Long-term effects of cumulative average fine particulate matter exposure on the risk of hemorrhagic stroke

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Directed by Professor Changsoo Kim

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ABSTRACT

Long-term effects of cumulative average fine particulate matter exposure on the risk of hemorrhagic stroke

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Background: Epidemiological studies have revealed associations between fine particle ($PM_{2.5}$; aerodynamic diameter <2.5 μm) exposure and cardiovascular disease. Researchers have also recently begun investigating the association between $PM_{2.5}$ exposure and hemorrhagic stroke (HS) and identifying subpopulations susceptible to $PM_{2.5}$ exposure. Long-term cumulative average $PM_{2.5}$ exposure may affect the risk of HS, and the effects may be modified by risk factors.

Methods: This retrospective study evaluated the effects of $PM_{2.5}$ on the time-to-first-diagnosis of HS among 62,676 Seoul metropolitan city

residents with 670,431 total person-years of follow-up; this cohort is a subset from a nationally representative cohort of 1,025,340 individuals from the Korean National Health Insurance Service database (2002–2013). A time-dependent Cox proportional hazards model was used to adjust for age, sex, household income, insurance type, body mass index, smoking status, medical history, and family history. The annual average $PM_{2.5}$ concentrations for 25 districts were used as the time-dependent variables. Subgroup analyses of the traditional risk factors of HS were performed to evaluate the potential effect modifications.

Results: Each 10-$\mu g/m^3$ increment in cumulative average $PM_{2.5}$ exposure was significantly associated with HS (hazard ratio [HR]: 1.43, 95% confidence interval [CI]: 1.09−1.88). The adverse effects of $PM_{2.5}$ exposure were modified by age ≥65 years (HR: 2.00, 95% CI: 1.32−3.02) and obesity (body mass index ≥25 kg/m^2; HR: 1.91, 95% CI: 1.28−2.84).

Conclusion: Cumulative average $PM_{2.5}$ exposure might increase the risk of HS. Elderly (≥65 years) and obese individuals may be more susceptible to the effects of $PM_{2.5}$ exposure.

Key words : particulate matter; chronic effect; cumulative average exposure; hemorrhagic stroke

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I. INTRODUCTION

Fine particulate matter ($PM_{2.5}$) is particles with a nominal mean aerodynamic diameter≤ 2.5 μm among particulate matter, a mixture of solid particles and liquid droplets found in the ambient air (Figure 1).[1] It is comprised of various components including metals, black carbon, or organic compounds.[2] Composition of the PM varies greatly and depends on many factors. The major components of PM are transition metals, ions (sulfate and nitrate), organic compounds, quinoid stable radicals of carbonaceous materials, minerals, reactive gases, and materials of biological origin.

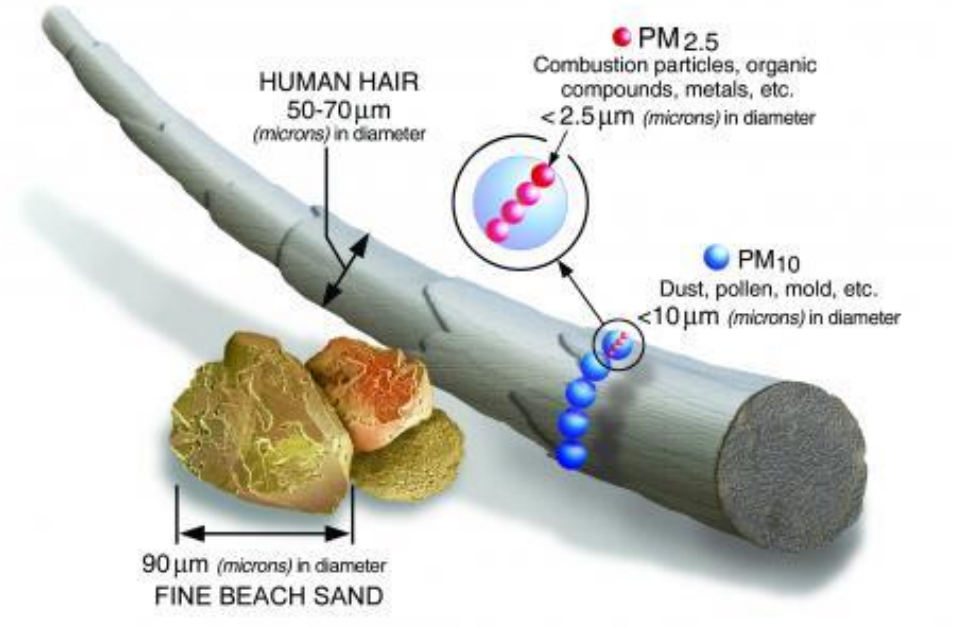


Figure 1. Size fractions of particulate matter.

Source: U.S. EPA. Particulate matter basics. Available at: https://www.epa.gov/pm-pollution/particulate-matter-pm-basics [Accessed 30 June 2019].

1. A landmark fine particulate matter study: Harvard six cites study

In 1993, Dockery et al. suggested that long-term exposure to fine-particulate air pollution could increase the risk of death.[3] At that time, fine-particulate matter had not been defined as being unhealthy by the World Health Organization (WHO) or U.S. Environmental Protection Agency (EPA). Hence, ground-breaking findings have generated many debates.[4] As always in public health and epidemiology,

important results require support from other studies with replication.[5] American Cancer Society II study, which was another large cohort study with long-term follow-up, showed that a significant association between fine particulate matter cardiopulmonary and lung cancer mortality.[6]

The results of the studies have been subject to debate with other scientists, members of the U.S. Congress, and industry representatives. Consequently, the reanalysis of the original data from two historical studies was requested to test the validity and robustness of the findings.[7] The reanalysis, which was independently performed by the Health Effects Institute, demonstrated that the data were of high quality and supported that the risk estimates published by the original investigators were not the results of inappropriate statistical methods or accidental errors.[8]

These two studies provided an important basis for the U.S. EPA to establish an air quality standard for the annual average $PM_{2.5}$ of 15 $\mu g/m^3$ in 1997 and for the WHO to adopt the annual average concentration of 10 $\mu g/m^3$ as the long-term guideline value for $PM_{2.5}$ in 2005.[9,10] Air quality standard specifies not just the concentration and the averaging time but the proportion of time that the standard must be met. This regulatory approach inherently assumes that maintaining target concentrations met by source control and emission reductions will reduce exposure to $PM_{2.5}$ and, subsequently, decrease risks of adverse health effects.

2. Frameworks for particulate matter research

Measuring the health impact of regulations or policies to improve air quality could be performed in different perspective across broad range of disciplines, including atmospheric science or engineering, exposure assessment technology, toxicology, biostatistics or epidemiology, public policy, and health economics. In 1998, the National Research Council's Committee on Research Priorities for Airborne Particulate Matter report set out a framework for connecting air pollution sources to adverse health effects (Figure 2).[11]

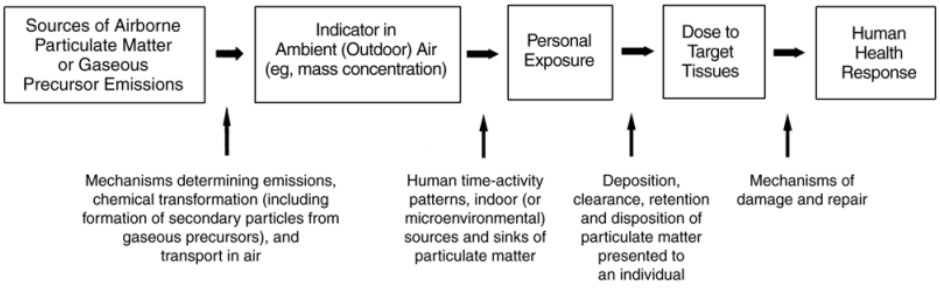


Figure 2. A framework for linking air pollution sources to adverse health effects. Source: National Research C. Research Priorities for Airborne Particulate Matter: I. Immediate Priorities and a Long-Range Research Portfolio. Washington, DC: The National Academies Press; 1998.

