates than non-smokers.[8,86] In terms of occupational exposures, the report also states that exposure to organic/inorganic dusts, chemical agents and fumes is an underappreciated risk factor for COPD.[8,84,85] An important hypothesis to note is that the sum of cumulative exposure over a person's life may be a reason as to why age is a risk factor for COPD.[8,87] Lung function declines naturally with age,[8,87] but historical evidence has demonstrated that cumulative exposure increases the rate of lung function decline.[88-90]

5.2.4.3 Supporting Evidence for the Impact of Cumulative Exposure to Cigarette Smoking and/or Workplace VGDF Exposure on Lung function

5.2.4.3.1 Study Characteristics

Seventeen studies were identified that presented evidence regarding the cumulative effect of occupational VGDF and/or smoking exposures on measures of lung impairment or the likelihood of having COPD.

All 17 studies included had an observational study design including, three observational cohort studies, (Bolund 2018, Soyseth 2016, and Liao 2015)[16,18,19] and 14 cross-sectional studies (Lehnert 2015, Vinnikov 2017, Doney 2019, Koh 2015, Sinha 2017, Liu 2015, Stoleski 2019, Stoleski 2017, Reynolds 2017, Dement 2015, Sumit 2020, van Koeverden 2015, Sadhra 2020 and Mabila 2018).[3,17,20-31] The studies were conducted in 11 different countries (Denmark, the U.S., Germany, the Republic of Belarus, Korea, India, China, Macedonia, Norway, the United Kingdom and Wales, and Bangladesh).

Studies had largely heterogeneous study populations (occupation and/or location) and exposures of interest (i.e., wood dust, welding fumes, metal dust, silica dust), with five studies evaluating VGDF

exposure in general. All studies but two utilized spirometry to measure lung function, while the remaining two studies relied on a self-reported diagnosis of COPD.[29]

The study characteristics for publications in which COPD is the primary focus and report supporting/inferential data towards Question 4 are presented in **Table 12.** Studies in which COPD is not the primary focus, but present supporting/inferential data regarding a variety of conditions related to lung function loss/impairment are included in the Data Extraction Workbook that accompanies this report.[91,92] Additionally studies where cumulative exposure is present but the data is not presented by varying duration or intensity are included in the Data Extraction Workbook.[5,32]

Table 12: Study Characteristics for Publications Providing Supporting Evidence for Question 4

Study Name Author, Year	Occupation(s)	Main Exposure of Interest	Method of Exposure Measurement	Stratified by Smoking Status *(Yes/No)*	Primary Outcome of Interest	Method of Outcome Assessment	Study Dates (year-year)	Country
Observational Cohort Studies								
Bolund 2018[16] REFID: 503	Woodworking	Wood Dust	Passive dust monitors	Yes	COPD	Spirometry	1998-2004	Denmark
Soyseth 2016[18] REFID: 3704	Aluminum workers	Molten aluminum fumes	Questionnaire	Yes	COPD	Spirometry	1986 - 1995	Norway
Liao 2015[19] REFID: 2350	More likely dust exposure[a] Less likely dust exposure	Dust	Job Exposure Matrices	Yes	COPD	Spirometry	N.R.	United States
Observational Studies – Cross-Sectional								
Doney 2019[29] REFID: 1000	N.R.	Mineral Dust Organic Dust Exhaust Fumes Other gases, vapours or fumes	Questionnaire	Yes	COPD	Self-reported	2007-2012	United States
Lehnert 2015[24] REFID: 2267	Welders	Welding fumes	Sampling of respirable particles in the workplace	Yes	Lung Function COPD	Spirometry	2007-2009	Germany
Vinnikov 2017[23] REFID: 4120	Tractor Plant workers	Metal dust	Sampling of total suspended particles in the workplace	No	COPD	Spirometry	N.R.	Republic of Belarus
Koh 2015 [17] REFID: 2044	Welder	Fumes	Sampling of respirable particles in the workplace	Yes	COPD	Spirometry	2010	Korea
Sinha 2017[25] REFID: 3639	N.R.	Dust, smoke, fumes, gas	Questionnaire	Yes	COPD	Spirometry	2012-2013	India
Liu 2015[26] REFID: 2409	Greenhouse workers	N.R.	Questionnaire	Yes	COPD	Spirometry	2006-2009	China
Stoleski 2019[21] REFID: 3749	Dairy Farmers Office workers	VGDF	Questionnaire Job Exposure Matrices	No	COPD	Spirometry	2017-2018	Macedonia

Stoleski 2017[20] REFID: 3750	Crop Farmers Dairy Farmers Office workers	VGDF	Questionnaire	Yes	COPD	Spirometry GOLD Assessment	2014 - 2015	Macedonia
Reynolds 2017 [22] REFID: 3293	Miners	Crystalline silica dust	Questionnaire	Yes	COPD	Spirometry	1975	Wales
Dement 2015[27] REFID: 921	Construction workers	Asbestos Silica Cement dust Man-made-mineral fibres Engine exhausts Acids Caustics Welding, thermal cutting, soldering or brazing Metal cutting, grinding, and machine aerosol Paint-related aerosols Isocyanates Organic solvents Wood dust Molds and spores Particulates not otherwise regulated	Questionnaire	Yes	COPD	Spirometry	2013	United States
Sumit 2020[28] REFID: 3787	Motor Vehicle Mechanic Cleaners Drivers Manager Clerk Housekeeper and related worker Administrative job	VGDF	Questionnaire, Job Exposure Matrix	Yes	COPD	Spirometry	2019-2020	Bangladesh

van Koeverden 2015[3] REFID: 4066	N.R.	VGDF Work second-hand smoke	Questionnaire, Job Exposure Matrix	No	COPD	Spirometry	2008-2011	United States
Sadhra 2020[30] REFID: 3400	N.R.	VGDF	Questionnaire	Yes	Airflow Obstruction COPD	Spirometry	2006-2010	United Kingdom
Mabila 2018[31] REFID: 2492	Miners	Mineral dust	Questionnaire	Yes	COPD	Self-reported	2006 - 2015	United States

Abbreviations: COPD: chronic obstructive pulmonary disease; GOLD: Global initiative for COPD; N.R.: not reported; VGDF: Vapour, Gas, Dust, Fume.
[a]Occupational dust exposures were classified into “more likely dust exposure” and “less likely dust exposure” based on the UCSF COPD Job Exposure Matrix (January 2009 revision). Details of the jobs categorized are found in Appendix C.

5.2.4.3.2 Findings

Nine studies reported evidence regarding cumulative exposure to VGDF and/or smoking on measures of lung function including FEV, FVC, and the C-reactive protein biomarker (Bolund 2018, Koh 2015, Soyseth 2016, Liao 2015, Stoleski 2017, Stoleski 2019, Reynolds 2017, Vinnikov 2017, and Lenhert 2015).[16-24]

Bolund et al., 2018 reported a significant reduction in spirometry measures of lung function in Danish male and female woodworkers exposed to organic wood dust in furniture factories compared to factory workers without dust exposure over a 6-year time period.[16,24] Both female and male woodworkers who smoked had a significant reduction in the change in z scores for FEV_1 (ΔFEV_1) and change in z scores for FVC (ΔFVC) over the 6-year follow-up when compared to female and male woodworkers who were non-smokers, respectively.[16] In the unexposed group, only the ΔFVC was found to be significantly decreased for female smokers compared to non-smokers over the 6-year follow-up (**Table 13**).[16] Absolute values of FEV_1 and FVC decreased slightly over the 6-year follow-up period and are not presented here, but can be found in the Data Extraction Workbook that accompanies this report.[16]

Low smoking (≤6 pack years), high smoking (>6 pack years), and weight change over the 6-year follow-up period were associated with a significant decrease in ΔFEV_1 for male wood workers.[16] Intermediate/high wood dust exposure (third quartile >3.75 to ≤4.71 mg/m^3 × year), high wood dust exposure (fourth quartile >4.71 to 7.55 mg/m^3 × year), ex-smoking status, high smoking (>6 pack years), and weight change during the 6-year follow-up period were all associated with a significant decrease in ΔFEV_1 for female wood workers (**Table 14**).[16]

Together these data suggest that smoking is a substantial contributor to the decrease in lung function for both male and female Danish workers (woodworkers and non-woodworkers). As noted by the authors, the negative correlation of increased occupational wood dust exposure and a decrease in lung function with Danish female wood workers indicates a dose-dependent association; however, estimates regarding the proportional contribution of occupational wood dust exposure and smoking on lung function impairment was not directly measured or discussed.

Similar to Bolund *et al*., 2018, Koh *et al.,* 2015 performed a multivariate linear regression to evaluate potential risk factors for decreased lung function among Korean welders, however none of the factors evaluated (age ≥40, smoking, never smoker) were significant (**Table 15**).[17]

Two studies compared lung function change per year among workers with differing occupational exposure levels (**Table 13**).[18,19] Soyseth *et al.,* 2016 conducted a prospective study to examine the impact of aluminum fumes on lung function measures over a follow-up period of up to ten years. This study found that the annual decline in FEV_1 for workers exposed to aluminum fumes in a potroom was greater than reference workers with no exposure to aluminum fumes (56.7±1.0mL/year compared to 36.8±2.7mL/year). However, there was no significant difference in annual decline in FVC between potroom workers and reference workers, which was supported by multivariate analyses.[18] Liao *et al.* 2015 also found that individuals categorized into “more likely dust exposure" had significantly greater mean loss of FEV_1/year over time compared with those categorized into “less likely dust exposure”.[19]

Two similar studies compared measures of lung function in farmers with >20 and <20 years occupational exposure, with both studies reporting non-significant trends (**Table 13**). Stoleski *et al.*, 2017 found elevated levels of C-reactive protein (a biomarker of inflammation) in dairy and crop farmers exposed over 20 years compared to ≤20 year exposure.[20] Stoleski *et al.*, 2019 found that spirometric measures of lung function were lower in dairy farmers exposed for >20 years compared to farmers with <20 years exposure (**Table 13**).[21]

Similarly, Reynolds *et al.*, 2017 also reported a trend towards longer exposure times leading to reduced lung function.[22] Slate miners had reduced FEV_1 (3.01L compared to 3.2L, $p<0.01$) and FVC (4.08L

compared to 4.28L, p<0.01) values compared to non-miners independent of smoking status (**Table 13**).[22] However, FEV_1/FVC values were not significantly different between slate miners and non-miners. Multivariate analysis also revealed that slate miners had reduced lung function regardless of smoking status.[22] Multivariate analysis also revealed a relationship between % predicted FEV_1 and years exposed in the age group 55+ (n=467) where 1-8 years exposure yielded a % predicted FEV_1 β value of 2.73 (95% CI, -9.06 – 14.51) and ≥25 years exposed yielded a % predicted FEV_1 β value of -7.65 (-14.47 – 0.82).[22]

Two studies looked at exposure intensity levels, as classified as 'high' and 'low' by both studies. Lenhert *et al.,* 2015 reported no association between the low and high intensity level of welding fume exposure and lung function in German welders (**Table 13**).[24] Similarly, Vinnikov *et al.*, 2017 did not find any difference in lung function between low and high occupational exposure to metal dust in tractor plant workers in the Republic of Belarus (not controlled for smoking status).[23] Interestingly, Vinnikov *et al*., 2017 reported that individuals with relatively better lung function held occupations classified as having higher dust exposure, suggesting that weak correlations between lung function and exposure levels may be attributed to a healthy worker effect (**Table 13**).[23]

While Research Question 4 aims to understand the impact of cumulative exposure on lung function loss/impairment, studies that presented data describing the increased likelihood of developing COPD following cumulative exposure were also included as lung function loss/impairment can be inferred based on the diagnosis of COPD. Twelve studies were identified that presented relevant data of this nature (Sinha 2017, Liu 2015, Bolund 2018, Koh 2015, Vinnikov 2017, Dement 2015, Stoleski 2019, Sumit 2020, van Koeverden 2015, Doney 2019 and Sadhra 2020; **Table 16**).[3,16,17,21,23,25-30] Of these 12 studies, many conducted multivariate regression analyses that provide evidence of the cumulative impact of VGDF exposure or smoking on the likelihood of developing COPD while controlling for other confounders.

Both Sinha *et al.,* 2017, and Liu *et al.,* 2015 present strong evidence of the impact of duration of exposure on the likelihood of developing COPD (**Table 16**).[25,26] Sinha *et al.,* 2017 found that the prevalence of COPD with no exposure to VGDF was 4%, while the prevalence of COPD in individuals with exposure of ≥20 years was 30.7%. Likewise, in individuals that did not smoke, the prevalence of COPD was 1.6%, whereas in individuals who smoked ≥20 pack-years the prevalence of COPD was 72.7%.[25] Of most relevance, this study demonstrates that cumulative exposure to smoking and occupational exposure increases the likelihood of COPD with longer duration of exposure resulting in higher likelihood of COPD. Only individuals with occupational exposure of >20 years had a significant increase in the likelihood of COPD relative to ≤ 10 years (OR: 6.91 [1.80-9.85]). Among current smokers, a significant increase of nearly 5-fold was observed among current smokers with 11-20 pack-years of exposure and nearly 13-fold increase among current smokers with >20 pack-years (OR: 4.87 [95%CI: 1.70-9.13] and OR: 12.95 [95% CI: 3.71-19.82]) relative to current smokers with ≤ 10 pack-years. Among ex-smokers, those with >20 pack-years exposure had a significant increase in the likelihood of COPD relative to ex-smokers with ≤ 10 pack-years (OR: 2.43[95% CI: 1.31-3.55]), yet ex-smokers with 11-20 pack-years exposure were observed to have a reduced likelihood of COPD (non-significant).[25]

Liu *et al.*, 2017 reported on working years, daily working hours, and pack-years of smoking, among greenhouse workers in Liaoning Province, China. Individuals who worked 3-5 years had the highest prevalence of COPD (28.2%) compared to individuals who worked <3 and >5 working years. Daily working hours was inversely related to COPD prevalence, as individuals who worked >5 hours daily had the lowest prevalence of COPD (9.3%) compared with individuals who worked 3-5 hours per day (22.6%), and those that worked <3 hours per day (34.9%). Individuals that smoked 1-4 pack-years had the highest prevalence of COPD (38.2%). Age (40-49, 50-59 and ≥60, relative to >40), current smoker (relative to non-smoker), 15-29 and ≥30 pack-years smoking (relative to 0 pack-years), being located in a mountain or coastal area (relative to plains), mushroom and flower greenhouses (relative to vegetable) and working in a greenhouse for 3-5 years (relative to <3 years) were all found to be risk factors associated with a

significant increase in the likelihood of COPD. Interesting, working for >5 years and all BMI categories ≥18.5 (relative to BMI <18.5) were significantly associated with a decreased likelihood of COPD.

Bolund *et al.,* 2018 assessed the association between COPD and dust exposure at baseline and after six years of follow up among wood workers with low and high dust exposure. There were no significant differences in OR observed at baseline relative to no exposure but after six years, female wood works with high exposure were significantly more likely to have COPD (OR: 12.0, 95% CI:1.3-111.0; **Table 16**).[16]

Koh *et al*., 2015 reported that Korean welders exposed to intermediate and high levels of welding fumes had a significant increased risk for the development of COPD compared to welders exposed to low welding fumes (**Table 16**).[17] Although, this suggested an increased risk of developing COPD with higher occupational exposure, these results were not stratified by smoking status. No significant increase in risk was found to be associated with the development of COPD when evaluating all welders by smoking pack years.[17] However, this result should be interpreted with caution as level of occupational exposure was not controlled for in this analysis.[17]

Vinnikov *et al.*, 2017 reported that higher exposure levels were associated with increased odds of developing COPD in tractor plant workers in the Republic of Belarus, when accounting for sex, age, smoking pack-years, and work duration(**Table 16**).[23] This is supported by Dement *et al.,* 2015, Stoleski *et al.,* 2019, Sumit *et al.,* 2020, and van Koeverden *et al.*, 2015, who all found that working in an occupation with VGDF exposure led to increased likelihood of developing COPD.

Dement *et al.,* 2015 found that when accounting for smoking, higher exposure levels (as categorized by exposure indices calculated from task frequency, job duration, work hours per week, and task exposure intensity) for common construction related exposures were related to increased likelihood of COPD(**Table 16**).[27] Overall, Dement *et al.,* 2015 found significant associations between exposure and the development of COPD for all exposures except man-made mineral fibers and painting aerosols after adjusting for age, gender, race/ethnicity, smoking status (current, past, never), cigarette pack-years, blood relative with COPD, and BMI.[27]

Stoleski *et al.*, 2019 found that exposure to either dust or gases/fumes by dairy farmers increased the likelihood of COPD, but only the high levels of exposure, as determined by a job exposure intensity matrix, significantly increased the likelihood of developing COPD(**Table 16**).[21] Odds ratios were adjusted for age and smoking habit.

Sumit *et al.,* 2020 found that individuals exposed to VGDF in their workplace had an over 6-fold increase in the likelihood of developing COPD (OR: 6.3; 95% CI 2.8 – 9.2). When exposures were stratified, the shorter exposure group (1-9 years) had an odds ratio of 1.1 (95% CI: 1.0 – 12.08) while individuals with longer exposure had an odds ratio of 2.8 (95% CI: 1.2 – 13.09) (**Table 16**).

Van Koeverden *et al.*, 2015 analysed the odds ratios for developing COPD after exposure with occupational second-hand smoke exposure, occupational VGDF exposure, and smoking using multivariable linear regression. Individuals exposed to occupational VGDF, occupational second-hand smoke exposure, and smoking all had a significant increased likelihood of developing COPD. Interestingly, when results were stratified by age (younger vs. older than 62 years of age), only the young group was found to have a significant association with COPD when exposed to occupational VGDF (OR: 1.46 95% CI: 1.00 – 2.13). Conversely, only the older group was found to have a significant association with COPD when exposed to occupational second-hand smoke (OR: 1.13 95% CI: 1.01 – 1.27). Smokers in both age groups had a significant risk of developing COPD (**Table 16**).[3]

Doney *et al.,* 2019 observed a trend of an increased prevalence odds ratio with any level of exposure to all VGDFs of interest (mineral dust, organic dust, exhaust fumes, other gases/vapours/fumes) relative to

no exposure. The prevalence odds ratio was not significant for each exposure level and did not increase in magnitude with years exposure categories for mineral dust, organic dust exposure, and other gases/vapours/fumes(**Table 16**).[29]

Sadhra *et al.,* 2020 reported adjusted prevalence ratios for the risk of airflow obstruction following occupational exposure, based on low, medium and high exposure levels relative to no exposure, and stratified by mixed smoking status and non-smokers.[30] Occupational exposure was assigned to individuals within the UK Biobank cohort using a job exposure matrix. Risk estimates increased significantly with high exposure levels of vapours (mixed and non-smokers), mineral dusts (mixed smoking status only), fumes (mixed only), mists (mixed only) and all VGDF(mixed only). Risk estimates also increased significantly with medium exposure to gases (mixed only), any dusts (mixed only), mineral dust (mixed only), and fumes (mixed only), as well as low exposure to biological dusts (mixed only). Of note, this study defined airflow obstruction as FEV_1/FVC< lower limit of normal, which is a commonly used measure for diagnosing COPD, however post-bronchodilator measurements were not available to confirm cases were COPD and not asthma, therefore, these rates may not be comprised of only COPD cases.[7,30]

Sinha present the proportion of individuals with COPD stratified by duration of exposure to occupational dust and fumes and to smoking, demonstrating a trend of increasing rates of COPD with longer duration.[25]

Mabila *et al.,* 2018 evaluated the likelihood of developing COPD in miners exposed to varying levels of mineral dust. Miners who had very high dust exposure (defined as workers who perform extraction) were at a significantly higher odds of developing COPD compared to those with low dust exposure (defined as various professions such as office and administration support, management, finance etc. (adjusted OR: 2.56 [1.29-5.12], p= <0.05); with the adjusted odds ratios of workers with either moderate or high dust exposure being non-significantly higher than those with low dust exposure.[31]

Together, the evidence from studies evaluating cumulative VGDF and/or smoking exposure demonstrate that increased intensity or duration result in greater lung function impairment and greater likelihood of developing COPD.

