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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. Other than cigarette smoking, previous studies showed air pollution (such as $PM_{2.5}$) exposure 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 association between $PM_{2.5}$ and COPD in non-smoking patients is still unclear.

Methods: Literature search was performed in 5 online medical databases (PubMed, EMBASE, ScienceDirect, EBSCOhost, and Cochrane Library) along with 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 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 study had important results with adjusted odds ratio 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 for 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, $PM_{2.5}$

INTRODUCTION

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

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 having 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 disease, including COPD.[3–5] One of the air pollutant component that may play significant role in the development of COPD is Particulate Matters (PM), along with Sulfur Oxide (SO), Ozone (O_3), and Nitric Oxide (NO).[4,6]

PM consists of solid and liquid droplets suspended in the atmosphere. PM can be divided into three categories, which are ultrafine (size <0.1 μm), fine particulate (size 0.1-2.5 μm), and coarse particulate (size 2.5-10 μm). $PM_{2.5}$ or fine particulate matter has small size with big superficial area that can make it easier to absorb toxic components in the air.[6] $PM_{2.5}$ is known as the 5th highest risk factor of death worldwide.[7]

$PM_{2.5}$ can enter lung via breathing and stay in terminal bronchiole and alveoli, especially if the respiratory system's clearance is inefective.[8] $PM_{2.5}$ exposure promotes macrophages recruitment and cytokines release, including TNF-α, IL-6, and IL-1β. Macrophage recruitment leads to eosinophil recruitment and production of IFN-γ and IL-17 by T cells. In addition, $PM_{2.5}$ can also make macrophage phagocytosis dysfunction by pulmonary oxidative stress activation. All of these process lead to chronic inflammation in airway and lung.[6,9] Furthermore, exposures to $PM_{2.5}$ was associated with DNA methylation conversion in lung tissue.[10]

The relationship between $PM_{2.5}$ and COPD has been explored in previous studies. Higher prevalence of COPD is found in patients with $PM_{2.5}$ exposure, especially in male, high genetic risk, and unhealthy lifestyle.[4,11] $PM_{2.5}$ is also associated with worse pulmonary function and increased risk of exacerbation, hospitalization, and death in COPD patients.[11–14] However, the cause and effect association between $PM_{2.5}$ and COPD in non-smoking patients is still unclear.

Case Illustration

A 45-year-old male came to pulmonary outpatient clinic with recurring shortness of breath since 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 chronic obstructive pulmonary disease (COPD). The physician had once read that one of the most common air pollutants around industrial areas is the Particulate Matter 2.5 ($PM_{2.5}$). He would like to know whether the exposure to $PM_{2.5}$ could rise the risk of developing COPD among non-smoking adults.

Clinical Question

Clinical question was formulated as follows:

- Patient (P): Non-smoking adults (aged 18 years or older)
- Indicator (I): Exposure to $PM_{2.5}$
- Comparison (C): No exposure to $PM_{2.5}$
- Outcome (O): 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

Strategy of Literature Searching

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, 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

Selection of articles was conducted based on the inclusion criteria, consisting of: (1) studies which included subjects were non-smoking adults; (2) observed determinants involved $PM_{2.5}$; (3) observed outcome was 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 over them led to the decision that there were 3 useful articles to be critically appraised (**Figure 1**).

Critical Appraisal

The three useful articles obtained in the literature searching 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.

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 of Taiwan Biobank Project, from 2008 until 2015. The data of exposure (air pollution) and outcome of interest (COPD) was 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 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 the 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 concentration increased the susceptibility to COPD among non-smokers.

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.

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 incident 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.

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 drawing conclusions. Fisher et al did not pass the importance appraisal because of the non significant outcome so we did not consider it for applicability appraisal.

DISCUSSION

Firstly, critical appraisal for validity of the case-control study by Huang et al.[15] 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 FEV_1/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.[18] 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. Furthermore, participants recruited by Huang et al.[15] were local

Taiwanese residents living in 74 municipalities, thus it could be inferred that the subjects' exposure to air pollution had even happened years prior to the data recording.

To reassure that the $PM_{2.5}$ preceded the COPD onset, the authors had 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 the exposure to $PM_{2.5}$ at concentration greater than 38.98 ug/m^3 and COPD, whereas such association did not show significance at lower concentrations. The "dechallenge-rechallenge" is not relevant in this study. The causal relationship in this study is similiar to Jo et al.[19] 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. 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. Thus, we decided that this study is valid be used.

