보건학석사 학위논문

대기오염과 알츠하이머 질환의 연관성 연구: 노인코호트 자료를 이용한 분석

Association between Exposure to Particulate Matter and Newly Diagnosed Alzheimer's disease in the elderly – Elderly Cohort

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서울대학교 보건대학원

보건학과 보건통계학전공

박 성 원

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지도 교수 김 호

이 논문을 보건학 석사 학위논문으로 제출함

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보건학과 보건통계학전공

박 성 원

박성원의 석사 학위논문을 인준함

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위 원 장 조 성 일 (인)

부위원장 황 승 식 (인)

위 원 김 호 (인)

Abstract

Seong-won Park

Department of Biostatistics and Epidemiology

Graduate School of Public Health

Seoul National University

Background: Air pollution is a growing concern all over the world. Of air pollution compound, Particulate matter (PM) is known to have adverse health effects on cardiovascular and cerebrovascular disease. Also, several studies has been made about relationship between air pollution and cognitive decline, dementia. However, the actual impact of air pollution on Alzheimer's disease (AD) in Korea has not been studied yet. Therefore, the purpose of this study is to investigate the association with air pollution and the risk of newly diagnosed Alzheimer's disease.

Method: We used Elderly Cohort data and the study periods were from 1 January, 2008 to 31 December, 2015 in this study. The Elderly Cohort participants composed of 558,147 individuals aged over 60 years were included at the baseline in 2002. The first diagnosed date was defined as newly diagnosed AD and selected as our outcome of interest. We regarded the annual average concentration (1, 2, 3, 4, 5 years) before event as exposure. Cox proportional hazard model was mainly implemented to investigate the association between air pollution and newly diagnosed AD. The effect of air

pollution on the risk of newly diagnosed AD was estimated as the hazard ratio (HR) per 1 ㎍/㎥ increase in PM10(aerodynamic diameter equal to or less than 10㎛) with 95% confidence intervals (CIs).

Result: The increased risk of newly diagnosed AD in relation to average 1 year concentration of PM10 was 1.15(95% CI: 1.05, 1.27), and 1.14(1.03, 1.25), 1.16(1.05, 1.28), 1.20(1.09, 1.32), 1.19(1.08, 1.30) for each 2, 3, 4, 5 years. After adjusting regional variables additionally from model 1, the risk of newly diagnosed AD was increased from 1.15 to 1.29 (95% CI: 1.14, 1.46) for average 1 year concentration, and increased from 1.14 to 1.34(95% CI: 1.17, 1.53), 1.16 to 1.41(1.23, 1.62), 1.20 to 1.50(1.31, 1.73), 1.19 to 1.49(1.30 1.71) for each average 2, 3, 4, 5 years concentration change of PM10.

Conclusion: Air pollution exposure increased the risk of newly diagnosed AD in the elderly in Korea.

Keywords: Air pollution, PM10, Alzheimer's disease, diagnosis, Elderly Cohort, Cox proportional hazard model

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Chapter 1. Introduction

1.1 Background

Air pollution is a complex mixture consisted of gases, particulate matter (PM), organic compounds from by-product of industrialization. Many people worldwide are exposed to air pollution chronically in concentrations above safety standards(Akimoto 2003). High level of air pollution become a major public health concern. Of air pollution compound, PM has been demonstrated to have adverse health effects in both developed and developing countries(Craig, Brook et al. 2008). Even though the mechanism of exposure to PM remains unclear, several studies suggested that particulate matter reaches central nerve system (CNS) and affects immune response. (Block and Calderón-Garcidueñas 2009, Genc, Zadeoglulari et al. 2012, Babadjouni, Hodis et al. 2017). PM may influence the nervous system by affecting cellular and molecular pathway of inflammatory response. Especially, PM can cause to increase in systemic-induced cytokine response and plasma cytokine concentration (interleukin-6(IL-6), granulocyte-macrophage colony-stimulating factor (GMCF)) that are produced by blood cells.

Also, Exposure to air pollution is associated with neuroinflammation and oxidative stress. Long term exposure to air pollution including ultrafine particulate matter(UFPM) and PM2.5 cause neuroinflammation and affect

innate immune responses, oxidative stress in children and young adults(Calderón-Garcidueñas, Solt et al. 2008). The epidemiological evidences have been reported that PM exposure can increases biomarkers of oxidative stress in blood (Delfino, Staimer et al. 2011).

As one of the factors of degenerative disorders, neuroinflammation and oxidative stress are important role on the cause of degenerative disorders such as Alzheimer's disease(AD) (Heusinkveld, Wahle et al. 2016). The clinical mechanisms of the relationships between neuroinflammation, oxidative stress and degenerative disorders have been indicated in the previous studies (Fukui and Moraes 2008, Zhao and Zhao 2013, Uchoa, Moser et al. 2016). Some studies showed that cytochrome oxidase activity was decreased and the evidence of oxidative damage was found in their cerebral cortex of AD patients(Beal 1995).

As described above, exposure to air pollution, especially PM, may contribute to progress of inflammation and oxidative stress, and which can be a risk factor of degenerative disorders. The epidemiological association between exposure to air pollution and neurodegenerative disease such as Alzheimer's disease and Parkinson's disease are revealed (Wu, Lin et al. 2015, Kioumourtzoglou, Schwartz et al. 2016). A significant number of epidemiological and biological studies suggest associations between air pollution and cognitive decline (Power, Adar et al. 2016, Cacciottolo, Wang et al. 2017). More notably, relationship between air pollution and cognitive decline has been reported primarily for the

elderly (Ranft, Schikowski et al. 2009, Weuve, Puett et al. 2012, Gatto, Henderson et al. 2014). Based on the earlier studies, chronic exposure to air pollution stimulating inflammatory process for long period might be able to accelerate cognitive impairment and onset of Alzheimer's disease. The prevalence of AD in Korea is 6.49% in 2008 which consists of 70.5% of all kinds of dementia (Kim and Han 2012). But relatively fewer studies about association between air pollution and Alzheimer's disease have been studied in Korea. In addition, few studies have aimed at entire elderly population in Korea. Therefore, it would be worthwhile to evaluate relationship between air pollution and Alzheimer's disease for the elderly in Korea.

1.2 Objectives

The objectives of this study were to evaluate effect of air pollution on the risk of Alzheimer's disease and explore association between air pollution and Alzheimer's disease in the elderly.