Table 13: Supporting Evidence for Research Question 4: Impact of Exposure on Lung Function

Study Name Author, Year	Occupation/ Group	Main Exposure of Interest	Method of Exposure Assessment	Exposure Measure (mg/m^3)	Smoking Status	Lung Function Tests			CRP (mg/mL) *Mean (SD)*
						FEV_1 (L) *Mean (SD), p value*	**FVC (L)** *Mean (SD), p value*	**FEV_1/FVC** *Mean (SD), p value*	
Observational Cohort Studies									
Bolund 2018[16] REFID: 503	Females	Wood Dust (Wood Worker) (n=185)	Passive dust monitors	-	Smoker (n=96)	Δ-0.22 (±0.76)[b], **<0.005**	**Δ-0.17 (±0.70)[b], <0.05**	Δ-0.11 (±0.84)[b]	-
					Non-Smoker (n=87)	Δ0.06 (±0.6)[b]	Δ0.05 (±0.42)[b]	Δ0.04 (±0.86)[b]	-
		No Exposure (Control Factory Worker[a]) (n=131)		-	Smoker (n=72)	Δ-0.03 (±0.53)[b]	Δ-0.07 (±0.48)[b], **<0.05**	Δ0.02 (±0.66)[b]	-
					Non-Smoker (n=58)	Δ0.12 (±0.53)[b]	Δ0.09 (±0.41)[b]	Δ0.02 (±0.64)[b]	-
	Males	Wood Dust (Wood Worker) (n=927)	Passive dust monitors	-	Smoker (n=429)	Δ-0.06 (±0.53)[b], **<0.001**	Δ-0.04 (±0.48)[b]	Δ-0.05 (±0.65)[b], **<0.005**	-
					Non-Smoker (n=494)	Δ0.06 (±0.50)[b]	Δ0.02 (±0.44)[b]	Δ0.06 (±0.61)[b]	-
		No Exposure (Control Factory Worker[a]) (n=104)		-	Smoker (n=55)	Δ-0.15 (±0.60)[b]	Δ-0.07 (±0.53)[b]	Δ-0.14 (±0.57)[b]	-
					Non-Smoker (n=49)	Δ0.05 (±0.60)[b]	Δ-0.02 (±0.47)[b]	Δ0.14 (±0.79)[b]	-
Stoleski 2019[21] REFID: 3749	Dairy Farmers	VGDF	Questionnaire Job Exposure Matrices	>20 years (n=59)	*adjusted*	85.3% (8.4), 0.503[c]	92.2% (9.4), 0.400[c]	72.2% (5.1), 0.087	-
	Office Workers	-		≤20 years (n=24)	*adjusted*	86.7% (9.1)[c]	94.1% (9.9)[c]	74.3% (4.8)	-
Stoleski 2017[20] REFID: 3750	Crop Farmers	Dust, fumes, vapours, pesticides	Questionnaire	>20 years (n=24)	-	-	-	-	3.7 (2.8)
				≤20 years (n=11)		-	-	-	3.2 (2.2), 0.646[d]
	Dairy Farmers	Dust, chemical hazards, vapours, gases		>20 years (n=22)	-	-	-	-	3.9 (2.9)
				≤20 years (n=10)		-	-	-	3.4 (2.2), 0.653[d]
Soyseth 2016[18] REFID: 3704	Aluminum (potroom) workers	Molten aluminum fumes	Questionnaire	Potroom workers (n=4,546)	-	Δ56.7(1.0) mL/yr[e]	Δ37.2(1.3) mL/yr[e]	-	-
				Reference workers (n=651)	-	Δ36.8 (2.7) mL/yr[e]	Δ47.5(3.8) mL/yr[e]	-	-

Study Name Author, Year	Occupation/ Group	Main Exposure of Interest	Method of Exposure Assessment	Exposure Measure (mg/m^3)	Smoking Status	Lung Function Tests			CRP (mg/mL) *Mean (SD)*
						FEV_1 (L) *Mean (SD), p value*	**FVC (L)** *Mean (SD), p value*	**FEV_1/FVC** *Mean (SD), p value*	
				Potroom workers compared to unexposed workers	-	**Δ13.5(3.5) mL/year, <0.001[e,f]**	Δ-8.0 (4.2), 0.060 mL/yr[e,f]	-	-
				Aluminum fumes	Never smokers	Δ48.2 (2.0)[e] mL/yr	Δ23.7 (2.6)[e] mL/yr	-	-
				No aluminum fumes – reference workers		Δ34.7 (5.9)[e] mL/yr	Δ43.8 (8.0)[e] mL/yr	-	-
				Aluminum fumes	Former smokers	Δ58.2 (3.2)[e] mL/yr	Δ48.2 (4.1)[e] mL/yr	-	-
				No aluminum fumes – reference workers		Δ52.3 (7.2)[e] mL/yr	Δ83.1 (11.1)[e] mL/yr	-	-
				Aluminum fumes	Current smokers	Δ59.6 (1.4)[e] mL/yr	Δ39.8 (1.6)[e] mL/yr	-	-
				No aluminum fumes – reference workers		Δ31.5 (4.0)[e] mL/yr	Δ32.8 (6.0)[e] mL/yr	-	-
Liao 2015[19] REFID: 2350	More likely dust exposure[g] Less likely dust exposure[g]	Dust	Job Exposure Matrices	More likely vs. less likely dust exposure	*adjusted*	-15.1 (41.6), 0.7173[h] mL	-	-0.0039 (0.0058), 0.503[h]	-
				Years after baseline age x more likely dust exposure	*adjusted*	**-4.5 (1.7), 0.0074[h] mL**	-	-0.0001 (0.0003), 0.6643[h]	
				-	Pack-years	**-2.8 (0.4), <0.0001[h] mL**	-	**-0.0004 (0.0000), <0.0001[h]**	-
Observational Studies – Cross-Sectional									
Lehnert 2015[24] REFID: 2267	Welders	Welding fumes (n=219)	Sampling of respirable particles in the workplace	1-9 years[i] (n=59)	-	4.4 (4.1 – 4.9)[j]	5.8 (5.3 – 6.4)[j]	0.77 (0.743 – 0.804)[j]	-
				10-19 years[i] (n=62)	-	4.3 (3.8 – 4.7)[j]	5.4 (4.9 – 6.0)[j]	0.774 (0.726 – 0.805)[j]	-
				20-29 years[i] (n=63)	-	4.1 (3.6 – 4.4)[j]	5.4 (4.9 – 5.9)[j]	0.753 (0.727 – 789)[j]	-

Study Name Author, Year	Occupation/ Group	Main Exposure of Interest	Method of Exposure Assessment	Exposure Measure (mg/m^3)	Smoking Status	Lung Function Tests			CRP (mg/mL) *Mean (SD)*
						FEV_1 (L) *Mean (SD), p value*	**FVC (L)** *Mean (SD), p value*	**FEV_1/FVC** *Mean (SD), p value*	
				≥30 years[i] (n=35)	-	3.8 (3.2 – 4.1)[j]	4.9 (4.5 – 5.6)[j]	0.752 (0.701 - 0.801)[j]	-
				<LOQ[k] (n=83)	-	4.2 (3.4 – 4.7)[j]	5.4 (4.7 – 6.0)[j]	0.77 (0.730 – 0.8807)[j]	-
				≥LOQ ≥1.18[k] (n=34)	-	4.1 (3.6 – 4.4)[j]	5.2 (4.7 – 6.0)[j]	0.755 (0.732 – 796)[j]	-
				>1.18 ≤2.36[k] (n=34)	-	4.2 (4.0 – 4.6)[j]	5.6 (5.2 – 6.0)[j]	0.770 (0.727 – 0.803)[j]	-
				>2.36 ≤4.88[k] (n=34)	-	4.2 (3.6 – 4.7)[j]	5.5 (5.0 – 5.9)[j]	0.760 (0.720 – 0.801)[j]	-
				>4.88[j] (n=33)	-	4.4 (4.0 – 4.5)[j]	5.6 (5.1 – 6.0)[j]	0.748 (0.720 – 0.802)[j]	-
				Low (0.1 – 10.1)[l] (n=73)	-	4.3 (3.9 – 4.8)[j]	5.7 (5.0 – 6.3)[j]	0.770 (0.730 – 0.810)[j]	-
				Medium (>10.1 – 37.8)[l] (n=72)	-	4.2 (3.7 – 4.6)[j]	5.4 (5.0 – 5.9)[j]	0.773 (0.720 – 0.801)[j]	-
				High (>37.8 – 78.9)[l] (n=55)	-	4.1 (3.6 – 4.4)[j]	5.3 (4.7 – 5.7)[j]	0.750 (0.725 – 0.803)[j]	-
				Substantial (>78.9)[l] (n=19)	-	4.0 (3.5 – 4.4)[j]	5.1 (4.7 – 5.5)[j]	0.753 (0.727 – 0.803)[j]	-
Vinnikov 2017[23] REFID: 4120	Tractor Plant workers	Metal dust (n=458)	Sampling of total suspended particles in the workplace	Low-exposure (<2) (n=367)	Mixed	96.1% (17)[c]	100% (17.4)[c]	0.808 (0.098)	-
				High-exposure (>2) (n=91)		94.5% (19.5)[c]	98.2% (20.3)[c]	0.805 (0.078)	-
Reynolds 2017 [22] REFID: 3293	Slate miners (n=726)	Crystalline silica dust	Questionnaire	-	-	**3.01 (1.03), <0.01[m]**	**4.08 (1.05), <0.01[m]**	0.75 (0.67 – 0.81), <0.5[m]	
	Non-miners (n=529)	-		-	-	3.20 (0.93)	4.28 (1.01)	0.76 (0.70 – 0.82)	
	All ages (n=1,255)	Mining		-	*adjusted*	-3.97 (-6.65, -1.29)[n]	-2.32 (-4.31, -0.33)[o]	-	-
		-		-	Smoking (ever)	-8.07 (-11.68, -4.46)[n]	-2.55 (-5.23, 0.13)[o]	-	-

Study Name Author, Year	Occupation/ Group	Main Exposure of Interest	Method of Exposure Assessment	Exposure Measure (mg/m^3)	Smoking Status	Lung Function Tests			CRP (mg/mL) *Mean (SD)*
						FEV_1 (L) *Mean (SD), p value*	**FVC (L)** *Mean (SD), p value*	**FEV_1/FVC** *Mean (SD), p value*	
	Age < 40 years (n=404)	Mining		No exposure (Ref.)	*adjusted*	-	-	-	-
				1 – 8 years	*adjusted*	0.51 (-2.92, 3.95)[n]	-0.13 (-2.70, 2.43)[o]	-	-
				≥9 years	*adjusted*	-2.00 (-6.18, 2.17)[n]	-0.89 (-4.00, 2.23)[o]	-	-
				-	Smoking (ever)	-3.14 (-6.78, 0.50)[n]	-1.00 (-3.72, 1.72)[o]	-	-
	Age 40 – 54 years (n=380)			No exposure (Ref.)	*adjusted*	-	-	-	-
				1 – 8 years	*adjusted*	-8.10 (-14.38, -1.83)[n]	-5.47 (-10.27, -0.67)[o]	-	-
				9 – 24 years	*adjusted*	-2.42 (-7.92, 3.07)[n]	-0.37 (-4.55, 3.80)[o]	-	-
				≥25 years	*adjusted*	-5.77 (-12.18, 0.65)[n]	-3.13 (-8.01, 1.74)[o]	-	-
				-	Smoking (ever)	-11.18 (-17.75, -4.60)[n]	-3.32 (-8.31, 1.67)[o]	-	-
	Age 55+ years (n=567)			No exposure (Ref.)	*adjusted*	-	-	-	-
				1 – 8 years	*adjusted*	2.73 (-9.06, 14.51)[n]	3.67 (-5.01, 12.35)[o]	-	-
				9 – 24 years	*adjusted*	-6.66 (-15.43, 2.11)[n]	-4.71 (-11.17, 1.75)[o]	-	-
				≥25 years	*adjusted*	-7.65 (-14.47, -0.82)[n]	-2.33 (-7.37, 2.72)[o]	-	-
				-	Smoking (ever)	-14.38 (-22.64, -6.12)[n]	-6.50 (-12.58, -0.42)[o]	-	-

Abbreviations: COPD: Chronic Obstructive Pulmonary Disease; CRP: C-reactive protein; FEV_1: Forced expiratory volume in 1 second; FVC: forced vital capacity; IQR: interquartile range; L: liter; mg/m^3: miligram/cubic meter; mg/mL: milligram/milliliter; mL/yr: milliliter/year; N.R. not reported; OR: odds ratio; Ref.: Reference group; SD: standard deviation; SE: standard error.

Bolded values indicate a significant difference was detected

[a] Workers from three factories with low organic dust exposure.

[b] Change in z score from baseline (6 years)

[c] % predicted

[d] p-value for t-test comparing exposed <20 years and exposed ≤20 years groups

[e] Annual decline (mL/year), mean (standard error)

[f] Multivariate analyses of annual decline FVC and FEV_1 during follow-up
[g] Occupational dust exposures were classified into “more likely dust exposure” and “less likely dust exposure” based on the UCSF COPD Job Exposure Matrix (January 2009 revision). Details of the jobs categorized are found in Appendix C.
[h] Estimate (SE), Linear mixed model
[i] Duration of employment as a welder (years)
[j] Median (IQR)
[k] Shift exposure to respirable welding fume
[l] Lifetime exposure to respirable welding fume (mg x years/m^3)
[m] P-value reported for comparison between slate miners and non-miners
[n] Adjusted regression analyses, FEV_1 predicted, β (95% CI)
[o] Adjusted regression analyses, FVC predicted, β (95% CI)

Table 14. Supporting Evidence for Question 4: Risk factors Associated with Change in Lung Function (ΔzFEV) for Danish Wood Workers over 6-year Follow-up from Bolund 2018[16]

Group	Exposure Measure *(mg/m³)*	*Female*			*Male*		
		Smoking Exposure Measure *(pack-years)*	**Multivariable Linear Regression[a] $\Delta zFEV_1$** *E (95% CI)*	**Significance** *(P value)*	**Smoking Exposure Measure** *(pack-years)*	**Multivariable Linear Regression[a] $\Delta zFEV_1$** *E (95% CI)*	**Significance** *(P value)*
Control	0	N.R.	0 (Ref.)	-	N.R.	0 (Ref.)	-
Current worker (1st Quartile Exposure)	>0 ≤2.97	N.R	0.02 (-0.18 – 0.23)	0.818	N.R.	0.09 (-0.03 – 0.21)	0.15
Current worker (2nd Quartile Exposure)	>2.97 ≤3.75	N.R.	-0.05 (-0.26 – 0.17)	0.674	N.R.	0.03 (-0.1 – 0.15)	0.672
Current worker (3rd Quartile Exposure)	>3.75 ≤4.71	N.R.	**-0.32 (-0.56- – 0.08)**	0.009	N.R.	0.05 (-0.07 – 0.17)	0.461
Current worker (4th Quartile Exposure)	>4.71 ≤7.55	N.R.	**-0.31 (-0.62- – 0.001)**	0.049	N.R.	0.08 (-0.04 – 0.20)	0.174
Ex-smoker	N/A	N.R.	**0.25 (0.04 – 0.46)**	0.018	N.R.	0.005 (-0.08 – 0.20)	0.904
Low Smoker	N/A	≤6[b]	-0.13 (-0.33 – 0.07)	0.188	≤6[b]	**-0.11 (-0.20 – -0.02)**	0.026
High Smoker	N/A	>6[b]	**-0.44 (-0.66 – -0.23)**	0.000	>6[b]	**-0.20 (-0.30 – -0.11)**	0.000

Abbreviations: CI: Confidence Interval; COPD: Chronic Obstructive Pulmonary Disease; E: Estimate; $\Delta zFEV_1$: change in z score Forced expiratory volume in 1 second; mg/m^3: milligram/cubic meter; N.R. not reported; OR: odds ratio; Ref.: Reference group; SD: standard deviation.

Bolded values indicate a significant difference was detected

[a] Multivariable linear regression comparing different levels of exposure in wood workers with controls. Adjusted for exposure length, smoking status, asthma and weight change.

[b] pack-years during the 6 year follow up period.

Table 15. Supporting Evidence for Question 4: Risk Factors associated with FEV_1 and FVC for Korean welders from Koh 2015 [17].

Group	Exposure Measure *(mg/m³)*	Smoking Exposure Measure *(pack-years)*	Multivariable Linear Regression FEV_1 (L) *β_{slope} (SE)*	Multivariable Linear Regression FVC (L) *β_{slope} (SE)*	Significance *(P value)*
All (n=240)	-	<3.5	Ref.	Ref.	N.S.
	-	3.5 – 16.4	-0.05 (0.07)	-0.12 (0.09)	N.S.
	-	16.5 – 64.5	-0.04 (0.08)	-0.12 (0.09)	N.S.
	<3.42	-	Ref.	Ref.	N.S.
	3.42 – 11.69	-	-0.13 (0.08)	-0.13 (0.10)	N.S.
	11.7 – 22.8	-	-0.09 (0.10)	-0.12 (0.12)	N.S.
Age ≥ 40 (n=169)	-	<6	Ref.	Ref.	N.S.
	-	6 – 16.9	-0.01 (0.09)	-0.03 (0.11)	N.S.
	-	17 – 64.5	-0.03 (0.09)	-0.11 (0.11)	N.S.
	<6	-	Ref.	Ref.	N.S.
	6 – 12.4	-	<0.01 (0.09)	-0.02 (0.11)	N.S.
	12.4 – 22.8	-	-0.06 (0.10)	-0.06 (0.12)	N.S.
Never smoker (n=76)	<2.8	-	Ref.	Ref.	N.S.
	2.8 – 8.51	-	-0.07 (0.14)	-0.18 (0.17)	N.S.
	8.52 – 21.1	-	-0.03 (0.16)	-0.25 (0.18)	N.S.

Abbreviations: β_{slope}: regression coefficient; COPD: Chronic Obstructive Pulmonary Disease; FEV_1: Forced expiratory volume in 1 second; L: liter; N.R. not reported; N.S. not significant; OR: odds ratio; Ref.: Reference group; mg/m^3: milligram/cubic meter; SE: standard error.
Bolded values indicate a significant difference was detected

Table 16. Supporting Evidence for Research Question 4: Increased likelihood of COPD following cumulative exposure

Study Name Author, Year	Occupation/ Group	Main Exposure of Interest	Method of Exposure Assessment	Exposure Measure (mg/m^3)	Smoking Status	COPD Diagnosis *n (%), p-value* †FEV_1/FVC <0.7 ‡FEV_1/FVC<5% LLN	COPD at Baseline *OR (95% CI), p-value*	COPD at Follow-up *OR (95% CI), p-value*
Studies Identified from Q2-6 Search								
Observational Cohort Studies								
Bolund 2018[16] REFID: 503	Females	Wood Dust (Wood Worker) (n=185)	Passive dust monitors	Low Exposure (>0 ≤0.972)	Current smoker[a] (n=96)	‡9 (9.6)	5.49 (0.6 – 48.7), 0.126 (n=139)	5.57 (0.6 – 52.2), 0.132 (n=141)
				High Exposure (>0.972 ≤ 1.61)			8.47 (0.9 – 82.4), 0.066 (n=139)	**12.0 (1.3 –111.0), 0.029** (n=141)
				-	Non-smoker (n=87)	‡0	-	-
		No Exposure (Factory Worker) (n=131)		-	Current smoker[a] (n=72)	‡1 (1.5)	-	-
				-	Non-smoker (n=58)	‡0	-	-
				No Exposure 0	-	-	-	1‡ (Ref.)
	Males	Wood Dust (Wood Worker) (n=927)	Passive dust monitors	-	Current smoker[a] (n=429)	‡22 (5.5)	**6.24 (2.5-15.6), 0.000** (n=916)	**7.05 (2.4-2076), 0.036** (n=900)
				-	Non-smoker (n=494)	‡4 (0.8)	-	-
				Low Exposure (>0 ≤0.972)	-	-	0.94 (0.3 – 3.0), 0.917 (n=916)	0.82 (0.3 – 2.7), 0.745 (n=900)
				High Exposure (>0.972 ≤ 1.61)	-	-	0.66 (0.2 – 2.2), 0.490 (n=916)	0.72 (0.2 – 2.4), 0.593 (n=900)
		No Exposure		-	Current smoker[a]	‡4 (7.6)	-	-

Study Name Author, Year	Occupation/ Group	Main Exposure of Interest	Method of Exposure Assessment	Exposure Measure (mg/m^3)	Smoking Status	COPD Diagnosis *n (%), p-value* †FEV_1/FVC <0.7 ‡FEV_1/FVC<5% LLN	COPD at Baseline *OR (95% CI), p-value*	COPD at Follow-up *OR (95% CI), p-value*
		(Factory Worker) (n=104)			(n=55)			
				-	Non-Smoker (n=49)	‡0	-	-
				No Exposure 0	-	-	-	1 (Ref.)
Stoleski 2019[21] REFID: 3749	Dairy farmers	Dust	Questionnaire Job Exposure Matrices	-	*adjusted*	†6 (85.7)	1.91 (0.43 – 3.90)	-
				Low	*adjusted*	†0	1.68 (0.30 – 3.73)	-
				Intermediate	*adjusted*	†2 (33.3)	**2.07 (1.03 – 4.15), <0.05**	-
				High	*adjusted*	**†4 (66.7), <0.05**	**3.12 (1.45 – 6.35), <0.05**	-
		Gases, fumes, vapours		-	*adjusted*	†5 (71.4)	1.74 (0.27 – 3.81)	-
				Low	*adjusted*	†1 (20)	1.61 (0.42 – 3.79)	-
				Intermediate	*adjusted*	†1 (20)	1.81 (0.53 – 3.92)	-
				High	*adjusted*	**†3 (60), <0.05**	**3.14 (1.75 – 6.25), <0.05**	-
		Dust		Rare	*adjusted*		1.63 (0.43 – 3.12)[a]	
				Sporadic	*adjusted*		1.83 (0.49 – 3.88)[a]	
				Regular	*adjusted*		**2.47 (1.26 – 5.29)[a], <0.05**	
		Gases, fumes, vapours		Rare	*adjusted*		1.67 (0.39 – 3.12)[a]	
				Sporadic	*adjusted*		1.85 (0.48 – 3.33)[a]	
				Regular	*adjusted*		**2.46 (1.25 – 5.17)[a], <0.05**	
Observational Studies – Cross-Sectional								
Koh 2015[17] REFID: 2044	Welder	Metal fumes	Environmental sampling	All (Mixed Exposure) (n=240)	Low Smoking (<3.5)	-	Ref.	-
					Intermediate Smoking (3.5 – 16.4)	-	0.65 (0.26 – 1.58)	-

Study Name Author, Year	Occupation/ Group	Main Exposure of Interest	Method of Exposure Assessment	Exposure Measure (mg/m^3)	Smoking Status	COPD Diagnosis *n (%), p-value* †FEV_1/FVC <0.7 ‡FEV_1/FVC<5% LLN	COPD at Baseline *OR (95% CI), p-value*	COPD at Follow-up *OR (95% CI), p-value*
					High Smoking (16.5 – 64.5)	-	0.90 (0.37 – 2.16)	-
				Low Exposure (<3.42)	All (Mixed Smoking) (n=240)	-	Ref.	-
				Intermediate Exposure (3.42 – 11.7)		-	**3.91 (1.36 – 13.33)**	-
				High Exposure (11.7 – 22.8)		-	**3.77 (1.03 – 16.21)**	-
				Low Exposure (<3.5)	Never-smoker (n=76)	-	Ref.	-
				Intermediate Exposure (3.5 – 16.4)		-	1.39 (0.3 – 7.01)	-
				High Exposure (16.5-64.5)		-	1.19 (0.22 – 6.97)	-
Vinnikov 2017[23] REFID: 4120	Tractor Plant workers	Metal dust (n=458)	Sampling of total suspended particles in the workplace	Low-exposure (<2) (n=367)	Mixed	†40 (11) ‡27 (7)	Ref.[c]	-
				High-exposure (>2) (n=91)		†7 (8) ‡3 (3)	2.10 (1.16 – 3.83)[c]	-
		Metal dust		Low-exposure (<2)	Non smoking	-	Ref.[d]	-