In the importance analysis of the study by Huang et al.[15], the adjusted OR is 1.29 (95%CI 1.01-1.65). The narrow confidence interval, which showed a clinically impotant higher risk of COPD among non-smokers, was the main reason for us to say that the valid results of this study are important.

Subjects enrolled in the case-control study by Huang et al.[15] are Taiwanese adults. The results of this study can be extrapolated to our patient because of their similar Asian racial. Based on the results in the study by Huang et al.[15], 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 patient about 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 is applicable for our patient.

Secondly, critical appraisal of validity of the retrospective cohort study by Prasad et al.[16] showed clear definitions of the exposed and unexposed group. Both groups were similar because there were adjustments done 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 were 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.[18] was 4.12 cases per 100 person-years during the same length of follow-up period. In addition, Kurniawan et al. also reported that the decline of pulmonary function could even be detected 6 months after exposure to forest fire in Riau.[20]

Prasad et al.[16] unfortunately did not provide any clear description about the attempt to determine the COPD status of subjects prior to the $PM_{2.5}$ exposure, so there is still a room of uncertainty whether the exposure truly preceded the outcome. 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.[21] in Taiwan which revealed a 39% increased risk of emergency presentation due to COPD for every 10 μg/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). As a support for the biological plausibility of the findings in this study, a study by Gaughan et al.[22] showed that a large decline in forced expiratory volume in one second (FEV_1) is associated with exposure to levoglucosan, which 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.

The OR in this study is 1.69 (95% CI 1.11-2.58).[16] 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 a decision that this study's valid results are also important.

Prasad et al.[16] 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 in this study also matches our patient's question. By using the OR reported in this study and the PEER based on the study by Huang et al.[15], 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 patient about the role of $PM_{2.5}$ exposure in increasing the risk of COPD development. Ultimately, we deached a conclusion that this evidence can be applied to our patient.

Thirdly, in the prospective cohort by Fisher et al.[17], 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 made both groups similiar. 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.

We could confidently identify that the the outcome occurred after exposure in the study by Fisher et al.[17] since the authors had excluded patients with frequent cases of COPD or asthma at baseline, as well as patients who had missing either exposure or 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. However, the consistent relationship was questionable since a cohort study by Jacquemin et al.[23] reported no relationship between $PM_{2.5}$ and incidence of COPD. Furthermore, a study by Schikowski et al.[24] stated that traffic intensity on the nearest major road had positive association with COPD incident among non-smokers and females. The biological evidence of airway damage and inflammation because of air pollution-induced oxidative stress supported the results of this study.[25]

Critical appraisal of the importance of the study by Fisher et al.[17] 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 of 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 applicability appraisal of this study.

Furthermore, the subjects included in this study were all female nurses implying that this study is not applicable for our patient.

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 which may explain the causal relationship between $PM_{2.5}$ exposure and COPD have been supported by prior studies. $PM_{2.5}$ can enter our lungs via breathing and can be retained in the terminal bronchiole or alveoli. This can be worsened especially if our respiratory system's clearance is ineffective.[8] $PM_{2.5}$ exposure promotes macrophages recruitment and cytokines release, including TNF-α, IL-6, and IL-1β. Macrophage recruitment leads to eosinophil recruitment and production of IFN-γ and IL-17 by T cells. $PM_{2.5}$ can also make macrophage phagocytosis dysfunction by pulmonary oxidative stress activation. All of these mechanism lead to chronic inflammation in airway, lung, and DNA methylation conversion in lung tissue.[6,9,10] In addition, a study by Churg et al. stated that long term exposure to high level of ambient $PM_{2.5}$ can also penetrate into and retain in the walls of small airways in non-smoker patients that might play an important role in small airway remodeling and chronic airway obstruction.[26] On the worst case scenario, $PM_{2.5}$ can even move to other tissues and organs via the circulation system causing multi-organ damage.[27]

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 smoking workers (incidence rate 4.21 vs 2.51 cases per 100 person-years).[18] A large sample prospective cohort by Wang et al showed that long term exposure to $PM_{2.5}$ was positively associated with higher risk of COPD (HR 2.5; 95%CI 1.15-1.19), with higher chance of adverse effects in individual with high genetic risk (HR 1.19; 95%CI 1.16-1.22) and unfavorable lifestyle (HR 1.24; 95%CI 1.21-1.26).[4] Another study by Doiron et al also found that COPD is related with higher concentration of $PM_{2.5}$ in never-smoker (OR 1.39; 95%CI 1.26-1.53).[11]

LIMITATION

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 was considerably not so 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 the COPD development among non-smoking adults. The results of this evidence-based case report could be pivotal for 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 to 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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