Literature Review

Risk of Developing Chronic Obstructive Pulmonary Disease in Non-Smoking Adults Exposed to Particulate Matter 2.5 Compared to Those Without Exposure

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) development involves a complex pathway of host and environmental factors. Besides cigarette smoking, previous studies showed exposure to air pollution, such as particulate matter sized 2.5 µm or less ($PM_{2.5}$), might also have an important role in COPD development because it might lead to airway remodeling and chronic lung inflammation. However, the cause-and-effect relationship between $PM_{2.5}$ and COPD in non-smoking patients is still unclear.

Methods: Literature searches were performed in five online medical databases (PubMed, EMBASE, ScienceDirect, EBSCOhost, and Cochrane Library) and hand-searching in Google Scholar. Filtering literature with the inclusion and exclusion criteria resulted in three relevant articles (1 case-control and 2 cohort studies). Critical appraisal was conducted using the Center of Evidence-Based Medicine (CEBM) worksheet from the University of Oxford for etiologic studies.

Results: All three articles were considered valid. The prospective cohort was decided unimportant because of the non-significant adjusted hazard ratio (HR 1.23; 95% confidence interval [CI]=0.50-3.06). The case-control and retrospective studies had important results with adjusted odds ratio of 1.29 (95% CI=1.01-1.65) and 1.69 (95% CI=1.11-2.58), respectively. The relatively low number needed to harm (NNH) of 10-23 indicated that $PM_{2.5}$ exposure was a meaningful factor for the risk of developing COPD in non-smoker adults. Both articles were considered applicable to our case.

Conclusion: Non-smoking adults with exposure to $PM_{2.5}$, compared to those without exposure, are at higher risk of developing COPD.

Keywords: chronic obstructive pulmonary disease, non-smoker, $PM_{2.5}$

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a pulmonary disease characterized by constant airflow limitation and respiratory symptoms caused by alveolar with or without airflow abnormality. The persistent airflow limitation causes patients with COPD to have a chronic cough, sputum production, and dyspnea. The disease ranks as the third cause of death in the world; 90% of these occur in middle-income countries.[1]

The risk of developing COPD involves a complex pathway of host and environmental factors. It is already well known that tobacco smoking has the highest risk of lung function deterioration and developing respiratory symptoms. However, there are other risk factors for COPD development, such as older age, female sex, occupational exposures, and also air pollution.[1,2] Air pollution from biomass, coal, dust, fumes, or gas is considered an important risk factor for respiratory diseases, including COPD.[3–5] One of the air pollutant components that may play a significant role in the development of COPD is particulate matter (PM), along with sulfur oxide (SO), ozone (O_3), and nitric oxide (NO).[4,6]

Solid and liquid droplets suspended in the atmosphere are the components of PM. There are three categories of PM: ultrafine (size <0.1 µm), fine (size 0.1–2.5 µm), and coarse particulate (size 2.5–10 µm). Particulate matter sized 2.5 µm or less ($PM_{2.5}$) or fine particulate matter has a small size with a big superficial area that can make it easier to absorb toxic components in the air.[6] It is known that

$PM_{2.5}$ has become the 5th highest risk factor of death worldwide.[7]

Exposure to $PM_{2.5}$ promotes macrophage recruitment and cytokine release, including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and IL-1β. Macrophage recruitment leads to eosinophil recruitment and production of interferon-γ (IFN-γ) and IL-17 by T cells. In addition, $PM_{2.5}$ can also cause macrophage phagocytosis dysfunction by pulmonary oxidative stress activation. All of these processes lead to chronic inflammation in the airway and lung.[6,8] Furthermore, exposures to $PM_{2.5}$ were associated with deoxyribonucleic acid (DNA) methylation conversion in lung tissue.[9]

The relationship between $PM_{2.5}$ and COPD has been explored in previous studies. A higher prevalence of COPD is found in patients with $PM_{2.5}$ exposure, especially in males, with high genetic risk, and an unhealthy lifestyle.[4,10] A worse pulmonary function and an increased risk of exacerbation, hospitalization, and death in COPD patients are also linked to $PM_{2.5}$ exposure.[10–13] However, the cause-and-effect relationship between $PM_{2.5}$ and COPD in non-smoking patients is still unclear.

A 45-year-old male came to a pulmonary outpatient clinic with recurring shortness of breath for the previous 3 months. Neither clinical nor supporting examination showed abnormality of cardiac function. On history-taking, the caring physician found no history of smoking habits, but the patient admitted that his house was located next to an industrial area. According to the clinical examination, which was confirmed by spirometry, he was diagnosed with COPD. The physician had once read that one of the most common air pollutants in industrial areas is $PM_{2.5}$. He would like to know whether exposure to $PM_{2.5}$ could raise the risk of developing COPD among non-smoking adults.

