Methodology of an Observational Cohort Study for Subjects with Chronic Obstructive Pulmonary Disease in Dusty Areas Near Cement Plants

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Abstract
Chronic Obstructive Pulmonary Disease (COPD) occurs in genetically susceptible individuals by chronic exposure to environmental factors. Although cigarette smoking is a major risk factor for this disease, environmental factors including vapor, gas, dust, and fumes can also impact lung function. Emissions from cement plants are known to have negative health effects; however, the effects of cement dust on COPD subjects living near cement plants have not been fully investigated. We plan to conduct a study to observe clinical outcomes of COPD areas near the cement plants in Korea. Here, we present methodology for an observational cohort study. Cement plants are mostly located in the Kangwon and Chungbuk provinces in Korea. COPD subjects in these areas are recruited for medical examinations consisting of a questionnaire of environmental exposure and health habits, symptom severity, pulmonary function testing, and computed tomography. Blood and urine samples are obtained and subjects will be followed up over 10 years. The patient cohort of this study differs from other COPD study populations in that the participants have been living in dusty areas near cement plants; we therefore termed this cohort COPD in dusty area.

Keywords: Chronic Obstructive Lung Disease (COPD); Cohort study; Cement; Dusty areas; Environmental exposure

Abbreviation: CAT: COPD Assessment Test; COPD: Chronic Obstructive Pulmonary Disease; CT: Computed Tomography; FEV₁: Forced Expiratory Volume in one second; FVC: Forced Vital Capacity; mMRC: The modified Medical Research Council dyspnea scale

Introduction
Chronic Obstructive Lung Disease (COPD) is a leading cause of morbidity and mortality worldwide [1]. It is characterized by airflow limitation that is not fully reversible [2], and cigarette smoking has been established as a major risk factor since the 1950s [3,4]. However, emerging evidence suggests that other risk factors, such as air pollutants and workplace exposure, are strongly associated with COPD [5]. Based on population-based studies, it is estimated that about a quarter of COPD cases occur in non-smokers [6-8].

Cement is one of the most important building materials in the world. A cement plant can be a significant source of air pollutants, and cement dust can affect respiratory symptoms and lung function. Previous studies indicate reduced lung function [9-11], a higher prevalence of chronic respiratory symptoms [11,12], and a higher prevalence of COPD in cement production workers [13]. While most studies on cement dust focus on the health effects of occupational exposure, few studies have investigated whether cement dust can affect residents living near cement plants [14,15].

In Korea, cement plants are mostly located in the Kangwon and Chungbuk provinces. Concerns have been raised that emissions from cement plants may have distinct clinical presentation and disease progression. To date, the health impact of cement dust on COPD subjects living near cement plants has not been fully investigated. Therefore, a long-term observational cohort study on COPD subjects in cement dusty areas is warranted. We plan a strategy to recruit and follow up a cohort of COPD subjects living near cement plants to investigate clinical outcomes of COPD developed in cement dusty areas of Korea.

Our hypothesis is that COPD subjects, who were exposed to cement dust by living in areas near cement plants, represent different clinical features from subjects of other COPD study cohorts.

Materials and Methods
Selection of regions for study population
Cement plants are mostly located in the Kangwon and Chungbuk provinces of the Republic of Korea. Most cement plants began operating before 1970 and have a production capacity of 5,000,000-10,000,000 tons of clinker per year. Several administrative districts have been selected for surveys on the health effects of cement dust on inhabitants, which have taken into consideration of distance from cement plants and wind direction based on meteorological data among areas surrounding cement plants, by the National Institute of Environmental Research of the Ministry since 2007. The administrative districts have areas of approximately 40-80 km² and thousands of residents.

Participant recruitment
A health survey on six Korea’s administrative districts of Korea has been performed since 2007. The participation rate in the health survey

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was approximately 40-60%. All subjects with respiratory symptoms or ventilatory dysfunction on health survey and volunteers among non-participants on initial survey are subjected to further examination. Subjects confirmed as having airflow limitation by spirometry are recruited to the cohort study, while subjects not having airflow limitation are recruited as controls.

Airflow limitation is defined as a post-bronchodilator forced expiratory volume in 1s over forced vital capacity value of less than 0.7 (FEV1/FVC%<70). Subjects will be recruited until the end of 2015 and will be followed up over 10 years (Figure 1).

