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ASSOCIATION BETWEEN PM2.5 AND THE COEXISTENCE OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND CORONARY HEART DISEASE

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CAPSTONE PROJECT PAPER

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Abstract

Aim: To identify PM2.5 as a risk factor for chronic obstructive pulmonary disease (COPD) and coronary heart disease (CHD) respectively, and to explore the magnitude of the association of PM2.5 with the coexistence of CHD and COPD, by using the combined dataset of 1999-2014 EPA Air Data and 2017 BRFSS SMART data (age 18 and older).

Methods: Cross-sectional study was designed to identify the association between PM2.5 exposure and COPD and CHD. The PM2.5 exposure values were adapted from the county-level EPA Air Data, the yearly mean values of PM2.5 were used to determine the association. Characteristics of sex, age, race, health status, and socioeconomic status were obtained from the BRFSS SMART data. Binary logistic regressions using binary/two-level ("high-level" and "low-level" determined by EPA National Ambient Air Quality Standards) PM2.5 exposure values and continuous PM2.5 exposure values respectively were applied to identity the association between PM2.5 exposure and target health outcomes.

Results: Adjusted odds ratios (AOR) (with adjustments of sex, race, education, and income) between binary PM2.5 and CHD among elderly group (with age equal to or older than 65) was 1.074 ($P<0.05$, 95% CI 1.017-1.134); the same association among younger group (with age younger than 65) was not significant. A significant association between binary PM2.5 and COPD was observed (for elderly group, AOR=1.129 95% CI 1.072-1.188; for younger group, AOR=1.195 95% CI 1.136-1.257). 2448 (1.4%) respondents reported that had ever been told have both CHD and COPD, there was a significant association between binary PM2.5 and the coexistence of COPD and CHD among the elderly population (AOR=1.168 95% CI 1.054-1.295). Associations between continuous PM2.5 (adjusted by per 5 μg/m^3 increase) and the outcomes suggested the same trend of results.

Conclusions: The association between PM2.5 and CHD was not as strong as the association between PM2.5 and COPD. However, the association between PM2.5 and the coexistence of CHD and COPD among elderly population was stronger than the associations between PM2.5 and either of them, according to the AOR. These finds may help with the diagnosis of CHD within populations that have COPD, especially in high PM2.5 exposure areas. Future studies that can determine the temporal sequence of association are required to figure out the association between COPD and CHD regarding to the PM2.5 exposure.

Introduction

COPD is the current fourth leading cause of death in the world. By 2020, COPD will be the third leading cause of death. COPD is a major cause of chronic morbidity and mortality around the world (Global Initiative for Chronic Obstructive Lung Disease, 2018). Back to 1993, (Dockery et al., 1993) conducted a population-based, cross-sectional studies of metropolitan areas in six US cities to study the effects of air pollution on mortality. After adjusting for smoking and other risk factors, including occupational exposure to dust, gases, or fumes there was a statistically significant associations between fine particles and mortality, they compared the adjusted mortality-rate of the most polluted cities and the least polluted cities, the rate ratio was 1.26 (95% CI, 1.08-1.47). In a cohort study of US veterans regarding to traffic density and mortality, PM2.5 had the largest RR among all the individual air quality measures, 1.118 (95% CI, 1.038-1.203), (Lipfert, Wyzga, Baty, & Miller, 2006).

COPD is characterized by persist respiratory symptoms and airflow limitation; the issues are due to airway and/or alveolar abnormalities that cause a decrease in the ratio of forced expiratory volume in 1 s (FEV1) to forced vital capacity (FVC); if the ratio is lower than 70%, it would be defined as a persist respiratory symptoms and airflow limitation, (Sin & Man, 2005). The adverse issues are usually caused by significant exposure to noxious particles or gases. Tobacco smoking is characterized as the main risk factor of COPD, (Loffredo et al., 2016); besides, the environmental exposure is also a risk factor. COPD can be resulted from host factors as well, including genetic abnormalities, abnormal lung development and accelerated aging, (Global Initiative for

Chronic Obstructive Lung Disease, 2018).

CHD is also called coronary artery disease (CAD). The buildup of plaque in the arteries of the heart can induce a reduction of blood flow to the heart muscle. The main symptom is angina (chest pain) which can usually last longer than 10 minutes, and even longer than 30 minutes. Other symptoms of CHD include shortness of breath, sleep problems, fatigue, lack of energy, (American Heart Association, 2019) Risk factors for CHD relate more to health behavior, such as tobacco smoking, inactivity, unhealthy diet, high blood pressure, diabetes, overweight and obesity, and host factors like aging and family history of heart disease, (Mendis et al., 2011). A study based on BRFSS and EPA Air Data illustrated a positive association between PM2.5 and cardiovascular disease (CVD), the multivariable-adjusted odds for the multiplicity of CVD outcomes increased by 1.32 (95% CI 1.23–1.43) times per 10 mg/m^3 increase in PM2.5, (Feng, Yang, & Cook, 2012). (Johnson & Parker, 2009) conducted a study based on the National Health Interview Survey (NHIS) from 1999 to 2005 and EPA Air Data, there was an association between $10mg/m^3$ increase in PM2.5 exposure and heart disease with a small elevated risk (AOR=1.08 95% CI 1.00-1.16).

A meta-analysis of 110 studies, dated to May 2011 was conducted for PM 2.5 and daily mortality and hospital admissions. According to this study, per 10 $\mu g/m^3$ increment in PM2.5 increased the risk of death due to COPD by 3.86%; around 2.30% increase in the risk of hospital admissions due to COPD among the population with ages older than 65 years; this meta-analysis also indicated that per 10 $\mu g/m^3$ increment in PM2.5 could cause 3.36% increase in the risk of death due to CHD; around 2.50%

increase in the risk of hospital admissions due to CHD among the population with ages older than 65 years, (Atkinson, Kang, Anderson, Mills, & Walton, 2014). A study of the association between PM2.5 and cardiovascular hospitalizations indicated that PM2.5 total mass and PM2.5 road dust were the main contributors to the hospitalization rate, (Bell et al., 2013).