Study Name Author, Year	Occupation/ Group	Main Exposure of Interest	Method of Exposure Assessment	Exposure Measure (mg/m^3)	Smoking Status	COPD Diagnosis *n (%), p-value* †FEV_1/FVC <0.7 ‡FEV_1/FVC<5% LLN	COPD at Baseline *OR (95% CI), p-value*	COPD at Follow-up *OR (95% CI), p-value*
				High-exposure (>2)		-	2.47 (1.02 – 5.97)[d]	-
Sumit 2020[28] REFID: 3787	Motor Vehicle Mechanic Cleaners Drivers Manager Clerk Housekeeper and related worker Administrative job	VGDF	Questionnaire	Unexposed (n=184)	-	23 (12.5)	Ref.	-
				Exposed (n=189)		104 (55)	**6.3 (2.8 – 9.2), 0.00**	-
			Job Exposure Matrix	Shorter exposure (1-9 years)[b] (n=170)		35 (20.6)	1.1 (1.0 – 12.08), 0.7	-
				Longer exposure (>9 years)[b] (n=169)		87 (51.5)	2.8 (1.2 – 13.09), 0.05	-
van Koeverden 2015[3] REFID: 4066	N.R.	Work second-hand smoke	Job Exposure Matrix	Intermediate or high-risk exposure to secondhand smoke	*adjusted*	-	**1.52 (1.16 – 1.98), <0.01[e]**	-
				Work secondhand smoke exposure (per 10 years)	*adjusted*	-	**1.12 (1.02 – 1.23), 0.01[e]**	-
		-	Questionnaire		Smoker (per 10 pack-years)	-	**1.17 (1.11 – 1.24), <0.01[e]**	-
		Occupational VGDF	Job Exposure Matrix	-	*adjusted*	-	**1.58 (1.21 – 2.05), <0.01[f]**	-
		Work second-hand smoke		>20 years work secondhand smoke exposure	*adjusted*	-	**1.45 (1.13 – 1.86), <0.01[f]**	-
		-	Questionnaire	-	>20 pack-years smoking	-	**2.41 (1.61 – 3.62), <0.01[f]**	-

Study Name Author, Year	Occupation/ Group	Main Exposure of Interest	Method of Exposure Assessment	Exposure Measure (mg/m^3)	Smoking Status	COPD Diagnosis *n (%), p-value* †FEV_1/FVC <0.7 ‡FEV_1/FVC<5% LLN	COPD at Baseline *OR (95% CI), p-value*	COPD at Follow-up *OR (95% CI), p-value*
	<62 years of age	Occupational VGDF	Job Exposure Matrix	Intermediate or high risk job	*adjusted*	-	**1.46 (1.00 – 2.13), 0.04[g]**	-
		Work second-hand smoke		Work secondhand smoke exposure (per 10 years)	*adjusted*	-	1.15 (0.99 – 1.33), 0.06[g]	-
		-	Questionnaire		Smoker (per 10 pack-years)	-	**1.25 (1.15 – 1.36), <0.01[g]**	-
	>62 years of age	Occupational VGDF	Job Exposure Matrix	Intermediate or high risk job	*adjusted*	-	1.34 (0.94 – 1.93), 0.10[g]	-
		Work second-hand smoke		Work secondhand smoke exposure (per 10 years)	*adjusted*	-	**1.13 (1.01 – 1.27), 0.03[g]**	-
		-	Questionnaire		Smoker (per 10 pack-years)	-	**1.16 (1.08 – 1.24), <0.01[g]**	-
Doney 2019[29] REFID: 1000	N.R.	Mineral Dust	Self-reported exposure	No exposure (n=4,971)	*adjusted*	(4.47)	Ref.	-
				- (n=10,764)		(3.05)	1.07 90.91 – 1.26)[h] **1.62 91.19 – 2.21)[i]**	-
				>0 – 9		-	0.92 (0.75 – 1.12)[h] **1.48 (1.02 – 2.15)[i]**	-
				10 – 19		-	1.08 (0.79 – 1.48)[h] **1.90 (1.25 – 2.89)[i]**	-
				≥20		-	**1.44 (1.13 – 1.85)[h] 1.69 (1.17 – 2.43)[i]**	-
			COPD-JEM Occupational exposures	Low (n=13,948)	*adjusted*	(3.35)	Ref.	-
				Medium (n=1,005)		(4.62)	0.85 (0.62 – 1.16)[h] **1.47 (1.02 – 2.10)[i]**	-

Study Name Author, Year	Occupation/ Group	Main Exposure of Interest	Method of Exposure Assessment	Exposure Measure (mg/m^3)	Smoking Status	COPD Diagnosis *n (%), p-value* †FEV_1/FVC <0.7 ‡FEV_1/FVC<5% LLN	COPD at Baseline *OR (95% CI), p-value*	COPD at Follow-up *OR (95% CI), p-value*
				High (n=778)		(4.41)	**1.44 (1.09 – 1.90)[h]** 1.40 (0.79 – 2.47)[i]	-
		Organic Dust	Self-reported exposure	No exposure (n=12,309)	*adjusted*	(3.06)	Ref.	-
				- (n=3,454)		(4.98)	**1.23 (1.02 – 1.44)[h]** **1.64 (1.29 – 2.08)[i]**	-
				>0 – 9		-	0.95 (0.78 – 1.15)[h] **1.50 (1.01 – 2.22)[i]**	-
				10 – 19		-	**1.61 (1.13 – 2.29)[h]** **2.18 (1.41 – 3.37)[i]**	-
				≥20		-	**1.73 (1.35 – 2.21)[h]** 1.52 (0.99 – 2.33)[i]	-
			COPD-JEM Occupational exposures	Low (n=13,638)	*adjusted*	(3.39)	Ref.	-
				Medium (n=1,302)		(5.32)	**1.34 (1.02 – 1.76)[h]** **1.71 (1.25 – 2.34)[i]**	-
				High (n=791)		(2.44)	1.45 (0.98 – 2.12)[h] 0.84 (0.51 – 1.39)[i]	-
		Exhaust Fumes	Self-reported exposure	No exposure (n=11,896)	*adjusted*	(2.89)	Ref.	-
				- (n=3,875)		(5.24)	1.13 (0.97 – 1.31)[h] **2.01 (1.48 – 2.74)[i]**	-
				>0 – 9		-	0.89 (0.73 – 1.09)[h] **1.83 (1.30 – 2.59)[i]**	-
				10 – 19		-	1.22 (0.91 – 1.63)[h] **2.15 (1.37 – 3.58)[i]**	-
				≥20		-	**1.65 (1.27 – 2.15)[h]** **2.22 (1.37 – 3.58)[i]**	-
		Other gases, vapours or fumes	Self-reported exposure	No exposure (n=10,780)	*adjusted*	(3.05)	Ref.	-
				- (n=4,991)		(4.43)	1.03 (0.89 – 1.19)[h] **1.47 (1.20 -1.79)[i]**	-

Study Name Author, Year	Occupation/ Group	Main Exposure of Interest	Method of Exposure Assessment	Exposure Measure (mg/m^3)	Smoking Status	COPD Diagnosis *n (%), p-value* †FEV_1/FVC <0.7 ‡FEV_1/FVC<5% LLN	COPD at Baseline *OR (95% CI), p-value*	COPD at Follow-up *OR (95% CI), p-value*
				>0 – 9		-	0.96 (0.81 – 1.14)[h] 1.19 (0.93 – 1.54)[i]	-
				10 – 19		-	0.99 (0.74 – 1.32)[h] **1.97 (1.35 – 2.87)[i]**	-
				≥20		-	1.23 (0.93 – 1.63)[h] **1.61 (1.16 – 2.23)[i]**	-
		Ever dust and/or fumes	Self-reported exposure	- (8,413)	*adjusted*	(4.50)	1.05 (0.90 – 1.23)[h] **2.04 (1.64 – 2.53)[i]**	-
		Combined Dust	COPD-JEM Occupational exposures	Low (n=11,973)	*adjusted*	(3.15)	Ref.	-
				Medium (n=2,316)		(5.19)	1.15 (0.92 – 1.44)[h] **1.81 (1.36 – 2.43)[i]**	-
				High (n=1,442)		(4.09)	**1.57 (1.21 – 2.04)[h]** **1.52 (1.03 – 2.24)[i]**	-
		Diesel Exhaust	COPD-JEM Occupational exposures	Low (n=13,404)	*adjusted*	(3.35)	Ref.	-
				Medium (n=1,184)		(3.16)	0.85 (0.66 – 1.09)[h] 1.02 (0.69 – 1.51)[i]	-
				High (n=1,143)		(5.36)	**1.44 (1.12 – 1.85)[h]** **1.82 (1.18 – 2.81)[i]**	-
		Vapour-gas	COPD-JEM Occupational exposures	Low (n=11,045)	*adjusted*	(3.23)	Ref.	-
				Medium (n=2,794)		(4.30)	1.15 (0.91 – 1.45)[h] **1.46 (1.05 – 2.02)[i]**	-
				High (n=1,892)		(4.11)	**1.31 (1.05 – 1.64)[h]** **1.39 (1.04 – 1.85)[i]**	-
		Sensitizers	COPD-JEM Occupational exposures	Low (n=10,514)	*adjusted*	(3.13)	Ref.	-
				Medium (n=2,844)		(4.31)	**1.27 (1.03 – 1.56)[h]** **1.43 (1.05 – 2.02)[i]**	-
				High (n=2,733)		(4.26)	**1.33 91.01 – 1.76)[h]** **1.50 (1.13 – 1.99)[i]**	-
		Fumes	COPD-JEM Occupational exposures	Low (n=14,689)	*adjusted*	(3.43)	Ref.	-
				Medium (n=567)		(3.68)	0.88 (0.60 – 1.28)[h] 1.20 (0.69 – 2.069)[i]	-

Study Name Author, Year	Occupation/ Group	Main Exposure of Interest	Method of Exposure Assessment	Exposure Measure (mg/m^3)	Smoking Status	COPD Diagnosis *n (%), p-value* †FEV_1/FVC <0.7 ‡FEV_1/FVC<5% LLN	COPD at Baseline *OR (95% CI), p-value*	COPD at Follow-up *OR (95% CI), p-value*
				High (n=475)		(4.99)	1.19 (0.80 – 1.77)[h] 1.43 (0.89 – 2.30)[i]	-
		Overall Exposure	COPD-JEM Occupational exposures	Low (n=9,592)	*adjusted*	(2.71)	Ref.	-
				Medium (n=3642)		(5.37)	**1.32 (1.08 – 1.61)[h] 2.20 (1.70 – 2.86)[i]**	-
				High (n=2,497)		(4.51)	**1.54 (1.21 – 1.96)[h] 2.02 (1.46 – 2.80)[i]**	-
Liu 2015[26] REFID: 2409	Greenhouse workers	N.R	Questionnaire		Non-smoker (n=3,505)	†500 (14.3)	Ref.	-
					Current smoker (n=1,915)	†447 (23.3)	**2.18 (1.84 – 2.59), <0.0005[j]**	-
				Vegetable greenhouse (n=2,167)	*adjusted*	†268 (12.4)	Ref.	-
				Mushroom greenhouse (n=1,085)	*adjusted*	†266 (24.5)	**1.46 (1.13 – 1.87), 0.004[j]**	-
				Flower greenhouse (n=1,355)	*adjusted*	†243 (17.9)	**1.55 (1.24 – 1.95), <0.0005[j]**	-
				Poultry greenhouse (n=813)	*adjusted*	†170 (20.9)	2.08 (0.67 – 6.49), 0.206[j]	-
				<3 working years (n=758)	*adjusted*	†137 (18.1)	Ref.	
				3 – 5 working years (n=485)	*adjusted*	†137 (28.2)	**1.52 (1.08 – 2.15), 0.017[j]**	
				>5 working years (n=4,177)	*adjusted*	†673 (16.1)	**0.51 (0.40 – 0.65), <0.0005[j]**	
				<3 working hours/day (n=604)	*adjusted*	†211 (34.9)	Ref.	

Study Name Author, Year	Occupation/ Group	Main Exposure of Interest	Method of Exposure Assessment	Exposure Measure (mg/m^3)	Smoking Status	COPD Diagnosis *n (%), p-value* †FEV_1/FVC <0.7 ‡FEV_1/FVC<5% LLN	COPD at Baseline *OR (95% CI), p-value*	COPD at Follow-up *OR (95% CI), p-value*
				3 – 5 working hours/day (n=2,162)	*adjusted*	†488 (22.6)	0.96 (0.76 – 1.21), 0.709[j]	
				>5 working hours/day (n=2,654)	*adjusted*	†248 (9.3)	1.09 (0.83 – 1.43), 0.548[j]	
				-	Smoker 0 pack-years (n=3,505)	†500 (14.3)	Ref.	
				-	Smoker 1 – 14 pack-years (n=55)	†21 (38.2)	0.93 (0.47 – 1.85), 0.844[j]	
				-	Smoker 15-29 pack-years (n=743)	†170 (22.9)	**2.39 (1.88 – 3.03), <0.0005[j]**	
				-	Smoker ≥30 pack-years (n=1,117)	†256 (22.9)	**2.17 (1.76 –2.66), <0.0005[j]**	
Sadhra 2020[30] REFID: 3400	UK Biobank (n=228,614)	Vapours	Questionnaire	-	-	‡3903 (19.2)	1.06 (1.02 – 1.10)[k]	-
					adjusted		1.03 (0.99 – 1.07)[k,l]	-
				Low	*adjusted*	‡2885	**1.00 (0.96 – 1.04)[k,l]**	-
				Medium		‡574	**1.05 (0.97 – 1.15)[k,l]**	-
				High		‡444	**1.26 (1.15 – 1.38)[k,l]**	-
				-	Never-smoker	‡1759	0.99 (0.94 – 1.04)[k,l]	-
				Low		‡1412	0.98 (0.92 – 1.03)[k,l]	-
				Medium		‡199	0.95 (0.83 – 1.08)[k,l]	-
				High		‡148	1.23 (1.05 – 1.43)[k,l]	-

Study Name Author, Year	Occupation/ Group	Main Exposure of Interest	Method of Exposure Assessment	Exposure Measure (mg/m^3)	Smoking Status	COPD Diagnosis *n (%), p-value* †FEV_1/FVC <0.7 ‡FEV_1/FVC<5% LLN	COPD at Baseline *OR (95% CI), p-value*	COPD at Follow-up *OR (95% CI), p-value*
		Gases		-	-	‡3135 (15.5)	1.08 (1.04 – 1.12)[k]	-
					adjusted		1.04 (1.00 – 1.08)[k,l]	-
				Low	*adjusted*	‡2841	**1.03 (0.99 – 1.07)[k,l]**	-
				Medium		‡256	**1.14 (1.01 – 1.29)[k,l]**	-
				High		‡38	**1.26 (0.92 – 1.72)[k,l]**	-
				-	Never-smoker	‡1429	1.02 (0.97 – 1.08)[k,l]	-
				Low		‡1318	1.02 (0.96 – 1.08)[k,l]	-
				Medium		‡100	1.05 (0.87 – 1.28)[k,l]	-
				High		‡11	1.12 (0.63 – 1.98)[k,l]	-
		Dusts		-	-	‡5745 (28.3)	1.08 (1.05 – 1.12)[k]	-
					adjusted		1.05 (1.01 – 1.08)[k,l]	-
				Low	*adjusted*	‡4146	**1.02 (0.99 – 1.06)[k,l]**	-
				Medium		‡965	**1.14 (1.07 – 1.22)[k,l]**	-
				High		‡634	**1.07 (0.99 – 1.16)[k,l]**	-
				-	Never-smoker	‡2473	1.01 (0.96 – 1.06)[k,l]	-
				Low		‡1938	1.0 (0.96 – 1.05)[k,l]	-
				Medium		‡335	1.06 (0.95 – 1.18)[k,l]	-
				High		‡200	0.97 (0.85 – 1.11)[k,l]	-

Study Name Author, Year	Occupation/ Group	Main Exposure of Interest	Method of Exposure Assessment	Exposure Measure (mg/m^3)	Smoking Status	COPD Diagnosis *n (%), p-value* †FEV_1/FVC <0.7 ‡FEV_1/FVC<5% LLN	COPD at Baseline *OR (95% CI), p-value*	COPD at Follow-up *OR (95% CI), p-value*
		Biological Dusts		-	-	‡3093 (15.2)	1.09 (1.05 – 1.13)[k]	-
					adjusted		1.05 (1.01 – 1.10)[k,l]	-
				Low	*adjusted*	‡2740	**1.05 (1.01 – 1.10)[k,l]**	-
				Medium		‡134	**1.04 (0.88 – 1.23)[k,l]**	-
				High		‡219	**1.09 (0.96 – 1.25)[k,l]**	-
				-	Never-smoker	‡1441	1.03 (0.97 – 1.09)[k,l]	-
				Low		‡1318	1.03 (0.98 – 1.09)[k,l]	-
				Medium		‡48	0.90 (0.68 – 1.18)[k,l]	-
				High		‡75	1.03 (0.83 – 1.28)[k,l]	-
		Mineral Dusts		-	-	‡3383 (16.7)	1.07 (1.03 – 1.11)[k]	-
					adjusted		1.03 (0.99 – 1.07)[k,l]	-
				Low	*adjusted*	‡2061	**0.98 (0.93 – 1.03)[k,l]**	-
				Medium		‡1110	**1.11 (1.04 – 1.18)[k,l]**	-
				High		‡212	**1.18 (1.03 – 1.35)[k,l]**	-
				-	Never-smoker	‡1351	0.97 (0.91 – 1.03)[k,l]	-
				Low		‡921	0.94 (0.88 – 1.01)[k,l]	-
				Medium		‡372	1.03 (0.93 – 1.01)[k,l]	-
				High		‡58	1.02 (0.79 – 1.30)[k,l]	-

Study Name Author, Year	Occupation/ Group	Main Exposure of Interest	Method of Exposure Assessment	Exposure Measure (mg/m^3)	Smoking Status	COPD Diagnosis *n (%), p-value* †FEV_1/FVC <0.7 ‡FEV_1/FVC<5% LLN	COPD at Baseline *OR (95% CI), p-value*	COPD at Follow-up *OR (95% CI), p-value*
		Fumes		-	-	‡3399 (16.8)	1.07 (1.04 – 1.11)[k]	-
					adjusted		1.02 (0.98 – 1.06)[k,l]	-
				Low	*adjusted*	‡2687	**1.0 (0.96 – 1.05)[k,l]**	-
				Medium		‡617	**1.09 (1.0 – 1.18)[k,l]**	-
				High		‡95	**1.26 (1.03 – 1.54)[k,l]**	-
				-	Never-smoker	‡1318	0.98 (0.92 – 1.04)[k,l]	-
				Low		‡1063	0.96 (0.90 – 1.03)[k,l]	-
				Medium		‡218	1.05 (0.92 – 1.19)[k,l]	-
				High		‡37	1.18 (0.86 – 1.60)[k,l]	-
		Diesel Fumes		-	-	‡1828 (9.0)	1.13 (1.08 – 1.19)[k]	-
					adjusted		1.04 (0.99 – 1.09)[k,l]	-
				Low	*adjusted*	‡1665	1.04 (0.99 – 1.10)[k,l]	-
				Medium		‡163	1.02 (0.87 – 1.20)[k,l]	-
				High		-	-	-
				-	Never-smoker	‡680	1.0 (0.93 – 1.09)[k,l]	-
				Low		‡607	1.0 (0.92 – 1.09)[k,l]	-
				Medium		‡73	1.01 (0.81 – 1.27)[k,l]	-
				High		-	-	-

Study Name Author, Year	Occupation/ Group	Main Exposure of Interest	Method of Exposure Assessment	Exposure Measure (mg/m^3)	Smoking Status	COPD Diagnosis *n (%), p-value* †FEV_1/FVC <0.7 ‡FEV_1/FVC<5% LLN	COPD at Baseline *OR (95% CI), p-value*	COPD at Follow-up *OR (95% CI), p-value*
		Fibers		-	-	‡1814 (8.9)	1.03 (0.98 – 1.08)[k]	-
					adjusted		0.98 (0.93 – 1.03)[k,l]	
				Low	*adjusted*	‡1460	0.96 (0.90 – 1.01)[k,l]	-
				Medium		‡310	1.08 (0.96 – 1.21)[k,l]	-
				High		‡44	1.16 (0.87 – 1.53)[k,l]	-
				-	Never-smoker	‡654	0.87 (0.80 - 0.95)*[,k,l]	-
				Low		‡549	**0.86 (0.78 – 0.93)[k,l]**	-
				Medium		‡94	**0.98 (0.80 – 1.19)[k,l]**	-
				High		‡11	**0.87 (0.49 – 1.55)[k,l]**	-
		Mists		-	-	‡2662 (13.1)	1.03 (0.99 – 1.08)[k]	-
					adjusted		1.01 (0.97 – 1.06)[k,l]	-
				Low	*adjusted*	‡1898	**0.97 (0.93 – 1.02)[k,l]**	-
				Medium		‡291	**1.0 (0.89 – 1.12)[k,l]**	-
				High		‡473	**1.22 (1.12 – 1.34)[k,l]**	-
				-	Never-smoker	‡1170	0.96 (0.91 – 1.02)[k,l]	-
				Low		‡897	0.94 (0.88 – 1.00)[k,l]	-
				Medium		‡113	0.93 (0.78 – 1.12)[k,l]	-
				High		‡160	1.15 (0.99 – 1.34)[k,l]	-

Study Name Author, Year	Occupation/ Group	Main Exposure of Interest	Method of Exposure Assessment	Exposure Measure (mg/m^3)	Smoking Status	COPD Diagnosis *n (%), p-value* †FEV_1/FVC <0.7 ‡FEV_1/FVC<5% LLN	COPD at Baseline *OR (95% CI), p-value*	COPD at Follow-up *OR (95% CI), p-value*
		VGDF		-	-	‡7205 (35.5)	1.09 (1.06 – 1.12)[k]	-
					adjusted		1.04 (1.01 – 1.07)[k,l]	-
				Low	*adjusted*	‡5123	**1.03 (0.99 – 1.06)[k,l]**	-
				Medium		‡949	**1.01 (0.95 – 1.08)[k,l]**	-
				High		‡1133	**1.14 (1.08 – 1.22)[k,l]**	-
				-	Never-smoker	‡3023	1.01 (0.97 – 1.05)[k,l]	-
				Low		‡2293	1.01 (0.96 – 1.05)[k,l]	-
				Medium		‡358	0.97 (0.87 – 1.07)[k,l]	-
				High		‡372	1.07 (0.97 – 1.18)[k,l]	-
		VGDFFiM		-	-	‡7218 (35.6)	1.09 (1.06 – 1.12)[k]	-
					adjusted		1.04 (1.01 – 1.07)[k,l]	-
(Sinha 2017[25] REFID: 3639	Occupational exposure	Dust, Fumes	Questionnaire	No exposure (n=706)	-	†28 (4.0)	Ref.	-
				Exposure present	-	-	**6.16 (3.30 – 10.22)**	
					adjusted		**7.97 (3.32 – 13.18)**	
				Exposure present	Smoker ≤10 pack-years	-	Ref.	
					Smoker 11-20 pack-years	-	2.52 (0.86 – 7.44)	
					Smoker ≥20 pack-years	-	**6.91 (1.80 – 9.85)**	
				≤10 years (n=190)	-	†8 (4.2)	-	-