The Health Effects Institute Accountability Working Group also developed another integrated framework for assessing the performance of air quality regulatory policies as well as for evaluating the extent to which those regulations improve public health (Figure 3).[12] These chains encompass air pollution sources including

emissions and the resulting concentrations of pollutants in air as well as individuals and population exposure levels, and finally the consequent adverse health outcomes.

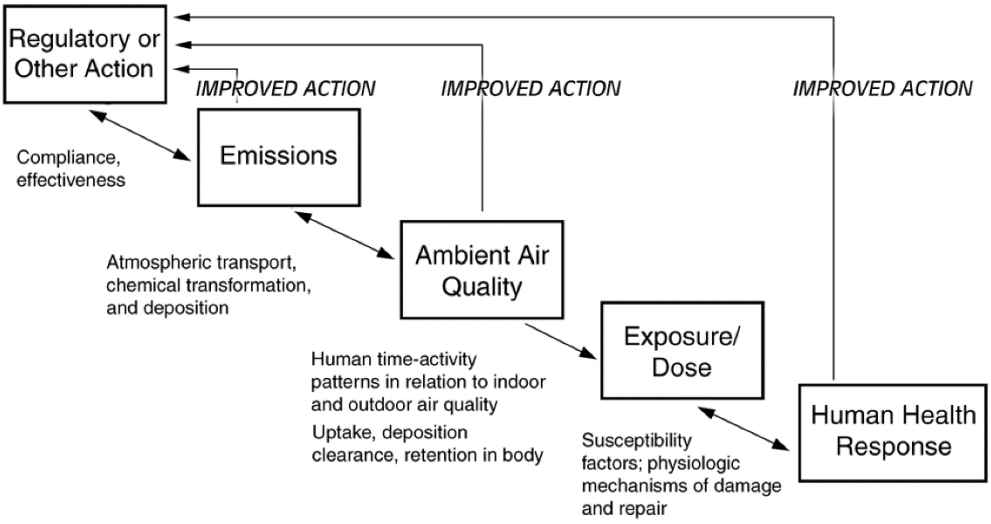


Figure 3. Chain of accountability. Each box represents a link between regulatory action and human health response to air pollution. Arrows connecting the links indicate possible directions of influence. Text below the arrows identifies the general indices of accountability at that stage. At several stages, knowledge gained from accountability assessment can provide valuable feedback for improving regulatory or other action. Source: Health Effects Institute Accountability Working Group. Assessing health impact of air quality regulations : concepts and methods for accountability research. Boston, MA: Health Effects Institute; 2003.

The U.S. EPA released a report that evaluated the policy-relevant scientific literatures aimed at characterizing exposures to ambient particulate matter and the

potential human health and welfare effects associated with these exposures.[13] In that report, U.S. EPA outlined the general framework for evaluating scientific evidence and drawing conclusions on the key policy-relevant questions including causal judgments, as a step in the general National Ambient Air Quality Standards review process (Figure 4).[14]

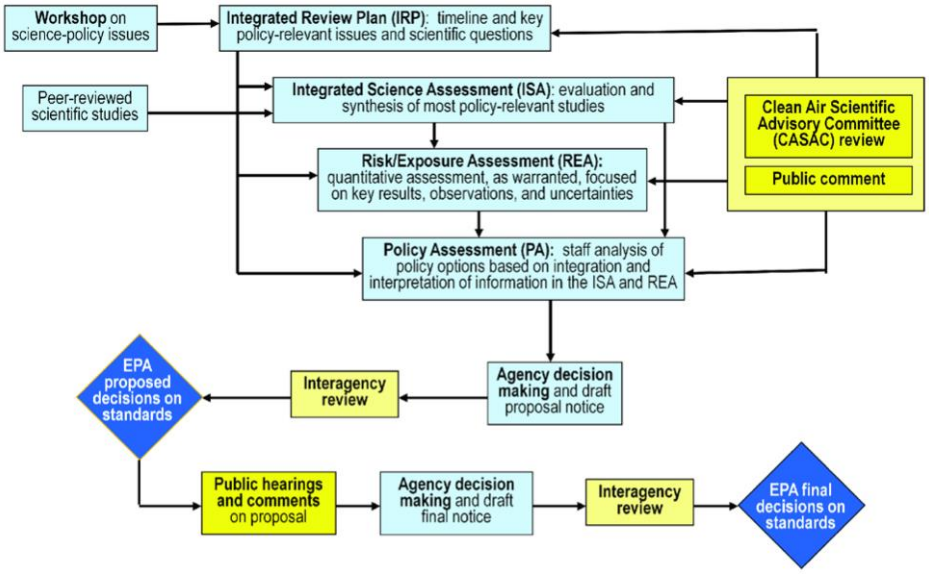


Figure 4. Schematic of the key steps in the review of the National Ambient Air Quality Standards. Source: National Center for Environmental Assessment. Preamble to the Integrated Science Assessments. Research Triangle Park, NC; 2015.

3. Assessment of the long-term exposure to fine particulate matter

The ideal way to estimate long term $PM_{2.5}$ exposure may be the integration of

breathing concentrations over time and across the microenvironments in which a person spends time during defined periods. Personal exposures including time-activity pattern, meteorological data, emission sources, and characteristics of microenvironments are not usually measured, surrogate exposure estimates are often used to represent personal exposure.[15] Depending on data availability and research purpose, epidemiological studies select surrogate exposure estimates such as ambient $PM_{2.5}$ concentration, non-ambient $PM_{2.5}$ concentration, total personal exposure to ambient $PM_{2.5}$, or overall total personal exposure.[16,17]

To assign exposure concentrations to study participants, epidemiologic studies use a variety of approaches including measurement methods (fixed-site monitor, microenvironmental monitor, or active/ passive personal exposure monitor) or modelling methods (data averaging, inverse distance weighting, kriging, land use regression, spatiotemporal model, chemical transport model, dispersion model, hybrid approaches, or microenvironmental modeling). Ozkaynak et al. developed a hierarchy of methods based upon complexity (Figure 5).[18] Common methods include using measurements from central-site or fixed-site ambient monitoring, selecting the closest monitor to represent population exposure concentration, and averaging concentrations from multiple monitors. Statistical adjustment methods trimming extreme values might be applied to improve the quality control of exposure concentration data set.