Chapter 2. Materials and Methods

2.1 Data

2.1.1 Study design

We established a population-based cohort study by obtaining all individual medical record from National Health Insurance Service (NHIS) database. The NHIS indicated that the National Sample Cohort data ensure representativeness and systematic stratified random sampling was constructed by 18 age group, two sex group, 41 groups according to participant's income level (Lee, Lee et al. 2016). The NHIS maintains individual registration files and longitudinal claim data of medical expenditures including hospitalization and inpatient expenditures. In that way, The Elderly Cohort is made especially for 5,580,000 registered people who was over 60 years old in 2002. The Elderly Cohort data is the registry of beneficiary data that 10 percent of the elderly registered people (558,147 subjects) were randomly and systemically selected by National Health Insurance Sharing Service (NHISS). The NHISS offers the registered people data about personal demographic information, medical utilization record, diagnosis details, information of health check-ups. The data is so anonymously composed that the need for consent from each subject is exempted. This study complied with academic research ethics and has been approved by the Seoul National University Institutional Review Board. (IRB No. E1710/001-005)

2.1.2 Study population

We used the Elderly Cohort data and the study periods were from 1 January, 2008 to 31 December, 2015 in this study. The Elderly Cohort participants composed of 558,147 individuals aged over 60 years were included at the baseline in 2002. We excluded people who censored or diagnosed prior to study period (from 2002 to 2007, n=86,631). 471,516 people were in the baseline study cohort in 2008. We excluded who had not undergone health check-ups or check-up data missing from 2008 to 2015 (n=182,349). In case participant took health check-ups more than one time from 2008 to 2015, the first health check-ups data was used in the analysis. After merging air pollution data, we excluded who had no air pollution information (n=1,057). As a result, we followed up 288,110 elderly aged over 60 years from 2008 to 2015. The cohort entry is organized with 288,110 individuals consisted of 9,166 cases and 278,944 controls. The follow-up time started from 1 January, 2008 to the diagnosis of AD, termination of insurance or death, or the end of the study period same as the 31 December 2015. In the study, 39,974 subjects were censored during follow-up period.

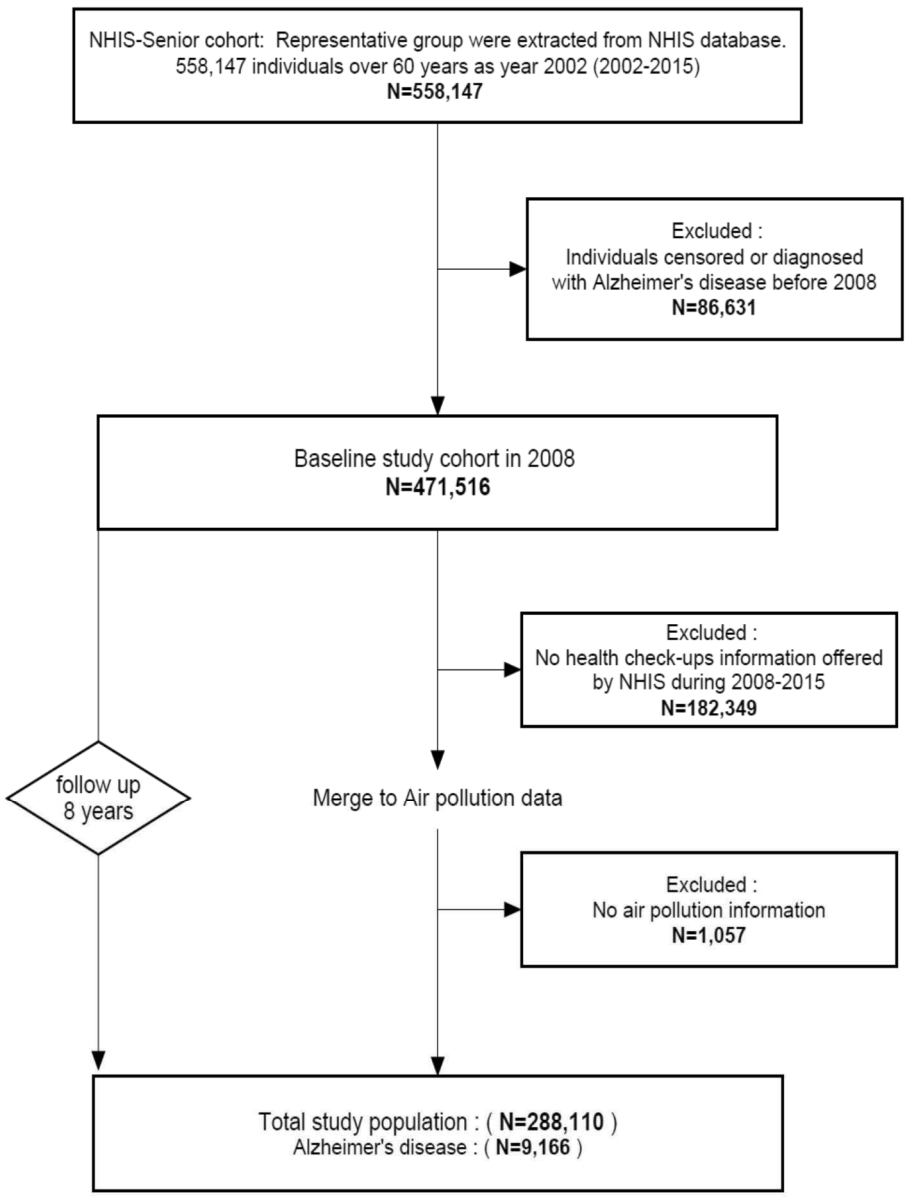

Figure 1. Flow chart of cohort data processing

2.1.3 Outcome of interest

The Elderly Cohort contains diagnosis records based on International Classification of Disease, 10th Revision, Clinical Modification (ICD-10-CM). We searched participants' data containing diagnosis code "G30", which is ICD-10-CM code of AD, in diagnosis records to discover the date of AD diagnosis from 1 January, 2008 to 31 December, 2015. Of them, the first diagnosed date was defined as newly diagnosed AD and selected as our outcome of interest.

In Korea, The diagnosis of AD is principally based on history of cognitive decline from caregivers, neurological examination, laboratory investigations, neuropsychological test, Korean version of Mini-Mental State Examination (K-MMSE), and brain MRI according to National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria and the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (Park, Na et al. 2011).

2.1.4 Study area and exposure measurement

The study area included 97 districts and 323 monitoring stations located in all over the country from 2002 through 2015. Hourly PM10 (particulate matter ≤ 10㎛) and other air pollutants such as SO2, O3, NO2, CO were continuously measured from the monitoring stations. The data is managed and provided by Korea National Institute of Environmental Research. We computed the monthly concentration of air pollutants and integrated them into 16 provinces. We also calculated the average concentration (from 1 year to 5 years) before event or censoring. Then, we regarded the mean concentration each year before event as exposure.