The clinical question was formulated as Patient (P) was non-smoking adults (aged 18 years or older); Indicator (I) was Exposure to $PM_{2.5}$; Comparison (C) was no exposure to $PM_{2.5}$; and Outcome (O) was development of COPD. So, our clinical question is: In non-smoking adult patients, does exposure to $PM_{2.5}$, compared with no exposure to $PM_{2.5}$, increase the risk of developing COPD?

METHODS

The article search was independently done by at least two authors. We performed the article search in PubMed, EMBASE, ScienceDirect, EBSCO*host*, and Cochrane on October 8, 2020. Hand searching was also carried out in Google Scholar on the same date. During the search, the keywords of “non-smokers”, “pm2.5”, and “chronic obstructive pulmonary disease” were used along with their related terms and synonyms. Table 1 summarizes the terminology used in each of the databases.

Selection of articles was conducted based on the inclusion criteria, consisting of: (1) studies that included subjects who were non-smoking adults; (2) observed determinants involved $PM_{2.5}$; (3) observed outcome was the development of COPD; and (4) meta-analysis/systematic review of observational studies, or individual observational studies (cohort or case-control studies). The exclusion criteria were: (1) irrelevant to the clinical question; (2) cross-sectional study; and (3) written neither in English nor in Bahasa Indonesia.

Literature searching yielded 166 articles from PubMed, 106 from EMBASE, 461 from ScienceDirect, 59 from EBSCO*host*, and 3 from Cochrane. Hand searching in Google Scholar found 333 related articles. By applying the inclusion criteria to all the gathered articles, we then obtained 3 articles from PubMed, 2 from EMBASE, 3 from ScienceDirect, 1 from EBSCO*host*, 0 from Cochrane, and 4 from Google Scholar. We screened each article’s title and abstract and found 5 articles with no duplication relevant to our clinical question. A thorough reading of them led to the decision that there were 3 useful articles to be critically appraised (Figure 1).

The three useful articles obtained in the literature search consisted of 1 prospective cohort, 1 retrospective cohort, and 1 case-control study. We conducted the critical appraisal using worksheets from the Center of Evidence-Based Medicine (CEBM), University of Oxford for etiologic studies.

Table 1. Searching Strategy

Database	Terms	Articles Found	Articles Used
PubMed	(((((((((Non-Smokers[MeSH Terms]) OR (Non-Smokers[Title/Abstract])) OR (Non-Smoker[Title/Abstract])) OR (Nonsmokers[Title/Abstract])) OR (Nonsmoker[Title/Abstract])) OR (never smoker[Title/Abstract])) OR (never-smoker[Title/Abstract])) AND (((((((((Particulate Matter[MeSH Terms]) OR (Particulate Matter[Title/Abstract])) OR (Particulate Matters[Title/Abstract])) OR (Particulate particle[Title/Abstract])) OR (Particulate