**Dietary assessment methods**

For the evaluation of dietary intake, we administer more than 6 times 24-hour dietary record (24-HDR) to all subjects over one-year period. The days that the 24-HDR are administered are chosen to ensure a balanced representation of weekdays and weekend days for each participant. All recalls are obtained by an unannounced in-person interview in the evening.

**Outcome measurement**

Outcome measurements for CODA cohort subjects are described in Table 1, along with the measurement interval and methods. At the enrollment visit, all patients were evaluated with medical interviews, physical examinations, spirometry, bronchodilator reversibility tests, laboratory test, and Computed Tomography (CT) scan. Initial questionnaire data include demographics, history of disease, habitant area, and environmental exposure. Intensity and durations for respiratory symptoms of cough, sputum, dyspnea, and wheezing were evaluated. Dyspnea was evaluated using the modified Medical Research Council Dyspnea grade. Health-related quality of life was evaluated by calculating the total score of patients reported COPD Assessment test (CAT). Environmental factors include occupational history, cooking fuels, heating fuels, and passive smoking exposure. The question for occupational exposure includes type and duration of job. The question for direct exposure history to cooking or heating fuels was “For cooking and/or heating, have you ever been exposed to fuels of wood or charcoal for one year or more?” Our COPD cohort will be compared with controls exposed or COPD not exposed, for clinical outcomes of respiratory symptoms, CAT, nutritional status, number of exacerbations, hospitalization, and FEV1 decline.

The methods for measuring volumetric CT scans are based on the reports of the Korean obstructive lung disease (KOLD) cohort study [16]. Upon enrollment, and then at 3-year intervals, volumetric CT scans are taken at full inspiration and expiration using 16-multidetector CT scanners produced by one manufacturer (Somatom Sensation 16, Siemens Medical Systems, Bonn, Germany). Images of the whole lung will be extracted automatically, and the attenuation coefficient of each pixel will be calculated. Emphysema index (volume fraction of the lung ≤950 HU), air trapping index (mean lung density at full expiration over mean lung density at full inspiration), and airway thickening (wall area percentage of two segmental bronchi; RBI and LBI+2) will be used for quantitative assessment using CT.

Spirometry is performed using an Easy One kit (NDD; Zurich, Switzerland). To assess post-bronchodilator FEV1 increases, spirometry is performed before bronchodilation and 15 minutes after inhalation of 400 μg of salbutamol through a metered-dose inhaler (MDI) with spacer. Bronchodilator reversibility is evaluated by assessing post-bronchodilator FEV1 increase in liters. All pulmonary function tests is performed as recommended by the American Thoracic Society (ATS)/European Respiratory Society (ERS) [17].

Serum, plasma, and urine samples are collected for biomarker and genetic/proteomic analysis. The descriptive statistics of the clinical variables will be expressed as means and standard deviations, and the Student's t and chi-square tests will be used to confirm statistical significance between the environmental exposures. And we will use mixed effect model for repetitive data as exacerbation and hospitalization. P values of less than 0.05 will be considered significant. All statistical analyses will be taken counsel form statisticians.

Our Institutional Review Board approved analyses of the clinical and imaging data (Institutional Review Board of Kangwon National University Hospital 2012-06-007-001). Individual informed written consent was obtained from all patients.

**Discussion**

COPD is caused by chronic exposure to environmental factors in genetically susceptible individuals. Since cigarette smoking is known as a major risk factor, most studies on the clinical characteristics of COPD have been conducted only in cigarette smokers. Although many risk factors of COPD have been reported, the association between air pollutants and clinical outcomes of COPD is not fully known. In the current CODA cohort study, we will investigate how environmental exposures of cement dust are associated with distinct clinical features in smokers and non-smokers with COPD.

Although COPD is defined by the presence of airflow limitation, significant variation in clinical presentation and disease progression exists among patients with a similar degree of airflow limitation. The identification and subsequent grouping of key elements of the COPD syndrome into clinically meaningful and useful subgroups, phenotypes, have been proposed as a potential solution to optimize diagnosis, assessment, and management [18]. Recently, it was reported that a history of inhalational exposure to sulfur-mine fires may be associated with constrictive bronchiolitis in soldiers serving in the Middle East [19]. This suggests that there may be a specific association between a specific respiratory condition and exposure to a particular inhalational dust. Therefore, it can also be assumed that chronic exposure of a
particular air pollutant, such as cement dust, may induce distinct clinical characteristics of respiratory disorders, as COPD. Therefore, long-term observational cohort studies on subjects exposed to an environmental factor are warranted to elucidate whether the factor is related to clinically meaningful outcomes of COPD. Such data will improve our understanding of COPD heterogeneity and pathophysiology.