Korea Meteorological Administration established the meteorological data that was measured from 94 monitoring stations. Of the meteorological data, we adjusted temperature and relative humidity in the statistical model. We converted daily mean temperature and relative humidity into monthly mean temperature and relative humidity by 16 provinces.

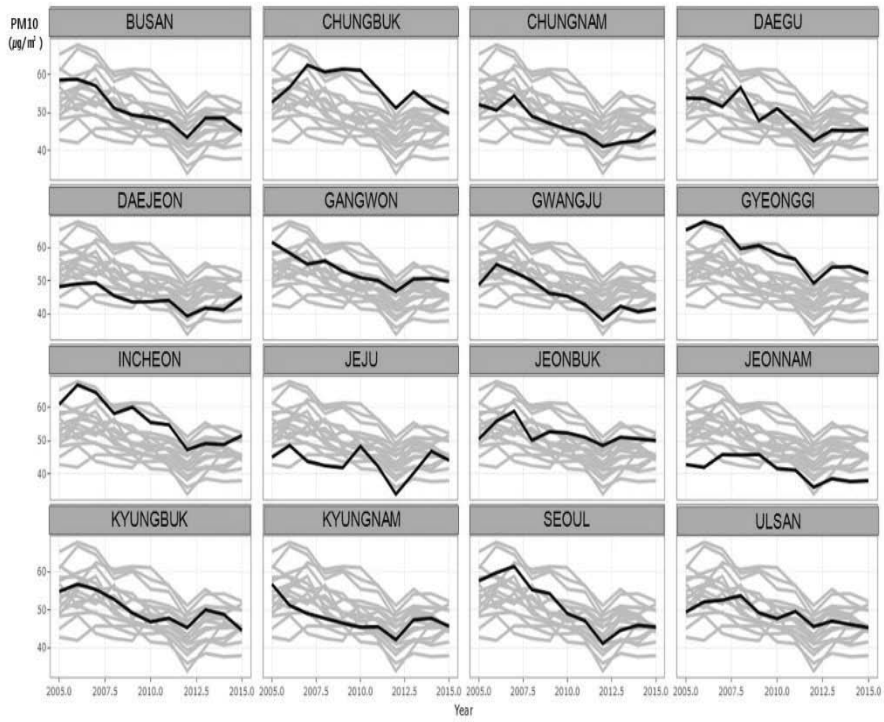

Figure 2. Time-series plots of monthly PM10 concentration by 16 provinces

2.1.5 Covariates

We adjusted personal characteristics and regional properties in this study. Adjusted characteristics of participants were gender, Age, BMI (less than 25 or not), income (medi-care recipients, 0-30%, 30-70%, 70-100%), insurance type (regional applicant, workplace applicant, medi-care recipients), smoking status (non-smoker, ex-smoker, smoker, no answer), alcohol consumption (never or more than one time in a week), and comorbidities including stroke, heart disease, hypertension, diabetes. Comorbidities is obtained from information of health check-ups which is conducted obligatorily every two years. Age was an indicator variable with 5-year groups from 60 (60-64, 65-69, 70-74, 75-79, 80-84, ≥85).

We also fitted regional properties obtained from Korean Statistical Information service. Gross Regional Domestic Product (GRDP), the number of medical institutes, the ratio of the elderly, green coverage area(㎡) were divided into five groups by percentile (0-20%, 20-40%, 40-60%, 60-80%, 80-100%) in each participant's residing provinces.

2.2 Statistical analysis

A Cox proportional hazard model was mainly implemented to investigate the association between air pollution and newly diagnosed AD. The primary outcome of this study was defined as the first diagnosed date of AD. Each observation time was censored when patient died, the insurance was terminated or the follow-up was ended. For the purpose of observing more detailed time effect of air pollution, the exposure period and the follow-up time of newly diagnosed AD was calculated in month from 1 January 2006.

We extended this study by establishing two models and comparing them. First. We fitted the first model which takes into account individual confounding factors. The following variables of the cohort data were adjusted in the model: Age, gender, BMI, income, insurance type, smoking status, alcohol consumption, and comorbidities including stroke, heart disease, hypertension, diabetes. Age and gender are stratified in the model. Second, in order to identify whether regional properties affect the association between air pollution and newly diagnosed AD or not, Gross Regional Domestic Product (GRDP), the number of medical institutes, the ratio of the elderly, green coverage area are included additionally in the first model, which is the second model. Comparisons were made in terms of air pollution exposure depending on period and adjustment of individual and regional confounding factors.

The effect of air pollution on the risk of newly diagnosed AD was estimated

as the hazard ratio (HR) per 1 $\mu g/m^3$ increase in PM10 with 95% confidence intervals (CIs).

All analyses in this study were carried out with SAS Enterprise guide version 7.13

Chapter 3. Results

3.1 Descriptive statistics

A total of 288,110 elderly Koreans older than 60 years consist of the study cohort from 1 January, 2008 to 31 December, 2015. The demographic characteristics of the 288,110 individuals are presented in Table 1. Among them, 9,166 individuals were diagnosed with AD more than one time and 278,944 were not diagnosed in the study period. In our study, there were more females than males, and most of participants were over 70 years old (especially 75-79 years), workplace applicants in both AD group and no AD group. These newly diagnosed AD individuals is comprised of 6,041 females (65.9%), 4,997 individuals in high income status (54.5%), 6,342 workplace applicants (69.2%). The common comorbidities was hypertension (43.8%) in AD individuals. The number of 5,309 people didn't answer the status of smoking. Most newly diagnosed AD individuals were females (IR = 48.3 per 10,000 person years) and from ages 75 to 79 (incidence rate (IR) = 34.9 per 10,000 person-years), and high income status (IR = 44.0 per 10,000 person-years), and workplace applicant (IR = 41.9 per 10,000 person-years), and non-smokers (IR = 45.4 per 10,000 person-years)

All individual confounding factors were significantly associated with AD (not shown).