Study Name Author, Year	Occupation/ Group	Main Exposure of Interest	Method of Exposure Assessment	Exposure Measure (mg/m^3)	Smoking Status	COPD Diagnosis *n (%), p-value* †FEV_1/FVC <0.7 ‡FEV_1/FVC<5% LLN	COPD at Baseline *OR (95% CI), p-value*	COPD at Follow-up *OR (95% CI), p-value*
				11 – 19 years (n=66)	-	†12 (18.2)	-	-
				≥ 20 years (n=241)	-	†74 (30.7)	-	-
	Tobacco smoke exposure	-		-	No exposure (n=744)	†12 (1.6)	Ref.	-
					Smoker ≤10 pack-years (n=248)	†21 (8.5)	-	-
					Current Smoker (≤10 pack-years)	-	Ref.	-
					Ex-smoker (≤10 pack-years)	-	Ref.	-
					Smoker 11-20 pack-years (n=134)	†33 (24.6)	-	-
					Current Smoker (11-20 pack-years)	-	**4.87 (1.70 – 9.13)**	-
					Ex-smoker (11-20 pack-years)	-	0.34 (0.68 – 1.69)	-
					Smoker ≥20 pack-years (n=77)	†56 (72.7)	-	-
					Current Smoker (≥20 pack-years)	-	**12.95 (3.71 – 19.82)**	
					Ex-smoker (≥20 pack-years)	-	**2.43 (1.31 – 3.55)**	
Dement 2015[27] REFID: 921	VGDF	Asbestos	Questionnaire	0.25[m]	*adjusted*	-	1.15 (1.05 – 1.26)[n]	-
				0.50[m]		-	1.31 (1.09 – 1.58)[n]	-
				0.75[m]		-	1.50 (1.14 – 2.00)[n]	-
				1.00[m]		-	1.72 (1.19 – 2.48)[n]	-
		Silica		0.25[m]	*adjusted*	-	1.21 (1.11 – 1.32)[n]	-
				0.50[m]		-	1.46 (1.3 – 1.74)[n]	-
				0.75[m]		-	1.77 (1.36 – 2.30)[n]	-
				1.00[m]		-	2.13 (1.50 – 3.03)[n]	-
		Cement dust		0.25[m]	*adjusted*	-	1.16 (1.05 – 1.25)[n]	-
				0.50[m]		-	1.31 (1.11 – 1.56)[n]	-
				0.75[m]		-	1.51 (1.17 – 1.94)[n]	-

Study Name Author, Year	Occupation/ Group	Main Exposure of Interest	Method of Exposure Assessment	Exposure Measure (mg/m^3)	Smoking Status	COPD Diagnosis *n (%), p-value* †FEV_1/FVC <0.7 ‡FEV_1/FVC<5% LLN	COPD at Baseline *OR (95% CI), p-value*	COPD at Follow-up *OR (95% CI), p-value*
				1.00[m]		-	1.73 (1.23 – 2.43)[n]	-
		Man-made mineral fibers		0.25[m]	*adjusted*	-	1.06 (0.97 – 1.16)[n]	-
				0.50[m]		-	1.13 (0.94 – 1.35)[n]	-
				0.75[m]		-	1.20 (0.92 – 1.57)[n]	-
				1.00[m]		-	1.28 (0.89 – 1.82)[n]	-
		Engine Exhausts		0.25[m]	*adjusted*	-	1.15 (1.05 – 1.26)[n]	-
				0.50[m]		-	1.33 (1.11 – 1.74)[n]	-
				0.75[m]		-	1.53 (1.17 – 2.00)[n]	-
				1.00[m]		-	1.76 (1.23 – 2.52)[n]	-
		Acids and caustics		0.25[m]	*adjusted*	-	1.46 (0.91 – 2.32)[n]	-
				0.50[m]		-	1.49 (1.09 – 2.04)[n]	-
				0.75[m]		-	1.51 (1.16 – 1.98)[n]	-
				1.00[m]		-	1.54 (1.07 – 2.22)[n]	-
		Welding, thermal cutting, soldering, brazing		0.25[m]	*adjusted*	-	1.11 (1.01 – 1.21)[n]	-
				0.50[m]		-	1.23 (1.03 – 1.46)[n]	-
				0.75[m]		-	1.36 (1.04 – 1.77)[n]	-
				1.00[m]		-	1.50 (1.05 – 2.14)[n]	-
		Metal cutting, grinding, and machining aerosol		0.25[m]	*adjusted*	-	1.09 (1.00 – 1.19)[n]	-
				0.50[m]		-	1.20 (1.01 – 1.42)[n]	-
				0.75[m]		-	1.31 (1.02 – 1.68)[n]	-
				1.00[m]		-	1.43 (1.02 – 2.00)[n]	-
		Paint-related aerosols		0.25[m]	*adjusted*	-	1.05 (0.96 – 1.15)[n]	-
				0.50[m]		-	1.10 (0.92 – 1.31)[n]	-
				0.75[m]		-	1.15 (0.89 – 1.50)[n]	-
				1.00[m]		-	1.21 (0.85 – 1.72)[n]	-
		Isocyanates		0.25[m]	*adjusted*	-	1.09 (0.83 – 1.42)[n]	-
				0.50[m]		-	1.22 (0.97 – 1.52)[n]	-
				0.75[m]		-	1.36 (1.03 – 1.80)[n]	-
				1.00[m]		-	1.52 (1.04 – 2.23)[n]	-
		Organic solvents		0.25[m]	*adjusted*	-	1.16 (1.07 – 1.26)[n]	-
				0.50[m]		-	1.34 (1.13 – 1.59)[n]	-
				0.75[m]		-	1.55 (1.20 – 2.01)[n]	-
				1.00[m]		-	1.80 (1.28 – 2.53)[n]	-

Study Name Author, Year	Occupation/ Group	Main Exposure of Interest	Method of Exposure Assessment	Exposure Measure (mg/m^3)	Smoking Status	COPD Diagnosis *n (%), p-value* †FEV_1/FVC <0.7 ‡FEV_1/FVC<5% LLN	COPD at Baseline *OR (95% CI), p-value*	COPD at Follow-up *OR (95% CI), p-value*
		Wood dust		0.25[m]	*adjusted*	-	1.36 (1.07 – 1.74)[n]	-
				0.50[m]		-	1.46 (1.10 – 2.00)[n]	-
				0.75[m]		-	1.36 (1.02 – 1.80)[n]	-
				1.00[m]		-	1.17 (0.80 – 1.69)[n]	-
		Molds and spores		0.25[m]	*adjusted*	-	1.12 (1.03[o] – 1.22)[n]	-
				0.50[m]		-	1.25 (1.05 – 1.49)[n]	-
				0.75[m]		-	1.40 (1.08 – 1.82)[n]	-
				1.00[m]		-	1.57 (1.11 – 2.23)[n]	-
		Particulates not otherwise regulated		0.25[m]	*adjusted*	-	1.21 (1.11 – 1.32)[n]	-
				0.50[m]		-	1.47 (1.23 – 1.74)[n]	-
				0.75[m]		-	1.78 (1.37 – 2.30)[n]	-
				1.00[m]		-	2.15 (1.52 – 4.04)[n]	-
		All VGDF		0.25[m]	*adjusted*	-	1.19 (1.09 – 1.30)[n]	-
				0.50[m]		-	1.42 (1.20 – 1.69)[n]	-
				0.75[m]		-	1.70 (1.31 – 2.20)[n]	-
				1.00[m]		-	2.03 (1.43 – 2.87)[n]	-
Mabila 2018{Mabila 2018 REFID: 2492	Miners	Mineral dust	Questionnaire	Low Dust	*adjusted*	-	Ref.	-
				Moderate Dust	*adjusted*	-	1.39 (0.62-3.14)[p]	-
				High Dust	*adjusted*	-	1.04 (0.56-1.95)[p]	-
				Very High Dust	*adjusted*	-	**2.56 (1.29-5.12)[p], <0.05**	-

Abbreviations: BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; FEV_1: Forced expiratory volume in 1 second; FVC (L): forced vital capacity; LLN: lower limit of normal; mg/m^3: miligram/cubic meter; N.R. not reported; Ref. Reference group; OR: odds ratio; SD: standard deviation; VGDF: Vapours, Gases, Dusts, Fumes; VGDFFiM: Vapours, Gases, Dusts, Fumes, Fibres or Mists.

*Significance at p<0.05

†FEV_1/FVC <0.7; ‡FEV_1/FVC < 5% LLN (lower limit of normal)

[a] Smoking status during the follow-up period

[b] Cumulative years exposed

[c] OR for FEV_1/FVC < 0.70; adjusted for sex, age, pack-years of smoking, and work duration.

[d] OR for FEV_1/FVC < 0.70; adjusted for sex, age, and work duration.

[e] Multivariate regression model adjusted for second-hand smoke exposure, intermediate or high risk exposure job, pack-years of smoking, age, and sex.

[f] Multivariate analysis of the population attributable risk fraction for COPD, adjusted for second-hand smoke exposure, occupational VGDF exposure, and pack-years of smoking.

[g] Multivariate estimate of the associations between secondhand smoke and job vapours, gas, dusts, and fume exposure likelihood and COPD, stratified by age.

[h] Prevalence odds ratio for airflow obstruction (FEV_1/FVC < LLN), adjusted for age, gender, race, smoking status
[i] Prevalence odds ratio for self-reported COPD, adjusted for age, gender, race, smoking status
[j] Multivariate regression model
[k] Prevalence ratios
[l] Adjusted for sex, study centre, age, lifetime smoking exposure (ever, pack-years, and year since quitting)
[m] Cumulative exposure indices identified for each exposure based on the product of task frequency, job duration, work hours per week, and task exposure intensity. See Appendix C for further details on the exposure concentrations used for intensity scoring.
[n] Logistic regression model adjusted for age, gender, race/ethnicity, smoking status (current, past, never), cigarette pack-years, blood relative with COPD, and BMI.
[o] Original text 1.12 (10.3 – 1.22) – updated in extraction based on assumption that 10.3 was a typo.
[p] Adjusted for race (black, white, other), smoking status (current, ex-smoker, never smoker), age (continuous), and sex (male, female)

5.2.4.4 Limitations

The data identified for Question 4 demonstrate that increased duration or intensity of exposure to various occupational VGDFs and/or smoking does increase measures of lung impairment and also increases the likelihood of developing COPD. While the evidence of this trend was significant in many studies, there were many studies that did not demonstrate significance. Additionally, differences were observed in the level of impact on lung impairment or likelihood of developing COPD when stratifying by or controlling for, potential confounders, such as gender, age, and type of exposure. This indicates that the impact of cumulative exposure is complex and quantifying the impact on lung impairment due to occupational exposure versus smoking is not feasible based on the evidence identified in this RLR. A deeper understanding of all the confounders influencing the values identified in these studies would be required, in order to ensure each study has controlled for the appropriate confounders, to isolate the effect of the exposure of interest.

Furthermore, a substantial amount of heterogeneity exists across the publications identified for Question 4 in relation to several factors such as, occupation, exposure of interest, exposure levels, geographical location, occupational environment, and subgroups stratification (i.e., smoker, non-smoker, ever-smoker, former smoker). The variability of the data identified within the last five years to answer Question 4 limits the ability for evidence synthesis to quantify the impact of cumulative exposure of cigarette smoking and or occupational VGDF exposure.

Lastly, three studies captured in this RLR cautioned a ‘healthy worker bias’, suggesting that individuals, particularly males, who have better lung function remain in jobs with higher occupational VGDF exposure while symptomatic workers moved to other work.[16,18,19]

5.2.4.5 Evidence Gaps

Based on the synthesis of evidence within the GOLD 2021 report, previous evidence has not been able to quantify the contribution of lung function loss/impairment by exposure type, and given the heterogeneity of available evidence published within the last five years, quantifying the contribution of either occupational VGDF exposure or cigarette smoking remains a challenge. Based on the evidence from this RLR, any attempt to quantify the contribution of occupational VGDF would need to be specific to the exposure type and the occupation. The standardization of reporting exposure intensity and duration, analysis of the impact of potential confounders and the inclusion of isolated smoking groups within longitudinal study designs would be next steps to further understanding and quantifying the contribution of lung function loss/impairment of occupational VGDF and cigarette exposure.

5.2.4.6 Conclusion

The evidence identified in this RLR suggest that cumulative exposure, as assessed by increased intensity and/or duration, to specific occupational VGDF and/or smoking does impact the extent of lung function impairment/loss. While there is considerable variability in the degree of impact reported, with numerous mitigating factors identified, the general trend observed from most studies was an increase in impairment or likelihood of developing COPD with greater exposure. Reliably quantifying the amount of lung function loss/impairment caused by smoking and that caused by workplace VGD exposure is not feasible based on the data identified in this study.

5.2.4.7 Clinical Comment

From the perspective of smoking related COPD, it is well recognized that the intensity and/or duration of exposure impacts the amount of lung function loss/impairment leading to accelerated loss of lung function. Thus the duration of smoking exposure will translate into an absolute increase in lung function loss. We know that earlier intervention with smoking cessation leads to a more typical rate of lung

function loss as discussed by Fletcher and Peto. [93] This recent data reinforces the previously recognized fact that occupational exposures do lead to COPD.

It is not possible to differentiate between smoking related lung function loss and that from occupational exposure related lung function loss as there is likely at least an additive effect. Additionally, there is likely tremendous individual variation in the personal experience of disease related to various factors (e.g. frequency of exacerbations, use of PPE, concomitant treatment, comorbid conditions etc.)

5.2.5 Research Question 5

Research Question 5: Are the effects of cigarette smoking and workplace VGDF exposure on lung function loss/impairment additive or multiplicative? If a person quits cigarette smoking and/or avoids workplace VGDF exposure, would that slow, stop or reverse their COPD or lung function loss/impairment?

5.2.5.1 Results

There were no studies identified in the last five years as a part of this RLR that directly addressed Question 5. However, there were four studies identified in the RLR presenting data regarding additive or multiplicative effects of smoking and workplace exposure in the development of lung function/impairment and/or COPD.[16-18,26] Additionally, six studies were identified that provided data relating to cessation of an exposure.[16,18,19,28,31,32] Supplemental information has also been included to provide contextual reference to established information and/or inferential data pertaining to Research Question 5.

5.2.5.2 Supplemental Information

The GOLD report does not speak directly to the additive or multiplicative effects or how lung impairment might alter with changes in exposure (either smoking or VGDF). However, it does state that '*the inflammatory and structural changes in the airways increase with disease severity and persist on smoking cessation,'* and that smoking cessation is a key intervention for COPD patients as it has the greatest capacity to influence the natural history of COPD.[8]

Previous studies report that former smokers have less lung function loss/impairment compared to current smokers.[93-95] Smoking has been shown to decrease expiratory airflow approximately two times of what would be expected for age-related loss.[93-95] Although former smokers remain at a higher risk for developing COPD compared to never smokers, sustained cessation results in a substantial decrease in the rate of loss of lung function over time when compared to continuing smokers.[96] Slowing the rate of decline in lung function suggests that the removal of exposure to cigarette smoking can alter the course of disease progression.[95,96]

The effect of removal of VGDF exposure on the disease process of COPD or lung function loss/impairment is less clear. Both the ATS 2019 review and GOLD 2021 report agree that occupational exposure accounts for approximately 10-20% of symptoms or lung functional loss/impairment consistent with COPD, however, neither directly address whether interventions that reduce occupational exposures also reduce COPD-related burden.[7,8] The GOLD report advises that it may be logical to advise patients to avoid ongoing exposure to irritants if possible.[8]

A recent publication by Henneberger *et al.,* 2020 reported that airflow obstruction defined as both FEV_1 and $FEV_1/FVC<LLN$ was associated with high total occupational VGDF exposure only among those who were smokers in a sample of rural residents in the state of Iowa, U.S. (OR: 1.81 [95% CI: 1.002-3.26]), suggesting an additive effect of VGDF and smoking.[97] This publication was not identified by the electronic search due to the focus on an outcome of 'airflow obstruction' as opposed to 'chronic airflow obstruction'; therefore, the data was not included as a part of this report. RLR by nature are less comprehensive in comparison to more a robust SLR. As such, it is possible that other publications that may address the research questions at hand are not included in this report.

5.2.5.3 Additive and/or Multiplicative Effects of Cigarette and Occupational VGDF Exposure on Decreased Lung Function

5.2.5.3.1 Study Characteristics

A total of four publications were identified for Research Question 5 that address a potential additive or multiplicative effect of VGDF and cigarette smoking on lung function loss/impairment. All studies were observational; two utilized a cross-sectional design and the remaining two were cohort studies. Two studies (Bolund 2018 and Soyseth 2016) were prospective longitudinal studies and provided follow-up data.[16,18] Two studies[16,18] reported lung function values for exposed workers by smoking status and two studies[17,26] reported the association of either duration and/or intensity of exposure (VGDF and/or smoking) controlling for other confounding factors (e.g. sex, age, smoking status, asthma).

Studies include populations from four countries (Denmark, Norway, Korea, and China) evaluating numerous exposure types from different occupations.

Study characteristics for the publications in which COPD is the primary focus and report supporting/inferential data towards Question 5 are presented in **Table 17**. Studies in which COPD is not the primary focus, but present supporting/inferential data regarding a variety of conditions associated with occupational exposure (e.g. emphysema, chronic bronchitis) related to lung function loss/impairment are included in the Data Extraction Workbook that accompanies this report.[91]

Table 17: Study Characteristics of Publications Providing Supporting Evidence for Question 5 Regarding Additive or Multiplicative Effects of VGDF and Smoking on Lung Function Loss/Impairment or the Association of COPD Development

Study Name Author, Year	Occupation(s)	Main Exposure of Interest	Method of Exposure Measurement	Stratified by Smoking Status *(Yes/No)*	Primary Outcome of Interest	Method of Outcome Assessment	Study Dates (year-year)	Country
Observational Cohort Studies								
Bolund 2018[16] REFID: 503	Woodworking	Wood Dust	Passive dust monitors	Yes	COPD	Spirometry	1998-2004[a]	Denmark
Soyseth 2016[18] REFID: 3704	Aluminum workers	Molten aluminum fumes	Questionnaire	Yes	COPD	Spirometry	1986 - 1995[a]	Norway
Observational Studies – Cross-Sectional								
Liu 2015[26] REFID: 2409	Greenhouse workers	N.R.	Questionnaire	Yes	COPD	Spirometry	2006-2009	China
Koh 2015 [17] REFID 2044	Welders	Welding fumes	Questionnaire	Yes	COPD	Spirometry	2010	Korea

Abbreviations: COPD: Chronic Obstructive Pulmonary Disease; VGDF: Vapours, Gases, Dusts, Fumes; N.R.: Not reported

[a] Includes follow up data

5.2.5.3.2 Findings- Effects of VGDF *and* Exposure on Lung Function Loss/Impairment

This RLR identified two studies published in the last five years that presented data regarding lung function loss/impairment for workers with occupational exposure who smoke compared to exposed/unexposed workers who do not smoke (Bolund 2018, Soyseth 2016).[16,18]

Bolund *et al.,* 2018[16] and Soyseth *et al.,* 2016[18] report decrease lung function values for smokers compared to non-smokers for wood dust and aluminum fume exposure, respectively **(Table 18)**. Bolund *et al.,* 2018 evaluated Danish wood workers over a 6-year time-period. At follow-up, the female woodworkers who smoke experienced a significant decline in both FEV_1 and FVC compared to their non-smoking woodworking counterparts.[16] Over the same time period, only the unexposed female smoking control cohort saw a significant decrease in FVC.[16] Male woodworkers who smoked experienced a significant decline in FEV_1 and FEV_1/FVC compared to their non-smoking woodworking counterparts.[16] During the same time period, no significant decline in lung function was detected for the male control cohort.[16]

Although Soyseth *et al.,* 2016 did not provide direct comparisons between smokers and non-smokers within aluminum potroom workers, aluminum potroom workers who smoke had the greatest annual decline (measured over 10-year follow-up period) in FEV_1 (Δ59.6 (1.4) mL/yr) followed by former smokers (Δ58.2 (3.2) mL/yr), and never smokers (Δ48.2 (2.0) mL/yr).[18] The annual decline in FVC did not follow a similar pattern, with former smokers having the greatest decline (Δ48.2 (4.1) mL/yr), followed by current smokers (Δ39.8 (1.6) mL/yr), and finally never smokers (Δ23.7 (2.6) mL/yr).[18] Over a 10-year period, aluminum potroom workers had a greater annual decline in FEV_1, but not FVC, when compared to controls (data not displayed: potroom vs reference annual decline Δ FEV_1:13.5 (3.5 SE), <0.001; ΔFVC: -8.0 (4.2 SE), 0.060).[18] The authors remark that although the decline in FEV_1 is more pronounced in potroom workers who also smoke compared to never smokers, this was not found to be statistically significant.[18] However, the authors suggest that this finding is clinically meaningful and recommend that aluminum potroom workers not smoke.[18]

Bolund *et al.,* 2018 and Soyseth *et al.,* 2016 demonstrated a change in lung function over time with combined VGDF and smoking exposure compared to non-smoking exposed and unexposed groups for woodworkers and aluminum potroom workers, respectively. The differences in the change in FEV_1 in the Bolund *et al.,* 2018 study would suggest the effect of exposure to both smoking and VGDF is greater than just an additive effect among female woodworkers but not among male woodworkers. The FEV_1 data from the Soyseth *et al.,* 2016 study would also suggest the effect of combined exposures is more than additive for aluminum potroom workers exposed to aluminum fumes, however based on the FVC data, it would appear the occupational exposure reduces the rate of decline in FVC compared to the reference worker, suggesting that other factors are involved in lung impairment. Although the prospective data collection is a clear strength of both studies, whether the data is generalizable to other occupations is unclear.