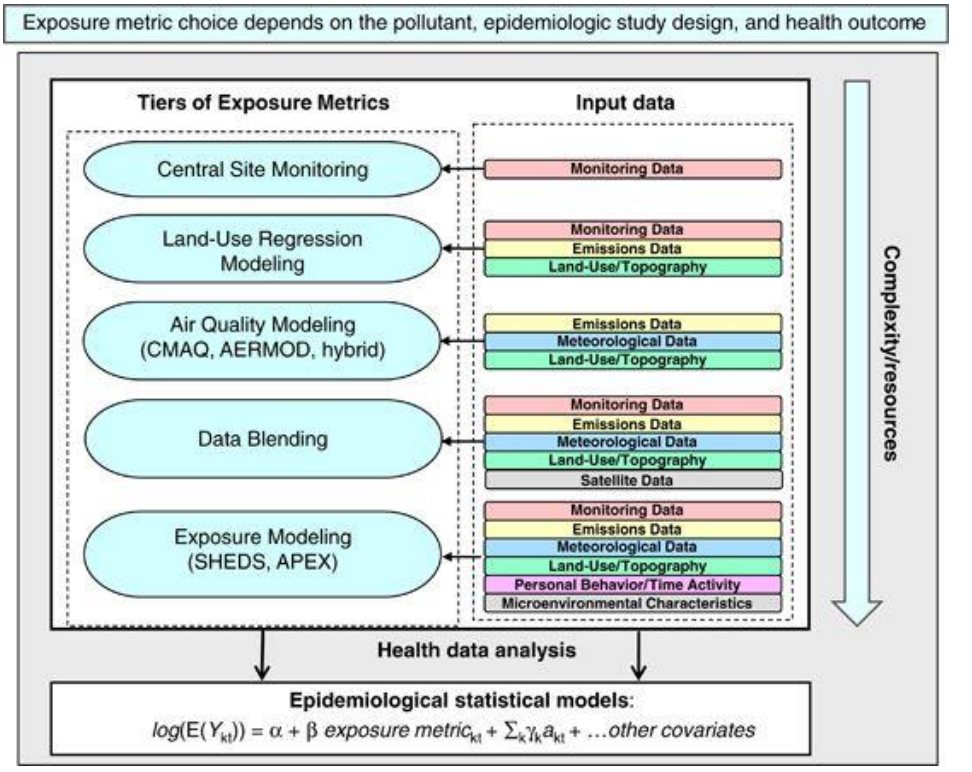


Figure 5. Tiers of exposure models relevant to epidemiology studies and input data types for each exposure model tier. CMAQ: Community Multiscale Air Quality; AERMOD: AMS (American Meteorological Society)/EPA (United States Environmental Protection Agency) Regulatory Model; SHEDS: Stochastic Human Exposure and Dose Simulation; APEX: Air Pollutants Exposure models. Source: Ozkaynak H, Baxter LK, Dionisio KL, Burke J. Air pollution exposure prediction approaches used in air pollution epidemiology studies. J Expo Sci Environ Epidemiol 2013;23:566-72.

There might be a difference between the actual $PM_{2.5}$ exposure and surrogate

exposure estimates.[19] When spatiotemporal variability or population groupings are incorrectly assigned, exposure error due to the usage of surrogate estimate could result in the exposure misclassification, either differential or nondifferential.[20] The quality of epidemiological study inference is determined by study design, data structure, appropriate adjustment of confounding, and the quality of the $PM_{2.5}$ exposure estimates. According to the type of exposure misclassification, the health effect estimate might be attenuated or overestimated. Exposure errors has two distinctive components, classical error and Berkson error (Figure 6).[21]

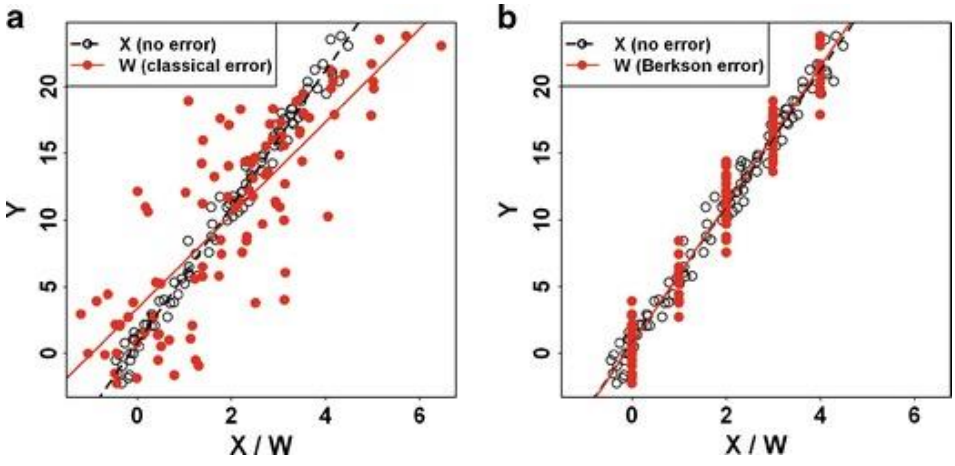


Figure 6. Examples of possible errors in a linear disease model relationship with surrogate exposures. a: classical error; b: Berkson measurement error; X: true exposure; W: surrogate exposure; Y: disease outcome. Source: Sheppard L, Burnett RT, Szpiro AA, Kim SY, Jerrett M, Pope CA, 3rd, et al. Confounding and exposure measurement error in air pollution epidemiology. Air Qual Atmos Health 2012;5:203-16.

A classical error is identified when the measurement varies randomly and independently around the true exposure, and it usually derived from the error of the ambient monitor. Classical error typically attenuates the effect estimates towards the null because the variation in the measurements tends to be greater than variation in the true exposures. A Berkson error is defined when the true exposure scattered around the measured concentrations of the surrogate exposure, which is the ambient monitoring measurement in most cases. The measured concentrations of surrogate exposure are less variable than the true personal exposure level and independent of the measured population average. A purely Berkson error tends not to cause bias in the health effect estimate.[22]

In longitudinal cohort studies, exposure surrogates are ambient concentrations aggregated over follow-up periods, such as several years or decades, and by unit region such as community.[3,23] Applying exposure surrogate with different degrees of measurement error can influence and determine bias in the health effect estimate.[24] Jerrett et al. compared the effect estimated using ground-based data or remote sensing with satellite data and found that the effect of $PM_{2.5}$ estimates modelled using ground data as well as remote sensing data was larger than that of $PM_{2.5}$ estimates from the satellite method alone.[25] Another study comparing the estimated bias and the inflation of the standard errors caused by the different exposure surrogates of traffic-related air pollution reported that measurement error typically biased the associations between exposure and health toward the null

and might reduce the ability to detect an adverse effect.[26] That is, validation studies and the related exposure models can substantially increase the likelihood of detecting significant associations. In other studies using the time-varying ambient source exposures, when nonambient sources are independent of ambient sources, the measurement error behaves like a Berkson measurement error and would result in a bias toward the null to underestimate the health effect of the exposure to ambient $PM_{2.5}$ with widening the confidence interval.[27]

Although $PM_{2.5}$ concentrations tend to be less spatially variable than other size fraction concentrations, spatial exposure error is another source of bias in long-term cohort studies.[28] Alexeeff et al. compared the bias and uncertainty measurement error correction strategies of land use regression, kriging, and satellite-based high resolution model.[29] Compared with the satellite-based model, the R^2 of the land use regression model was 71-84% and that of the kriging model was 24-44%. The effect estimates from the land use regression or kriging models sometimes worked well but other times were biased away from the null. In some large epidemiological cohort studies, the measurement error of $PM_{2.5}$ exposure resulted in a bias toward the null to underestimate the health effect estimates, which were lower than those estimated using the $PM_{2.5}$ exposure modelled with the error correction method.[30-32] Other studies reported consistent findings that exposure concentration of $PM_{2.5}$ with a greater spatial resolution (50 m) resulted in higher mortality effect estimates than those obtained with a 10-km resolution.[33,34] Sheppard et al. emphasized that exposure assessment is necessary to capture the underlying exposure variability

for the pollutants in the estimation of the health effect.[21] Cefalu and Dominici conducted a simulation study to evaluate the joint effect of $PM_{2.5}$ exposure measurement error and confounding and found that, a more accurate prediction of the exposure does not always reduce the bias in the health effect estimation in the presence of uncontrolled spatial confounding adjustment.[35]

4. Evaluation of the cardiovascular health effects of long-term $PM_{2.5}$ exposure

The extended follow-up of the Harvard Six Cities study showed that the city-specific reduction of $PM_{2.5}$ were associated with reduced mortality risk suggesting that recent or lifetime cumulative exposures would have effect on survival and public health benefit.[36,37] The results of extended follow-up and spatial analysis of the American Cancer Society study consolidate earlier findings.[38] Dr. Krewski's team repeated a spatial analysis designed to explore whether more recent exposures to air pollution are more or less strongly associated with mortality than exposures further in the past.[39] Exposure profiles for this analysis were constructed from average $PM_{2.5}$ concentrations for periods 1 to 5 years, 6 to 10 years, and 11 to 15 years prior to death.