Table 1. Summary statistics of the study cohort from 1 January, 2008 to December 31, 2015

Characteristic		Total(%) (n=288,110)	AD(%) (n=9,166)	no AD(%) (n=278,944)	Person-years	IR(per 10000 person year)
Gender	Male	123,653 (42.9)	3,125 (34.1)	120,528 (43.2)	911,480	34.3
	Female	164,457 (57.1)	6,041 (65.9)	158,416 (56.8)	1,247,756	48.4
Age	65-69	1,198 (0.4)	386 (4.2)	812 (0.3)	2,578	1,497.2
	70-74	69,746 (24.2)	2,222 (24.2)	67,524 (24.2)	519,482	42.8
	75-79	116,994 (40.6)	3,118 (34)	113,876 (40.8)	892,162	34.9
	80-84	65,480 (22.7)	2,159 (23.6)	63,321 (22.7)	492,435	43.8
	≥85	34,692 (12)	1,281 (14)	33,411 (12)	252,579	50.7
Income	medical care recipients	7,023 (2.4)	255 (2.8)	6,768 (2.4)	53,277	47.9
	0-30%	71,810 (24.9)	2,134 (23.3)	69,676 (25)	535,355	39.9
	30-70%	58,446 (20.3)	1,780 (19.4)	56,666 (20.3)	435,825	40.8
	70-100%	150,831 (52.4)	4,997 (54.5)	145,834 (52.3)	1,134,779	44.0
Insurance type	regional applicant	79,534 (27.6)	2,569 (28)	76,965 (27.6)	591,292	43.4
	workplace applicant	201,553 (70)	6,342 (69.2)	195,211 (70)	1,514,667	41.9
	medical care recipients	7,023 (2.4)	255 (2.8)	6,768 (2.4)	53,277	47.9
Smoking Status	Never	218,485 (75.8)	7,471 (81.5)	211,014 (75.7)	1,645,159	45.4
	Ever	32,672 (11.3)	813 (8.9)	31,859 (11.4)	244,043	33.3
	Present	31,644 (11)	698 (7.6)	30,946 (11.1)	231,224	30.2
	Not answer	5,309 (4.8)	184 (2)	5,125 (1.8)	38,810	47.4
Drinking Status	No	222,127 (77.1)	7,612 (83.1)	214,515 (76.9)	1,663,949	45.7
	Yes	65,983 (22.9)	1,554 (17)	64,429 (23.1)	495,287	31.4

Body mass index	< 25	192,203 (66.7)	6,457 (70.5)	185,746 (66.6)	1,426,289	45.3
	25 ≤	95,907 (33.3)	2,709 (29.6)	93,198 (33.4)	732,947	37.0
Stroke	No	279,019 (96.8)	8,648 (94.4)	270,371 (96.9)	2,094,162	41.3
	Yes	9,091 (3.2)	518 (5.7)	8,573 (3.1)	65,074	79.6
Heart disease	No	268,811 (93.3)	8,475 (92.5)	260,336 (93.3)	2,016,067	42.0
	Yes	19,299 (6.7)	691 (7.5)	18,608 (6.7)	143,169	48.3
Hypertension	No	166,422 (57.8)	5,150 (56.2)	161,272 (57.8)	1,242,821	41.4
	Yes	121,688 (42.2)	4,016 (43.8)	117,672 (42.2)	916,415	43.8
Diabetes	No	245,345 (85.2)	7,504 (81.9)	237,841 (85.3)	1,842,049	40.7
	Yes	42,765 (14.8)	1,662 (18.1)	41103 (14.7)	317,187	52.4

AD: Alzheimer's disease,
IR: Incidence rate
Gross Regional Domestic Product (GRDP, unit: one million won (Korean currency unit))
the number of medical institutes,
the ratio of the elderly,
green coverage area(m^2)

3.2 Distribution of air pollution

Distribution of annual average concentration of each year were described in Table 2. For the mean concentration of PM10, individuals with AD exposed to higher concentration than individuals without AD. In terms of mean concentration difference, individuals with AD were exposed more about 2 μg/㎥. Generally, the average concentration of PM10 exposures was increased by gradually in both AD and no AD group from previous 1 year to 5 years.

Table 2. Distribution of PM10 concentration by previous exposure years

Exposure	AD	N	Mean	SD	Max	Min	Range	Q1	Q3
PM10(㎍/㎥)									
the average concentration of previous 1 year	No	278,944	46.6	4.1	64.8	33.2	31.7	44.5	49.8
	Yes	9,166	49.0	5.9	66.0	34.0	32.0	45.1	52.3
the average concentration of previous 2 years	No	278,944	47.7	4.4	66.7	35.9	30.7	46.0	50.8
	Yes	9,166	49.5	5.9	66.9	36.2	30.8	45.4	53.3
the average concentration of previous 3 years	No	278,944	47.6	4.6	66.9	37.2	29.7	45.1	50.3
	Yes	9,166	50.0	6.0	66.9	37.2	29.7	45.5	53.3
the average concentration of previous 4 years	No	278,944	47.0	4.6	66.5	37.5	29.0	44.2	51.0
	Yes	9,166	50.6	6.1	66.6	37.5	29.1	45.9	54.7
the average concentration of previous 5 years	No	278,944	47.8	4.7	66.8	38.5	28.4	45.1	51.4
	Yes	9,166	51.3	6.1	67.0	38.5	28.5	46.5	55.6

AD: Alzheimer's disease, SD: standard deviation

3.3 Association between air pollution and Alzheimer's disease

We examined the relationship between air pollution and Alzheimer's disease using Cox proportional model. In Cox proportional hazard models with stratified by age and gender, PM10 exposures were significantly associated with an increased risk of newly diagnosed AD after adjusting individual and regional confounding factors. The risk of newly diagnosed AD is shown as the hazard ratio (HR) per 1 $\mu g/m^3$ increase in PM10 with 95% confidence intervals (CIs) in Table 3. In model 1, we considered exposure as annual average concentration of PM10 and fitted only individual variables in the model. The increased risk of newly diagnosed AD in relation to average 1 year concentration of PM10 was 1.15(95% CI: 1.05, 1.27), and 1.14(1.03, 1.25), 1.16(1.05, 1.28), 1.20(1.09, 1.32), 1.19(1.08, 1.30) for each 2, 3, 4, 5 years. After adjusting regional variables additionally from model 1, the risk of newly diagnosed AD was increased from 1.15 to 1.29 (95% CI: 1.14, 1.46) for average 1 year concentration, and increased from 1.14 to 1.34(95% CI: 1.17, 1.53), 1.16 to 1.41(1.23, 1.62), 1.20 to 1.50(1.31, 1.73), 1.19 to 1.49(1.30, 1.71) for each average 2, 3, 4, 5 years concentration change of PM10. The hazard ratios in relation to average 4 years concentration was the highest value in both model 1 and model 2. The hazard ratios of each models were indicated by plot in Figure 3.

Regarding hazard ratio and attributable risk by regions, when we adjusting individual factors only in the model, the hazard ratios were similar between regions. But, when we adjusting individual and regional factors, the hazard ratios were widely different by regions and tended to be increased in the long period (Table S1-S10).