Table 18: Study Outcomes of Publications Providing Supporting Evidence for Question 5 Towards Additive or Multiplicative Effects of Cigarette Smoking and VGDF Exposure on Lung Function Loss/Impairment

Author, Year	Occupation/ Group	Main Exposure of Interest	Method of Exposure Assessment	Exposure Measure *(mg/m³)*	Smoking Status	Lung Function				
						FEV_1 (L) *Mean (SD) Median [IQR]*	**p-value, or Difference (95%CI)**	**FVC (L)** *Mean (SD) Median [IQR]*	**p-value, or Difference (95% CI)**	**FEV_1/FVC** *Mean (SD), p value* ***% [95% CI]***
Observational Cohort Studies										
Bolund 2018[16] REFID: 503	Females	Wood Dust (Wood Worker) (n=185)	Passive dust monitors	N.R.	Smoker (n=96)	**Δ-0.22 (±0.76)[a,b]**	<0.005	**Δ-0.17 (±0.70)[a,b]**	<0.05	Δ-0.11 (±0.84)[b]
					Non-Smoker (n=87)	Δ0.06 (±0.6)[b]		Δ0.05 (±0.42)[b]		Δ0.04 (±0.86)[b]
		No Exposure (Factory Worker) (n=131)	-	N.R.	Smoker (n=72)	Δ-0.03 (±0.53)[b]	N.S.	**Δ-0.07 (±0.48), <0.05[a,b]**	<0.05	Δ0.02 (±0.66)[b]
					Non-Smoker (n=58)	Δ0.12 (±0.53)[b]		Δ0.09 (±0.41)[b]		Δ0.02 (±0.64)[b]
	Males	Wood Dust (Wood Worker) (n=927)	Passive dust monitors	N.R.	Smoker (n=429)	**Δ-0.06 (±0.53)[a,b]**	0.001	Δ-0.04 (±0.48)[b]	N.S.	**Δ-0.05 (±0.65), <0.005 [a,b]**
					Non-Smoker (n=494)	Δ0.06 (±0.50)[b]		Δ0.02 (±0.44)[b]		Δ0.06 (±0.61)[b]
		No Exposure (Factory Worker) (n=104)	-	N.R.	Smoker (n=55)	Δ-0.15 (±0.60)[b]	N.S.	Δ-0.07 (±0.53)[b]	N.S.	Δ-0.14 (±0.57)[b]
					Non-Smoker (n=49)	Δ0.05 (±0.60)[b]		Δ-0.02 (±0.47)[b]		Δ0.14 (±0.79)[b]

Author, Year	Occupation/ Group	Main Exposure of Interest	Method of Exposure Assessment	Exposure Measure *(mg/m³)*	Smoking Status	Lung Function				
						FEV_1 (L) *Mean (SD) Median [IQR]*	**p-value, or Difference (95%CI)**	**FVC (L)** *Mean (SD) Median [IQR]*	**p-value, or Difference (95% CI)**	**FEV_1/FVC** *Mean (SD), p value* ***% [95% CI]***
Soyseth 2016[18] REFID: 3704	Aluminum (potroom) workers	Aluminum fumes	Questionnaire and Spirometry (annually for 10 years 1986-1995)	-	Never smokers	Δ48.2 (2.0)[c] mL/yr	14.3 (2.1 to 26.4)	Δ23.7 (2.6)[c] mL/yr	-20.2 (-36.7 to -3.6)	-
	Reference workers	No aluminum fumes				Δ34.7 (5.9)[c] mL/yr		Δ43.8 (8.0)[c] mL/yr		-
	Aluminum (potroom) workers	Aluminum fumes		-	Former smokers	Δ58.2 (3.2)[c] mL/yr	6.2 (-9.2 to 21.6)	Δ48.2 (4.1)[c] mL/yr	-34.9 (-58.0 to -11.8)	-
	Reference workers	No aluminum fumes				Δ52.3 (7.2)[c] mL/yr		Δ83.1 (11.1)[c] mL/yr		-
	Aluminum (potroom) workers	Aluminum fumes		-	Current smokers	Δ59.6 (1.4)[c] mL/yr	29.0 (20.8 to 37.2)	Δ39.8 (1.6)[c] mL/yr	7.1 (-5.1 to 19.2)	-
	Reference workers	No aluminum fumes				Δ31.5 (4.0)[c] mL/yr		Δ32.8 (6.0)[c] mL/yr		-

Abbreviations: COPD: Chronic Obstructive Pulmonary Disease; FEV_1: Forced expiratory volume in 1 second; FVC (L): forced vital capacity; IQR: interquartile range; L: Liter; LLN: lower limit of normal; mg/m^3: milligram/cubic meter; N.R.: not reported; N.S.: Not Significant; SD: standard deviation;

Bolded values indicate a significant difference was detected

[a] Significant difference from non-smoker in same exposure category

[b] Mean change in z-scores for lung function during the follow-up period over 6 years

[c] Mean annual decline (standard error)

5.2.5.3.3 Findings- Effects of VGDF *and* Exposure on Likelihood of Developing COPD

Similar to Research Question 4, studies that presented data describing the increased likelihood of developing COPD where the effect of smoking or VGDF exposure could be isolated were also included as lung function loss/impairment can be inferred based on the diagnosis of COPD.

This RLR identified two studies published in the last 5-years that report data regarding the likelihood of developing COP by level or duration of exposure to smoking and occupational VGDF (Liu 2015, and Koh 2015; (**Table 19**)[17,26]

Liu *et al.,* 2015 evaluated the likelihood of various greenhouse workers' developing COPD based on different levels of exposure including smoking by pack years, daily working hours, and working years. Greenhouse workers who reported smoking both 15-29 pack years, and 30 or greater pack years were at a significantly greater odds for developing COPD compared to no pack years (15-29 pack years: OR: 2.39 [95% CI: 1.88-3.03], *p*= <0.0005; ≥30 years OR: 2.17 [95% CI: 1.76-2.66], *p*= <0.0005) than those who reported 1-14 pack years.[26] Although, daily working hours were not found to significantly increase likelihood of COPD development, greenhouse workers who reported 3-5 exposure years were at a significantly higher odds for developing COPD compared to those who reported less than three exposure years (3-5 working years: OR: 1.52 [95% CI 1.08-2.15], *p*= 0.017). Interestingly, greenhouse workers reporting >5 years of exposure were found to be less likely to develop COPD compared to those who reported <3 years exposure (>5 working years: OR: 0.51 [95%CI: 0.40-0.65], *p*= <0.0005).[26] The authors hypothesized that airway enhancement and tolerability may explain this finding but that further investigation was needed.[26]

Lastly, Koh *et al.*, 2015 reported that welders exposed to intermediate and high levels of welding fumes at Korean shipyards, were at a significantly higher risk for developing COPD when compared to welders with low exposure (intermediate OR: 3.91 [95% CI: 1.36-13.33], *p*= <0.05; high OR: 3.77 [95% CI: 1.03-16.21], *p*= <0.05].[17] Smoking by pack years was not found to be significantly associated with the development of COPD. The author's suggest that a healthy worker effect may be the reason for the contrast of a non-significant association of cigarette smoke with the development of COPD against the well-established association reported in the literature.[17]

Liu *et al.,* 2015 demonstrated an increased odds of developing COPD with increased duration of exposure to VGDF and to smoking, however the OR results was lower among those with the highest level of exposure. Koh *et al*.,2015 reported no significant association with cigarette smoking to COPD among Korean welders. Together these studies do not provide a clear trend on any additive or multiplicative effect of smoking and VGDF exposure.

Table 19: Study Outcomes of Publications Providing Supporting Evidence for Question 5 Towards Additive or Multiplicative Effects of Cigarette Smoking and VGDF Exposure Associated with Lung Function Loss/Impairment or the Development of COPD

Study Name Author, Year	Occupation/ Group	Main Exposure of Interest	Method of Exposure Assessment	Exposure Measure (mg/m^3)	Smoking Status	Development of COPD	
						Unadjusted/Crude OR (95% CI), p-value	*Adjusted OR (95% CI), p-value*
Observational Studies – Cross-Sectional							
Liu 2015[26] REFID: 2409	Greenhouse workers	Occupational exposure	Questionnaire and Spirometry	-	0 pack years (ref)	-	Ref.
				-	1-14 pack years	-	0.93 (0.47-1.85), 0.844
				-	15-29 pack years	-	**2.39 (1.88-3.03), <0.0005**
				-	≥30 pack years	-	**2.17 (1.76-2.66), <0.0005**
				<3 working hours (Ref.)	*adjusted*	-	Ref.
				3-5 working hours	*adjusted*	-	0.96 (0.76-1.21, 0.709
				>5 working hours	*adjusted*	-	1.09 (0.83-1.43), 0.548
				<3 working years (Ref.)	*adjusted*	-	Ref.
				3-5 working years	*adjusted*	-	**1.52 (1.08-2.15), 0.017**
				>5 working years	*adjusted*	-	**0.51 (0.40-0.65), <0.0005**
Koh 2015 [17] REFID 2044	Welders	Welding Fumes	Questionnaire and Spirometry	-	<3.5 pack years *(ref)*	-	Ref.
				-	3.5-16.4 pack years	-	0.65 (0.26-1.58)
				-	16.5-64.5 pack years	-	0.90 (0.37-2.16)
				<3.42 *(ref)*	-	-	Ref.
				3.42-11.7	-	-	**3.91 (1.36-13.33), <0.05**
				11.7-22.8	-	-	**3.77 (1.03-16.21), <0.05**
				<2.80 (*ref)*	Never Smoker	-	Ref.

Study Name Author, Year	Occupation/ Group	Main Exposure of Interest	Method of Exposure Assessment	Exposure Measure (mg/m^3)	Smoking Status	Development of COPD	
						Unadjusted/Crude OR (95% CI), p-value	*Adjusted OR (95% CI), p-value*
				2.8-8.51		-	1.39 (0.30-7.07)
				8.52-21.1		-	1.19 (0.22-6.97)

Abbreviations: COPD: Chronic Obstructive Pulmonary Disease; mg/m^3: milligram/cubic meter; SD: standard deviation; OR: odds ratio; FEV_1: Forced expiratory volume in 1 second; N.R. not reported; Ref.: Reference group.

Bolded values indicate a significant difference was detected

[a] Adjusted for age and smoking habit

[b] Adjusted for race (black, white, other), smoking status (current, ex-smoker, never smoker), age (continuous), and sex (male, female)

[c] Cumulative exposure indices identified for each exposure based on the product of task frequency, job duration, work hours per week, and task exposure intensity. See Appendix C for further details on the exposure concentrations used for intensity scoring.

[d] Logistic regression model adjusted for age, gender, race/ethnicity, smoking status (current, past, never), cigarette pack-years, blood relative with COPD, and BMI.

5.2.5.4 Effects of Exposure (Cigarette and/or Occupational VGDF) Cessation on the Course of COPD Lung Function Loss/Impairment

5.2.5.4.1 Study Characteristics

Six studies were published in the last five years, that were identified in this RLR provided data regarding the cessation of either VGDF or cigarette smoking exposure in the occupational setting (Bolund 2018, Soyseth 2016, Sumit 2020, Toren 2017, Mabila 2018, and Liao 2015).[16,18,19,28,31,32] All six studies are observational in nature. Two studies (Bolund 2018 and Soyseth 2016) utilize a prospective longitudinal study design, and the remaining four studies (Sumit 2020, Toren 2017, Mabila 2018, and Liao 2015) are cross-sectional in design.

Studies report on populations from five countries including Denmark, Norway, Bangladesh, Sweden, and the U.S. Two of the six studies evaluate VGDF exposure pooled from variety of occupations (Sumit 2020 and Toren 2017), and four studies examine specific exposures related to wood dust, molten aluminum fumes, mineral dust, and dust (Bolund 2018, Soyseth 2016, Mablia 2018, and Liao 2015).

Study characteristics for the publications in which COPD is the primary focus and report supporting/inferential data towards Question 5 are presented in (**Table 20**). Studies in which COPD is not the primary focus and instead present supporting/inferential data regarding a variety of conditions associated with occupational exposure (e.g. emphysema, chronic bronchitis) related to cessation of exposure are included in the Data Extraction Workbook that accompanies this report.[91,98]

Table 20: Study Characteristics of Publications Providing Supporting Evidence for Question 5 Regarding the Effects of VGDF or Cigarette Smoking Cessation on Lung Function Loss/Impairment or the Association of COPD Development

Study Name Author, Year	Occupation(s)	Main Exposure of Interest	Method of Exposure Measurement	Stratified by Smoking Status *(Yes/No)*	Primary Outcome of Interest	Method of Outcome Assessment	Study Dates (year-year)	Country
Observational Cohort Studies								
Bolund 2018[16] REFID: 503	Woodworking	Wood Dust	Passive dust monitors	Yes	COPD	Spirometry	1998-2004	Denmark
Soyseth 2016[18] REFID: 3704	Aluminum workers	Molten aluminum fumes	Questionnaire	Yes	COPD	Spirometry	1986 - 1995	Norway
Observational Studies – Cross-Sectional								
Sumit 2020[28] REFID: 3787	Motor Vehicle Mechanic Cleaners Drivers Manager Clerk Housekeeper and related worker Administrative job	VGDF	Questionnaire	Yes	COPD	Spirometry	2019-2020	Bangladesh
Toren 2017[32] REFID: 3961	The Swedish CArdioPulmonary BioImage Study (SCAPIS)	VGDF	Questionnaire	No	COPD	Spirometry	N.R.	Sweden
Mabila 2018[31] REFID: 2492	Miners	Mineral dust	Questionnaire	Yes	COPD	Self-reported	2006 - 2015	United States
Liao 2015[19] REFID: 2350	More likely dust exposure Less likely dust exposure	Dust	Job Exposure Matrices	Yes	COPD	Spirometry	N.R.	United States

Abbreviations: COPD: Chronic Obstructive Pulmonary Disease; N.R. not reported; SCAPIS: The Swedish CArdioPulmonary BioImage Study; VGDF: Vapours, Gases, Dusts, Fumes.

5.2.5.4.2 Findings- Effects of Cessation of Occupational VGDF or Cigarette Exposure on Lung Function Loss/Impairment

This RLR identified three studies published in the last 5-years that report inferential data regarding the effects of cessation of occupational exposure or smoking on lung function loss/impairment within the occupational setting (Bolund 2018, Soyseth 2016, and Liao 2015).[16,18,19]

Bolund *et al.,* 2018 was one of the few studies captured in this RLR that evaluated the cessation of occupational exposure on the change in lung function over the 6-year follow-up period comparing current to ex-wood workers. A regression model was utilized to investigate whether multiple variables including being a current or ex-wood worker could significantly predict a change in FEV1. Although the model explained only 10% (R^2= 0.10) of the variance, being a current wood worker was found to be a significant predictor of declining FEV1 over the 6-year time period. The model showed that, being a current worker was responsible for an estimated 0.37(p=0.003) and 0.11(p=0.003) decrease in lung function z-score for FEV1, among females and males, respectively.(**Table 21**)

Both Soyseth *et al.,* 2016 and Liao *et al.,* 2015 assessed lung function within occupational exposure by smoking status, including former smokers (**Table 22**). Both current and former smokers had experienced a significant main effect of decreased FEV1, but not FVC, compared to never smokers (current vs. never: -43.6 [SE:9.1] mL, *p*=<0.001; former vs never: -41.3 [SE:12.3] mL, *p*=.001).[18] Although, there was a significant main effect of decreased FEV1 for former smokers vs. never smokers, significant annual decline in FEV1 was not detected.[18]

Liao *et al.,* 2015 compared current vs. never smokers and former vs. never smokers within various occupations that experience dust exposure. Both current and former smokers who have occupational dust exposure, had a significant decrease in FEV1 and FEV1/FVC compared to never smokers, with a greater magnitude of decrease observed in current smokers (FEV1: current vs. never: -135.9 [SE: 22.4], *p*=<0.0001; former vs. never: -92.8 [SE: 19.6], *p*= <0.0001)(FEV1/FVC: current vs. never: -0.0175 [SE: 0.0036], *p*=<0.0001; former vs. never: -0.0125 [SE: 0.0031], *p*= <0.0001) (**Table 22**).

Although none of these three studies directly evaluated the effects of cessation of either occupational VGDF or cigarette smoking cessation on lung function impairment, inferential data suggest that current exposure to occupational wood dust as a current woodworker is a significant predictor of a change in lung function compared to ex-wood workers. Similarly, both current and former smokers have a significantly greater decline in lung function compared to non-smokers. Although not directly compared, smokers appear to have an overall greater mean decline in lung function when compared to former smokers. In summation, inferentially, these data appear to support continued exposure is associated with lung function loss/impairment while cessation of smoking slows lung function decline. However, whether the cessation of VGDF exposure (specifically wood dust) or smoking slows, stops, or reverses lung function loss/impairment requires further research.

Table 21: Supporting Evidence for Question 5: Cessation of Workplace Exposure on the Change in Lung Function (ΔzFEV) for Danish Wood Workers over 6-year Follow-up 2018[16]

Author, Year	Group	Exposure Measure (mg/m^3)	*Female*			*Male*		
			Smoking Exposure Measure *(pack-years)*	**Multivariable linear regression $\Delta zFEV_1$** *E (95% CI)*	**Significance** *(P value)*	**Smoking Exposure Measure** *(pack-years)*	**Multivariable linear regression $\Delta zFEV_1$** *E (95% CI)*	**Significance** *(P value)*
Bolund 2018[16] REFID: 503	**Ex-worker**	-	*adjusted*	0 (ref.)	-	*adjusted*	0 (Ref.)	-
	Current worker	-	*adjusted*	**-0.37**	0.003	*adjusted*	**-0.11**	0.003

Abbreviations: CI: Confidence Interval; COPD: Chronic Obstructive Pulmonary Disease; $\Delta zFEV_1$: Change in z score Forced expiratory volume in 1 second; E: E: Estimate; Ref.: Reference group.

Bolded values indicate a significant difference was detected

Table 22: Supporting Evidence for Question 5: Effects Cigarette Smoking Cessation on Lung Function Loss/Impairment

Author, Year	Occupation/ Group	Main Exposure of Interest	Method of Exposure Assessment	Exposure Measure *(mg/m³)*	Smoking Status	Lung Function				
						FEV_1 (L) *Mean (SD/SE)*	**p-value, or Difference (95% CI)**	**FVC (L)** *Mean (SD)*	**p-value, or Difference (95% CI)**	**FEV_1/FVC** *Mean (SD/SE), p value*
Soyseth 2016[18] REFID: 3704	Aluminum (potroom) workers	Aluminum fumes	Questionnaire and Spirometry (annually for 10 years 1986-1995)	Annual Decline	Current vs. never smoking	**Δ 10.6 (2.2 SE) mL/yr**	<0.001	**Δ 5.8 (2.6) mL/yr**	0.023	-
					Former vs. never smoking	Δ 4.0 (3.2 SE) mL/yr	0.202	Δ -2.9 (3.8 SE) mL/yr	0.446	-
				Main Effect	Current vs. never smoking	**-43.6 (9.1 SE) mL**	<0.001	-11.3 (10.0 SE) mL	0.259	-
					Former vs. never smoking	**-41.3 (12.3 SE) mL**	<0.001	-25.7 (14.2 SE) mL	0.070	-
Liao 2015[19] REFID: 2350	Framingham Heart Study Population	Occupational Dust Exposure	Job Exposure Matrices		Current vs. never smoker	**-135.9 (22.4 SE) mL**	<0.0001	-	-	**-0.0175 (0.0036 SE), <0.0001**
					Former vs. never smoker	**-92.8 (19.6 SE) mL**	<0.0001	-	-	**-0.0125 (0.0031 SE), <0.0001**

Abbreviations: Δ: Change/year; CI: Confidence Interval; FEV_1: Forced expiratory volume in 1 second; FVC: Forced Vital Capacity; mg/m^3: milligram/cubic meter; mL/yr: milliliter per year; SD: Standard deviation; SE: Standard Error.

Bolded values indicate a significant difference was detected

5.2.5.4.3 Findings- Effects of Cigarette Smoking Exposure/Cessation on the Likelihood of Developing COPD or Lung Function Loss/Impairment

This RLR identified three studies published in the last 5-years that evaluated the effect of smoking status on the likelihood of developing COPD or lung function loss/impairment within occupational exposure groups (Sumit 2020, Toren 2017, and Mabila 2018; **Table 23**).[28,31,32]

As previously discussed, Sumit *et al.,* 2020 evaluated the likelihood of developing COPD among exposed and unexposed workers by smoking status. When compared to unexposed workers, exposed smokers, former smokers and non-smokers had a significantly greater odds of developing COPD (OR: exposed smoker: 7.4, *p*= <0.05; exposed former smoker: 7.2, *p*= <0.05; exposed non-smoker: 12.7, *p*= <0.05), noting the interesting observation that exposed non-smokers had the highest odds ratio among these comparisons.

Interestingly, Mabila *et al.,* 2018 reported that former smokers within the general U.S. mining population were at a significantly higher odds of developing COPD compared to non-smokers (OR: 2.99 [95% CI: 1.21, 7.43], *p*= <0.05) than current smokers (OR: 1.76 [95% CI: 0.73, 4.24, *p*= n.s).[31] The authors did not discuss as to why former smokers had a higher likelihood of developing COPD than current smokers.

Lastly, Toren *et al.,* 2017 evaluated the likelihood of lung function loss/impairment and the development of COPD by smoking status within individuals 50-64 years of age from the Swedish CArdioPulmonoary BioImage Study (SCAPIS) who reported having occupational exposure. Both current and former smoking was associated with all three measures of lung function loss/impairment evaluated (FEV1/FVC <0.7 pre-bronchodilation, FEV1/FCV <0.7 post-bronchodilation, and FEV1/FVC post-bronchodilation <LLN), with higher odds reported for current smoking (**Table 23**).[32] Though both current and former smoking was associated with increased odds of developing COPD, the reported odds for current smokers were greater than former smokers, although significance was not detected (OR: current smoker: 4.0 [95% CI: 1.5-10.4]; former smoker: 1.4 [95% CI: 0.6-3.5]).

The results from these three studies show differing inferential results regarding the impact of smoking cessation on the odds of developing COPD. The odds of developing COPD were reportedly higher for current smokers than for former smokers in two out of three studies with the exception of Mabila *et al.,* 2018 in which former smokers had higher odds of developing COPD than current smokers in the U.S. general mining population. However, Sumit *et al.,* 2020 found the odds of developing COPD among exposed workers was higher among non-smokers than former or current smoker, when compared to unexposed non-smokers. Both Toren *et al.,* 2017 and Sumit *et al.,* 2020 evaluated population with various occupational exposures suggesting that results may be more generalizable, however Toren *et al.,* 2017 is limited to individuals 50-64 years of age. Further investigation regarding whether cessation of cigarette smoking or VGDF exposure slows, stops, or reverses COPD or lung function loss/impairment is warranted.