Many recent epidemiologic studies as well as subsequent analyses of two landmark studies demonstrated consistent positive associations and supported a strong relationship between long-term $PM_{2.5}$ exposure and risk of cardiovascular disease and mortality. Some well-conducted prospective studies indicate an

association between long-term exposure to $PM_{2.5}$ and ischemic heart disease (IHD). Miller et al. analyzed the cohort of 65,893 postmenopausal women in 36 U.S. metropolitan areas followed for a median duration of 6 years and found that annual average of $PM_{2.5}$ from the monitor located nearest to the residence of each women might increase risk of cerebrovascular events and stroke [co-pollutants adjusted hazard ratio [HR]: cerebrovascular events: 1.16 (95% confidence interval [CI]: 1.04, 1.30) and HR stroke: 1.13 (95% CI: 1.04, 1.30)].[40] Cesaroni et al. conducted a meta-analysis of 11 European prospective cohort studies with a median follow-up of 11.5 years and supported that annual average $PM_{2.5}$ estimated by land use regression was associated with an increased incidence of IHD.[41] Some studies reported no association between $PM_{2.5}$ exposure and the incidence of myocardial infarction (MI) or coronary events.[42,43] Adar et al. found that the intima-medial thickness (IMT) of the common carotid artery was associated with long-term $PM_{2.5}$ concentrations and greater reductions in $PM_{2.5}$ are related to slower IMT progression.[44] The association was consistent with that from other studies which considered $PM_{2.5}$ components.[28,45] Several studies also explored the potential effect modification by past medical history of diabetes, cardiac disorders, and MI as well as by individual and neighborhood level socioeconomic status (SES).[46-49]

Although consistency of associations varied with the specific outcome and exposure definition, several epidemiologic studies have reported an association between $PM_{2.5}$ exposure and various outcomes related to cardiovascular disease including atherosclerosis progression.[50,51] The Multi-Ethnic Study of

Atherosclerosis (MESA) analyses supported the effect of $PM_{2.5}$ exposure on coronary artery calcium score among middle to older aged adults, while the Framingham Heart Study offspring study found no such association.[52,53] A small number of studies provide evidence supporting a possible relationship between $PM_{2.5}$ and heart failure (HF).[48,54] Liao et al. reported that 365-day $PM_{2.5}$ concentrations were not associated with the most frequent forms of arrhythmia in the general population (supraventricular or ventricular ectopy).[55] Another study did not find any arrhythmogenic effects of $PM_{2.5}$.[54] The meta-analysis of European cohorts reported a weak positive association of residential traffic exposure with arrythmia in contrast to exposure modeled by land use regression.[56] Similarly, Coogan et al. reported no association between long-term $PM_{2.5}$ exposure and hypertension in the Black Women's Health Study, which was based on exposure estimated at all residential locations over follow-up with a hybrid model incorporating land use regression and Bayesian Maximum Entropy techniques.[57,58] A longitudinal analysis of postmenopausal women in the Women's Health Initiative Hormone Therapy trials found no evidence of an association between venous thromboembolism and long-term exposure to $PM_{2.5}$ and that of effect modification by hormone therapy.[59] Another Nurses' Health Study reported exposure to $PM_{2.5}$ is positively associated with pulmonary embolism.[60]

Recent epidemiologic studies focusing on the health effects of long-term $PM_{2.5}$ exposure controlled for the potential confounding effect of co-pollutants.[61,62] Some studies often examined traffic-related pollutants such as ozone (O_3), nitrogen

dioxide (NO_2), Nitrogen oxide (NO_X), or carbon monoxide (CO), whereas others adjusted for the size of particles such as $PM_{10-2.5}$ or ultra-fine particulate matter. The $PM_{2.5}$ associations with effects were relatively unchanged in co-pollutant models. In a multipollutant model adjusting for NO_2, the effect estimates for the association of $PM_{2.5}$ and MI risk was remained largely unchanged.[47] Madrigano et al. distinguished area $PM_{2.5}$ from local traffic-related $PM_{2.5}$ and reported that the association with area $PM_{2.5}$ was maintained after adjusting for local traffic-related $PM_{2.5}$[61] . Puett et al. reported that the health effect of long-term $PM_{2.5}$ exposure was similar to that in the co-pollutant model incorporating $PM_{10-2.5}$.[63] The correlations coefficient between co-pollutants and $PM_{2.5}$ were usually less than 0.7.

Another important consideration for the long-term $PM_{2.5}$ exposure effect on cardiovascular health is whether the concentration-response relationship is linear or whether there is a threshold for the health effect. Recent epidemiologic studies on the shape of the concentration response curve provide evidence of a linear no-threshold relationship between long-term $PM_{2.5}$ exposure and cardiovascular effects IHD, coronary artery calcification, hypertension and mortality. Some studies found that the effect on cardiovascular mortality or the steeper slope at lower $PM_{2.5}$ concentrations was within ranged within 5-15 $\mu g/m^3$. Qian et al. reported an almost linear relationship between $PM_{2.5}$ exposure and all-cause mortality with a steeper slope below 12 $\mu g/m^3$ and no sign of threshold down to 5 $\mu g/m^3$.[62] Dorans et al. found non-linearity in the associations of $PM_{2.5}$ with log-transformed coronary artery calcium score and Kaufman et al. reported that the concentration-response

curve suggests an attenuation of the association at higher concentrations.[52,53]

Some studies have investigated the relationship between exposures to $PM_{2.5}$ components and sources and health effects to evaluate whether specific components or sources are more strongly associated with health effects than $PM_{2.5}$ mass. In a multicenter study of 11 European cohorts, exposure to $PM_{2.5}$ components of iron and potassium was positively associated with coronary events.[64] Gan et al. found an association between long-term traffic-related fine particulate black carbon exposure and coronary heart disease hospitalizations.[65] Exposure to $PM_{2.5}$ components of elemental carbon, organic carbon, sulfur, and possibly silicon was associated with common carotid artery IMT.[28,45] These findings supported that any one source and/or component is not consistently more strongly associated with health effects than $PM_{2.5}$ mass.

There are several biologically plausible pathways connecting long-term exposure to $PM_{2.5}$ to cardiovascular health effects (Figure 7).[66] Respiratory tract injury and inflammation might spread into the circulatory system and induce a series of pathophysiological responses that could ultimately result in IHD, stroke, HF, or thromboembolic disease elsewhere in the body. Hajat et al. identified an association between $PM_{2.5}$ and IL-6 levels among participants from the Multi-Ethnic Study of Atherosclerosis.[67] In a longitudinal study of the Heinz Nixdorf Recall Study, Viehmann et al. demonstrated the effect of $PM_{2.5}$ estimates modeled at each participant's residence by the chemistry transport model on pathways of