Table 3. Hazard ratios of newly diagnosed AD in two models

Exposure	HR(95% CI)
Model 1 - Individual factors	
the average concentration of previous 1 year	1.15 (1.05, 1.27)
the average concentration of previous 2 years	1.14 (1.03, 1.25)
the average concentration of previous 3 years	1.16 (1.05, 1.28)
the average concentration of previous 4 years	1.20 (1.09, 1.32)
the average concentration of previous 5 years	1.19 (1.08, 1.30)
Model 2 - Individual and regional factors	
the average concentration of previous 1 year	1.29 (1.14, 1.46)
the average concentration of previous 2 years	1.34 (1.17, 1.53)
the average concentration of previous 3 years	1.41 (1.23, 1.62)
the average concentration of previous 4 years	1.50 (1.31, 1.73)
the average concentration of previous 5 years	1.49 (1.30, 1.71)

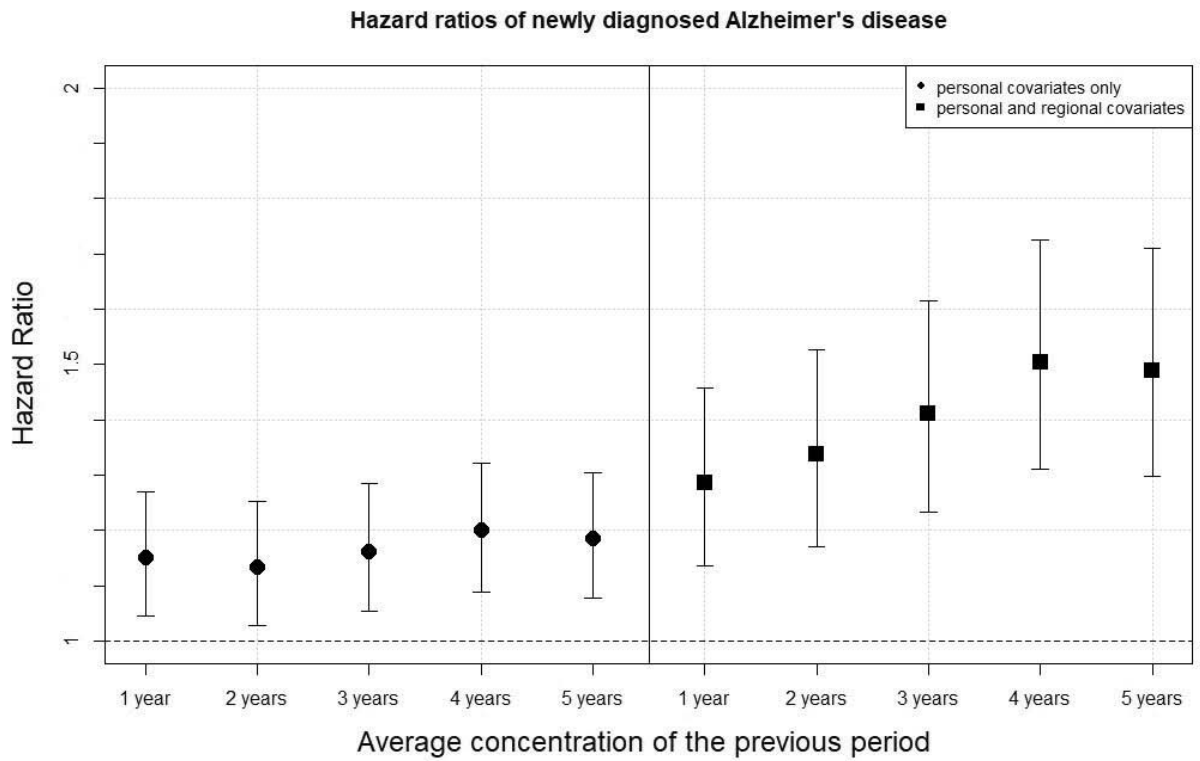

Figure 3. Hazard ratios of newly diagnosed AD for annual average concentration of PM10 after adjusting individual and regional variables.

Chapter 4. Discussion

In this study, the object of the study was to research the influence of air pollution exposure on newly diagnosed AD in the elderly. The result suggest a significant association between air pollution exposure and Alzheimer's disease occurrence. In the present population-based cohort study, we observed long-term (annual average concentration) exposure of air pollution on the risk of newly diagnosed Alzheimer's disease. We found long-term exposure enhanced the risk of newly diagnosed AD by from 13.5% to 20.0% according to previous period and adjusting individual variables only. In addition, when regional properties was adjusted in the long-term exposure model, regional covariates could affect and enhance the risk of newly diagnosed AD by from 28.7% to 50.4%.

The findings of the increased risk of newly diagnosed AD by air pollution exposure were consistent with the recent studies (Jung, Lin et al. 2015). This previous study demonstrated that the risk of newly diagnosed AD was 138% per increase of 4.34 μg/㎥ in PM2.5 and the risk was increased to over 200% (217~243%) after controlling other air pollutant. A study in Spain examined the association between daily mean concentrations (μg/m3) of air pollutants (PM2.5) and emergency hospital admissions due to AD (Culqui, Linares et al. 2017). The result in this study showed that PM2.5 concentrations can aggravate the symptoms of AD, leading to emergency hospital admissions. Other study

reported that the elderly living in areas with higher PM2.5 concentrations had decrease in cognitive function (Ailshire and Crimmins 2014).

The previous study found that not only PM10 but other air pollutant such as nitrogen compound also could raise the risk of Alzheimer's disease incidence. Participants with high nitrogen oxide exposure were more likely than those with low exposure to be diagnosed with dementia (Alzheimer's disease or vascular dementia), with the risk 143% (Oudin, Forsberg et al. 2016).

In terms of biochemical mechanism, the most recent study suggested that long-term exposure to air pollution is related to onset of gene mutation, which could act synergistically to increase and exacerbate AD (Wu, Chen et al. 2017). This previous study found that higher percent of candidate genes associated with AD was noticeable in the AD group with increased air pollution levels.

Alzheimer's disease is increasing steeply and become a global concern in all over the world. Age-standardized prevalence of AD for the elderly aged over 60 years ranged from 5% to 7% in most world region, and expected number of patients is estimated almost double every 20 years (Prince, Bryce et al. 2013). In Seoul, capital of Korea, the previous study reported that dementia prevalence was varied from 2.6% in people aged 65 to 69, to 32.6% in people aged over 85, and age-standardized prevalence for AD was 5.4% (Lee, Lee et al. 2002). There are many risk factors for the risk of AD such as age, being male, lower education level, illiteracy, smoking, head trauma history, depression and so on (Kim, Park et al. 2011).