particles[Title/Abstract])) OR (pm2.5[Title/Abstract])) OR (pm2,5[Title/Abstract])) OR (pm 2.5[Title/Abstract])) OR (pm 2,5[Title/Abstract]))) AND (((((((((Chronic Obstructive Pulmonary Disease[MeSH Terms]) OR (Chronic Obstructive Pulmonary Disease[Title/Abstract])) OR (Chronic Obstructive Lung Disease[Title/Abstract])) OR (Chronic Obstructive Pulmonary Diseases[Title/Abstract])) OR (COAD[Title/Abstract])) OR (COPD[Title/Abstract])) OR (Chronic Obstructive Airway Disease[Title/Abstract])) OR (Chronic Airflow Obstruction[Title/Abstract])) OR (Chronic Airflow Obstructions[Title/Abstract]))) NOT (cross-sectional[Title/Abstract])	166	1
EMBASE	('never smoker'/exp OR 'never smoker' OR 'never smokers' OR 'neversmoker' OR 'neversmokers' OR 'non smoker'/exp OR 'non smoker' OR 'non-current smoker' OR 'non-current smokers' OR 'non-smoker' OR 'non-smokers' OR 'noncurrent smoker' OR 'noncurrent smokers' OR 'nonsmoker' OR 'nonsmokers' OR 'not-current smoker' OR 'not-current smokers') AND ('pm2.5 exposure'/exp OR 'pm 2.5 exposure' OR 'pm2.5 exposure' OR 'exposure to pm 2.5' OR 'exposure to pm2.5' OR 'fine particle exposure' OR 'fine particulate matter exposure' OR 'particulate matter 2.5 exposure' OR 'particulate matter'/exp OR 'particulate matter') AND ('chronic obstructive lung disease'/exp OR 'chronic airflow obstruction' OR 'chronic airway obstruction' OR 'chronic obstructive bronchopulmonary disease' OR 'chronic obstructive lung disease' OR 'chronic obstructive lung disorder' OR 'chronic obstructive pulmonary disease' OR 'chronic obstructive pulmonary disorder' OR 'chronic obstructive respiratory disease' OR 'chronic pulmonary obstructive disease' OR 'chronic pulmonary obstructive disorder' OR 'copd' OR 'lung chronic obstructive disease' OR 'lung disease, chronic obstructive' OR 'obstructive chronic lung disease' OR 'obstructive chronic pulmonary disease' OR 'obstructive lung disease, chronic' OR 'pulmonary disease, chronic obstructive' OR 'pulmonary disorder, chronic obstructive')	106	1
ScienceDirect	(“never smoker” OR “non-smoker”) AND (“pm2.5” OR “pm 2.5” OR “fine particle” OR “particulate matter” OR “fine particulate matter”) AND (“chronic obstructive pulmonary disease” OR “copd”)	461	0
EBSCO*host*	TX (non-smoker or never smoker) AND TX particulate matter 2.5 AND TX (chronic obstructive pulmonary disease or copd or chronic obstructive airway disease or chronic obstructive lung disease)	59	0
Cochrane	(("Non-Smoker" OR "Nonsmokers" OR "Never smoker" OR "Never-smoker"):ti,ab,kw) AND (("Particulate Matters" OR "Particulate Particle" OR "Particulate Particles" OR "PM2.5" OR "PM2,5" OR "PM 2.5" OR "PM 2,5"):ti,ab,kw) AND (("Chronic Obstructive Lung Disease" OR "Chronic Obstructive Pulmonary Diseases" OR "COAD" OR "COPD" OR "Chronic Obstructive Airway Disease" OR "Chronic Airflow Obstruction" OR "Chronic Airflow Obstruction"):ti,ab,kw)	3	0