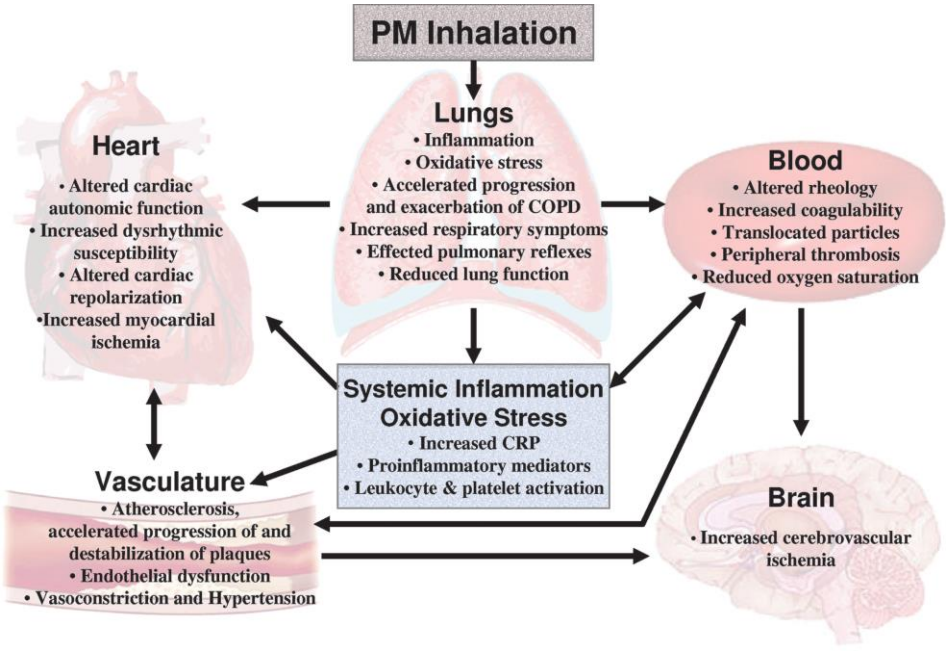


Figure 7. Potential general pathophysiological pathways linking PM exposure with cardiopulmonary morbidity and mortality. Source: Pope CA, 3rd, Dockery DW. Health effects of fine particulate air pollution: lines that connect. J Air Waste Manag Assoc 2006;56:709-42.

inflammation (high-sensitive C-reactive protein [hs-CRP]; an independent predictor of cardiovascular disease) and coagulation (platelets).[68] Hennig et al. also investigated the associations between source-specific $PM_{2.5}$ exposure and hs-CRP and reported that systemic inflammation was more strongly associated with local traffic-specific $PM_{2.5}$ exposure than industry-specific or total $PM_{2.5}$ exposure.[69] In recent studies, the long-term exposure to particulate air pollution was found to be associated with an increase in CRP and more strongly associated with CRP level

than short-term exposure.[70,71] Certain subgroup of older patient with diabetes, smokers, the unmarried, people with high blood pressure, or those who were using hormone therapy were more susceptible to the effects of long-term exposure to $PM_{2.5}$ on CRP.[72] Animal experiments have shown that vascular or cardiac dysfunction might be impaired due to systemic inflammation in response to long-term $PM_{2.5}$ exposure.[73,74] Chronic air pollution exposure has also been found to induce the accumulation of oxidized lipids in macrophage and atherosclerosis progression.[75]

Modulation of the autonomic nervous system is another mechanism for the incidence of cardiovascular diseases. Studies using $PM_{2.5}$ exposure assigned using 30-day or 60-day averages showed elevated systolic blood pressure (SBP), pulse pressure (PP), and mean arterial pressure (MAP) but not diastolic blood pressure (DBP).[76,77] Chen et al. supports that estimates of long-term exposure to $PM_{2.5}$ at participants' postal-code residences derived from satellite observations increase the risk of the incident hypertension.[78] In an animal study, chronic $PM_{2.5}$ exposure resulted in a cardiac phenotype consistent with HF.[79] In another study, the centrally acting α2a agonist guanfacine attenuated the basal BP increase after long-term $PM_{2.5}$ exposure, suggesting a role of sympathetic activation, which was accompanied by the hypothalamic inflammation.[80] Hypertension can lead to HF or arrhythmia through cardiac remodeling and contribute to impaired vascular function and atherosclerosis.[81,82] These studies might provide additional biologically plausible mechanisms for the association between long-term exposure to $PM_{2.5}$ and

cardiovascular mortality or morbidity including cerebrovascular disease.

5. Backgrounds of this study

Despite improvements in managing cardiovascular risk factors, cerebrovascular disease remains a major cause of death and morbidity. For example, 90% of the total stroke risk can be attributed to 10 major risk factors, including acute events (e.g., emotional stimulus) and medical conditions (e.g., atrial fibrillation or history of hypertension).[83] In addition, fine particulate matter ($PM_{2.5}$; particulate matter with an aerodynamic diameter of <2.5 μm) has also emerged as a risk factor for stroke.[84,85]

During the last decade, epidemiological studies have revealed that particulate matter exposure may be associated with respiratory and cardiovascular diseases.[81] Long-term $PM_{2.5}$ exposure has also been shown to be associate with increased cardiovascular morbidity and mortality.[86,87] In a recent study, each increment of 10 μg per cubic meter in $PM_{2.5}$ was associated with an increase in all-cause mortality of 7.3% (95% confidence interval [CI]: 7.1–7.5%).[88] Various biological mechanisms for the effects of $PM_{2.5}$ on cardiovascular disease have been proposed,[89,90] and these mechanisms may be relevant to the development of cerebrovascular events. Growing amounts of evidence also support the association between $PM_{2.5}$ and stroke. Meta-analyses have summarized the short-term effects of peak $PM_{2.5}$ exposure on stroke hospitalization and mortality.[91,92] A recent meta-

analysis also found that incremental increases in $PM_{2.5}$ were associated with acute stroke morbidity and mortality (relative risk: 1.011 per 10 μg/m^3, 95% CI: 1.011–1.012).[93] The reported associations of long-term $PM_{2.5}$ exposure with stroke are less consistent than those for cardiovascular events,[40,42,94] and a recent meta-analysis investigated the long-term effects of particulate matter on the incidence of stroke in European cohorts (hazard ratio [HR]: 1.19, 95% CI: 0.88-1.62).[85]

Although individuals with underlying conditions could have a higher risk of nonfatal and fatal stroke events, few studies have investigated the modifying effects of $PM_{2.5}$ exposure in these patients. In this context, the key modifiers of hemorrhagic stroke (HS) risk include age, sex, ethnicity, family history of stroke, hypertension, cigarette smoking, heart disease, diabetes, and obesity.[95] Stafoggia et al. observed associations among those ≥ 60 years of age, never-smokers, and participants with $PM_{2.5}$ exposure < 25 μg/m^3. Hart et al. reported higher risks in women with diabetes, older women (≥70 years), and obese individuals.[96] Recently, Lin et al. also observed stronger effects of long-term $PM_{2.5}$ exposure among individuals with greater physical activity, whereas mitigated effects were seen among those with fruit and vegetable intake.[94] However, it is still unclear whether there are population subgroups that are more susceptible to the adverse effects of $PM_{2.5}$ exposure.

6. Objectives of this study

Therefore, this retrospective study was designed to evaluate residents in a

metropolitan city, a subpopulation in a nationally representative cohort of the Korean population, by linking death certificates and district-level $PM_{2.5}$ exposure concentrations using the individuals' residential addresses.

The aim of this study was to investigate the effects of long-term $PM_{2.5}$ exposure on HS, and to analyze whether the effect modifications were associated with modifiable risk factors.

II. MATERIALS AND METHODS

1. Ethical considerations

The study was performed in accordance with the Declaration of Helsinki, and was approved by the institutional review board of the Yonsei University Health System Clinical Trial Centre (4-2015-1191).

2. Data source

Data were extracted from the National Health Insurance Service-National Sample Cohort (NHIS-NSC), which is a nationally representative cohort of 1,025,340 Korean individuals (approximately 2% of the Korean population that was covered by the NHIS in 2002). Individuals were sampled using the systematic stratified random method, and followed annually for 12 years (2002–2013). A detailed profile

of the NHIS-NSC cohort has been reported.[97] Anonymous claims-based data were collected for all individuals who were covered by the NHIS. The NHIS insurance eligibility records consist of 14 criteria, including the participants' identifier, birthdate, date of death, status of disability, and demographic and socioeconomic characteristics (e.g. sex, income, district of residence, and type of health insurance). Data regarding causes of death were obtained from Statistics Korea.[98] The individuals' treatment records were obtained from medical claims records, which contained specific treatment information (e.g., prescription drugs and procedure codes). Detailed diagnoses were coded using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM). Records were also obtained from the questionnaire-based nationwide health examination of citizens (2002–2013), which provided information regarding each individual's physical status, blood test results, urine test results, lifestyle, and family history. To protect privacy, each Korean Resident Registration Number (a unique identification number) was replaced with a new eight-digit personal identifier.