Smoking is the main risk factor for both COPD and CHD. With symptoms of simple chronic bronchitis, the risk of death due to coronary events increases 50%. The decrease of the ratio FEV1 to FVC increases the risk of a coronary event by 30%. As 10% decrease in FEV1, all-cause mortality increases 14%, cardiovascular mortality increases 28%, non-fatal coronary events increases 20%. Coexistence of extrapulmonary comorbidities, such as coronary heart disease, heart failure, ischemic heart disease, systemic venous thromboembolism, hypertension, anxiety and depression, osteoporosis, metabolic syndrome and diabetes, sleep disturbance, influence the prognosis of patients with COPD, (Cavaillès et al., 2013; Global Initiative for Chronic Obstructive Lung Disease, 2018). Coexistence of COPD and coronary heart disease can not only worsen the prognosis of COPD, but also worsen the prognosis of CHD. Coronary heart disease is often unrecognized in COPD, (Cavaillès et al., 2013).

Several previous studies indicated the associations between PM2.5 and COPD or CHD regarding to other health outcomes. (McCormack et al., 2015) conducted a study on the effects of indoor PM on COPD among obese and non-obese participants. The results showed that obesity modified the effects of indoor PM on COPD respiratory outcomes; PM2.5 increases were associated with greater increases in nocturnal symptoms, dyspnea and rescue medication use among obese participants. There are studies on the associations between PM2.5 and CHD regarding to hypertension, (Johnson & Parker, 2009). This study suggested that a 10 mg/m^3 increase in PM2.5 exposure was associated with an elevated risk of hypertension among non-Hispanic white people (AOR=1.10 95% CI 1.04-1.17).

Methods

Individual-Level Data

Data on COPD, CHD status and individual covariates were obtained from the U.S. Behavioral Risk Factor Surveillance System (BRFSS), SMART: City and County Survey Data. BRFSS, which is conducted by the Centers for Disease Control and Prevention (CDC), is the nation's premier system of health-related telephone surveys that collect state data about U.S. residents (18+ years old and non-institutionalized) regarding their health-related risk behaviors, chronic health conditions, and use of preventive services. BRFSS now collects data in all 50 states as well as the District of Columbia and three U.S. territories. The survey is based on Random Digit Dialing (RDD) techniques on both landlines and cell phones and a standardized core questionnaire, as well as optional modules, and state-added questions. Since 2005, BRFSS began to monitor cardiovascular disease (CVD) status among U.S. adults. In the section of CVD, angina or coronary heart disease (CHD) status is collected by the question "(Ever told) you had angina or coronary heart disease?", (Centers for Disease Control and Prevention, 2019).

BRFSS data are state-level, for this study, area-level data are required to correspond the city-level ambient air pollution data. The SMART project of BRFSS produces data set with localized health information for metropolitan and micropolitan statistical areas (MMSAs) which have geographic subdivisions designated by the U. S. Office of Management and Budget and used by the U. S. Census Bureau as of June 2003. For the 2017 BRFSS combined landline telephone and cellular telephone data that have 500 or more respondents, MMSAs would be selected in the SMART BRFSS data, (Centers for Disease Control and Prevention, 2017a).

The general concept of a metropolitan or micropolitan statistical area is that of a core area containing a substantial population nucleus, together with adjacent communities and all having a high degree of economic and social integration. Metropolitan statistical areas are the groups of counties that contain at least one urbanized area of 50,000 or more inhabitants; micropolitan statistical areas are the groups of counties that contain at least one urban cluster of at least 10,000 but less than 50,000 inhabitants; metropolitan divisions are smaller groups of counties within a metropolitan statistical area of 2.5 million or more inhabitants, (U.S. Census Bureau, 2019)

This study applied the BRFSS SMART data set of 2017. There were 136 MMSAs selected in the data set; 230875 respondents participated in this SMART project. 167032 (72.35%) respondents were non-Hispanic white; 23484 (10.17%) respondents were non-Hispanic black; 22022 (9.54%) respondents were Hispanic; except for 4799 (2.08%) invalid respondents, the other race had respondents of 13538 (5.86%).

Ambient air pollution data

Particulate Matter (PM) is defined as the term for a mixture of solid particles and liquid droplets found in the air. PM2.5 are fine inhalable particles, with aerodynamic diameters of 2.5 micrometers or less, (U.S. Environmental Protection Agency, 2018). Concentrations of PM2.5 were extracted primarily from the Air Quality System (AQS) database, also called Air Data, which is conducted by U.S. Environmental Protection

Agency (EPA).

The years of Air Data ranged from 1999 to 2014; and there was no systematic sampling of PM2.5 before 1999. The dataset was national-wide and in counties or core based statistical areas (CBSA) level with exceptional events. Exceptional events, such as high winds and wildfire, were flagged by states. The dataset contained values of 24-hr mean of PM2.5 concentrations from 615 monitoring sites. 24-hr mean of PM2.5 was the Weighted Annual Mean by calendar quarter for the year, (U.S. Environmental Protection Agency, 1999-2014). The monitoring sites with at least 50% of observations (percent of observations calculated as the ratio of valid years for the year of 1999 to 2014) were referred to provide ambient air pollution data for PM2.5 (total 343 sites). The yearly mean level values of PM2.5 mean was calculated. (Table 1)

Statistical Analysis

Valid number of respondents in the 2017 BRFSS SMART survey was 230,875; the respondents were above the age of 18 years and lived in the metropolitan or micropolitan statistical areas of the U.S. Valid number of air monitoring sites was 343 in the U.S.

Core based statistical areas (CBSA) consists of metropolitan statistical areas and micropolitan statistical areas, so, CBSA and MMSA represent the same locating strategy. The BRFSS SMART data and the EPA Air Data were merged by the common variable, CBSA (also known as MMSA). The number of monitoring sites in the overlap of the two datasets sorted by statistical areas was 106. 175,328 (76.0%) respondents lived in these 106 areas and were selected for the statistical analysis. Binary logistic regression was applied to obtain the model and the adjusted odds ratio. For statistical analysis of PM2.5, the mean values were used as both a binary variable and a continuous variable separately. Because these two types are common in the previous studies, so that we can compare the results to prior results by setting PM2.5 as both binary variable and continuous variable. When considered as a binary variable, the mean values of PM2.5 was defined into two levels of exposure. According to EPA National Ambient Air Quality Standards (NAAQS), the primary standard for PM2.5 is 12 $\mu g/m^3$ which is an annual arithmetic mean that is averaged over 3 years. The primary standards are set to protect public health. 12 $\mu g/m^3$ was used as the cut point. According to EPA's rounding rule for annual values, exposures which were equal to or below that 12.04 $\mu g/m^3$ were defined as "low-exposure", otherwise, the exposures were defined as “high-exposure”. The continuous mean values of PM2.5 were used to calculate adjusted odds ratios by per 5 μg/m^3 PM2.5 exposure increase.