Table 23: Supporting Evidence for Question 5: Association of Cigarette Smoking Cessation on Lung Function Loss/Impairment and the Development of COPD

Study Name Author, Year	Occupation/ Group	Main Exposure of Interest	Method of Exposure Assessment	Exposure Measure (mg/m^3)	Smoking Status	Lung Function *Adjusted OR (95% CI), p-value*	Development of COPD	
							Unadjusted/Crude OR (95% CI), p-value	*Adjusted OR (95% CI), p-value*
Sumit 2020[28] REFID: 3787	Exposed smoker (n=106)	Various occupational exposures	ALOHA-JEM	-	Current smoker	-	**7.4, <0.05**	-
	Unexposed smoker (n=74)	No occupational exposure		-		-	(Ref.)	-
	Exposed former smoker (n=31)	Various occupational exposures		-	Former smoker	-	**7.2, <0.05**	-
	Unexposed former smoker (n=35)	No occupational exposure		-		-	(Ref.)	-
	Exposed non-smoker (n=52)	Various occupational exposures		-	Non-smoker	-	**12.7, <0.05**	-
	Unexposed non-smoker (n=75)	No occupational exposure		-		-	(Ref.)	-
Toren 2017[32] REFID: 3961	The Swedish CArdioPulmonary BioImage Study (SCAPIS)	Occupational VGDF	Questionnaire and Spirometry	-	Current smoking	*FEV_1/FVC<70% Pre BD:* 2.1 (1.3-3.6) *FEV_1/FVC<70% Post BD:* 3.6 (1.8-7.2) *FEV_1/FVC<LLN Post BD:* 3.8 (1.9-7.6)	-	4.0 (1.5-10.4)
				-	Former smoking	*FEV_1/FVC<70% Pre BD:* 1.3 (0.8-2.0) *FEV_1/FVC<70% Post BD:* 1.3 (0.7-2.4) *FEV_1/FVC<LLN Post BD:* 1.4 (0.7-2.7)	-	1.4 (0.6-3.5)
Mabila 2018[31] REFID: 2492	Miners	Mineral dust	Questionnaire		Never smoker	-	Ref.	-
				-	Current smoker	-	1.76 (0.73, 2.26)	-

Study Name Author, Year	Occupation/ Group	Main Exposure of Interest	Method of Exposure Assessment	Exposure Measure (mg/m^3)	Smoking Status	Lung Function *Adjusted OR (95% CI), p-value*	Development of COPD	
							Unadjusted/Crude OR (95% CI), p-value	*Adjusted OR (95% CI), p-value*
				-	Former smoker	-	**2.99 (1.21, 7.43), <0.05**	-

Abbreviations: ALOHA-JEM: community based Job Exposure Matrix; CI: Confidence Interval; FEV_1: Forced expiratory volume in 1 second; FVC: Forced Vital Capacity; LLN: Lower Limit of Normal; mg/m^3: milligram/cubic meter; mL/yr: milliliter per year; OR: Odds Ratio; Pre-BD: Pre-bronchodilation; Post-BD: Post-bronchodilation; Ref.: Reference group; SD: Standard deviation; SE: Standard Error.

Bolded values indicate a significant difference was detected

5.2.5.5 Limitations

While inferential data was identified in this RLR demonstrating an additive and multiplicative effect of smoking and occupational-VGDF exposure, there was a substantial amount of heterogeneity (e.g., occupation, exposure, race, study design, results) associated with the studies identified for Research Question 5, restricting a comprehensive synthesis of the evidence. It is important to consider that different occupational exposures may have variable effects on lung function; therefore, results of any one study on the additive or multiplicative effects of cigarette smoking and occupational VGDF exposure may not be generalizable to other occupational populations. While three studies actively measured workplace exposures, the remaining studies relied on self-reported retrospective recall of exposure, limiting the reliability of the exposure measurement.

Bolund *et al.,* 2018 and Soyseth *et al.,* 2016 are the only studies identified in this RLR that reported lung function results stratified by both smoking and VGDF exposure status, allowing for an assessment of the effect of both exposures.[16,18] However, both studies demonstrate inconsistent results, with the Bolund *et al.,* 2018 study demonstrating a potential multiplicative effect among the Danish female woodworkers only, and the Soyseth *et al.,* 2016 study demonstrating conflicting evidence based on the measure of lung function considered within a cohort of Norwegian aluminum potroom workers. These results highlight the complex interaction of numerous risk factors that result in lung function impairment. Additionally, these results may not be generalizable to other occupations or populations.

For odds ratio data providing inferential evidence of the additive or multiplicative effect of exposures, Liu *et al.,* 2015 and Koh *et al.,* were the only studies identified that presented odds ratio data for both exposure types (pack years of smoking within an exposure group), within Chinese greenhouse workers and Korean shipyard welders, respectively. However, any comparison between magnitudes of the different groups (e.g. smokers vs. non-smokers for Koh *et al.* 2015) need to be approached with caution as different reference cases were used for each exposure type.[17,26]

For the cessation of exposure data, Bolund *et al.,* 2018 was the only study that investigated the impact of cessation of occupational-VGDF exposure, the remaining studies present data regarding cessation of smoking.[16] The Bolund *et al.,* 2018 study is a woodworking population; therefore, these results may not be generalizable to other occupations or non wood-dust exposures.

Lastly, the Henneberger *et al.,* 2020 study was identified outside of this RLR as having relevant data to addressing Research Question 5. This highlights the limitations of a RLR as this methodology is not as comprehensive as a SLR.

5.2.5.6 Evidence Gaps

The evidence identified from Research Question 5, together with the supplemental information, provide strong evidence for an additive or multiplicative effect of smoking with occupational exposure. Quantify the effect remains challenging given the heterogeneity of available evidence published within the last five years. Additionally, limited evidence was identified addressing the potential impact of cessation of occupational exposures. This is a key evidence gap where future research is required.

5.2.5.7 Conclusion

Based on the evidence identified in this RLR, evidence would suggest that there may be an additive or multiplicative effect of smoking and workplace VGDF exposure on lung function/loss and odds of developing COPD. However, none of the studies captured in the last five years directly evaluated either an additive or multiplicative effect of exposure on lung function loss/impairment; therefore, only inferences can be made. The magnitude of the effect did vary across studies and when considering other factors (e.g. gender, exposure type, cumulative exposure) demonstrating the complex interaction of smoking and occupational exposure with other mitigating risk factors.

None of the studies captured in this RLR specifically evaluated whether exposure cessation slows, stops or reverses COPD or lung function loss/impairment. Studies that included either former smokers or former workers provide data that inferentially suggest that the removal of exposure results in reduce lung function impairment or lower odds of developing COPD, however, some of these studies had conflicting data, namely the Mabila *et al.* 2018 and Sumit *et al.* 2020 studies.[28,31] Only one study was identified that provided relevant data regarding cessation of exposure to an occupational-VGDF,[16] demonstrating a gap in the current literature. Further research is warranted to better understand the impact of cessation of exposures, particularly occupational VGDF exposures, on lung function impairment/loss.

5.2.5.8 Clinical Comment

There may be at least an additive effect of smoking and workplace VGDF on lung function loss. It is not possible clinically to distinguish the magnitude of this effect.

From a clinical perspective, cessation of occupational VGDF exposure is anticipated to slow COPD by analogy with smoking cessation, but reversal of COPD would not occur since lung function has been lost. However, clinical symptoms such as cough, exacerbations and dyspnea may improve significantly with removal from exposure (VGDF or smoking).

5.2.6 Research Question 6

Research Question 6: Is COPD a disease or injuring process that, once triggered, follows its own course for progression of disease, similar to cancer? If yes, does this occur regardless of cause and/or continued (or discontinued) exposure?

5.2.6.1 Results

The focus for Research Question 6 was to identify data related to the progression of COPD following diagnosis. There were no studies identified in the last five years as a part of this RLR that directly addressed Research Question 6. Additionally, there were no studies presenting inferential data to provide insight into the progression of COPD following diagnosis. Supplemental information has been included to provide contextual reference as to what is currently understood regarding the course of COPD disease progression.

5.2.6.1.1 Supplemental Information

While some populations with COPD have been followed longitudinally for up to 20 years, no studies have monitored the progression of the disease throughout its entire course.[8] As a result, the current understanding of the disease course and risk factors for COPD is incomplete.[8] As previously addressed in Research Question 5, the pathological inflammatory and structural changes that take place in the lungs of individuals with COPD continue and increase in some aspects when smoking is stopped, suggesting that the pathophysiology of COPD remains with discontinued exposure.[8,99] It is unknown at this time as to why inflammation persists following cessation. However, it has been well established since 1977 that cessation of smoking can reduce the rate of lung function decline and improve survival among COPD patients.[93] More recent studies have also demonstrated that sustained cessation of cigarette smoking results in a substantial decrease in the rate of lung function loss/impairment over time when compared to individuals who continue to smoke (not specific to a COPD population.[96] However, it is important to note that former smokers remain at a higher risk for developing COPD compared to never smokers (please see Research Question 5). Slowing the rate of decline in lung function suggests that the removal of exposure to cigarette smoking can alter the course of disease progression.[95,96] Evidence on the reduction of occupational exposure and the effects on COPD progression are lacking.

Effective interventions such as pulmonary rehabilitation, have also been shown to improve shortness of breath, health status, and exercise tolerance in patients with COPD.[100] Often individuals with COPD have been reported to decrease engagement in physical activity which predisposes them to a reduced quality of life, as well as increased rates of hospitalization and mortality.[101-104]

5.2.6.1.2 Supporting Evidence

There were no studies identified that followed the disease progression of COPD patients. While numerous studies reported factors influencing the likelihood of developing COPD, none of these studies reported further information pertaining to progression of COPD. Similarly, the lung function impairment data from the studies conducted in the past five years did not present data specific to a COPD population, or data that showed change in lung function impairment from diagnosis of COPD or based on stage of COPD.

5.2.6.2 Limitations

The key limitation to Research Question 6 is that there were no appropriate studies identified from the past five years as part of this RLR that investigated COPD following diagnosis or reported inferential data that could provide insight into the progression of disease. Based on the paucity of data from Question 3, it is apparent that limited research has been conducted in the past five years to further understand the pathogenesis and resulting pathology of COPD. This evidence is required to understand first, if COPD is

a disease or injury process, and then to inform on the course of progression. Additionally, clinical tools need to be sensitive enough to be able to identify the initiation of disease and/or injury and to reliably measure progression overtime. These tools need to be reliably utilized in future studies to help differentiate the impact of various risk-factors. The availability and reliability of spirometry testing can be a key limitation to this type of research.[8,79]

The key limitation to the second part of Question 6 is the inability to clinically distinguish the cause of COPD (see Research Question 2 for further information).

5.2.6.3 Evidence Gaps

There is a large gap in the literature from the past 5 years, and presumably historically based on the lack of data within the GOLD 2021 report, evaluating the pathophysiology of COPD to understand if it is a disease or injury process, and the progressive nature of COPD. Additionally, the impact of continued or discontinued exposure on COPD disease progression is not fully known at this time, particularly in regard to occupational VGDF exposure.

Future investigations will need to utilize various types of study designs from the cellular and molecular level through epidemiological studies with large sample sizes, to properly capture and isolate the substantial complexities associated with COPD progression.

5.2.6.4 Conclusion

This RLR did not identify any studies directly or indirectly evaluated whether COPD is a disease or injuring process that once triggered follows its own course for progression of disease (similar to cancer) or the progression of disease with discontinued exposure. Current studies are focused on understanding risk factors associated with the development of COPD rather than the progression of the disease following diagnosis. Different study designs and clinical assessments from what is currently observed in the literature over the last five years are required to provide further evidence addressing this research question.

5.2.6.5 Clinical Comment

Occupational exposure of individuals and the effect that occurs is also dependent on disease exacerbations. It is not possible to determine when the disease process is triggered as this will occur sometime before the condition becomes clinically symptomatic or detectable. Occupational surveillance of at risk working populations might allow early detection however lung function loss is not reversible.

The clinical course of COPD is not predictable the way it is for cancer. As far as it is known treatment and modification of contributing factors can change the course however there can be considerable individual variability. Respiratory infections with exacerbations can significantly contribute to disease progression. Other comorbidities such as cardiac disease osteoporosis etc. may be likely to contribute to the decline in overall health (frailty) and therefore morbidity and mortality.

6 Clinical Expert Commentary

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The review is a rapid literature review covering a 5-year period (2015-2020) examining the association of COPD, exposure to tobacco smoke, and workplace exposures to VGDF. The type and quantity of evidence found that could answer the questions posed was limited. This is not considered surprising as the clinicians were not aware of key studies done in the past 5 years that are omitted from the evidence captured. In the preceding 10 years there was more published work of relevance however identifying and summarizing this work would be a substantial undertaking.

Although the GOLD report is updated bi-annually the review group does not have a specific focus on occupational COPD. In particular, it is noted that the GOLD spirometric definition (fixed post-bronchodilator ratio of FEV_1/FVC below 0.7) is not that typically used for occupational purposes where the American Thoracic Society recommendation is for the 5th percentile lower limit of normal (LLN) of the ratio of FEV_1 to VC.[40] "The LLN approximates the one-sided 95% confidence limit for the expected value and identifies approximately 5% of healthy never-smokers as abnormal".[81]

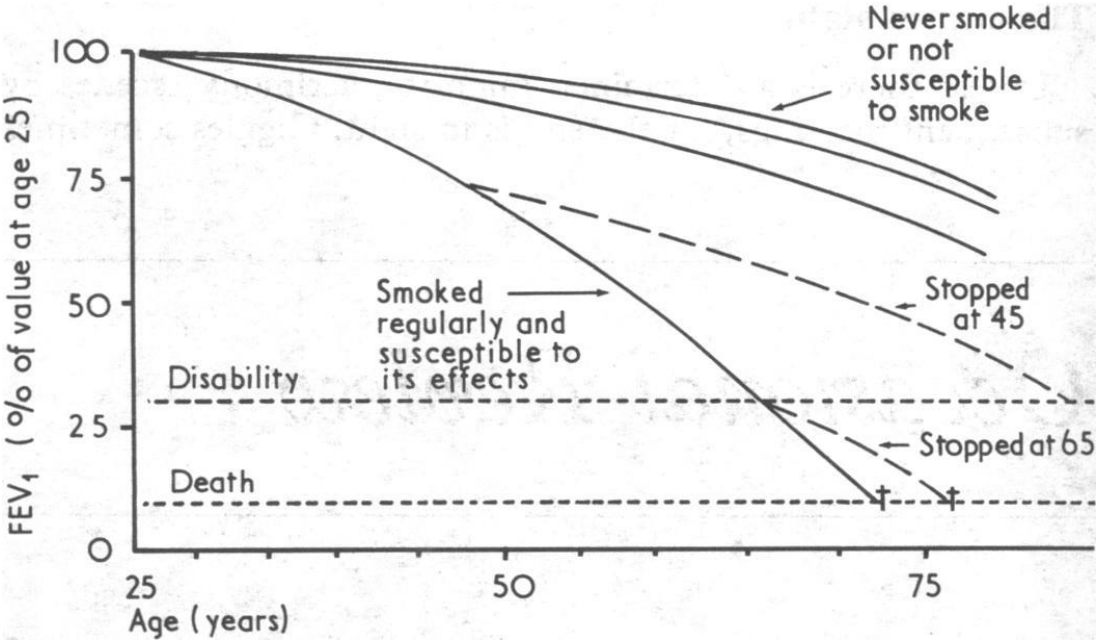
Cessation of smoking is known to slow the accelerated rate of lung function decline and improves survival compared with continued smoking even in severe chronic obstructive pulmonary disease as was demonstrated by the classic work of Fletcher and Peto.[93] A cohort of 792 working males was followed with 6 monthly spirometry for eight years. This allowed the data to be presented as the plotted averages of FEV_1 for the cohort grouped by smoking status (**Figure 4**). In this paper the authors also comment, "Unfortunately, FEV_1 slopes of individuals could not be measured accurately enough to be useful but averages of the FEV_1 slopes of groups of a dozen or more men were accurate enough for our analysis of causal factors." More recently Hnidzo *et al.,* 2007 identified that the measurement errors that occur during repeated spirometry can substantially affect the observed within person variation of longitudinal spirometry results and therefore calculation of the rate of FEV_1 decline.[81] These concerns apply even with adherence to American Thoracic Society and European Thoracic society guidelines for spirometry. There is also the consideration of the frequency of longitudinal spirometry which in many workplace programs is annually or less frequent. Such data may have limitations for individual applicability but still be meaningful on a group monitoring basis for health surveillance purposes. This paper reports on the use of paired estimates of lung function for within person variation of lung function to calculate the limit of longitudinal decline (LLD) being the approximate one-sided 95% confidence limit for longitudinal decline. The American Thoracic Society recommended criterion of 15% annual decline in FEV_1 is considered excessive by these authors, except for workers who have airways disease associated with bronchial hyper-reactivity, and detection of a 10% or less decline is advised as achievable for good quality workplace monitoring programs.[81]

In 2014 the American Thoracic Society produced a report on "Spirometry in the Occupational Setting" that discussed the selection of appropriate criteria for assessing excessive lung function decline.[105] In this report it is noted that the typical rate of decline in FEV_1 in nonsmokers is 29 ml/yr and that a rate of decline of about 50–90ml/yr, has been associated with increased morbidity and mortality from chronic obstructive pulmonary disease. Three methods of detection of excessive decline in FEV_1 are discussed: 1. A 15% decline from baseline FEV_1 (plus expected age-related loss) on either a percent predicted method or a volume method; 2. limit of longitudinal decline (LLD); 3. Linear regression. It is noted that the methods are most effective over relatively long periods of time ≥ 5 years. In addition to recommending

these methods it is stated, “Spirometry measurements should be evaluated relative to workers’ baseline or prior tests, in addition to comparing to population normal ranges. This is particularly important when baseline measurements exceed predicted values”.[105]

The challenges of identifying spirometry data of sufficient quality from existing occupational cohorts or the expense of conducting research that is not otherwise occupationally required are the main reasons for the paucity of studies in this area. In the case of diagnosis of occupational asthma there are tests that can be performed such as serial peak flow recording, specific IgE blood tests to suspected workplace allergens that assist in the attribution to work. By contrast in the clinical assessment of COPD there are no similar tests or biomarkers as identified by this literature review. Having established a diagnosis of COPD the clinician is reliant on the exposure history to infer likely causation, a decision which is easier in the smaller number of COPD patients who have never smoked.

Figure 4: From Fletcher and Peto (1977) showing the risk of lung function decline with continued smoking and with cessation.[93]



A community-based study by Darby *et al.,* 2012 among the residents of Sheffield, an industrialized area in the UK used three methods of exposure assessment: self-reported ever exposure to VGDF, then selection from a specific exposure checklist and separately the use of a job exposure matrix (JEM). [71] Based on the 231 people with COPD, emphysema or chronic bronchitis, with or without concomitant asthma, there was an OR 32.04 (CI95, 15.92-64.47) with both high smoking and exposure to VGDF, and OR 5.63 (2.60-12.20) for never smoking and exposure to VGDF.[71] The population attributable risk fraction (PAR%) for occupational VGDF exposure was estimated as 20%; 95% CI -7.2 to 40.3%. The key findings are summarized in (**Table 24**). In this study the ORs for occupational VGDF exposure alone and low smoking are similar, whereas the combined effect is four times that of low smoking alone.[71]

Table 24: Chronic obstructive pulmonary disease among residents of a historically industrialized area: effect of smoking and occupational VGDF exposure. Adapted from Darby *et al.*, 2012.

Cigarettes/VGDF Exposure	Subjects (n= 1183)	Risk of COPD	Excess risk	Adjusted OR *(95% CI)*
Never/No	530	0.02	0	1.0 (Ref.)
Never /Yes	302	0.08	0.06	5.63 (2.60-12.20)
Low[a]/No	248	0.07	0.05	3.96 (1.77-8.89)
Low[a]/Yes	279	0.18	0.16	15.68 (7.62-32.28)
High[b]/No	186	0.15	0.13	10.44 (4.91-22.20)
High[b]/Yes	338	0.31	0.29	32.04 (15.92-64.47)

Abbreviations: Ref.: Reference group; VGDF= Vapours, Gas, Dust or Fumes by Job Exposure Matrix.
[a] Low= 20 pack-years or less
[b] High= >20 pack-years

Another study by Blanc, Iribarren *et al.,* 2009 used a nested case referent design within the Function, Living, Outcomes and Work (FLOW) prospective study of COPD.[72] VGDF exposure was both self-reported, and based on a job exposure matrix (JEM) for probability of exposure related to occupation. They found that self-reported workplace / occupational exposure to VGDF was associated with an increased risk of developing COPD (OR 2.11; 95% CI 1.59-2.82) and a population attributable fraction (PAF) of 31%. When attribution of exposure by JEM was used the risk of COPD was similar (OR 2.27; 95%CI 1.46-3.52) although the PAF was lower (13%; 95% CI 8-18%). The latter finding was due to the lower exposure prevalence when applying the JEM. When the analysis was restricted to participants with COPD GOLD II criteria or higher the results for VGDF exposure were essentially the same OR 2.13 (1.55 to 2.93) PAF 31% (21 to 41%), and using JEM little different OR 2.33 (1.45 to 3.72), PAF 14% (8 to 20%). The authors emphasized that concomitant action on smoking cessation at a population level and reduction of workplace exposures is necessary to reduce the global burden of COPD (**Table 25**).[72]

Table 25: Occupational exposures and the risk of Chronic Obstructive Pulmonary Disease. Adapted from Blanc, Iribarren *et al.,* 2009.[72]

Exposure	Unadjusted OR *(95% CI)*	Adjusted OR *(95% CI)*	PAF % *(95% CI)*
VGDF exposure	2.18 (1.69 – 2.83)	2.11 (1.59 – 2.82)	31 (22 – 39)
JEM exposure probability			
Low (referent)	1.0 (Ref.)	1.0 (Ref.)	Ref.
Intermediate	1.64(1.00 – 2.67)	1.27 (0.74 – 2.19)	2 (-2 – 6)
High	2.66 (1.80 – 3.94)	2.27 (1.46 – 3.52)	13 (8 – 18)
Cigarette Smoking			
Never	1.0 (Ref.)	1.0 (Ref.)	Ref.
Current Smoker	31 (17 – 58)	31 (17 – 58)	32 (30 – 33)
Past Smoker	4.67(3.50 – 6.23)	4.52 (3.35 – 6.09)	42 (37 – 46)

Abbreviations: JEM: Job Exposure Matrix; OR: Odds Ratio; PAF: Population Attributable Fraction; Ref.: Reference group; VGDF= Vapours, Gas, Dust or Fumes by Job Exposure Matrix.

A multi-centre ecological analysis of occupational contribution to the COPD from 45 sites in three cohort studies, the Burden of Obstructive Lung Disease (BOLD) study, and one each from Latin America, and Europe confirmed a worldwide association between dusty trades and COPD among both males and females. The data used for the analysis included the participants with COPD GOLD stage II and above a 0.8% increase in COPD prevalence was found for each 10% increase in exposure prevalence. The observed mean population COPD prevalence was 3.4% and the model predicted a 20% reduction in disease (COPD) burden by achieving a 5.4% reduction in overall smoking rates or a reduction of 8.8% reduction in the prevalence of occupational exposures (**Table 26**).[106] Since two of the cohort studies only enquired about “dusty work” exposures to vapours, gases and fumes may be underestimated.