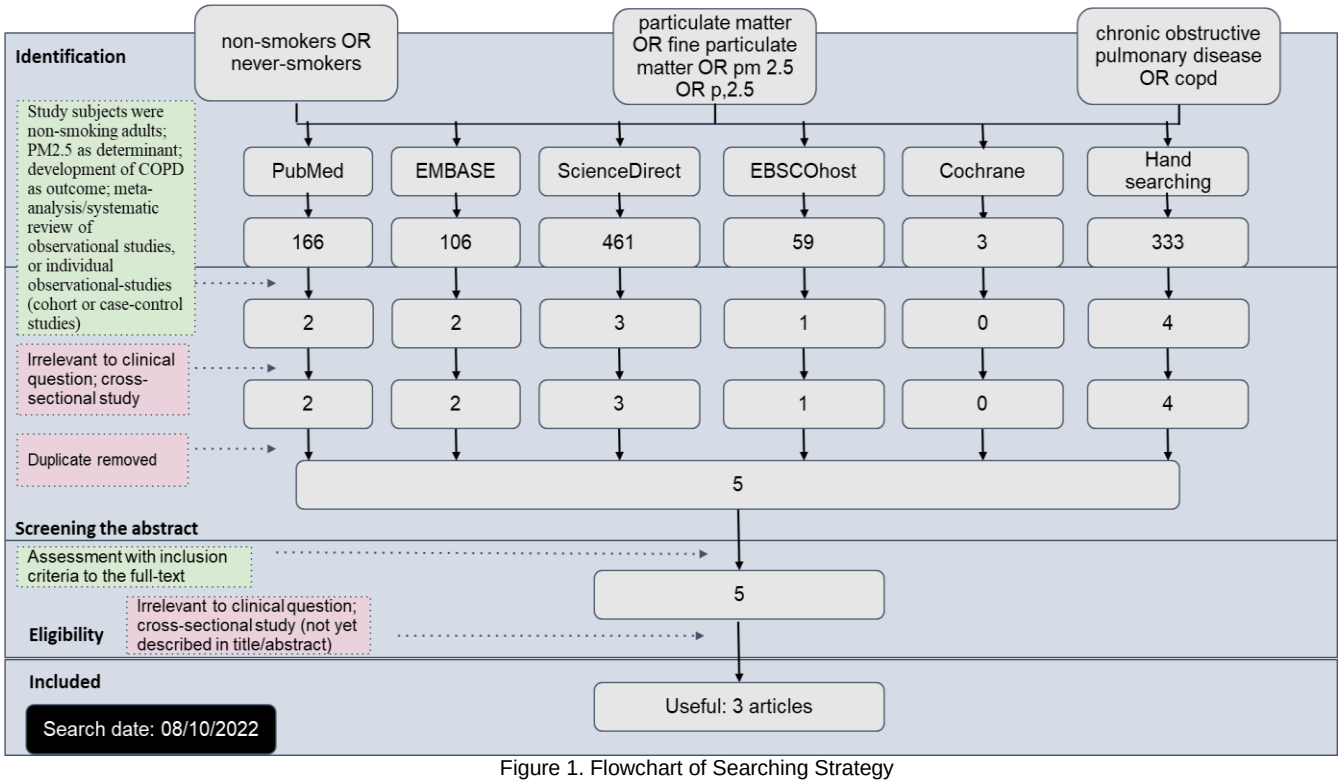

Figure 1. Flowchart of Searching Strategy

RESULTS

A case-control study by Huang et.al. aimed to examine the relationship between exposure to $PM_{2.5}$ and COPD among 3,941 non-smokers adults in Taiwan, who were also participants in Taiwan Biobank Project, from 2008 until 2015. The data on exposure (air pollution) and outcome of interest (COPD) were collected from two different data sources. Air pollution data was obtained from the Air Quality Monitoring Database (AQMD) from 2006 until 2011, while the COPD used the data from the National Health Insurance Research Database (NHIRD). In this study, the adjusted odds ratio (OR) of COPD development in non-smoking adults exposed to $PM_{2.5}$ at a concentration >38.98 ug/m^3 was 1.29 (95% confidence interval [95% CI]=1.01-1.65). They concluded that exposure to $PM_{2.5}$ at such concentrations increased the susceptibility to COPD among non-smokers.[14]

A longitudinal, retrospective-cohort study by Prasad et al investigated the clinical respiratory outcome more than 3.5 years after the prolonged air pollution from the Hazelwood coal mine fire in 2014 and their association with individual-level coal-mine fire $PM_{2.5}$ exposure. The mentioned clinical respiratory outcome was the possibility of developing COPD and related respiratory symptoms. They included 519 adults (aged more than 18 years old at the time of the mine fire). Subgroup analysis revealed that participants consisted of 167 subjects living in Morwell (exposed group) and 82 subjects living in Sale (unexposed group). In this study, the adjusted OR of COPD development among non-smokers exposed to $PM_{2.5}$ was 1.69 (95% CI=1.11-2.58). They suggested that COPD was associated with mean $PM_{2.5}$ exposure among non-smoking adults 3.5 years after exposure.[15]

A prospective cohort study by Fisher et al evaluated the relationship between long-term exposure to $PM_{2.5}$ air pollution and incident cases of chronic respiratory disease, specifically COPD and adult-onset asthma, in the US Nurses' Health Study (NHS) from 1992 to 2000. This study enrolled 121,701 female nurses aged between 30 and 55 years old at the beginning of the study. The adjusted hazard ratio (HR) of COPD incidence with 4-year cumulative average $PM_{2.5}$ exposure among never-smokers was 1.23 (95% CI=0.50-3.06). However, there was no observed statistically significant association among this subpopulation. They found

no evidence in this cohort that long-term exposure to $PM_{2.5}$ can increase the risk of developing COPD.[16]

The summary of each useful article's characteristics and relevant outcome can be seen in Table 2. Results of the critical appraisal of the useful articles are reported in Table 3 (validity) and Table 4 (importance and applicability). After conducting the critical appraisal, we found that only 2 studies (Huang et al and Prasad et al) will be used for discussion and conclusion.[14,15] Fisher et al did not pass the importance appraisal because of the non-significant outcome, so we did not consider it for the applicability appraisal.[16]

Table 2. Characteristics and relevant outcome of the useful articles.