Variables of sex, age above 65 or not, COPD and CHD status, smoking status, and the education levels were used in as the original coding methods. Variable of race was classified into four catalog: non-Hispanic White, non-Hispanic Black, Hispanic, and other races; variable of obese was calculated by BMI values (BMI greater than or equal to 30 was classified as obese); women with hypertension only during pregnancy were classified as “no hypertension” (also applicable in diabetes); the number of “not sure and missing” in the variable of income was classified as a category (unknown) in the regression because it took 17% of the number of the entire study sample. All the unknown/unsure and missing values were treated as missing values (classified as “Unknown”) in the regression, expect for the income values.

The respondents were stratified into two groups by age (equal to or older than 65, and younger than 65), due to the large portion of elderly population, and strong associations between age and the outcomes; also, age may be a confounder for some of the covariables. Logistic regressions for three outcomes were conducted by using binary PM2.5 values and continuous PM2.5 values, respectively. Each logistic regression was basically adjusted for sex, race, education levels, and income levels. Variables of hypertension, obese, diabetes, and smoking status were included individually in different logistic regressions.

SAS (v9.4; SAS Institute Inc., Cary, NC, USA) was used to merge the EPA Air

Data and the BRFSS SMART data. Variables of CBSA and yearly 24-h PM2.5 mean values in the EPA Air Data and variables in the BRFSS SMART data of annual sequence number (SEQNO), MMSANAME, "(Ever told) you had angina or coronary heart disease?" (CVDCRHD4) "(Ever told) you have chronic obstructive pulmonary disease, C.O.P.D., emphysema or chronic bronchitis?" (CHCCOPD1), whether the age is older than 65 (_AGE65YR), sex (SEX), race (_RACE), hypertension (BPHIGH4), diabetes (DIABETE3), whether BMI is greater than 30 (_BMI5), education levels (EDUCA), income levels (_INCOMG), and smoking status (_SMOKER3) were output to the merged dataset. SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) was used to output descriptive statistics and frequency distributions; to calculate the crude bivariate odds ratios among the variables; and to compute the logistic regressions.

Results

Among the 175,328 respondents, 44.1% were male (55.8% female); 33.7% were equal to or older than 65; non-Hispanic White took the largest composition of 73.9%, followed by Hispanic (9.6%) and non-Hispanic Black (9.0%). 7.8% respondents reported being told have COPD (47.6% of these respondents lived in “high” exposure areas); 5.3% respondents reported being told have CHD (45.5% of these respondents lived in “high” exposure areas); and 1.4% respondents reported “Yes” for both CHD and COPD. (Table 2)

When age was considered as a covariable and had not been stratified, crude odds ratios between age and the outcomes were 4.512 (95% CI 4.314-4.719), 2.312 (95% CI 2.232-2.395), 3.684 (95% CI 3.387-4.007), for COPD, CHD, and the coexistence, respectively. The prevalence of COPD in elderly group and younger group were 12.2% and 5.7%, respectively; the prevalence of CHD in elderly group and younger group were 10.8% and 2.6%, respectively; the prevalence of COPD in elderly group and younger group were 2.7% and 0.7%, respectively.

Association between PM2.5 and COPD

Binary PM2.5. In the logistic regression in which PM2.5 values were used as a binary variable, the crude odds ratio between PM2.5 and COPD was 1.150 (95% CI 1.094-1.208) in the elderly group. When adjusted for variables of age, sex, race, education, and income, the AOR between PM2.5 and COPD was 1.129 (95% CI 1.072-1.188); adjustments for hypertension, obese, diabetes, and smoking status in additional models did not show magnitude differences. Among the younger group, crude OR and AOR were higher than those among the elderly group, 1.195 (95% CI 1.136-1.257) and 1.174 (95% CI 1.113-1.238), respectively. Also, adjustments for hypertension, obese, diabetes, and smoking status in additional models did not show magnitude differences.

Continuous PM2.5. In the logistic regression in which PM2.5 values were used as a continuous variable, the AOR in the elderly group was 1.191 (95% CI 1.133-1.246) when included age, sex, race, education, and income in the model; variables of hypertension, obese, diabetes, and smoking status did not affect the results. In the younger group, the AOR was lower than those in the elderly group, 1.168 (95% CI 1.111-1.228). The additional adjustments for hypertension, obese, diabetes, and smoking status made no differences to the results. (Table 3)

Association between PM2.5 and CHD

Binary PM2.5. Crude OR between binary PM2.5 and CHD among the elderly group was 1.079 (95% CI 1.024-1.137). The adjusted model for age, sex, race, education, and income suggested that odds increased 7.4% in high PM2.5 exposure area; additional model adjustments for hypertension, obese, diabetes, and smoking status did not distinctly change the results. However, among the younger group, PM2.5 mean values were no longer a significant risk factor.

Continuous PM2.5. In the logistic regression model using continuous PM2.5 values, elevated odds for an increase of 5 $\mu g/m^3$ PM2.5 exposure were about 7.8% (AOR=1.078 95% CI 1.025-1.133). Additional model adjustments for hypertension, obese, diabetes, and smoking status did not distinctly change the results. Among the younger group, the associations between PM2.5 and the outcomes were no longer significant. (Table 4)

Association between PM2.5 and both CHD and COPD

Among the respondents that reported being told ever had COPD and the respondents that reported being told ever had CHD, 2448 (1.4%) respondents reported "Yes" in both questions; 1584 (64.7% of these respondents) respondents were belong to the elderly group.

Binary PM2.5. Among the elderly group, the crude odds ratio was 1.183 (95% CI 1.071-1.307). AOR for basic variables of sex, race, education levels, and income levels was 1.168 (95% CI 1.054-1.295). Adjustments for the additional variables of hypertension, obese, diabetes, and smoking status made no obvious differences. Among the younger group, PM2.5 did not have associations with the outcome of the coexistence of COPD and CHD.