Table 26: Prevalence of occupational exposure and Cigarette smoking as predictors of COPD prevalence: Multiple linear regression analysis. Adapted from Blanc, Menezes *et al.,* 2009.[106]

Independent variable	Increase in COPD prevalence per 10% increase in exposure	p-value
All observations (n=90)		
Dusty/ dirty jobs	**0.8 (0.3 – 1.3)**	0.003
Cigarette ever-smokers	**1.3 (0.7 – 1.8)**	<0.0001
Males only (n=45)		
Dusty/ dirty jobs	**0.8 (0.3 – 1.3)**	0.004
Cigarette ever-smokers	**0.9 (0.1 – 1.8)**	0.04
Females only (n=45)		
Dusty/ dirty jobs	**1.0 (0.1 – 11.9)**	0.03
Cigarette ever-smokers	**1.1 (0.4 – 1.8)**	0.005

Abbreviations: COPD: Chronic Obstructive Pulmonary Disease.
Bolded values indicate a significant difference was detected

Further work by Blanc, Eisner *et al.,* 2009 reported on a US case referent study from California, again using VGDF exposure self-reported and assigned by JEM.[107] Based on a definition of COPD that included a physician diagnosis of chronic bronchitis OR 2.5 (CI95, 1.9 to 3.4) with a PAF 32% (21 to 41%) for self-reported VGDF. **Table 27** shows the effect of cigarette smoking and VGDF exposure which is this case is less than an additive effect. However, the study authors do note limitations relating to the referents being combined with light smokers, the small numbers affecting stratification by sex and age, geographical area, the referents with a younger age of and an earlier interview time amongst some others.[107]

Table 27. Combined Cigarette Smoking and Occupational Risk. Adapted from Blanc, Eisner *et al.*, 2009.[107]

Cigarette Smoking and Occupational Exposure Categories [case number]	OR (95% CI)
Model I: Cases = COPD by Spirometry ≥ GOLD I or Current Chronic Bronchitis	Risk of COPD or Bronchitis (Cases=98; Referents=1652)
Minimal Smoking (Never up to 10 Pack Years), No Exposure [n=18 cases]	1.0 (Ref.)
Minimal Smoking; VGDF Exposure [n=20 cases]	3.2 (1.6 to 6.2)
Smoker (> 10 Pack years); No VGDF Exposure [n=32 cases]	3.3 (1.8 to 5.9)
Smoker and VGDF Exposure [n=28 cases]	5.6 (2.9 to 5.6)

Abbreviations: CI: Confidence Interval; COPD: Chronic Obstructive Pulmonary Disease; GOLD: Global Initiative for Chronic Obstructive Pulmonary Lung Disease; OR: Odds Ratio; Ref.: Reference Group; VGDF: Vapour, Gas, Dust, Fume.

Illustrative Case Example

A 55 year old man, worked for 23 years with Toronto Transit Commission as a welder in tunnels, he was exposed to dusts, as well as welding and diesel fumes (included stainless steel welding and manganese), mostly arc welding.

He had progressive shortness of breath on exertion for 2 years, with difficulty climbing 10 steps, he had a cough and clear sputum at work. He had smoked 2-3 cigarettes per day for 20 years (3 pack years), he quit smoking 10 years ago.

Pulmonary Function Tests: FEV_1 47%, FEV_1/VC 40%, FEV_1 ↑ 14% (>200ml) post-bronchodilator. He had moderate hyperinflation, severe gas trapping, normal gas transfer (DLCO).

Allergy skin prick tests all negative, including Nickel, and Chromium salts.

Serial Peak Expiratory Flow Recordings 320-360 L/min, the higher range was after bronchodilators taken as needed.

CT scan of the chest showed mosaic attenuation, bronchial wall thickening, mucus plugs – no Asbestos-related changes.

Diagnosis: Occupational COPD with asthmatic component and likely component of bronchiolitis

Occupational outcome: Changed work to outdoor delivery for TTC

Treated with a combination Long acting beta agonist and inhaled steroid + tiotropium + Short acting beta agonist.

Follow-up Pulmonary Function Tests: FEV_1 58%, FEV_1/FVC 46%, no further bronchodilator response.

Symptomatically he was improved with outdoor work. The WSIB claim was accepted for occupational COPD.

Clinical approach

There are no specific tests for occupational COPD. Epidemiologic studies (as summarized in the Background Section of this document) have shown that occupational exposures to VGDF contribute to approximately 13-15% of all COPD. Risk of COPD increases with smoking alone, VGDF exposure alone and is disproportionately higher with the combination of smoking and VGDF (Blanc *et al.,* Thorax and JOEM 2009, Darby *et al.,* Thorax 2012).[71,72]

The diagnosis of COPD is made on the basis of a clinical history, physical examination, pulmonary function tests and chest imaging. Considerations in the differential diagnosis include asthma, bronchiectasis and bronchiolitis (that may account for the clinical findings or may be co-existent diagnoses as in the case example).

Once a diagnosis of COPD is reached, consideration of an occupational component is based on the exposure history and smoking history, as well as consideration of other possible contributing factors (previous significant tuberculosis, biomass exposure, wildfire smoke exposure etc.). Even with these other contributing factors, significant occupational exposure to VGDF can have played a role in the COPD as noted above, that may be more than a simple additive effect. The extent of this proportionate effect is difficult to quantify on a clinical basis however when other factors are present, and it is simplest to provide a quantitative attribution in patients who are non-smokers and have no other factors contributing to COPD.

7 Discussion

The aim of this RLR was two-fold in nature, 1) to define COPD and whether it is a single disease or group of diseases, and 2) to identify and interpret evidence published in the last five years regarding the relationships between COPD, and exposure to cigarette smoke and/or occupational VGDF. Two separate search strategies were executed to identify evidence relative to each aim, the results of which are summarized in the following discussion.

7.1 Research Question 1

A total of 51 publications were identified through electronic search, which resulted in the inclusion of 6 studies. An additional publication was identified via bibliography screen (n=1) of the included studies, and a targeted grey literature search of selected organizations (6). Overall, 13 publications from the last five years met criteria for inclusion for Research Question 1.

What is COPD? Is it a single disease or group of diseases/conditions?

a) How is COPD diagnosed? How is severity determined?

b) What are the causes of COPD? Do different causes result in different changes (at the cellular, tissue or structural level) within the lung? Does COPD onset or progression differ according to cause?

COPD is defined on the basis of persistent airflow limitation and is generally described by the consensus statements identified in this RLR as a disease of multifactorial origin. It is diagnosed based on an FEV_1/FVC ratio being <70% or <LLN, depending on the recommendation followed.[8,12] FEV_1 is further used to determine severity of disease. The GOLD 2021 report highlights the nuanced nature of COPD development, and that a combination of lifestyle, environmental including workplace, genetic, and pathobiological factors may impact the development of the disease.[8] Smoking is identified as the most common risk factor, however, occupational exposure is recognized as a substantial contributor to COPD, with estimates between 10-20% of cases being attributable to workplace exposure.[7-9] Inhalation of tobacco smoke and/or toxic particles has been found to trigger pulmonary inflammation leading to a pathological changes believed to lead to progressive airflow limitation.[8] The evidence from this RLR did not identify a difference in the pathogenesis due to specific irritants. Cigarette smoke has been well studied as a risk factor, however the development of chronic airflow limitation among non-smokers is recognized, demonstrating the complicated and multi-faceted nature of COPD.

7.2 Research Questions 2-6

An inherent challenge of this RLR was that no information on the causal relationship between COPD and exposure to cigarette smoke and/or occupational VGDF was identified. For many questions, there was no direct evidence identified to support the research question, however, all relevant supportive evidence identified was included in this report. Such data is presented for inferential purposes only and should be interpreted with caution. The results, conclusion, and clinical commentary for each Research question are provided in detail within each respective section of the report, and are briefly summarized below.

A total of 30 publications were identified from the literature search that provided supportive, or inferential data on the differences between exposure due to smoking and/or occupational VGDF exposure on COPD or lung function loss/impairment. Of the 30 publications, 20 met criteria for reporting (i.e., COPD as the primary outcome of interest, appropriate stratification/adjustment of data for VGDF and/or smoking exposure). The remaining eight publications determined to be ineligible for reporting are captured in the Data Extraction Workbook that accompanies this report.

7.2.1 Research Question 2

Is it possible to differentiate clinically between COPD, or lung function loss/impairment, caused by cigarette smoking and that caused by workplace VGDF exposures?

There were no studies identified in the last five years as a part of this RLR that directly addressed Research Question 2. One study provided evidence of lung damage following VGDF exposure that persisted when controlling for smoking status.[14] However, the study did not provide any information as to whether the cause of lung damage could be differentiated by specific irritants. Based on the historical evidence offered by the GOLD report and the lack of any new evidence identified through the RLR, the cause of COPD by exposure type cannot be clinically differentiated at this time.

7.2.2 Research Question 3

Is COPD, or lung function loss/impairment, caused by cigarette smoking and that caused by workplace VGDF exposures separate diseases or conditions, or disease or injuring processes?

There were no studies identified in the last five years as a part of this RLR that directly addressed Research Question 3. One study was identified that offered inferential data that the HMOX1 L+ genotype is significantly associated with higher odds of developing COPD; however, these results failed to be replicated within another cohort thereby challenging the validity of the findings. Historical evidence highlights that chronic inflammation is a hallmark of COPD but does not provide any data demonstrating unique pathophysiological inflammatory pathways, or biochemical markers exclusive to any given exposure type. Based on the evidence identified in this RLR, whether lung function loss/impairment caused by smoking and that caused by workplace VGDF exposure are separate diseases or conditions, or a disease or injuring process, is not known at this time.

7.2.3 Research Question 4

Do cumulative exposures (intensity x duration) to cigarette smoking and/or workplace VGDF exposures impact the amount of lung function loss/impairment? Is it possible to estimate the amount of lung function loss/impairment caused by cumulative exposures to cigarette smoking (pack-years) and that caused by workplace VGDF exposures (mg/m3-years)?

This RLR identified several studies that were published within the last five years that provide data demonstrating that cumulative exposure to occupational VGDF, and duration of cigarette smoking, impact the amount of lung function loss/impairment. Studies were also identified that demonstrated a dose-dependent relationship on the increased odds of developing COPD with cumulative exposure to VGDF and smoking. Although not all studies found a significant association of cumulative exposure and the development of COPD, most studies reported an increase in lung function loss/impairment or greater odds of developing COPD with greater exposure. However, the substantial variability across studies regarding exposure type, intensity, duration, and analysis makes it challenging to synthesize and quantify the impact, as well as generalize results to a broader population.

7.2.4 Research Question 5

Are the effects of cigarette smoking and workplace VGDF exposure on lung function loss/impairment additive or multiplicative? If a person quits cigarette smoking and/or avoids workplace VGDF exposure, would that slow, stop or reverse their COPD or lung function loss/impairment?

There were no studies identified in the last five years as a part of this RLR that directly addressed Research Question 5. However, several studies were identified in the RLR that provided inferential data regarding additive or multiplicative effects of smoking and workplace exposure. In general, the evidence captured in this RLR suggests that there may be an additive or multiplicative effect of smoking and workplace VGDF exposure on lung function loss/impairment. Similar to the other research questions in

this RLR, the data captured for Research Question 5 included a wide variety of occupations, and therefore the magnitude of effect varied across studies.

None of the studies captured in this SLR specifically evaluated whether exposure cessation slows, stops, or reverses COPD or lung function loss/impairment. However, a few studies provided data on either ex-workers or ex-smokers which inferentially suggested that former workers and former smokers have lower odds of developing COPD when compared to current workers or smokers, respectively. It is important to note that these findings should be interpreted with caution as only one study evaluated ex-workers exposed to wood dust,[16] and one reported conflicting results that former ex-smokers were more likely to develop COPD than smokers.[31]

Although previous studies have demonstrated a decline in the rate of lung function loss/impairment with sustained smoking cessation,[93,96] the results of this RLR suggest that the effect of the removal of VGDF exposure on the disease process of COPD is not well understood.

7.2.5 Research Question 6

Is COPD a disease or injuring process that, once triggered, follows its own course for progression of disease, similar to cancer? If yes, does this occur regardless of cause and/or continued (or discontinued) exposure?

There were no studies identified in the last five years as a part of this RLR that directly addressed Research Question 6. Additionally, there were no studies presenting inferential data to provide insight into the progression of COPD. Evidence identified in this RLR is largely focused on identifying risk factors associated with the development of COPD or lung function loss/impairment highlighting a substantial evidence gap regarding the progression of COPD post diagnosis.

7.3 Limitations and Strengths

7.3.1 Limitations

Several limitations across the research questions were identified. Firstly, the lack of causal data for smoking and/or occupational VGDF exposures and the development of COPD limited the degree to which the research questions could be directly addressed. A further limitation was that among the identified publications, the appropriate study design and/or subgroup stratifications and comparisons necessary to elucidate comparative lung function outcomes of interest were not consistently reported. Finally, the considerable heterogeneity across included publications (e.g., occupation type, exposure type and level, geographical location) limits both the generalizability of the data and the ability to synthesize findings.

The methodology of a RLR sacrifices the rigor of a SLR for accelerated timelines to provide decision makers with timely evidence.[10] The streamlined approach to the methodology introduces some inherent limitations. Search strategies for RLR are not intended to be comprehensive, and instead are more focused to address a particular question(s) at hand; therefore, evidence identified via RLR is not intended to be exhaustive. Additionally, RLR may be performed by a single reviewer as opposed to two independent reviewers and as such, are not as rigorous as an SLR. Further, RLR can be restricted (e.g., search is designed to capture evidence within a designated timeframe), lending to limited or cautious interpretations of the evidence. Lastly, the purpose of an RLR is to provide timely information regarding pertinent and available evidence for a given topic; no statistical analyses were performed as a part of this review; therefore, only narrative synopses of the outcomes are provided.

7.3.2 Strengths

Although this RLR was restricted to the last 5-years, evidence from two reputable organizations (i.e., GOLD and ATS) were presented to provide historical context for each research question where

applicable. Findings from this RLR demonstrated that no new evidence has been published in the last 5-years that significantly change what is currently know about the relationships between COPD, and exposure to cigarette smoke and/or occupational VGDF.

Single reviewers were utilized for this RLR, however, pilot screening and QC processes were performed throughout the screening process to monitor screener agreement. Further, an audit using AI was performed throughout the screening process to identify the potential for any wrongfully excluded publications, thereby increasing the methodological rigor of this RLR.

Finally, a great strength of this RLR is the involvement of key stakeholders (i.e., practicing respirologists) who are well-versed in the diagnosis and management of COPD, and provided their clinical interpretation of the findings of this report.

7.4 Clinical Interpretation

The absence of longitudinal data from large studies with well conducted lung function assessment is not surprising. Where such studies exist a limitation is often the exposure quantification which tends to rely on estimation from either job exposure matrices, or a self report often only asking about dust or “dirty work”. The definitions of COPD also vary with some relying on report of a physician diagnosis, others based on spirometric criteria with or without post bronchodilator results, and using either $FEV_1/FVC < 70\%$ or $FEV_1/FVC <$ lower limit of normal (LLN). The available studies show heterogeneity of exposed populations by various demographic factors, as well as similar issues with comparator groups, the exposure types and exposure magnitude also show variation. This is true of the range of historical evidence on occupational COPD as well as for the present study. The evidence available in the last 5 years is however supportive of the known effects of occupational VGDF exposure and shows some new directions such as the indication of possible additional genetic susceptibility factors.

As the general population rate of smoking declines this will impact the prevalence of COPD, however the importance of occupational and other environmental factors to the COPD disease burden will relatively increase. Some studies in this and earlier evidence have shown multiplicative effects of occupational VGDF exposure with smoking, whereas others have shown additive or less contribution. It seems likely that the effect of occupational VGDF exposure is at least additive to that of smoking. In the clinical situation there is notable variation in the symptoms experienced by comparable patients with otherwise similar lung function results. COPD exacerbations, especially when accompanied by infection, can lead to disease progression.

There are knowledge gaps concerning the effect of withdrawal from occupational VGDF exposure on COPD disease progression and socioeconomic outcomes, early and especially presymptomatic detection of the effects of VGDF exposure, the absence of biomarkers of effect before detectable lung function loss, and the contribution of frailty to morbidity and mortality. The inclusion of occupational history information in electronic medical records together with Patient Reported Outcome Measures (PROMS) would be helpful to aid research in this area using administrative health records.

7.5 Conclusion

The evidence from this RLR did not identify any significant changes in the understanding of COPD in regards to occupational VGDF and smoking exposure. Cumulative smoking and occupational VGDF exposure are known risk factors to lung impairment and the development of COPD, with evidence demonstrating an additive and multiplicative effect of these combined exposures. The evidence of cessation of exposure is anticipated to reduce the rate of decline of lung impairment, however there is limited novel evidence from the past five years. At present, it is not possible to distinguish between causes of COPD and there is limited pathophysiology or etiology evidence to support a greater

understanding of the disease or injury process of COPD and COPD progression, in relation to potential causes. Further primary research is warranted to explore these questions further.

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9 Appendix A: Search Strategies

9.1 Electronic Database Search for Research Question 1

Search number	Query	Results
1	exp pulmonary disease, chronic obstructive/	56185
2	(COPD or COAD or AECB, obstructive pulmonary disease$ or obstructive airway disease$ or obstructive lung disease$ or emphysema$ or chronic airflow obstruction$).ti,ab,kw.	75674
3	bronchitis, chronic/	1769
4	(chronic$ adj3 bronchiti$).ti,ab,kw.	11217
5	pulmonary emphysema/	15895
6	emphysema$.ti,ab,kw.	26549
7	or/1-6 [COPD]	99585
8	Consensus/ or (guideline or "Consensus Development Conference, NIH" or "Consensus Development Conference").pt.	40264
9	7 and 8	201
10	limit 9 to english [Q1]	130
11	limit 10 to last 5 years [Q1]	51

9.2 Electronic Database Search for Research Questions 2-6

Search number	Query	Results
1	exp pulmonary disease, chronic obstructive/	56185
2	(COPD or COAD or AECB, obstructive pulmonary disease$ or obstructive airway disease$ or obstructive lung disease$ or emphysema$ or chronic airflow obstruction$).ti,ab.	75674
3	bronchitis, chronic/	1769
4	(chronic$ adj3 bronchiti$).ti,ab.	11217
5	pulmonary emphysema/	15895
6	emphysema$.ti,ab.	26549
7	or/1-6 [COPD]	99585
8	exp smoking/ or exp tobacco smoking/	148084
9	(smoking or smoke$).ti,ab.	284223
10	dust/ or asbestosis/ or silicosis/ or pneumoconiosis/ or anthracosis/ or anthracosilicosis/ or berylliosis/ or byssinosis/	38005
11	("interstitial fibrosis" or asbestosis or "diffuse pleural thickening" or "asbestos-related pleural disease" or "asbestos-related pleural diseases" or silicosis or pneumoconiosis or pneumokoniosis or pneumoconioses or anthracosis or "black lung$" or coalworker or coal miner or anthracosilicosis or berylliosis or byssinosis or siderosis or "brown lung$" or aluminosis or "caplan syndrome" or baritosis or chalicosis or bagassosis or "hypersensitivity pneumonitis" or "restrictive lung disorders" or "restrictive lung diseases").ti,ab,kf.	28132
12	(vapo?r$ or gas or gases or fume or fumes).ti,ab.	352800
13	or/8-12 [Smoking, vapors, dusts, gases or fumes]	719417
14	exp industry/	316415
15	workplace/	23180
16	(workplace$ or work-site$ or wokrsite$ or ((work or job) adj3 (location$ or site$ or place$))).ti,ab.	49452
17	occupational health/	33607
18	((health or safety) adj3 (occupation$ or industr$)).ti,ab.	29431
19	occupational medicine/	23328
20	((occupation$ or industr$) adj3 medicine$).ti,ab.	7504
21	occupational diseases/	83489
22	((occupation$ or industr$) adj3 (illness$ or disease$)).ti,ab.	11580
23	occupational exposure/	54996
24	(occupation$ adj3 exposure$).ti,ab,kf.	27306