3. Study population

The NHIS-NSC included 218,005 residents from Seoul, a metropolitan city, during 2002–2013. Seoul was chosen because $PM_{2.5}$ measurement data were only available for all districts in this metropolitan city, and several previous studies have evaluated the effects of particulate matter on cardiovascular events in Seoul.[99-101] A

total of 67,597 individuals were lost to follow-up (e.g., emigration, missing, or moving from Seoul), and another 87,732 individuals were excluded because of their age, unavailable health examination data, or a history of HS. A wash-out period of 1 year was used to eliminate potential cases of pre-existing HS. Accordingly, the final analyses included 62,676 adults (≥20 years old) who lived in the 25 districts of Seoul during 2002–2013 (Figure 8).

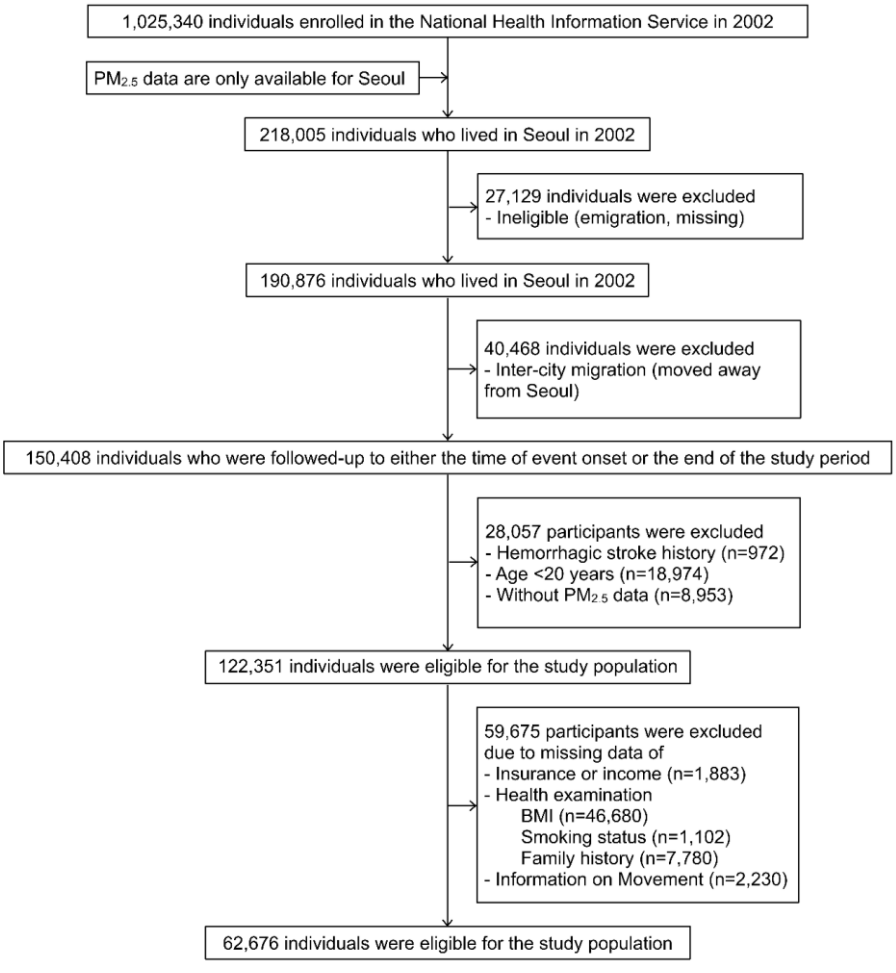


Figure 8. Study flowchart.

4. Study outcome

The study outcome was defined as the first diagnosis of non-fatal HS or death because of HS (ICD-10-CM codes I60–I62). The death records were updated every month, and all other records were updated annually after January 1, 2002. The index date was defined using the instance of an outcome event. The diagnosis of HS was robust, as computed tomography is covered by insurance and performed as the baseline examination for almost all stroke symptoms.[102,103] The 1-year wash-out period was used to ensure that only new-onset HS was included in the analyses.

5. Air pollution data

We obtained $PM_{2.5}$ data from 27 outdoor automated fixed-site monitoring stations, which are maintained by the Research Institute of Public Health and Environment (Seoul Metropolitan Government) [104]. Two outdoor automated fixed-site monitoring stations were closed during the study period (Figure 9). For each year, the individuals were assigned the annual average $PM_{2.5}$ exposure of hourly-monitored data in the district in which they were living. The long-term exposure variable of interest was the time-varying cumulative average $PM_{2.5}$ exposure during the follow-up period, which was calculated based on the annual average $PM_{2.5}$ exposures for each district during 2003–2013. To reflect the effects of any intra-city relocation,

the individuals' estimated $PM_{2.5}$ exposures were calculated by averaging the annual $PM_{2.5}$ exposure (January 1 to December 31) in the district where each individual had lived before the year of the event. $PM_{2.5}$ exposure was additionally categorized into tertiles, which were defined by the cumulative average $PM_{2.5}$ distribution. The last 3-year or 5-year average $PM_{2.5}$ exposures were calculated by averaging the annual mean $PM_{2.5}$ concentrations during last 3 or 5 years.

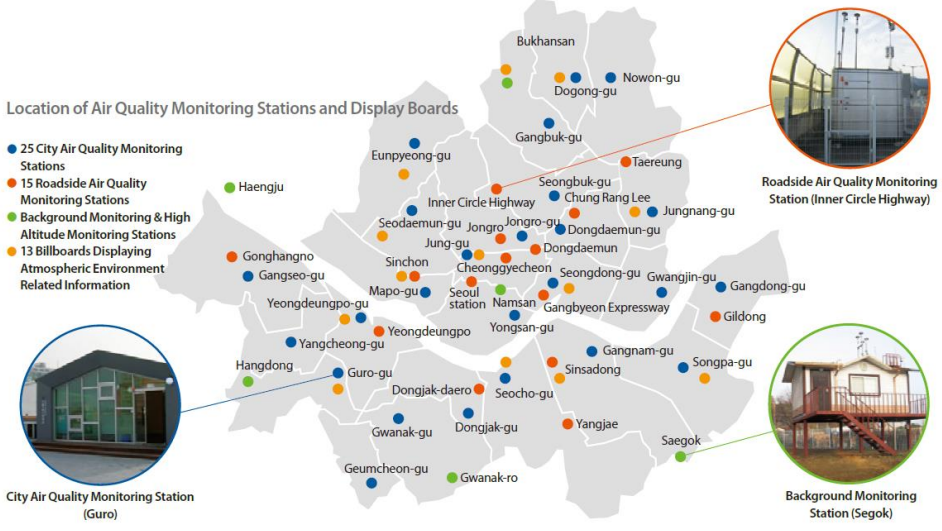


Figure 9. Locations of 25 city air quality monitoring stations in Seoul. Source: Seoul Solution. Air Pollution Monitoring Network. Available at: https://seoulsolution.kr/en/node/6540 [Accessed 25 June 2019].

6. Statistical analysis

The time-dependent Cox proportional hazards regression model was used to

estimate the adjusted hazard ratios (HRs) for stroke events. The follow-up duration was calculated as the time (in years) since enrolment. Each individual was followed-up annually until the first instance of the index date, death due to another cause, relocation outside of Seoul, or the end of the follow-up (December 31, 2013). Individuals were censored at the date of any non-index event. The main time-related variable of interest was the cumulative average $PM_{2.5}$ exposure, which was calculated as a continuous variable. Other time-related covariates were updated annually.