Continuous PM2.5. Among elderly group, AOR for basic variables of sex, race, education levels, and income levels was 1.228 (95% CI 1.116-1.357). Additional models included variables of hypertension, obese, diabetes, and smoking status did not affect the AOR obviously. Among younger group, the basic AOR for variables of sex, race, education levels, and income levels was 1.168 (95% CI 1.030-1.323). Additional adjusted models for hypertension and diabetes indicated that PM2.5 was not a significant risk factor for the coexistence of COPD and CHD; however, adjusted models for obese and smoking status suggested significant associations between

PM2.5 and the coexistence of COPD and CHD, (AOR=1.168 95% CI 1.030-1.336, AOR=1.156 95% CI 1.020-1.323, respectively). (Table 5)

Associations between the covariables and the outcomes

Adjusted OR for variables of sex, race, education levels, and income levels were obtained from the logistic regressions involved with these variables. Adjusted OR for hypertension, obese, diabetes, and smoking status were obtained from the separate logistic regressions included each of these variables respectively.

Sex had significant associations with CHD among both elderly group and younger group (male as reference, OR=2.191 95% CI 2.074-2.315, OR=1.543 95% CI 1.431-1.663, respectively); also, sex had a significant associations with the coexistence of COPD and CHD among the elderly group (OR=1.663 95% CI 1.498-1.846). Lower education levels and income levels were involved with higher odds ratios; overall, the odds ratios among the younger group were correspondingly higher than the odds ratios among the elderly group. Variables of specific characteristics of hypertension, obese, diabetes, and smoking status had significant associations with the three outcomes among the two age stratified groups. (Table 6 & 7)

Discussion

The weighting methodology of 2017 BRFSS is comprised of two sections: design weight and raking. Design weighting is conducted to reduce bias due to unequal probability of selection; raking is used to adjust for demographic differences between those persons who are sampled and the population that they represent.

The weight of each geographic stratum, the number of landline phones within a household, and the number of adults who use those phones are considered when calculating design weights. In addition, 2017 BRFSS also includes cellular telephone respondents, for the respondents use both cell phone and landline telephone, an adjustment to the design weights to account for the overlapping sample frames has been used. The combined landline and cell phone design weight has been truncated based on quartiles prior to raking. So that to prevent any adults in a state from carrying extremely large weights into the raking, and to prevent any adults from having extremely small design weights. Nine state level margins and allows up to eight additional margins are used to adjust sub-state populations within the raking; four additional margins if a county has at least 500 interviews available, and four additional margins if multiple regions have been defined for a state and each region has at least 500 interviews, (Centers for Disease Control and Prevention, 2017b). As a telephone-based survey, BRFSS may call recall bias due to the self-reported information, in addition, persons without a telephone or a cell phone are not included; BRFSS does not address geographic and social disparities, so the socioeconomic status from BRFSS do not represent the national status, (Ali H. Mokdad, 2003; Institute of Medicine (US) Committee on a National Surveillance System for Cardiovascular and Select Chronic Diseases, 2011).

The percentages of the elderly group with the three outcomes were 52.7% (for COPD), 68.0% (for CHD), and 65.2% (for coexistence of COPD and CHD). The odds ratios had not been changed obviously when stratified by age, and no evidence that indicates the relationship between PM2.5 exposure and age, so, there was no confounding by age.

It suggested that high level PM2.5 or a 5 $\mu g/m^3$ increase of PM2.5 could increase the odds of COPD by 10-20% among both elderly group and younger group. (Liu et al., 2017) reported the strong association between PM2.5 exposure and COPD, OR=2.416 95% CI 1.417-4.118 with PM2.5 level at >35 and ≤75 $\mu g/m^3$, OR=2.530 95% CI 1.280-5.001 with PM2.5 level at >75 $\mu g/m^3$. However, Liu's study was conducted in a province of China in which there had a relatively high PM2.5 concentration, thus the PM2.5 cut point(s) was higher than this study and PM2.5 had more classification levels, which provided more beneficial PM2.5 distribution. The EPA air monitoring sites which were not in the metropolitan and micropolitan statistical areas were not included in this study. Also, when setting cut points for the exposure, non-differential misclassification may be brought to this study; the exposure used in this study is from ambient air, so technically, the exposures had no difference between the populations who had or not had the outcomes.

For CHD, PM2.5 had no significant associations with the outcomes in the younger group. Compared with the elderly group, covariables of education and income had stronger association with the outcomes in the younger group. Socio-economic variables had been proved that have associations with CVD (Psaltopoulou et al., 2017), according to a recent study about the associations among socioeconomic variables, pollution levels, and self-reported histories of asthma, stroke, and heart attack in the U.S., higher income levels were associated with lower PM2.5; when income levels were included as a predictor, PM2.5 would not have significant association with heart attack. (Cox, 2017) In this study, higher income levels were associated with the three outcomes, especially in the younger group in which income levels had stronger associations with the three outcomes than the elderly group; in the younger group, income levels had stronger associations with the coexistence outcome. Thus, income may affect the association between PM2.5 and CHD in this study. In addition, income had stronger association with the coexistence of COPD and CHD in both age groups.

Smoking is a risk factor for COPD, in this study, current heavy smoker had the strongest association with COPD in both age groups, however, when considering smoking as predictor for CHD, former smoker had the strongest association with CHD in both age groups; so we can assume that smoking may cause a long-term effect on cardiovascular; and the association between smoking and the coexistence of COPD and CHD was not stronger than the associations with each outcome.

In the elderly group, the associations between PM2.5 and the coexistence of COPD and CHD were stronger than the associations with each outcome separately when adjusted for hypertension, obese, diabetes, and smoking status, respectively.

Limitations

The ambient air pollution data was collected from monitoring sites in the metropolitan and micropolitan statistical areas where had a high degree of social and economic integration. In this study, 40.2% of the respondents had college or high education level, 42.9% of the respondents were in income level of $50,000 or more. According to previous studies, people with the high social degree and economic integration were more likely to answer and finish the telephone survey. Income levels may confounding the association between PM2.5 and CHD (Cox, 2017), so future studies should consider income as a stratified variable, especially for younger population.