Article	Country	Study Design	Participants	Definition of $PM_{2.5}$ Exposure	Diagnosis of COPD	Relevant Outcome
Huang et al (2019)[14]	Taiwan	Case-control	3,941 subjects	Exposure to $PM_{2.5}$ at a concentration >38.98 ug/m^3 according to data from the Air Quality Monitoring Database (AQMD) by the Environmental Protection Agency (EPA) from 2006–2011.	History of 2 outpatient visits or 1 hospitalization with a diagnosis of COPD as evidenced by the ICD-9 CM diagnosis code of 490, 491, 492, 494, and 496 from 2000–2015.	After multivariate adjustments, exposure to $PM_{2.5}$ at a concentration >38.98 ug/m^3 increased the risk of COPD (adjusted odds ratio [OR]=1.29; 95% CI=1.01-1.65).
Prasad et al (2020)[15]	Australia	Retrospective cohort (follow-up time: 4 years)	519 subjects (subgroup analysis for non-smoking subjects: 167 persons in the exposed group, 82 persons in the unexposed group)	Mean $PM_{2.5}$ exposure across all the locations visited by subjects over the 6-week exposure period (9 February–31 March 2014)	Post-bronchodilator FEV_1/FVC <5th percentile of predicted (lower limit of normal with FEV_1/FVC z-scores <-1.645) on spirometry	There was a 69% increase in the odds of COPD among non-smokers who were exposed to $PM_{2.5}$ compared with those who were not exposed (adjusted OR=1.69; 95% CI=1.11-2.58).
Fisher et al (2016)[16]	United States	Prospective cohort (follow-up time: 8 years)	121,701 subjects	The 4-year cumulative average ambient exposure to $PM_{2.5}$, which was assessed by using the nationwide spatiotemporal models	Subjects who reported a physician diagnosis of COPD on the validated questionnaire and reported a diagnostic test at the time of COPD diagnosis on the supplemental questionnaire	Among never-smokers, there was a suggestion of a higher risk of COPD due to $PM_{2.5}$ exposure, but the association was not statistically significant (adjusted hazard ratio [HR]=1.23; 95% CI=0.50-3.06).

Table 3. Critical appraisal results of the validity of the useful articles

Article (Year)	Study Design	Level of Evidence	Similarity between Two Groups	Same way Measurement	Adequate Time for Follow-Up	Exposure Preceding Outcome	Dose-Response Gradient	Dechallenge-Rechallenge	Consistent Association	Biological Sense
Huang et al. (2019)[14]	Case-control	3b	**Yes** Adjustments were done for sex, age, education, alcohol drinking, physical activity, body mass index (BMI), second-hand smoke, and FEV1/FVC.	**Yes** Study data for the case group and the control group were obtained from the same three databases: (1) Taiwan Biobank; (2) the National Health Insurance Research Database; and (3) the Air Quality Monitoring Database.	**Yes** Subjects were recruited in the Taiwan Biobank project between 2008 and 2015. Air pollution data between 2006 and 2011 were obtained from the Air Quality Monitoring Database.	**Yes** The air pollution data were from 2006-2011, while the diagnosis period was traced from 2000–2015	**Yes** Exposure to $PM_{2.5}$ greater than 38.98 ug/m^3 was significantly associated with COPD (OR=1.29; 95% CI=1.01-1.65). Meanwhile, exposures to concentrations of 32.07-38.98 ug/m^3 (OR=1.12; 95% CI=0.88-1.44) and 29.38-32.07 ug/m^3 (OR=1.09; 95% CI=0.84-1.41) did not show significance.	**Not applicable** It is not possible to intentionally manipulate the exposure and re-exposure of $PM_{2.5}$ to the study subjects. Additionally, COPD is a chronic disease that cannot completely disappear.	**Yes** A study by Jo et al. in Korea also reported that there was a significant increase in COPD-related visits in the $PM_{2.5}$ area of Chungcheon[19]	**Yes** Single nucleotide polymorphisms, which were found as the secondary outcome of this study, are likely to raise the risk of COPD.
Prasad et al. (2020)[15]	Retrospective cohort	2b	**Yes** Adjustments were made for the location of the participants, body mass index category, occupational exposure, employment status, and highest educational qualification.	**Yes** The exposure status of all subjects was assessed based on a chemical transport model provided by the Australian Commonwealth Scientific and Industrial Research Organization's (CSIRO) Oceans & Atmosphere. The outcome was also measured in the same way as spirometry for all subjects.	**Yes** The outcome was measured 3.5 to 4 years after the prolonged exposure.	**No** No statement clearly describes whether there was an attempt to ascertain the COPD status of participants before the exposure.	**Yes** Among non-smokers, there was a dose-response relationship between 10 ug/m^3 increases in mean $PM_{2.5}$ exposure and chest tightness in the previous 12 months (OR=1.46; 95% CI=1.07-2.00).	**Not applicable** It is not possible to intentionally manipulate the exposure and re-exposure of $PM_{2.5}$ to the study subjects. Additionally, COPD is a chronic disease that cannot completely disappear.	**Yes** The association between $PM_{2.5}$ exposure and a higher risk of COPD was also found in a Taiwanese study by Guo et al[21]	**Yes** Smoke exposure is reported to be linked with a decline in lung function, particularly FEV1.