The strength of the present study is the first study of investigating the influence of air pollution, especially PM10, on the risk of newly diagnosed AD in the elderly in Korea. There are few studies about relationship between air pollution and dementia in Korea. Also, we used longitudinal population-based Elderly-cohort data that contains high-quality medical records of 580,000 sampled people, who consisted 10% of almost every elderly over 60 years in Korea. Also, we followed up over ten years from 1 January 2002 to 31 December 2015, and of them, we mainly analyzed over 288,000 people from 1 January 2008 to 31 December 2015 in this study. It means that our study can be interpreted with the generalizability of the findings.

With respect to this study's limitation, this study design is based on ecological design that means no causal relationship can be demonstrated between increases in PM10 concentrations and AD. Also, Newly diagnosed AD is not the first day of onset of AD. AD is a progressive disease that absolute incidence date cannot be figured out. Therefore, we defined the date of newly diagnosed AD as a proxy definition of incidence date of AD. The diagnosed date and the health check-up date were not same because the diagnosed date was a point date and the health check-up was undergone biennially. Thus, we used the first health check-ups data after 1 January 2006. We cannot take into account participant's characteristics which might be associated with AD like education level, illiteracy, cognitive decline degree, head trauma history, depression or other mental illness in our study due to absence of data. There might be

limitation in the assessment of exposure. We received air pollution data collected from monitoring stations all over the regions in Korea. However, as distribution of monitoring stations is not spread out equally in all regions and the air pollution data was not fitted in the individual exposure measurement model, we cannot measure actual exposure of individuals. So we matched air pollution data and individual data by using district code (Si-do code) and considered them as a measurement of exposure. Limitations regarding composition of participants who are female or came from families with high income are present. Because those who are male or those with low household income were underrepresented, the result should be understood with this limitation.

Despite these limitations, our findings can suggest that air pollution is associated with the first diagnosis of Alzheimer's disease. Air pollution and Alzheimer's disease can worsen the quality of life, and they are important issues in recent days. As many people live longer with a good memory and fresh air, the further studies about air pollution and Alzheimer's disease should be made.

Appendix

Table S1. Hazard ratio and attributable risk of newly diagnosed AD by regions in relation to average 1 year concentration after adjusting only individual factors

Region	No. of individuals	HR	95% CI	Attributable Risk
Seoul	43,299	1.00	Reference	
Busan	19,597	0.99	0.92 - 1.05	-1.2%
Daegu	12,519	1.01	0.94 - 1.08	0.7%
Incheon	11,724	1.03	0.96 - 1.1	2.6%
Gwangju	7,047	1.02	0.94 - 1.1	2.2%
Daejeon	6,777	1.04	0.96 - 1.11	3.6%
Ulsan	3,702	0.99	0.9 - 1.09	-0.7%
Gyeonggi	52,100	1.02	0.97 - 1.08	2.3%
Gangwon	12,842	1.02	0.96 - 1.09	2.2%
Chungbuk	12,340	1.02	0.96 - 1.09	2.3%
Chungnam	17,932	1.05	0.98 - 1.12	4.6%
Jeonbuk	17,078	1.04	0.98 - 1.11	4.2%
Jeonnam	21,094	1.05	0.97 - 1.12	4.3%
Kyungbuk	24,776	1.02	0.95 - 1.08	1.8%
Kyungnam	21,698	1.02	0.95 - 1.08	1.8%
Jeju	3,585	0.99	0.87 - 1.1	-1.1%

Table S2. Hazard ratio and attributable risk of newly diagnosed AD by regions in relation to average 2 years concentration after adjusting only individual factors

Region	No. of individuals	HR	95% CI	Attributable Risk
Seoul	43,299	1.00	Reference	
Busan	19,597	0.99	0.92 - 1.05	-1.3%
Daegu	12,519	1.01	0.94 - 1.08	0.7%
Incheon	11,724	1.03	0.96 - 1.1	2.6%
Gwangju	7,047	1.02	0.94 - 1.1	2.2%
Daejeon	6,777	1.04	0.96 - 1.11	3.6%
Ulsan	3,702	0.99	0.9 - 1.09	-0.7%
Gyeonggi	52,100	1.02	0.97 - 1.08	2.2%
Gangwon	12,842	1.02	0.96 - 1.09	2.2%
Chungbuk	12,340	1.02	0.96 - 1.09	2.2%
Chungnam	17,932	1.05	0.98 - 1.12	4.6%
Jeonbuk	17,078	1.04	0.98 - 1.11	4.1%
Jeonnam	21,094	1.04	0.97 - 1.12	4.2%
Kyungbuk	24,776	1.02	0.95 - 1.08	1.7%
Kyungnam	21,698	1.02	0.95 - 1.08	1.7%
Jeju	3,585	0.99	0.87 - 1.1	-1.2%

Table S3. Hazard ratio and attributable risk of newly diagnosed AD by regions in relation to average 3 years concentration after adjusting only individual factors

Region	No. of individuals	HR	95% CI	Attributable Risk
Seoul	43,299	1.00	Reference	
Busan	19,597	0.99	0.92 - 1.05	-1.2%
Daegu	12,519	1.01	0.94 - 1.08	0.9%
Incheon	11,724	1.03	0.96 - 1.1	2.8%
Gwangju	7,047	1.03	0.95 - 1.11	2.4%
Daejeon	6,777	1.04	0.96 - 1.12	3.8%
Ulsan	3,702	0.99	0.9 - 1.09	-0.6%
Gyeonggi	52,100	1.03	0.97 - 1.08	2.4%
Gangwon	12,842	1.02	0.96 - 1.09	2.3%
Chungbuk	12,340	1.02	0.96 - 1.09	2.3%
Chungnam	17,932	1.05	0.98 - 1.12	4.8%
Jeonbuk	17,078	1.04	0.98 - 1.11	4.2%
Jeonnam	21,094	1.05	0.97 - 1.12	4.4%
Kyungbuk	24,776	1.02	0.96 - 1.08	1.8%
Kyungnam	21,698	1.02	0.96 - 1.08	1.8%
Jeju	3,585	0.99	0.87 - 1.11	-1.0%

Table S4. Hazard ratio and attributable risk of newly diagnosed AD by regions in relation to average 4 years concentration after adjusting only individual factors

Region	No. of individuals	HR	95% CI	Attributable Risk
Seoul	43,299	1.00	Reference	
Busan	19,597	0.99	0.93 - 1.06	-0.9%
Daegu	12,519	1.10	0.94 - 1.08	9.2%
Incheon	11,724	1.03	0.96 - 1.1	3.1%
Gwangju	7,047	1.03	0.95 - 1.11	2.7%
Daejeon	6,777	1.04	0.97 - 1.12	4.0%
Ulsan	3,702	1.00	0.9 - 1.09	-0.4%
Gyeonggi	52,100	1.03	0.97 - 1.08	2.6%
Gangwon	12,842	1.03	0.96 - 1.1	2.6%
Chungbuk	12,340	1.03	0.96 - 1.09	2.4%
Chungnam	17,932	1.05	0.98 - 1.12	5.0%
Jeonbuk	17,078	1.05	0.98 - 1.11	4.5%
Jeonnam	21,094	1.05	0.98 - 1.12	4.8%
Kyungbuk	24,776	1.02	0.96 - 1.09	2.1%
Kyungnam	21,698	1.02	0.96 - 1.09	2.2%
Jeju	3,585	0.99	0.88 - 1.11	-0.6%