Regional disparity of PM2.5 was not considered due to the data source, because the distributions of the air monitoring sites were not concentrated enough to reflect the air quality in one statistical area. The study of (Johnson & Parker, 2009) used annual air quality estimates that were averaged from monitors within 20 miles of the respondent's residential block group; this method can be applied in the future study to control the underestimates or overestimates caused by inaccurate PM2.5 in a relatively large area. In addition, occupational exposure also relates to PM2.5 exposure. The sources of PM2.5 have a broad range, including incomplete combustion, automobile emissions, dust, cooking, and chemical reactions in the atmosphere, etc. For further studies of PM 2.5 sources, personal monitoring can be applied for specific situations, such as occupational exposures and extreme high ambient exposure, (Moore et al., 2016). Apart from the sources of PM2.5, the accumulation of PM2.5 also relates to geography and meteorology. A study from Korea indicated that climate factors also have effects on the development and severity of respiratory diseases. With the decrease of relative humidity, the effect of PM on respiratory diseases would be increased, (Jo et al., 2017).

There is an estimated 25-45% of patients with COPD are non-smokers (Salvi & Barnes, 2009), since smoking can affect both PM2.5 exposure and the outcomes, thus, smoking may be a confounder for the associations between PM2.5 and the outcomes; future studies can be conducted with stratification of smoking status.

There is not enough epidemiology studies of the coexistence of COPD and CHD; for now, the link between COPD and CHD has been found that is independent of any other confounding coronary risk factors, such as smoking status, cholesterol, systemic hypertension and BMI (Sin & Man, 2005). However, there were strong associations between PM2.5 and hypertension, BMI, and smoking, so, the regression models in this study could not indicate the associations among the other health outcomes (e.g., hypertension, obese, and smoking) and the coexistence of COPD and CHD properly.

Conclusions

The findings in this study indicate that among the elderly population with ages that are equal to or greater than 65, PM2.5 is a risk factor for COPD, CHD, and the coexistence of COPD and CHD which has a magnitude with association of PM2.5. But the association between PM2.5 and CHD was not as strong as the association between PM2.5 and COPD.

These finds may help with the diagnosis of CHD within the populations with COPD, especially in high PM2.5 exposure areas. Future studies that can determine the temporal sequence of association are required to figure out the association between COPD, CHD, and the PM2.5 exposure.

For the areas where have complex topography and the areas where have more concentrated industries and mining, more monitoring sites are required to measure more representative PM2.5 values. If possible, BFRSS may be set for specific areas regarding to pollutions to provide evidence for pollution-related adverse health outcomes.

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Table 1. Distributions of PM2.5, 1999–2014 from 106 sites in contiguous U.S. region.

	Number of Monitoring Sites	Yearly Mean Levels (μg/m3)						
		Mean	25% Q1	50% Median	EPA NAAQS (Primary) [a]	75% Q3	100% Max	Interquartile Range
PM2.5 Mean	106	11.9	9.8	11.4	12.0	14.2	20.5	4.4

a. EPA regulates particulate matter in primary level and secondary level. Primary standards set limits to protect public health, including the health of "sensitive" populations such as asthmatics, children, and the elderly. Secondary standards set limits to protect public welfare, including protection against decreased visibility, damage to animals, crops, vegetation, and buildings

Table 2. Characteristics of sample.

	N	% of Total
Sex		
Male	77311	44.1%
Female	97899	55.8%
Unknown [a]	118	0.1%
Age		
>=65	59041	33.7%
<65	113765	64.9%
Unknown [a]	2522	1.4%
Race		
Non-Hispanic white	129588	73.9%
Non-Hispanic black	15831	9.0%
Hispanic	16875	9.6%
Other	9635	5.5%
Unknown [a]	3399	1.9%
Hypertension		
Yes	69928	39.9%
No	104838	59.8%
Unknown [a]	562	0.3%
Obese		
BMI>=30	48948	27.9%
BMI<30	111857	63.8%
Unknown [a]	14523	8.3%
Diabetes		
Yes	25619	14.6%
No	149415	85.2%
Unknown [a]	294	0.2%
Education		
Less than high school or GED	11318	6.5%
High school graduate	43737	24.9%
Some college or technical school	49095	28.0%
College and higher education	70501	40.2%
Unknown [a]	677	0.4%

Income		
Less than $15,000	13010	7.4%
$15,000 to less than $25,000	22444	12.8%
$25,000 to less than $35,000	14647	8.4%
$35,000 to less than $50,000	20411	11.6%
$50,000 or more	75198	42.9%
Unknown [b]	29618	16.9%
Smoking		
Heavy Smoker	16104	9.2%
Light Smoker	7123	4.1%
Former Smoker	46746	26.7%
Never	97840	55.8%
Unknown [a]	7515	4.3%
CHD		
Yes	9347	5.3%
No	164620	93.9%
Unknown [a]	1361	0.8%
COPD		
Yes	13671	7.8%
No	160840	91.7%
Unknown [a]	817	0.5%
CHD and COPD		
Yes	2448	1.4%
No	172880	98.6%
Unknown [a]	237	0.1%

a. “Unknown” was identified as missing values and not included in the adjusted models

b. “Unknown” of variable of income was included as a catalog in the adjusted models

Table 3. Crude and adjusted odds ratios (OR) and 95% confidence interval (CI) for associations between PM2.5 and COPD, stratified by age.

>=65 years		95% Confidence Interval			95% Confidence Interval	
	Binary PM2.5	**Lower**	**Upper**	**Continuous PM2.5**	**Lower**	**Upper**
Crude OR	1.150	1.094	1.208	-	-	-
Adjusted OR [a]	1.129	1.072	1.188	1.191[b]	1.133	1.246
&Hypertension	1.118	1.062	1.177	1.179[b]	1.122	1.234
&Obese	1.127	1.069	1.189	1.179[b]	1.122	1.240
&Diabetes	1.121	1.065	1.181	1.179[b]	1.127	1.240
&Smoking	1.137	1.078	1.200	1.174[b]	1.116	1.234
<65 years						
Crude OR	1.195	1.136	1.257	-	-	-
Adjusted OR [a]	1.174	1.113	1.238	1.168[b]	1.111	1.228
&Hypertension	1.148	1.088	1.211	1.145[b]	1.094	1.203
&Obese	1.162	1.100	1.228	1.162[b]	1.105	1.221
&Diabetes	1.152	1.092	1.216	1.150[b]	1.094	1.203
&Smoking	1.163	1.100	1.228	1.156[b]	1.100	1.215

a. Adjusted for: sex, race, education level, and income level

b. Adjusted by per 5 μg/m^3 PM2.5 increase

Table 4. Crude and adjusted odds ratios (OR) and 95% confidence interval (CI) for associations between PM2.5 and CHD, stratified by age.