Article (Year)	Study Design	Level of Evidence	Similarity between Two Groups	Same way Measurement	Adequate Time for Follow-Up	Exposure Preceding Outcome	Dose-Response Gradient	Dechallenge-Rechallenge	Consistent Association	Biological Sense
Fisher et al. (2016)[16]	Prospective cohort	2b	**Yes** There were adjustments for age, time period, geographic region, body mass index, alcohol consumption, physical activity, census-tract median household income, and Western dietary pattern.	**Yes** The measurement of exposure used previously validated spatiotemporal exposure models. All participants were also sent questionnaires every 2 years on a multitude of risk factors and health outcomes.	**Yes** The duration of follow-up was 8 years, from 1992 until 2000.	**Yes** This study excluded patients with prevalent cases of asthma or COPD at baseline, as well as participants missing exposure or years of diagnosis.	**No** There was no statistically significant association observed for residential proximity to roads with incident COPD.	**Not applicable** It is not possible to intentionally manipulate the exposure and re-exposure of $PM_{2.5}$ to the study subjects. Additionally, COPD is a chronic disease that cannot completely disappear.	**Unclear** A study of four cohorts participating in the ESCAPE project found no association between $PM_{2.5}$ and incident COPD, but traffic intensity on the nearest major road was positively associated with incident COPD in females and never-smokers.	**Yes** The airway damage and inflammation due to pollution-induced oxidative stress and free radical reactions are considered the pathophysiological mechanisms in COPD development induced by ambient air pollution.

Table 4. Critical appraisal results of the importance and applicability of the useful articles

Article (Year)	Importance		Applicability			
	Magnitude of the Association between Exposure and Outcome	Precision of the Estimate of the Association between Exposure and Outcome	Capability of Extrapolation to the Patient	Patient's Risks of the Adverse Outcome	Patient's Preferences and Concerns	Availability of Alternative Treatments
Huang et al (2019)[14]	Adjusted OR=1.29	95% CI=1.01-1.65	**Yes** The participants of this study are Taiwanese adults. The Asian race of the participants matches with our patients in Indonesia.	**NNH = 23** According to results from Huang et al, we consider the PEER=0.20	**Yes** The results of this study can help us explain to our patients whether $PM_{2.5}$ exposure could increase the risk of COPD development.	**Not relevant** This study is not a clinical trial.
Prasad et al (2020)[15]	Adjusted OR=1.69	95% CI=1.11-2.58	**Yes** The exposed group in this study are people who live near an industrial area and are exposed to PM2.5. This geographical background is similar to our patient's.	**NNH = 10** According to results from Huang et al, we consider the PEER= 0.20	**Yes** The results of this study can help us explain to our patients whether $PM_{2.5}$ exposure could increase the risk of COPD development.	**Not relevant** This study is not a clinical trial.
Fisher et al (2016)[16]	Adjusted HR=1.23	95% CI=0.50-3.06	---*	---*	---*	---*

Note: *The critical appraisal for the applicability of the study by Fisher et al. was not done because the results were considered not important in answering the clinical question.

DISCUSSION

Firstly, the critical appraisal of the validity of the case-control study by Huang et al.[14] found that the COPD group and the control group were distinctly defined. Adjustments for sex, age, education, alcohol, physical activity, body mass index (BMI), secondhand smoke, and the ratio between the forced expiratory volume in 1 second (FEV_1) and the forced vital capacity (FVC) ensured the similarity of both groups. The same three databases--i.e. Taiwan Biobank, the NHIRD, and the AQMD--were used as the source of all participants' data. The time interval between subject recruitment (Taiwan Biobank data from 2008-2015) and analysis of exposure history (the AQMD data from 2006–2011) implied that there was a 2–9-year interval between the recording of $PM_{2.5}$ exposure data and the observation of COPD outcome.

It is considerably sufficient, as Tung et al reported that the incidence rate of COPD among non-smokers exposed to $PM_{2.5}$ in the shipyard was 4.12 cases per 100 person-years during a 4-year follow-up period.[17] Furthermore, participants recruited by Huang et al were local Taiwanese residents living in 74 municipalities; thus, it could be inferred that the subjects' exposure to air pollution had even happened years before the data recording.[14]

To reassure that $PM_{2.5}$ preceded the COPD onset, the authors traced the diagnosis period from 2000–2015, while the air pollution data were taken from 2006–2011. The dose-response gradient was highlighted by the significant association found between exposure to $PM_{2.5}$ at concentrations greater than 38.98 ug/m^3 and COPD, whereas such an association did not show significance at lower concentrations. The "dechallenge-rechallenge" is not relevant in this study.