The individual-level covariates were recorded based on the health examination results, and were incorporated into the various study models. Each individual underwent at least one health examination (not necessarily on an annual basis), and the values from the previous examination were carried forward until the next examination. The study covariates were age (20–39 years, 40–49 years, 50–59 years, 60–69 years, and ≥70 years), sex, self-reported family history of ischemic heart disease or stroke, smoking status (never, former, or current), body mass index (BMI) variables (a continuous variable and five categorical variables: <18.5 kg/m^2, 18.5–22.9 kg/m^2, 23.0–24.9 kg/m^2, 25.0–29.9 kg/m^2, and ≥30 kg/m^2), the number of times moving within Seoul during the follow-up period (0, 1, or 2 times), and medical histories of congestive heart failure (ICD-10-CM code I50), hypertension (ICD-10-CM code I10-15), diabetes (ICD-10-CM code E10-14), or aortic atherosclerosis (ICD-10-CM code I70.0). To control for economic and social factors,

we also adjusted for two individual-level socioeconomic covariates: the household income decile based on the national incomes (1–20% [lowest], 21–40%, 41–60%, 61–80%, and 81–100% [highest]) and the type of health insurance (employee health insurance or community health insurance).

The possibility of non-linear relationships between the $PM_{2.5}$ exposure and the HR of HS incidence was considered non-parametrically with restricted cubic splines. Splines in the Cox regression models were performed using the LGTPHCURV9 macro.[105] To estimate the concentration-response curve of air pollution and HS, we fit a Cox regression model with a penalized spline of $PM_{2.5}$ adjusted for all variables incorporated in our main analysis model.[106]

Adjusted HRs and 95% CIs were estimated for the risk of stroke events based on 10-$\mu g/m^3$ increments of $PM_{2.5}$ exposure. We also evaluated effect modifications by performing subgroup analyses for the various risk factors, which were considered a priori as potential effect modifiers through stratification.

7. Sensitivity analyses

Sensitivity analyses were conducted to examine the robustness of the results. With respect to differences in the adjusted covariates, the sample size used in each analysis model was different and we compared the extent of variation in our estimates of HS risk. As part of the sensitivity analyses, we performed the same analyses with different wash-out periods. The analyses were also repeated to test for

any possible advantage in the cumulatively updated average over the annual average, the last 3-year or last 5-year average $PM_{2.5}$ concentrations. We additionally adjusted for the district-level variables of population density, proportion of married population, and deprivation index to control for the potential residual confounding.

All analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, North Carolina) and R software version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria) with the pspline and smoothHR packages.[106]

III. RESULTS

The study population's demographic characteristics are shown in Table 1. HS patients were more likely to be aged>60 years and to have overweight or obese whereas were less likely to have jobs or to move than individuals without HS. HS patients were more likely to have family history of ischemic heart disease and to have medical history of congestive heart failure, hypertension, or diabetes than individuals without HS (Table 1).

Table 1. Demographic characteristics of the study population

	Total		No event		Hemorrhagic stroke	
	N	%	N	%	N	%

Sex (female)	31,750	50.7	31,495	50.7	255	49.8
Age, years						
20–39	19,849	31.7	19,784	31.8	65	12.7
40–49	18,223	29.1	18,125	29.2	98	19.1
50–59	14,065	22.4	13,927	22.4	138	27.0
60–69	7,499	12.0	7,358	11.8	141	27.5
≥70	3,040	4.9	2,970	4.8	70	13.7
Health insurance type						
Community	18,448	29.4	18,257	29.4	191	37.3
Employee	44,228	70.6	43,907	70.6	321	62.7
Income decile, %						
1–20 (lowest)	8,094	12.9	8,023	12.9	71	13.9
21–40	10,197	16.3	10,116	16.3	81	15.8
41–60	11,480	18.3	11,393	18.3	87	17.0
61–80	13,279	21.2	13,168	21.2	111	21.7
81–100 (highest)	19,626	31.3	19,464	31.3	162	31.6
Family history						
Stroke	3,869	6.2	3,836	6.2	33	6.4
Ischemic heart disease	2,538	4.0	2,526	4.1	12	2.3
Medical history						

Congestive heart failure	1,053	1.7	1,026	1.7	17	3.3
Hypertension	11,725	18.7	11,514	18.5	118	23.0
Diabetes	6,912	11.0	6,801	10.9	65	12.7
Aortic plaque	42	0.1	42	0.1	0	0.0
Smoking status						
Never	42,101	67.2	41,743	67.2	358	69.9
Former	5,338	8.5	5,308	8.5	30	5.90
Current	15,237	24.3	15,113	24.3	124	24.2
Body mass index, kg/m^2						
<18.5	2,894	4.6	2,867	4.6	27	5.3
18.5–22.9	24,668	39.4	24,498	39.4	170	33.2
23.0–24.9	15,229	24.3	15,099	24.3	130	25.4
25.0–29.9	17,582	28.1	17,417	28.0	165	32.2
≥30	2,303	3.7	2,283	3.7	20	3.9
Number of moves, times						
0	48,530	77.4	48,087	77.4	443	86.5
1	10,051	16.0	9,997	16.1	54	10.5
≥2	4,095	6.5	4,080	6.6	15	2.9
Total	62,676	100	62,164	99.0	512	1.00

During the 12-year follow-up of 62,676 adults (670,431 total person-years, median follow-up of 11 years), we detected incident HS in 512 patients (1.0%). Annually, the number of non-fatal hemorrhagic stroke cases was 45 and that of fatal hemorrhagic stroke cases was 2 (Figure 10).