>=65 years		95% Confidence Interval			95% Confidence Interval	
	Binary PM2.5	**Lower**	**Upper**	**Continuous PM2.5**	**Lower**	**Upper**
Crude OR	1.079	1.024	1.137	-	-	-
Adjusted OR [a]	1.074	1.017	1.134	1.078 [b]	1.025	1.133
&Hypertension	1.058	1.001	1.117	1.062 [b]	1.010	1.116
&Obese	1.087	1.028	1.149	1.089 [b]	1.036	1.145
&Diabetes	1.060	1.004	1.120	1.067 [b]	1.015	1.122
&Smoking	1.083	1.025	1.145	1.083 [b]	1.030	1.139
<65 years						
Crude OR	1.041	0.968	1.121	-	-	-
Adjusted OR [a]	1.027	0.953	1.108	1.010 [b]	0.946	1.078
&Hypertension	0.991	0.918	1.070	0.985 [b]	0.923	1.057
&Obese	1.018	0.942	1.100	1.015 [b]	0.951	1.089
&Diabetes	0.993	0.920	1.071	0.980 [b]	0.914	1.046
&Smoking	1.031	0.954	1.113	1.010 [b]	0.942	1.078

a. Adjusted for: sex, race, education level, and income level

b. Adjusted by per 5 μg/m^3 PM2.5 increase

Table 5. Crude and adjusted odds ratios (OR) and 95% confidence interval (CI) for associations between PM2.5 and the coexistence of COPD and CHD, stratified by age.

>=65 years		95% Confidence Interval			95% Confidence Interval	
	Binary PM2.5	**Lower**	**Upper**	**Continuous PM2.5**	**Lower**	**Upper**
Crude OR	1.183	1.071	1.307	-	-	-
Adjusted OR [a]	1.168	1.054	1.295	1.228[b]	1.116	1.357
&Hypertension	1.143	1.031	1.268	1.209[b]	1.100	1.330
&Obese	1.177	1.059	1.309	1.240[b]	1.122	1.370
&Diabetes	1.149	1.036	1.274	1.215[b]	1.100	1.336
&Smoking	1.182	1.063	1.313	1.228[b]	1.111	1.350
<65 years						
Crude OR	1.122	0.979	1.285	-	-	-
Adjusted OR [a]	1.070	0.930	1.231	1.168[b]	1.030	1.323
&Hypertension	1.013	0.880	1.168	1.116[b]	0.985	1.271
&Obese	1.059	0.916	1.223	1.168[b]	1.030	1.336
&Diabetes	1.029	0.892	1.185	1.127[b]	0.995	1.284
&Smoking	1.069	0.927	1.234	1.156[b]	1.020	1.323

a. Adjusted for: sex, race, education level, and income level

b. Adjusted by per 5 μg/m^3 PM2.5 increase

Table 6. Adjusted odds ratios (OR) and 95% confidence interval (CI) for associations between covariables and outcomes among respondents who are equal to or older than 65 years old.

	COPD			CHD			CHD and COPD		
	Adjusted OR	95% Confidence Interval		Adjusted OR	95% Confidence Interval		Adjusted OR	95% Confidence Interval	
		Lower	Upper		Lower	Upper		Lower	Upper
Sex [a]									
Male	ref			ref			ref		
Female	1.045	0.990	1.102	2.191	2.074	2.315	1.663	1.498	1.846
Race [a]									
White, non-Hispanic	ref			ref			ref		
Black, non-Hispanic	0.788	0.716	0.868	0.905	0.816	1.004	1.523	1.217	1.905
Hispanic	0.392	0.339	0.455	0.645	0.559	0.744	0.455	0.343	0.604
Others	1.162	1.022	1.323	1.021	0.884	1.178	0.874	0.728	1.051
Education [a]									
College and higher education	ref			ref			ref		
Some college or technical school	1.521	1.418	1.631	1.291	1.204	1.384	1.782	1.539	2.064
High school graduate	1.673	1.559	1.795	1.258	1.169	1.353	1.870	1.612	2.169
Less than high school or GED	2.329	2.103	2.579	1.515	1.353	1.697	2.699	2.220	3.282
Income [a]									
$50,000 or more	ref			ref			ref		
$35,000 to less than $50,000	1.523	1.395	1.662	1.136	1.040	1.241	1.348	1.120	1.622
$25,000 to less than $35,000	1.606	1.461	1.765	1.256	1.141	1.384	1.563	1.289	1.896
$15,000 to less than $25,000	2.091	1.924	2.273	1.459	1.338	1.591	2.143	1.814	2.532
Less than $15,000	3.104	2.805	3.434	1.704	1.521	1.909	3.418	2.826	4.135
Missing	1.363	1.256	1.478	1.117	1.029	1.213	1.274	1.072	1.514
Hypertension [b]	1.521	1.439	1.609	2.593	2.431	2.766	2.819	2.466	3.222
Obese [b]	1.262	1.193	1.335	1.401	1.322	1.485	1.717	1.543	1.910
Diabetes [b]	1.393	1.316	1.475	2.237	2.113	2.368	2.430	2.189	2.698
Smoking [b]									
Non-smoker	ref			ref			ref		
Former smoker	3.495	3.282	3.721	1.485	1.401	1.573	2.756	2.431	3.125
Current light smoker	5.476	4.783	6.269	1.351	1.139	1.602	4.447	3.506	5.640
Current heavy smoker	6.571	5.996	7.202	1.026	0.908	1.158	3.231	2.685	3.889

a. Adjusted odds ratios are obtained from the logistic regressions with variables of sex, race, education levels, and income levels

b. Adjusted odds ratios are obtained from the separate logistic regressions with variables of sex, race, education levels, income levels, and each specific characteristic respectively

Table 7. Adjusted odds ratios (OR) and 95% confidence interval (CI) for associations between covariables and outcomes among respondents who are younger than 65 years old.