The causal relationship in this study is similar to Jo et al which found that the number of COPD-related hospital visits in South Korea was significantly and proportionally increased with $PM_{2.5}$ concentration after adjusting for meteorological covariates.[18] The pathophysiological mechanism in the rise of COPD risk due to $PM_{2.5}$ exposure is supported by the role of single nucleotide polymorphisms, as evidenced by the secondary outcome of this study.[14] Therefore, we decided that this study is valid to be used.

In the importance analysis of the study by Huang et al, the adjusted OR is 1.29 (95% CI=1.01-1.65). The narrow confidence interval, which showed a clinically important higher risk of COPD among non-smokers, was the main reason for us to say that the valid results of this study are important.[14]

Subjects enrolled in the case-control study by Huang et al.[14] are Taiwanese adults. The results of this study can be extrapolated to our patient because of their similar Asian race. Based on the results of the study by Huang et al**,** the patient's expected event rate (PEER) is 0.20. So, with the aforementioned OR and PEER in this study, the number needed to harm (NNH) is 23, meaning that we can find 1 incidence of COPD by only having 23 non-smoking adults exposed to $PM_{2.5}$. These findings can also help us explain to our patients the higher risk of COPD development due to $PM_{2.5}$ exposure. At last, we decided that this valid and important evidence of this study applies to our patient.[14]

Secondly, the critical appraisal of the validity of the retrospective cohort study by Prasad et al showed clear definitions of the exposed and unexposed groups.[15] Both groups were similar because there were adjustments made for the location of the participants, BMI category, employment status, highest educational qualification, and also occupational exposure. Assessment of the $PM_{2.5}$ exposure and spirometry for COPD diagnosis was conducted in the same fashion among both groups. The 4-year follow-up was considered adequate since the incidence rate of COPD among non-smokers exposed to $PM_{2.5}$ in the shipyard, which was reported in the study by Tung et al was 4.12 cases per 100 person-years during the same length of follow-up

period.[17] In addition, Kurniawan et al. also reported that the decline of pulmonary function could even be detected 6 months after exposure to the forest fire in Riau.[19]

Prasad et al unfortunately did not provide any clear description of the attempt to determine the COPD status of subjects before the $PM_{2.5}$ exposure, so there is still room for uncertainty as to whether the exposure truly preceded the outcome.[15] The "dechallenge-rechallenge" concept is not applicable in this study either. A dose-response gradient was reflected by the significant association between 10 ug/m^3 increases in mean $PM_{2.5}$ exposure and chest tightness in the prior 12 months. The findings in this study are in line with a study by Guo et al in Taiwan, which revealed a 39% increased risk of emergency presentation due to COPD for every 10 $\mu g/m^3$ increase in 0-7 days' moving average of coal-fire-related $PM_{2.5}$ (OR=1.39; 95% CI=1.06-1.83).[20]

As a support for the biological plausibility of the findings in this study, a study by Gaughan et al showed that a large decline in forced expiratory volume in one second (FEV_1) is associated with exposure to levoglucosan, whose concentration measurement represents the level of fine and ultrafine smoke particles from biomass burning. Hence, we concluded that the results of this study are valid.[21]

The OR in this study is 1.69 (95% CI=1.11-2.58). The 95% confidence interval is narrow and reflects a precision of higher risk of COPD development due to $PM_{2.5}$ exposure. Therefore, we came to the decision that this study's valid results are also important.

Prasad et al recruited people who lived near an industrial area with $PM_{2.5}$ exposure into the exposed group. This environmental setting is similar to our patient's, thus our patient is comparable with the subjects included in the study. The outcome of this study also matches our patient's question.[15] By using the OR reported in this study and the PEER based on the study by Huang et al, the NNH found in this study is 10, indicating that we only need to have 10 non-smoking adults exposed to $PM_{2.5}$ to find 1 new case of COPD. We can also use the results of this study when explaining to our patients the role of $PM_{2.5}$ exposure in increasing the risk of COPD development. Ultimately, we concluded that this evidence can be applied to our patient.[14]

Thirdly, in the prospective cohort by Fisher et al, a critical appraisal of validity found that the exposed and unexposed groups were clearly described. Adjustments had been made for age, geographic region, time, period, physical activity, household income, BMI, alcohol consumption, and dietary pattern, thus making both groups similar. No difference was found in the measurement of exposure and outcome between both groups. The follow-up period was 8 years and was considered long enough.[16]