Table S5. Hazard ratio and attributable risk of newly diagnosed AD by regions in relation to average 5 years concentration after adjusting only individual factors

Region	No. of individuals	HR	95% CI	Attributable Risk
Seoul	43,299	1.00	Reference	
Busan	19,597	0.99	0.93 - 1.06	-1.0%
Daegu	12,519	1.01	0.94 - 1.08	1.0%
Incheon	11,724	1.03	0.96 - 1.1	2.9%
Gwangju	7,047	1.03	0.95 - 1.11	2.5%
Daejeon	6,777	1.04	0.97 - 1.12	3.9%
Ulsan	3,702	1.00	0.9 - 1.09	-0.5%
Gyeonggi	52,100	1.03	0.97 - 1.08	2.5%
Gangwon	12,842	1.03	0.96 - 1.09	2.5%
Chungbuk	12,340	1.02	0.96 - 1.09	2.3%
Chungnam	17,932	1.05	0.98 - 1.12	4.9%
Jeonbuk	17,078	1.05	0.98 - 1.11	4.4%
Jeonnam	21,094	1.05	0.98 - 1.12	4.5%
Kyungbuk	24,776	1.02	0.96 - 1.08	2.0%
Kyungnam	21,698	1.02	0.96 - 1.09	2.1%
Jeju	3,585	0.99	0.88 - 1.11	-0.7%

Table S6. Hazard ratio and attributable risk of newly diagnosed AD by regions in relation to average 1 year concentration after adjusting individual and regional factors

Region	No. of individuals	HR	95% CI	Attributable Risk
Seoul	43,299	1.00	Reference	
Busan	19,597	1.37	1.37 - 1.15	27.1%
Daegu	12,519	1.24	1.24 - 1.02	19.4%
Incheon	11,724	1.15	1.15 - 0.94	13.3%
Gwangju	7,047	1.43	1.43 - 1.19	30.2%
Daejeon	6,777	1.42	1.42 - 1.18	29.5%
Ulsan	3,702	0.97	0.97 - 0.74	-2.7%
Gyeonggi	52,100	1.54	1.54 - 1.34	35.2%
Gangwon	12,842	1.53	1.53 - 1.3	34.6%
Chungbuk	12,340	1.39	1.39 - 1.18	28.1%
Chungnam	17,932	1.35	1.35 - 1.13	25.7%
Jeonbuk	17,078	1.75	1.75 - 1.53	43.0%
Jeonnam	21,094	1.68	1.68 - 1.45	40.3%
Kyungbuk	24,776	1.58	1.58 - 1.35	36.7%
Kyungnam	21,698	1.40	1.4 - 1.12	28.4%
Jeju	3,585	1.46	1.46 - 1.22	31.7%

Table S7. Hazard ratio and attributable risk of newly diagnosed AD by regions in relation to average 2 years concentration after adjusting individual and regional factors

Region	No. of individuals	HR	95% CI	Attributable Risk
Seoul	43,299	1.00	Reference	
Busan	19,597	1.61	1.61 - 1.38	37.9%
Daegu	12,519	1.53	1.53 - 1.3	34.6%
Incheon	11,724	1.39	1.39 - 1.17	28.1%
Gwangju	7,047	1.96	1.96 - 1.71	49.1%
Daejeon	6,777	1.95	1.95 - 1.7	48.8%
Ulsan	3,702	1.20	1.2 - 0.96	16.5%
Gyeonggi	52,100	2.09	2.09 - 1.89	52.2%
Gangwon	12,842	2.01	2.01 - 1.77	50.2%
Chungbuk	12,340	1.76	1.76 - 1.51	43.2%
Chungnam	17,932	1.59	1.59 - 1.35	37.1%
Jeonbuk	17,078	2.33	2.33 - 2.09	57.0%
Jeonnam	21,094	2.35	2.35 - 2.11	57.4%
Kyungbuk	24,776	1.91	1.91 - 1.65	47.5%
Kyungnam	21,698	1.99	1.99 - 1.57	49.6%
Jeju	3,585	1.96	1.96 - 1.71	48.9%

Table S8. Hazard ratio and attributable risk of newly diagnosed AD by regions in relation to average 3 years concentration after adjusting individual and regional factors

Region	No. of individuals	HR	95% CI	Attributable Risk
Seoul	43,299	1.00	Reference	
Busan	19,597	1.85	1.85 - 1.63	45.9%
Daegu	12,519	1.69	1.69 - 1.46	40.7%
Incheon	11,724	1.52	1.52 - 1.3	34.1%
Gwangju	7,047	2.55	2.55 - 2.29	60.7%
Daejeon	6,777	2.60	2.6 - 2.34	61.6%
Ulsan	3,702	1.33	1.33 - 1.09	24.6%
Gyeonggi	52,100	2.23	2.23 - 2.03	55.1%
Gangwon	12,842	2.57	2.57 - 2.33	61.1%
Chungbuk	12,340	1.90	1.9 - 1.65	47.5%
Chungnam	17,932	1.85	1.85 - 1.62	46.0%
Jeonbuk	17,078	2.94	2.94 - 2.69	65.9%
Jeonnam	21,094	2.54	2.54 - 2.29	60.6%
Kyungbuk	24,776	2.10	2.1 - 1.83	52.3%
Kyungnam	21,698	2.98	2.98 - 2.61	66.5%
Jeju	3,585	2.68	2.68 - 2.42	62.7%

Table S9. Hazard ratio and attributable risk of newly diagnosed AD by regions in relation to average 4 years concentration after adjusting individual and regional factors

Region	No. of individuals	HR	95% CI	Attributable Risk
Seoul	43,299	1.00	Reference	
Busan	19,597	2.35	2.35 - 2.12	57.4%
Daegu	12,519	1.98	1.98 - 1.74	49.4%
Incheon	11,724	1.78	1.78 - 1.55	43.7%
Gwangju	7,047	3.58	3.58 - 3.29	72.0%
Daejeon	6,777	3.80	3.8 - 3.51	73.7%
Ulsan	3,702	1.65	1.65 - 1.4	39.2%
Gyeonggi	52,100	2.60	2.6 - 2.39	61.6%
Gangwon	12,842	3.49	3.49 - 3.22	71.3%
Chungbuk	12,340	2.39	2.39 - 2.1	58.2%
Chungnam	17,932	2.54	2.54 - 2.29	60.6%
Jeonbuk	17,078	3.84	3.84 - 3.57	74.0%
Jeonnam	21,094	3.08	3.08 - 2.81	67.5%
Kyungbuk	24,776	2.75	2.75 - 2.48	63.6%
Kyungnam	21,698	2.90	2.9 - 2.59	65.5%
Jeju	3,585	4.19	4.19 - 3.88	76.1%