	COPD			CHD			CHD and COPD		
	Adjusted OR	95% Confidence Interval		Adjusted OR	95% Confidence Interval		Adjusted OR	95% Confidence Interval	
		Lower	Upper		Lower	Upper		Lower	Upper
Sex [a]									
Male	ref			ref			ref		
Female	0.714	0.676	0.754	1.543	1.431	1.663	1.031	0.897	1.186
Race [a]									
White, non-Hispanic	ref			ref			ref		
Black, non-Hispanic	0.650	0.597	0.707	0.806	0.712	0.911	0.604	0.484	0.756
Hispanic	0.262	0.236	0.290	0.517	0.454	0.588	0.206	0.154	0.277
Others	0.891	0.805	0.985	1.005	0.874	1.155	1.140	0.905	1.435
Education [a]									
College and higher education	ref			ref			ref		
Some college or technical school	1.983	1.837	2.141	1.451	1.313	1.604	2.386	1.899	3.000
High school graduate	2.485	2.300	2.685	1.443	1.300	1.602	2.750	2.187	3.458
Less than high school or GED	4.125	3.727	4.565	2.038	1.765	2.353	4.836	3.702	6.319
Income [a]									
$50,000 or more	ref			ref			ref		
$35,000 to less than $50,000	1.864	1.691	2.056	1.357	1.182	1.558	2.033	1.495	2.763
$25,000 to less than $35,000	2.286	2.057	2.539	1.534	1.314	1.792	2.665	1.937	3.669
$15,000 to less than $25,000	3.596	3.309	3.907	2.653	2.366	2.976	5.793	4.570	7.343
Less than $15,000	5.864	5.383	6.388	3.851	3.416	4.340	10.289	8.137	13.010
Missing	2.109	1.931	2.303	1.612	1.426	1.822	3.034	2.343	3.929
Hypertension [b]	2.725	2.582	2.875	6.495	5.967	7.071	7.600	6.398	9.027
Obese [b]	1.545	1.462	1.633	1.896	1.755	2.048	2.137	1.851	2.467
Diabetes [b]	2.572	2.413	2.741	4.929	4.549	5.340	5.334	4.622	6.157
Smoking [b]									
Non-smoker	ref			ref			ref		
Former smoker	3.327	3.096	3.575	2.463	2.250	2.696	4.610	3.774	5.631
Current light smoker	3.897	3.527	4.306	1.875	1.616	2.175	4.127	3.169	5.375
Current heavy smoker	5.163	4.794	5.561	1.842	1.646	2.061	4.484	3.632	5.537

a. Adjusted odds ratios are obtained from the logistic regressions with variables of sex, race, education levels, and income levels

b. Adjusted odds ratios are obtained from the separate logistic regressions with variables of sex, race, education levels, income levels, and each specific characteristic respectively

References

1. Ali H. Mokdad, D. F. S., Wayne H. Giles. (2003). Public Health Surveillance for Behavioral Risk Factors in a Changing Environment Recommendations from the Behavioral Risk Factor Surveillance Team. *National Center for Chronic Disease Prevention and Health Promotion*.

2. American Heart Association. (2019). Retrieved from https://www.heart.org/en

3. Atkinson, R. W., Kang, S., Anderson, H. R., Mills, I. C., & Walton, H. A. (2014). Epidemiological time series studies of PM 2.5 and daily mortality and hospital admissions: a systematic review and meta-analysis. *Thorax, 69*(7), 660. doi:10.1136/thoraxjnl-2013-204492

4. Barratt, B., Chatzidiakou, L., Moore, E., Quint, J., Beevers, S., Kolozali, S., . . . Smeeth, L. (2017). Characterisation of COPD exacerbations using personal environmental exposure monitoring. *Eur. Resp. J., 50*(s61). doi:10.1183/1393003.congress-2017.PA421

5. Bell, M. L., Ebisu, K., Leaderer, B. P., Gent, J. F., Lee, H. J., Koutrakis, P., . . . Peng, R. D. (2013). Associations of PM2.5 Constituents and Sources with Hospital Admissions: Analysis of Four Counties in Connecticut and Massachusetts (USA) for Persons ≥ 65 Years of Age. *Environmental Health Perspectives, 122*(2). doi:10.1289/ehp.1306656

6. Cavaillès, A., Brinchault-Rabin, G., Dixmier, A., Goupil, F., Gut-Gobert, C., Marchand-Adam, S., . . . Diot, P. (2013). Comorbidities of COPD. *European respiratory review : an official journal of the European Respiratory Society, 22*(130), 454-475. doi:10.1183/09059180.00008612

7. Centers for Disease Control and Prevention. (2017a). SMART: BRFSS City and County Data and Documentation. Retrieved from https://www.cdc.gov/brfss/smart/Smart_data.htm

8. Centers for Disease Control and Prevention. (2017b). Weighting the BRFSS Data. https://www.cdc.gov/brfss/annual_data/2017/pdf/weighting-2017-508.pdf

9. Centers for Disease Control and Prevention (Producer). (2019). Behavioral Risk Factor Surveillance System.

10. Chow, J. C. (2006). Health Effects of Fine Particulate Air Pollution: Lines that Connect. *Journal of the Air & Waste Management Association, 56*(6), 707-708. doi:10.1080/10473289.2006.10464484

11. Cox, L. A. (2017). Socioeconomic and air pollution correlates of adult asthma, heart attack, and stroke risks in the United States, 2010–2013. *Environmental Research, 155*, 92-107. doi:10.1016/j.envres.2017.01.003

12. Dockery, D. W., Pope, C. A., Xu, X., Spengler, J. D., Ware, J. H., Fay, M. E., . . . Speizer, F. E. (1993). An Association between Air Pollution and Mortality in Six U.S. Cities. *The New England Journal of Medicine, 329*(24), 1753-1759. doi:10.1056/NEJM199312093292401

13. Feng, J., Yang, W., & Cook, A. R. (2012). Effects of Particulate Air Pollution on Cardiovascular Health: A Population Health Risk Assessment. *PloS one., 7*(3), e33385. doi:10.1371/journal.pone.0033385

14. Global Initiative for Chronic Obstructive Lung Disease. (2018). *Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease*.