We could confidently identify that the outcome occurred after exposure in the study by Fisher et al since the authors had excluded patients with frequent cases of COPD or asthma at baseline, as well as patients who had missed either exposure or a year of diagnosis. It is worth considering that no dose-response gradient was proven in this study because the association between the residential accessibility to roads and the COPD incident was not significant. The concept of "dechallenge-rechallenge" is also not relevant in this study.[16]

However, the consistent relationship was questionable since a cohort study by Jacquemin et al reported no relationship between $PM_{2.5}$ and the incidence of COPD.[22] Furthermore, a study by Schikowski et al stated that traffic intensity on the nearest major road had a positive association with COPD incidence among non-smokers and females.[23] The biological evidence of airway damage and inflammation because of air pollution-induced oxidative stress supported the results of this study.[24]

Critical appraisal of the importance of the study by Fisher et al found that the hazard ratio (HR) of COPD development among non-smokers exposed to $PM_{2.5}$ is 1.23 (95% CI=0.50-3.06). However, the 95% confidence interval crosses 1.00, implying the possibility of no true difference in COPD risk between the exposed and unexposed groups in this study. Since the precision of this study's result is not so good, we made a decision that the evidence of this article is valid yet not important to answer our clinical question. Hence, we did not carry on with the applicability appraisal of this study. Furthermore, the subjects included in this study were all female nurses, implying that this study does not apply to our patients.[16]

In general, we obtained 2 valid, important, and applicable articles to answer our clinical question. Those two articles emphasized the higher risk of COPD development among non-smoking adults exposed to $PM_{2.5}$. Possible mechanisms that may explain the causal relationship between $PM_{2.5}$ exposure and COPD have been supported by prior studies. The particles can enter the lungs via breathing and can be retained in the terminal bronchiole or alveoli. This can worsen, especially if our respiratory system's clearance is ineffective.[25] Exposure to $PM_{2.5}$ can also cause macrophage phagocytosis dysfunction by pulmonary oxidative stress activation. All of these mechanisms lead to chronic inflammation in the airway, lung, and DNA methylation conversion in lung tissue.[6,8,9]

In addition, a study by Churg et al. revealed that long-term exposure to high levels of ambient $PM_{2.5}$ can also penetrate and retain in the walls of small airways in non-smoker patients. It might play an important role in small airway remodeling and chronic airway obstruction.[26] In the worst-case scenario, $PM_{2.5}$ can even move to other tissues and organs via the circulation system, causing multi-organ damage.[27]

An association between $PM_{2.5}$ and COPD has also been found in other studies. In a prospective cohort study by Tung et al., 115 shipyard workers were recruited to evaluate the effect of welding fume $PM_{2.5}$ on lung function. The incidence rate of COPD in non-smoking workers was higher than in smoking workers (incidence rate 4.21 vs. 2.51 cases per 100 person-years).[17]

A large sample prospective cohort by Wang et al. showed that long-term exposure to $PM_{2.5}$ was positively associated with a higher risk of COPD (HR=2.5; 95% CI=1.15-1.19), with a higher chance of adverse effects in individuals with high genetic risk (HR=1.19; 95% CI=1.16-1.22) and an unfavorable lifestyle (HR=1.24; 95% CI=1.21-1.26).[4] Another study by Doiron et al. also found that COPD is related to a higher concentration of $PM_{2.5}$ in never-smokers (OR=1.39; 95% CI=1.26–1.53).[10]

LIMITATIONS

This evidence-based case report was limited in that systematic review/meta-analysis of cohort studies relevant to our clinical question was not available in any databases; however, we used cohort and case-control studies as the best available evidence. In addition, the individual lung function after $PM_{2.5}$ exposure was not analyzed in this case report because the indicator and outcome were categorical data. Moreover, we did not specify the length of exposure time $PM_{2.5}$ in the process of literature search; however, the follow-up periods among studies that we critically appraised were considerably less heterogeneous.

Overall, to our knowledge, this is the first evidence-based case report to assert that $PM_{2.5}$ exposure is the risk factor for COPD development among non-smoking adults. The results of this evidence-based case report could be pivotal for the prevention of the disease.

CONCLUSION

Non-smoking adults with exposure to $PM_{2.5}$, compared to those without exposure, are at higher risk of developing COPD. Therefore, adults who do not have a tobacco smoking habit should still be aware that exposure to air pollution, particularly $PM_{2.5}$, can still increase their risk of getting COPD. We recommend stakeholders apply strict policies in regulating the management of air pollution to prevent COPD problems in communities. In addition, further research is needed to assess the association between the duration of $PM_{2.5}$ exposure and COPD incidence.

CONFLICT OF INTEREST

All authors have no conflict of interest to declare.

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