Exposure to cement dust has been demonstrated to have adverse effects on human health. Because of the volatility of cement dust, the main targets in the human body are the respiratory system, skin, and eyes. It has been reported that cement dust in work environments are associated with a higher prevalence of chronic respiratory symptoms and reduced lung function [10-12]; however, no difference in mortality rates was seen in a cohort study of cement workers in a plant in Central Italy [20]. Furthermore, a recent survey found that cement workers were at a higher risk of developing COPD (prevalence of 18.8%) than the administrative workers of the same factory (prevalence of 4.8%), independent of smoking habits [21]. However, it is not certain how these workplace-based exposures interact with tobacco exposure and how cement dust exposure is associated with COPD. Because most studies have focused on occupational exposure or been conducted in a cross-sectional design, we may understand only a fragment knowledge about environmental exposure of cement dust and clinical outcomes of COPD.

Furthermore, there have been only a few studies that have focused specifically on the emission health effects on the population living in the proximity of cement plants, even results of the few studies have been conflicting. In a Portland study, the incremental individual risk increase due to emissions of the cement plant were found to be very low not only with regard to health effects, but also in relation to toxicological and cancer risks produced by pollutants emitted by the cement kiln [14].

Table 1: Summary of clinical measures collected in the chronic obstructive lung disease in dusty area cohort.

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
</tr>
<tr>
<td>Physical examination</td>
<td>By trained nurses</td>
</tr>
<tr>
<td>Age, gender, height, weight,</td>
<td></td>
</tr>
<tr>
<td>Clinical history</td>
<td>Using a uniform questionnaire</td>
</tr>
<tr>
<td>Habitat area</td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
</tr>
<tr>
<td>Environmental exposure</td>
<td>Cooking and heating fuels</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>Current/ex/- never, (pack years)</td>
</tr>
<tr>
<td>Quality of life</td>
<td>CAT</td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td>Cough, sputum, dyspnea†, wheezing</td>
</tr>
<tr>
<td>Medical illness</td>
<td></td>
</tr>
<tr>
<td>Pulmonary function test (pre- and post-spirometry)</td>
<td>As per ATS/ERS task force recommendations</td>
</tr>
<tr>
<td>FEV/FVC</td>
<td>Ratio</td>
</tr>
<tr>
<td>FEV₁</td>
<td>Liter, % of predicted</td>
</tr>
<tr>
<td>FVC</td>
<td>Liter, % of predicted</td>
</tr>
<tr>
<td>Inspiratory V₉₅₀ (%)</td>
<td>Chest CT scan</td>
</tr>
<tr>
<td>Wall area (%)</td>
<td>Mean lung density ratio</td>
</tr>
<tr>
<td>Laboratory test</td>
<td>CBC, chemistry, electrolyte, CRP</td>
</tr>
<tr>
<td>Blood, urine sample</td>
<td>Storage‡</td>
</tr>
<tr>
<td>Every 3 months</td>
<td></td>
</tr>
<tr>
<td>Clinical history</td>
<td>Telephone interviews</td>
</tr>
<tr>
<td>Every years</td>
<td></td>
</tr>
<tr>
<td>Clinical history</td>
<td></td>
</tr>
<tr>
<td>Pulmonary function test</td>
<td></td>
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<tr>
<td>Every 3 years</td>
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<td>Clinical history</td>
<td>Clinical history</td>
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<td>Clinical history</td>
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<td>Pulmonary function test</td>
<td>Pulmonary function test</td>
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<tr>
<td>Pulmonary function test</td>
<td>Pulmonary function test</td>
</tr>
<tr>
<td>Chest CT scan</td>
<td></td>
</tr>
</tbody>
</table>