25	miners/	172
26	(labo?rer or construction or constructors or firefight$ or miner or miners or mining or mine worker$ or agriculture).ti,ab.	188771
27	or/15-26 [Occupation]	420621
28	7 and (13 or 27) [COPD and smoking-VGDF or occupation]	24908
29	(catalogs or comment or editorial or essays or historical article or interview or journal correspondence or news or newspaper article or note or clinical Conference or congress or meeting abstract or poster or overall).pt.	1884255
30	(review not systematic review).pt.	2602796
31	case study/ or letter/ or historical article/ or case report.tw.	3436821
32	(exp animal experiment/ or exp animal model/ or exp transgenic animal/ or animal/ or chordata/ or vertebrate/ or tetrapod/ or amniote/ or exp amphibia/ or mammal/ or exp reptile/ or therian/ or placental mammals/ or exp marsupial/ or euarchontoglires/ or exp xenarthra/ or primate/ or exp scandentia/ or haplorhini/ or exp prosimian/ or simian/ or exp tarsiiform/ or catarrhini/ or exp platyrrhini/ or ape/ or exp cercopithecidae/ or hominid/ or exp hylobatidae/ or exp chimpanzee/ or exp gorilla/ or (animal or animals or pisces or fish or fishes or catfish or catfishes or sheatfish or silurus or arius or heteropneustes or clarias or gariepinus or fathead minnow or fathead minnows or pimephales or promelas or cichlidae or trout or trouts or char or chars or salvelinus or salmo or oncorhynchus or guppy or guppies or millionfish or poecilia or goldfish or goldfishes or carassius or auratus or mullet or mullets or mugil or curema or shark or sharks or cod or cods or gadus or morhua or carp or carps or cyprinus or carpio or killifish or eel or eels or anguilla or zander or sander or lucioperca or stizostedion or turbot or turbots or psetta or flatfish or flatfishes or plaice or pleuronectes or platessa or tilapia or tilapias or oreochromis or sarotherodon or common sole or dover sole or solea or zebrafish or zebrafishes or danio or rerio or seabass or dicentrarchus or labrax or morone or lamprey or lampreys or petromyzon or pumpkinseed or pumpkinseeds or lepomis or gibbosus or herring or clupea or harengus or amphibia or amphibian or amphibians or anura or salientia or frog or frogs or rana or toad or toads or bufo or xenopus or laevis or bombina or epidalea or calamita or salamander or salamanders or newt or newts or triturus or reptilia or reptile or reptiles or bearded dragon or pogona or vitticeps or iguana or iguanas or lizard or lizards or anguis fragilis or turtle or turtles or snakes or snake or aves or bird or birds or quail or quails or coturnix or bobwhite or colinus or virginianus or poultry or poultries or fowl or fowls or chicken or chickens or gallus or zebra finch or taeniopygia or guttata or canary or canaries or serinus or canaria or parakeet or parakeets or grasskeet or parrot or parrots or psittacine or psittacines or shelduck or tadorna or goose or geese or branta or leucopsis or woodlark or lullula or flycatcher or ficedula or hypoleuca or dove or doves or geopelia or cuneata or duck or ducks or greylag or graylag or anser or harrier or circus pygargus or red knot or great knot or calidris or canutus or godwit or limosa or lapponica or meleagris or gallopavo or jackdaw or corvus or monedula or ruff or philomachus or pugnax or lapwing or peewit or plover or vanellus or swan or cygnus or columbianus or bewickii or gull or chroicocephalus or ridibundus or albifrons or great tit or parus or aythya or fuligula or streptopelia or risoria or spoonbill or platalea or leucorodia or blackbird or turdus or merula or blue tit or cyanistes or pigeon or pigeons or columba or pintail or anas or starling or sturnus or owl or athene noctua or pochard or ferina or cockatiel or nymphicus or hollandicus or skylark or alauda or tern or sterna or teal or crecca or oystercatcher or haematopus or ostralegus or shrew or shrews or sorex or araneus or crocidura or russula or european mole or talpa or chiroptera or bat or bats or eptesicus or serotinus or myotis or dasycneme or daubentonii or pipistrelle or pipistrellus or cat or cats or felis or catus or feline or dog or dogs or canis or canine or canines or otter or otters or lutra or badger or badgers or meles or fitchew or fitch or foumart or foulmart or ferrets or ferret or polecat or polecats or mustela or putorius or weasel or weasels or fox or foxes or vulpes or common seal or phoca or vitulina or grey seal or halichoerus or horse or horses or equus or equine or equidae or donkey or donkeys or mule or mules or pig or pigs or swine or swines or hog or hogs or boar or boars or porcine or piglet or piglets or sus or scrofa or llama or llamas or lama or glama or deer or deers or cervus or elaphus or cow or cows or bos taurus or bos indicus or bovine or bull or bulls or cattle or bison or bisons or sheep or sheeps or ovis aries or ovine or lamb or lambs or mouflon or mouflons or goat or goats or capra or caprine or chamois or rupicapra or leporidae or lagomorpha or lagomorph or rabbit or rabbits or oryctolagus or cuniculus	4778553

	or laprine or hares or lepus or rodentia or rodent or rodents or murinae or mouse or mice or mus or musculus or murine or woodmouse or apodemus or rat or rats or rattus or norvegicus or guinea pig or guinea pigs or cavia or porcellus or hamster or hamsters or mesocricetus or cricetulus or cricetus or gerbil or gerbils or jird or jirds or meriones or unguiculatus or jerboa or jerboas or jaculus or chinchilla or chinchillas or beaver or beavers or castor fiber or castor canadensis or sciuridae or squirrel or squirrels or sciurus or chipmunk or chipmunks or marmot or marmots or marmota or suslik or susliks or spermophilus or cynomys or cottonrat or cottonrats or sigmodon or vole or voles or microtus or myodes or glareolus or primate or primates or prosimian or prosimians or lemur or lemurs or lemuridae or loris or bush baby or bush babies or bushbaby or bushbabies or galago or galagos or anthropoidea or anthropoids or simian or simians or monkey or monkeys or marmoset or marmosets or callithrix or cebuella or tamarin or tamarins or saguinus or leontopithecus or squirrel monkey or squirrel monkeys or saimiri or night monkey or night monkeys or owl monkey or owl monkeys or douroucoulis or aotus or spider monkey or spider monkeys or ateles or baboon or baboons or papio or rhesus monkey or macaque or macaca or mulatta or cynomolgus or fascicularis or green monkey or green monkeys or chlorocebus or vervet or vervets or pygerythrus or hominoidea or ape or apes or hylobatidae or gibbon or gibbons or siamang or siamangs or nomascus or symphalangus or hominidae or orangutan or orangutans or pongo or chimpanzee or chimpanzees or pan troglodytes or bonobo or bonobos or pan paniscus or gorilla or gorillas or troglodytes).ti,ab,kf.) not (human/ or (human$ or man or men or woman or women or child or children or patient$).ti,ab,kf.)	
33	randomized controlled trials as topic/ or randomized controlled trial/ or random allocation/ or double blind method/ or single blind method/ or clinical trial/ or exp clinical trials as topic/ or placebos/	1189352
34	(clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt.	1027297
35	(("phase i" or "phase ii" or "phase iii" or "phase iv" or random* or multicenter or multi-center or multicentre or multi-centre) adj3 (trial or study)).tw.	434569
36	(((clinical adj3 trial$) or ((singl$ or doubl$ or treb$ or tripl$) adj3 (blind$3 or mask$3)) or placebo$ or randomly allocated or (allocated adj2 random$) or random) adj2 allocat*).tw.	35156
37	or/29-36 [Exclusions]	12674036
38	28 not 37	16013
39	Consensus/ or (guideline or "Consensus Development Conference, NIH" or "Consensus Development Conference").pt.	40264
40	7 and 39 [COPD Guidelines]	201
41	(clinical Conference or congress or meeting abstract or poster or overall).pt.	76392
42	40 not 41 [Exclude conferences]	200
43	38 or 42	16186
44	limit 43 to english	13509
45	limit 44 to last 5 years	4550

10 Appendix B: Glossary of Terms

Term	Definition
Vapour	The gaseous state of a substance that is solid or liquid at room temperature.
Dust	Fine particles of organic or inorganic material produced by mechanical disruption.
Gas	A substance that is in its gaseous state at room temperature.
Fume	Solid particles produced from the condensation of a substance from its gaseous state. Often produced following a chemical reaction.
Pack-years	A measurement of the amount a person has smoked over a period of time. Calculated by multiplying the number of packs of cigarettes smoked per day by the number of years a person has smoked. 1 pack-years is equal to smoking 1 pack per day for 1 year.

11 Appendix C: List of Occupations and Occupational Exposures

List of occupations for Würtz *et al.*, 2020 selected from the Danish adaptation of the International Standard Classification of Occupations, revision 1988. Inserted from Würtz *et al.*, 2020.[15]

Job description[a]	Unit group[a]		
	ISCO-88	ISCO-88 (COM)	DISCO-88
General managers in agriculture, hunting, forestry and fishing	1311	1311	1311
General managers in manufacturing	1312	1312	1312
General managers in construction	1313	1313	1313
General managers in personal care, cleaning and related services	1318	1318	1318
Agronomists and related professionals	2213	2213	2213
Veterinarians	2223	2223	2223
Veterinary assistants	3227	3227	3227
Fire-fighters	5161	5161	5161
Field crop and vegetable growers	6111	6111	6111
Dairy and livestock producers	6121	6121	6121
Poultry producers	6122	6122	6122
Market-oriented animal producers and related workers not elsewhere classified	6129	6129	6129
Market-oriented crop and animal producers	6130	6130	6130
Forestry workers and loggers	6141	6141	6141
Miners and quarry workers	7111	7111	7111
Stone splitters, cutters and carvers	7113	7113	7113
Builders, traditional materials	7121	7121	7121
Bricklayers and stonemasons	7122	7122	7122
Concrete placers, concrete finishers and related workers	7123	7123	7123
Carpenters and joiners	7124	7124	7124
Roofers	7131	7131	7131
Floor layers and tile setters	7132	7132	7132
Plasterers	7133	7133	7133
Insulation workers	7134	7134	7134
Painters and related workers	7141	7141	7141
Varnishers and related painters	7142	-	7142
Building structure cleaners	7143	7143	7143
Metal moulders and coremakers	7211	7211	7211
Welders and flamecutters	7212	7212	7212
Sheet-metal workers	7213	7213	7213
Structural-metal preparers and erectors	7214	7214	7214
Riggers and cable splicers	7215	7215	7215

Job description[a]	Unit group[a]		
	ISCO-88	ISCO-88 (COM)	DISCO-88
Metal wheel-grinders, polishers and tool sharpeners	7224	7224	7224
Butchers, fishmongers and related food preparers	7411	7411	7411
Bakers, pastry-cooks and confectione-ry makers	7412	7412	7412
Tobacco preparers and tobacco products makers	7416	7416	7416
Wood treaters	7421	7421	7421
Woodworking-machine setters and setter-operators	7423	7423	7423
Mining-plant operators	8111	8111	8111
Mineral-ore- and stone-processing-plant operators	8112	8112	8112
Well drillers and borers and related workers	8113	8113	8113
Ore and metal furnace operators	8121	8121	8121
Metal melters, casters and rolling-mill operators	8122	8122	8122
Metal-heat-treating-plant operators	8123	8123	8123
Glass and ceramics kiln and related machine operators	8131	8131	8131
Wood-processing-plant operators	8141	8141	8141
Papermaking-plant operators	8143	8143	8143
Crushing-, grinding- and chemical-mixing-machinery operators	8151	8151	8151
Chemical-heat-treating-plant operators	8152	8152	8152
Cement and other mineral products machine operators	8212	8212	8212
Ammunition- and explosive-products machine operators	8222	8222	8222
Metal finishing-, plating- and coating-machine operators	8223	8223	8223
Wood-products machine operators	8240	8240	8240
Bookbinding-machine operators	8252	8252	8252
Paper-products machine operators	8253	8253	8253
Fibre-preparing-, spinning- and winding-machine operators	8261	8261	8261
Grain- and spice-milling-machine operators	8273	8273	8273
Baked-goods, cereal and chocolate-products machine operators	8274	8274	8274
Sugar production machine operators	8276	8276	8276
Tea-, coffee-, and cocoa-processing-machine operators	8277	8277	8277
Tobacco production machine operators	8279	8279	8279
Wood and related products assemblers	8285	8285	8285
Motorised farm and forestry plant operators	8331	8331	8331
Earth-moving- and related plant operators	8332	8332	8332
Garbage collectors	9161	9161	9161
Sweepers and related labourers	9162	9162	9162
Farm-hands and labourers	9211	9211	9211
Forestry labourers	9212	9212	9212
Mining and quarrying labourers	9311	9311	9311
Construction and maintenance labourers: roads, dams and similar constructions	9312	9312	9312
Building construction labourers	9313	9313	9313
Transport labourers and freight handlers	-	9330	9330

ISCO-88: The International Standard Classification of Occupations, revision 1988
ISCO-88 (COM): The International Standard Classification of Occupations, revision 1988 for the European Union (Eurostat)
DISCO-88: Danish adaptation of The International Standard Classification of Occupations, revision 1988
[a] Statistics Denmark (3 April, 2014): http://www.dst.dk/da/Statistik/dokumentation/Nomenklaturer/DISCO-88/Sammenlignende.aspx

List of occupations for Liao *et al.*, 2015. Inserted from Liao *et al.*, 2015.[19]

Dust exposure groups	Job categories
More likely dust exposure	Factory/assembly/mechanic
	Skilled labor (e.g., plumber, carpenter, painter, hairdresser)
	General labor (e.g., custodian, delivery, mailman, truck driver)
	Heavy labor (e.g., construction, landscaping)
Less likely dust exposure	Nurse/medical personnel/laboratory technician
	Physical/occupational/speech therapist
	Homemaker
	Self-employed business owner
	Physician/dentist/scientist/research
	Lawyer/judge
	Psychologist/social worker/mental health counselor
	Engineer/computer science
	banker/accountant
	Manager/consultant (e.g., production manager)
	Administrative (e.g., personnel)
	Educator
	Secretary/clerk/data entry
	Retail/cashier
	Sales/marketing/insurance
	Realtor
	Police/fire/security/military
	Restaurant/food worker
	Writer/editor
	Artist/graphic Designer/craftsperson
	Musician
	Clergy (minister, priest, rabbi)
	Sports pro/coach/exercise instructor/other
	Statistician
	Student

List of exposures for Dement *et al.*, 2015. Inserted from Dement *et al.*, 2015.[27]

Agent or exposure	Reference concentration for intensity scoring
Asbestos	2 f/cc
Silica	0.1 mg/m^3 respirable
Cement dust	5 mg/m^3 respirable
Man-made-mineral-fibers	1 f/cc
Engine exhausts	100 μg/m^3 respirable elemental carbon
Acids	Ceiling 5 ppm as HCL
Caustics	Ceiling 2 mg/m^3 as sodium hydroxide
Welding, thermal cutting, soldering, or brazing	5 mg/m^3 as total aerosol
Metal cutting, grinding, and machining aerosol	5 mg/m^3 as total aerosol
Paint-related aerosols	1 mg/m^3 as total aerosol
Isocyanates	0.02 ppm
Organic solvents	100 ppm as toluene
Wood dust	1 mg/m^3 as total aerosol
Molds and spores	Exposure above typical background
Particulates not otherwise regulated (PNOR)	10 mg/m^3 as total aerosol

12 Appendix D: Quality Appraisal

National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies															
Study Name Author, Year	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**9**	**11**	**12**	**13**	**14**	**Overall assessment** *Good, Fair, Poor*
Bolund 2018[16] REFID: 503	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Doney 2019[29] REFID: 1000	Yes	Yes	Yes	Yes	Yes	NA	No	NA	Yes	Yes	Yes	No	NA	No	Good
Würtz 2020[15] REFID: 4320	Yes	Yes	Yes	Yes	Yes	NA	No	NA	Yes	NA	Yes	NA	NA	No	Fair
LeVan 2017[83] REFID: 2290	Yes	Yes	Yes	Yes	Yes	NA	No	NA	Yes	No	Yes	No	NA	NA	Good
Sinha 2017[25] REFID: 3639	Yes	Yes	Yes	Yes	Yes	NA	No	NA	Yes	No	NA	NA	NA	No	Good
Lehnert 2015[24] REFID: 2267	Yes	Yes	Yes	Yes	Yes	NA	No	NA	Yes	NA	Yes	No	NA	Yes	Good

Vinnikov 2017[23] REFID: 4120	Yes	Yes	Yes	Yes	Yes	NA	No	NA	Yes	No	Yes	No	NA	Yes	Fair
Koh 2015[17] REFID:2044	Yes	Yes	Yes	Yes	Yes	NA	No	NA	Yes	NA	Yes	No	NA	Yes	Good
Liao 2015[19] REFID: 2350	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Soyseth 2016[18] REFID: 3704	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Liu 2015[26] REFID: 2409	Yes	Yes	Yes	Yes	Yes	NA	No	NA	Yes	NA	Yes	No	NA	Yes	Good
Stoleski 2019[21] REFID: 3749	Yes	Yes	Yes	Yes	Yes	NA	No	NA	Yes	NA	Yes	No	NA	Yes	Good
Dement 2015[27] REFID: 921	Yes	Yes	Yes	Yes	Yes	NA	No	NA	Yes	NA	Yes	No	NA	Yes	Good
Stoleski 2017[20] REFID: 3750	Yes	Yes	Yes	Yes	Yes	NA	No	NA	Yes	NA	Yes	No	NA	Yes	Good
Mabila 2019[108] REFID: 2492	Yes	Yes	Yes	Yes	Yes	NA	No	NA	Yes	NA	Yes	No	NA	Yes	Good

Sumit 2020[28] REFID: 3787	Yes	Yes	Yes	Yes	Yes	NA	No	NA	Yes	NA	Yes	No	NA	Yes	Good
Paulin 2018[14] REFID: 3053	Yes	Yes	Yes	Yes	Yes	NA	No	NA	Yes	NA	Yes	No	NA	Yes	Good
Sadhra 2020[30] REFID: 3400	Yes	Yes	Yes	Yes	Yes	NA	No	NA	Yes	NA	Yes	No	NA	Yes	Good
Reynolds 2017[22] REFID: 3293	Yes	Yes	Yes	Yes	Yes	NA	No	NA	Yes	NA	Yes	No	NA	Yes	Good
Van Koeverden 2015[3] REFID: 4066	Yes	Yes	Yes	Yes	Yes	NA	No	NA	Yes	NA	Yes	No	NA	Yes	Good
Toren 2017[32] REFID: 3961	Yes	Yes	Yes	Yes	Yes	NA	No	NA	Yes	NA	Yes	No	NA	Yes	Good

Abbreviations: NA: Not Applicable.

1: Was the research question or objective in this paper clearly stated? *Did the authors describe their goal in conducting this research? Is it easy to understand what they were looking to find? This issue is important for any scientific paper of any type. Higher quality scientific research explicitly defines a research question.*

2: Was the study population clearly specified and defined? *Did the authors describe the group of people from which the study participants were selected or recruited, using demographics, location, and time period? If you were to conduct this study again, would you know who to recruit, from where, and from what time period? Is the cohort population free of the outcomes of interest at the time they were recruited?*

3: Was the participation rate of eligible persons at least 50%? *If fewer than 50% of eligible persons participated in the study, then there is concern that the study population does not adequately represent the target population. This increases the risk of bias.*

4: Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? *Were the inclusion and exclusion criteria developed prior to recruitment or selection of the study population? Were the same underlying criteria used for all of the subjects involved?*

5: Was a sample size justification, power description, or variance and effect estimates provided? *Did the authors present their reasons for selecting or recruiting the number of people included or analyzed? Do they note or discuss the statistical power of the study? This question is about whether or not the study had enough participants to detect an association if one truly existed.*

A paragraph in the methods section of the article may explain the sample size needed to detect a hypothesized difference in outcomes. You may also find a discussion of power in the discussion section (such as the study had 85 percent power to detect a 20 percent increase in the rate of an outcome of interest, with a 2-sided alpha of 0.05). Sometimes estimates of variance and/or estimates of effect size are given, instead of sample size calculations. In any of these cases, the answer would be "yes." However, observational cohort studies often do not report anything about power or sample sizes because the analyses are exploratory in nature. In this case, the answer would be "no." This is not a "fatal flaw." It just may indicate that attention was not paid to whether the study was sufficiently sized to answer a prespecified question–i.e., it may have been an exploratory, hypothesis-generating study.

6: For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured? *For some prospective cohort studies, the investigator enrolls the cohort and then determines the exposure status of various members of the cohort. Therefore, you begin the study in the present by looking at groups that were exposed (or not) to some biological or behavioral factor, intervention, etc., and then you follow them forward in time to examine outcomes. If a cohort study is conducted properly, the answer to this question should be "yes," since the exposure status of members of the cohort was determined at the beginning of the study before the outcomes occurred.*

For retrospective cohort studies, the same principal applies. The difference is that, rather than identifying a cohort in the present and following them forward in time, the investigators go back in time (i.e., retrospectively) and select a cohort based on their exposure status in the past and then follow them forward to assess the outcomes that occurred in the exposed and nonexposed cohort members. Because in retrospective cohort studies the exposure and outcomes may have already occurred (it depends on how long they follow the cohort), it is important to make sure that the exposure preceded the outcome.

Sometimes cross-sectional studies are conducted (or cross-sectional analyses of cohort-study data), where the exposures and outcomes are measured during the same timeframe. As a result, cross-sectional analyses provide weaker evidence than regular cohort studies regarding a potential causal relationship between exposures and outcomes. For cross-sectional analyses, the answer to Question 6 should be "no."

7: Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? *Did the study allow enough time for a sufficient number of outcomes to occur or be observed, or enough time for an exposure to have a biological effect on an outcome? Cross-sectional analyses allow no time to see an effect, since the exposures and outcomes are assessed at the same time, so those would get a "no" response.*

8: For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)? *If the exposure can be defined as a range (examples: drug dosage, amount of physical activity, amount of sodium consumed), were multiple categories of that exposure assessed? In any case, studying different levels of exposure (where possible) enables investigators to assess trends or dose-response relationships between exposures and outcomes–e.g., the higher the exposure, the greater the rate of the health outcome. The presence of trends or dose-response relationships lends credibility to the hypothesis of causality between exposure and outcome.*

If there are only two possible exposures (yes/no), then this question should be given an "NA," and it should not count negatively towards the quality rating.

9: Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? *Were the exposure measures defined in detail? Were the tools or methods used to measure exposure accurate and reliable–for example, have they been validated or are they objective? This issue is important as it influences confidence in the reported exposures. When exposures are measured with less accuracy or validity, it is harder to see an association between exposure and outcome even if one exists. Also as important is whether the exposures were assessed in the same manner within groups and between groups; if not, bias may result.*

10: Was the exposure(s) assessed more than once over time? *Was the exposure for each person measured more than once during the course of the study period? Multiple measurements with the same result increase our confidence that the exposure status was correctly classified. Also, multiple measurements enable investigators to look at changes in exposure over time, for example, people who ate high dietary sodium throughout the follow-up period, compared to those who started out high then reduced their intake, compared to those who ate low sodium throughout. Once again, this may not be applicable in all cases. In many older studies, exposure was measured only at baseline. However, multiple exposure measurements do result in a stronger study design.*

11: Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? *Were the outcomes defined in detail? Were the tools or methods for measuring outcomes accurate and reliable–for example, have they been validated or are they objective? This issue is important because it influences confidence in the validity of study results. Also important is whether the outcomes were assessed in the same manner within groups and between groups. Results may be biased if one group is seen more frequently than another group because more frequent encounters with the health care system increases the chances of outcomes being detected and documented.*

12: Were the outcome assessors blinded to the exposure status of participants? *Blinding means that outcome assessors did not know whether the participant was exposed or unexposed. It is also sometimes called "masking." The objective is to look for evidence in the article that the person(s) assessing the outcome(s) for the study (for example, examining*

medical records to determine the outcomes that occurred in the exposed and comparison groups) is masked to the exposure status of the participant. Sometimes the person measuring the exposure is the same person conducting the outcome assessment. In this case, the outcome assessor would most likely not be blinded to exposure status because they also took measurements of exposures. If so, make a note of that in the comments section. As you assess this criterion, think about whether it is likely that the person(s) doing the outcome assessment would know (or be able to figure out) the exposure status of the study participants. If the answer is no, then blinding is adequate.

13: Was loss to follow-up after baseline 20% or less? *Higher overall follow-up rates are always better than lower follow-up rates, even though higher rates are expected in shorter studies, whereas lower overall follow-up rates are often seen in studies of longer duration. Usually, an acceptable overall follow-up rate is considered 80 percent or more of participants whose exposures were measured at baseline. However, this is just a general guideline.*

14: Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)? *Were key potential confounding variables measured and adjusted for, such as by statistical adjustment for baseline differences? Logistic regression or other regression methods are often used to account for the influence of variables not of interest. This is a key issue in cohort studies, because statistical analyses need to control for potential confounders, in contrast to an RCT, where the randomization process controls for potential confounders. All key factors that may be associated both with the exposure of interest and the outcome–that are not of interest to the research question–should be controlled for in the analyses.*