15. Gunen, H., Gulbas, G., In, E., Yetkin, O., & Hacievliyagil, S. S. (2010). Venous thromboemboli and exacerbations of COPD. *The European respiratory journal, 35*(6), 1243-1248. doi:10.1183/09031936.00120909

16. Institute of Medicine (US) Committee on a National Surveillance System for Cardiovascular and Select Chronic Diseases. (2011). *A Nationwide Framework for Surveillance of Cardiovascular and Chronic Lung Diseases*. Washington (DC): National Academies Press (US).

17. Jo, E.-J., Lee, W.-S., Jo, H.-Y., Kim, C.-H., Eom, J.-S., Mok, J.-H., . . . Park, H.-K. (2017). Effects of particulate matter on respiratory disease and the impact of meteorological factors in Busan, Korea. *Respiratory Medicine, 124*, 79-87. doi:10.1016/j.rmed.2017.02.010

18. Johnson, D., & Parker, J. D. (2009). Air pollution exposure and self-reported cardiovascular disease. *Environmental Research, 109*(5), 582-589. doi:10.1016/j.envres.2009.01.001

19. Lipfert, F. W., Wyzga, R. E., Baty, J. D., & Miller, J. P. (2006). Traffic density as a surrogate measure of environmental exposures in studies of air pollution health effects: Long-term mortality in a cohort of US veterans. *Atmospheric Environment, 40*(1), 154-169. doi:10.1016/j.atmosenv.2005.09.027

20. Liu, S., Zhou, Y., Liu, S., Chen, X., Zou, W., Zhao, D., . . . Ran, P. (2017). Association between exposure to ambient particulate matter and chronic obstructive pulmonary disease: results from a cross-sectional study in China. *Thorax, 72*(9), 788. doi:10.1136/thoraxjnl-2016-208910

21. Loffredo, C., Tang, Y., Momen, M., Makambi, K., Radwan, G., & Aboul-Foutoh, A. (2016). PM sub(2.5) as a marker of exposure to tobacco smoke and other sources of particulate matter in Cairo, Egypt. *International Journal of Tuberculosis and Lung Disease, 20*(3), 417-422. doi:10.5588/ijtld.15.0316

22. McCormack, M. C., Belli, A. J., Kaji, D. A., Matsui, E. C., Brigham, E. P., Peng, R. D., . . . Hansel, N. N. (2015). Obesity as a susceptibility factor to indoor particulate matter health effects in COPD. *The European respiratory journal, 45*(5), 1248. doi:10.1183/09031936.00081414

23. Mendis, S., Puska, P., Norrving, B., World Health, O., World Heart, F., & World Stroke, O. (2011). *Global atlas on cardiovascular disease prevention and control*. Geneva: Geneva : World Health Organization in collaboration with the World Heart Federation and the World Stroke Organization.

24. Miller, K. A., Siscovick, D. S., Sheppard, L., Shepherd, K., Sullivan, J. H., Anderson, G. L., & Kaufman, J. D. (2007). Long-Term Exposure to Air Pollution and Incidence of Cardiovascular Events in Women. *The New England Journal of Medicine, 356*(5), 447-458. doi:10.1056/NEJMoa054409

25. Moore, E., Chatzidiakou, L., Jones, R. L., Smeeth, L., Beevers, S., Kelly, F. J., . . . Barratt, B. (2016). Linking e-health records, patient-reported symptoms and environmental exposure data to characterise and model COPD exacerbations: protocol for the COPE study. *BMJ open, 6*(7), e011330-e011330. doi:10.1136/bmjopen-2016-011330

26. Polverino, F., & Celli, B. (2018). The Challenge of Controlling the COPD Epidemic: Unmet Needs. *The American Journal of Medicine, 131*(9), 1-6.

doi:10.1016/j.amjmed.2018.05.001

27. Pope, C. A., Krewski, D., Gapstur, S. M., Turner, M. C., Jerrett, M., & Burnett, R. T. (2017). Fine Particulate Air Pollution and Mortality: Response to Enstrom's Reanalysis of the American Cancer Society Cancer Prevention Study II Cohort. *Dose-Response, 15*(4). doi:10.1177/1559325817746303

28. Psaltopoulou, T., Hatzis, G., Papageorgiou, N., Androulakis, E., Briasoulis, A., & Tousoulis, D. (2017). Socioeconomic status and risk factors for cardiovascular disease: Impact of dietary mediators. *Hellenic Journal of Cardiology, 58*(1), 32-42. doi:10.1016/j.hjc.2017.01.022

29. Salvi, S. S., & Barnes, P. J. (2009). Chronic obstructive pulmonary disease in non-smokers. *The Lancet, 374*(9691), 733-743. doi:10.1016/S0140-6736(09)61303-9

30. Sin, D. D., & Man, S. F. P. (2005). Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality. *Proceedings of the American Thoracic Society, 2*(1), 8-11. doi:10.1513/pats.200404-032MS

31. Tofler, H. G., & Muller, E. J. (2006). Triggering of Acute Cardiovascular Disease and Potential Preventive Strategies. *Circulation, 114*(17), 1863-1872. doi:10.1161/CIRCULATIONAHA.105.596189

32. U.S. Census Bureau. (2019). Metropolitan and Micropolitan. Retrieved from https://www.census.gov/programs-surveys/metro-micro.html

33. U.S. Environmental Protection Agency. (1999-2014). Air Data: Air Quality Data Collected at Outdoor Monitors Across the US. https://www.epa.gov/outdoor-air-quality-data/download-daily-data

34. U.S. Environmental Protection Agency. (2018). Particulate Matter (PM) Pollution. Retrieved from https://www.epa.gov/pm-pollution.

35. Van Eeden, S., Hiraiwa, K., Elliott, M., & Hogg, J. (2015). Effect Of Statins On The Retention Of Ambient Particulate Matters (pm) In COPD. *Am. J. Respir. Crit. Care Med., 191*.

36. Xing, Y.-F., Xu, Y.-H., Shi, M.-H., & Lian, Y.-X. (2016). The impact of PM2.5 on the human respiratory system. *Journal of thoracic disease, 8*(1), E69-E74. doi:10.3978/j.issn.2072-1439.2016.01.19