†Dyspnea is graded with modified Medical Research Council dyspnea scale.
‡Blood and urine sample will be in storage for future genetic study and we have plan to measure the level of heavy metal poisoning (lead, mercury, cadmium).
CAT=COPD assessment test, ATS=American Thoracic Society, ERS=European Respiratory Society
FEV₁=forced expiratory volume in 1 second, FVC=forced vital capacity.
V₉₅₀=volume fraction of the lung below -950 HU, Wall area (%)=wall area/(wall area * lumen area)*100
Mean lung density ratio=mean lung density ratio of full expiration and inspiration
CBC=complete blood count, CRP=C-reactive protein.
contrast, a case-control study in Italy reported an association between exposure to cement plant emissions and the risk of hospital admission for cardiovascular or respiratory causes, particularly among children [15]. The latter study was reported more recently and appears to be reliable because it used more precise methods, like iso-concentration maps of the pollutants to estimate the average exposure for each person, compared to the Portland study. However, neither study produced direct evidence for the relationship between cement dust exposure and clinical outcomes of COPD because of their cross-sectional design and because they focused on acute health effects. Therefore, a longitudinal cohort study, such as the proposed COPD cohort, may bring further insight.

Currently, the majority of data on the pathophysiology, mechanisms, and response to treatment regarding COPD is based on its relationship to cigarette smoking. Although risk factors other than smoking, such as air pollutants and workplace exposure to dust, have been reported, little is known about the clinical characteristics of non-smokers with COPD. Conflicting results on the association between occupational exposure and COPD among never smokers have been reported. While the European Community Respiratory Health Survey (ECRHS) found no association between chronic bronchitis and dust and fume exposure in never smokers [22], a significant association between dust exposure and spirometry-defined COPD was reported in a sample of never-smoker patients in the United States referred to a pulmonary function laboratory [23]. In a patient series of COPD, occupational exposure was associated with distinct clinical characteristics; older male patients reported increased work-related respiratory disability, more asthma-like symptoms, and atopy in smokers and ex-smokers with COPD [18]. In addition, in an Asian cohort, history of exposure to biomass fuels or dusty jobs was related to the frequency of symptoms, severe airflow limitation, and poor quality of life [24]. However, to date, there is insufficient evidence to support an association between air pollutants and distinct clinical outcomes of COPD. Data from non-smoker subjects in the COPD cohort will give us additional information into the different clinical features compared to smoker COPD patients.

This study has several limitations. First, there was only a 50% participation rate for health surveys in the target areas. The relatively low response rate may have introduced selection bias and therefore makes the cohort not representative of the general population. Second, the intensity and duration of past exposure to cement dust may not be accurate because it is collected based on participant memory and questionnaires on residence duration. However, this is currently the best method available to us. Third, the adverse respiratory health effects in patients with COPD may not only be attributable to cement dust. Adverse effects on the environment and/or human health occur (or may occur) as a consequence of exposure to one or more physical, chemical, or biological agent. Smoking history should be considered in further analyses. Fourth, it is not currently clear whether this study will investigate clinical characteristics in COPD patients caused by past exposure of cement dust or respiratory effects of cement dust for COPD caused by any causes.

In conclusion, the COPD cohort in dusty area study is a unique study aimed at demonstrating that environmental exposures to cement dust are associated with distinct clinical features and natural history in smokers and non-smokers with COPD. Through this, a more comprehensive understanding of the relative contribution of environmental exposure to COPD features will offer an important platform on which to construct targeted and effective interventions to reduce the burden of disease.

Summary

We plan to conduct a study to determine the impact of dust from the cement industry on clinical outcome of COPD subjects. This cohort study differs from other COPD study populations in that the participants have been living in dusty areas near cement plants.

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Notation of prior abstract publication/presentation

The abstract was submitted and presented at the “Airway Vista 2013” held on 29-31 Mar 2013 at Asan Medical Center, Seoul, Korea.

Author Contributions

Dr WJ Kim: takes responsibility for the veracity and completeness of the data and the data analyses. The authors developed the design and concept, approved the statistical plan, had full access to, and interpreted the data, wrote the article, and was responsible for decisions with regard to publication.

Dr Y Hong: contributed to developing the study protocol, approved the statistical plan, interpreted study data, wrote and reviewed drafts of the manuscript, and approved the final version of the manuscript.

Dr JW Kwon, Prof SA Lee, Prof. YJ Han, Prof. JY Moon, Dr HY Kim, Dr SS Han, and Dr SJ Lee contributed to developing the study protocol, was a study investigator, interpreted study data, contributed to and reviewed drafts of the manuscript, and approved the final version of the manuscript.

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