Table S10. Hazard ratio and attributable risk of newly diagnosed AD by regions in relation to average 5 years concentration after adjusting individual and regional factors

Region	No. of individuals	HR	95% CI	Attributable Risk
Seoul	43,299	1.00	Reference	
Busan	19,597	2.32	2.32 - 2.08	56.9%
Daegu	12,519	2.15	2.15 - 1.91	53.6%
Incheon	11,724	1.93	1.93 - 1.7	48.1%
Gwangju	7,047	3.76	3.76 - 3.47	73.4%
Daejeon	6,777	4.03	4.03 - 3.73	75.2%
Ulsan	3,702	1.83	1.83 - 1.57	45.4%
Gyeonggi	52,100	2.62	2.62 - 2.41	61.8%
Gangwon	12,842	3.68	3.68 - 3.41	72.8%
Chungbuk	12,340	2.92	2.92 - 2.58	65.8%
Chungnam	17,932	2.54	2.54 - 2.27	60.6%
Jeonbuk	17,078	4.03	4.03 - 3.76	75.2%
Jeonnam	21,094	4.01	4.01 - 3.72	75.1%
Kyungbuk	24,776	3.08	3.08 - 2.8	67.5%
Kyungnam	21,698	2.26	2.26 - 1.96	55.7%
Jeju	3,585	4.45	4.45 - 4.14	77.5%

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국문초록

대기오염과 알츠하이머 질환의 연관성 연구
노인코호트 자료를 이용한 분석

박성원

보건학과 보건통계학전공

서울대학교 보건대학원

연구배경: 대기오염은 산업화로 인한 가스상 물질, 미세먼지(particulate matter), 유기 화합물 등으로 구성되며, 전세계적인 문제가 되고 있다. 대기 오염은 다양한 건강 관련 지표들과 함께 연구되고 있으며, 건강에 좋지 않은 영향을 미치는 것으로 밝혀져 있다. 대기오염은 신경계 퇴행성 질환의 원인으로 작용할 수 있는 신경계 염증반응(neuroinflammation)이나 산화적 손상(oxidative stress)과 관련이 있는 것으로 밝혀졌다. 또한 이전의 연구에서 대기오염과 인지 기능 저하 및 치매와의 연관성에 대해 다뤘으며, 이들 연구 결과에서 유의한 상관관계를 나타내었다. 그러나 우리나라에서는 아직 치매의 상당 부분을 차지하는 알츠하이머 질환(Alzheimer's disease)과 대기 오염에 대한 연구가 부족한 실정이다. 그래서 이번 연구에서는 대기오염과 알츠하이머 질환의 연관성에 대해 연구해보

고자 한다.

목적: 본 연구는 한국에서 대기오염이 알츠하이머 진단에 미치는 단기적 및 장기적 영향을 알아보고자 하며, 그 영향을 위험비를 통해 파악하고자 한다.

연구방법: 본 연구는 대기오염의 영향을 추정하기 위해 콕스비례위험모형(Cox proportional hazard model)을 사용하여 분석을 수행하였다. 자료는 국민건강보험자료 공유서비스에서 제공하는 노인코호트 자료를 이용하였다. 2002년 1월 1일부터 2015년 12월 31일까지 약 58만명에 해당하는 자료로, 그 중 조작적 정의에 해당하며 결측치가 없는 약 28만명에 대해 추적 조사를 하였다. 종속변수로는 알츠하이머 질환을 처음으로 진단 받은 날짜이며 주된 설명 변수로는 진단받기 이전까지의 평균 대기오염 농도이다. 그 외에 알츠하이머 질환에 영향을 미치는 개인 변수 및 지역별 변수를 고려하여 분석하였다. 대기오염에 대한 정보는 알츠하이머 질병 진단 및 중도 절단 이전까지의 1년, 2년, 3년, 4년, 5년 간의 평균 농도를 노출로 평가하여 분석에 사용하였다.

결과: 대기오염 노출에 대한 알츠하이머 질환의 연관성은 콕스비례위험모형에서 제시되는 위험비(Hazard ratio)를 통해 계산하였으며, 그 값은 95% 신뢰수준으로 표시하였다. 진단 이전 1년간의 평균 농도를 노출로 평가하여 분석에 사용한 경우의 위험비는 1.15(95% 신뢰구간: 1.05, 1.27)이었으며, 2년 간의 평균 농도를 사용한 경우는 1.14(1.03, 1.25), 3년 간의 평균의 경우 1.16(1.05, 1.28), 4년 간의 평균은 1.20(1.09, 1.32), 5년 간의 평균은 1.19(1.08, 1.30)로

기간이 길어짐에 따라 증가하는 추세를 나타냈다. 지역 변수를 추가적으로 고려한 모델에서는 개인변수만 고려했을 때 보다 약 2배 정도 증가한 것으로 나타냈다. 이전 1년간의 노출에 따른 위험비가 1.29 (1.14, 1.46)로 높아졌고, 2년 간의 노출에는 1.34(1.17, 1.53), 3년 간의 노출에는 1.41(1.23, 1.62), 4년 간의 노출에는 1.50(1.31, 1.73), 5년 간의 노출에는 1.49(1.30, 1.71)으로 높아졌으며, 기간이 길어짐에 따라 전반적으로 증가하는 추세를 보였다.

결론: 본 연구에서는 대기오염 노출과 알츠하이머를 처음으로 진단받을 위험에 대한 연관성에 대해 파악해보았다. 연구 결과에서 대기오염 노출에 따라 알츠하이머를 진단받을 위험성이 13%에서 20%까지 증가하는 것을 관찰하였다. 그리고 지역변수를 추가한 모델에서는 위험비가 더 증가하는 것으로 나타났다. 또한 진단 이전까지의 기간이 길어짐에 따라 점점 위험비가 증가하는 경향을 나타냈다. 노출 기간에 따른 영향은 다르지만, 전반적으로 대기오염 노출에 따라 알츠하이머를 진단 받을 위험이 증가하는 것으로 나타났다.

주요어: 대기오염, PM10, 알츠하이머 질환, 진단, 노인코호트, 콕스 비례위험 모형

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