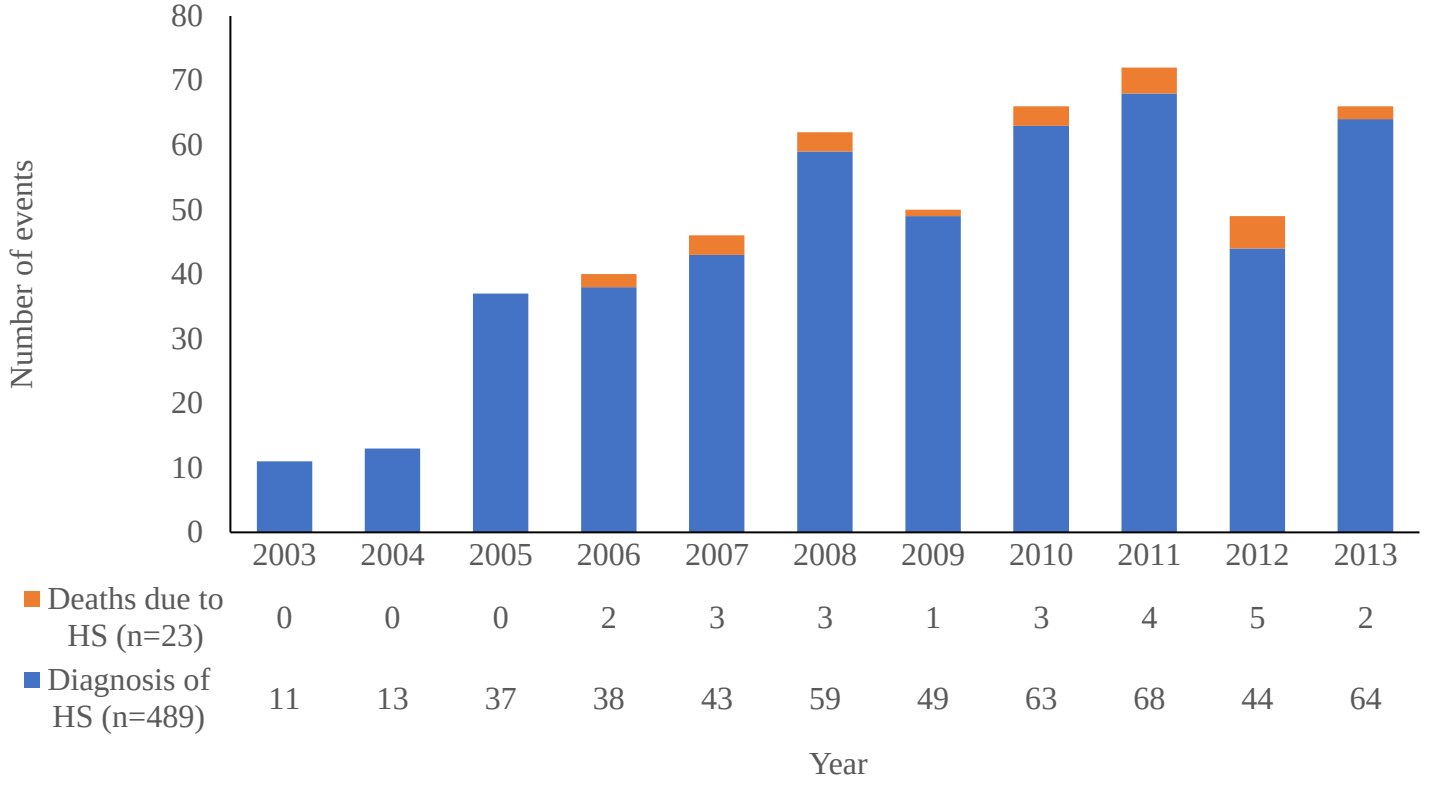


Figure 10. Incidence of hemorrhagic stroke. HS: hemorrhagic stroke.

The annual average $PM_{2.5}$ concentration in Seoul was 38.9 μg/m^3 in 2002, and decreased to 25.1 μg/m^3 in 2013 (Figure 11).

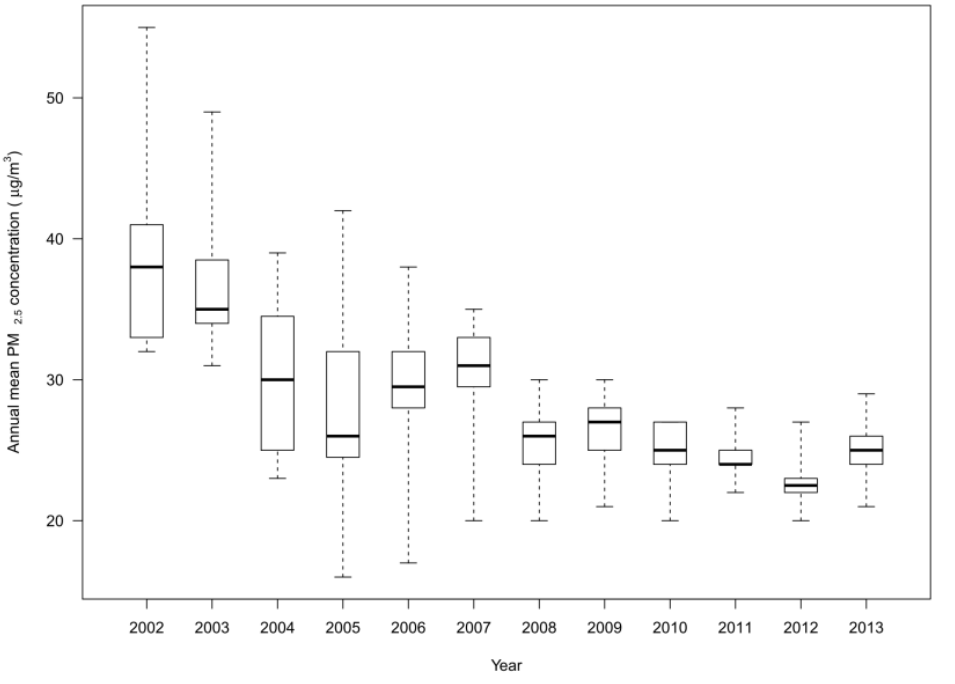


Figure 11. Annual average $PM_{2.5}$ concentrations in Seoul, 2002–2013. $PM_{2.5}$: particulate matter with an aerodynamic diameter of <2.5 μm.

The cumulative average $PM_{2.5}$ concentrations were positively correlated with the annual average $PM_{2.5}$ concentrations until 2009 (Figure 12, Figure 13). Since 2010, the annual average $PM_{2.5}$ concentrations were negatively correlated with those before 2010. This negative correlations also affected the correlations between cumulative average $PM_{2.5}$ concentrations and annual average $PM_{2.5}$ concentrations.

The last 3-year or last 5-year average $PM_{2.5}$ concentrations were more reflective of the recent annual average $PM_{2.5}$ concentrations than annually updated cumulative average $PM_{2.5}$ concentrations (Appendix Figure 4.).

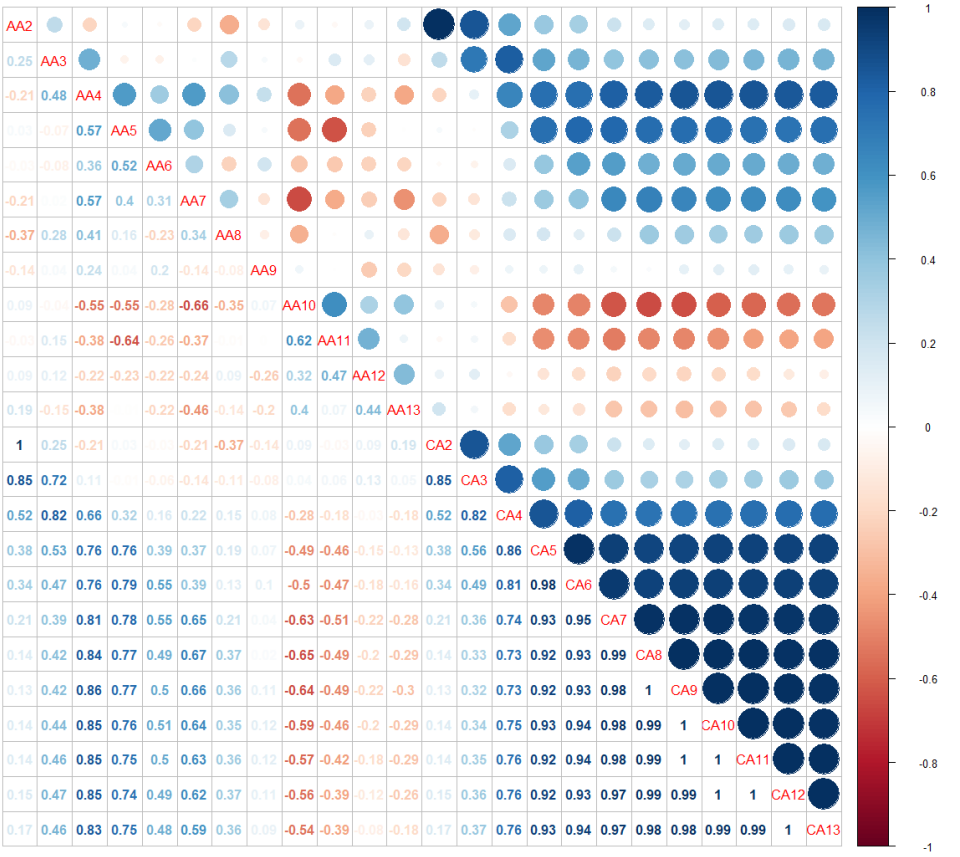


Figure 12. Correlation between annual average $PM_{2.5}$ concentrations and cumulative average $PM_{2.5}$ concentrations; AA2: annual average $PM_{2.5}$ concentrations in 2002, CA13: cumulative average $PM_{2.5}$ concentrations until 2013, $PM_{2.5}$: particulate matter with an aerodynamic diameter of <2.5 μm.

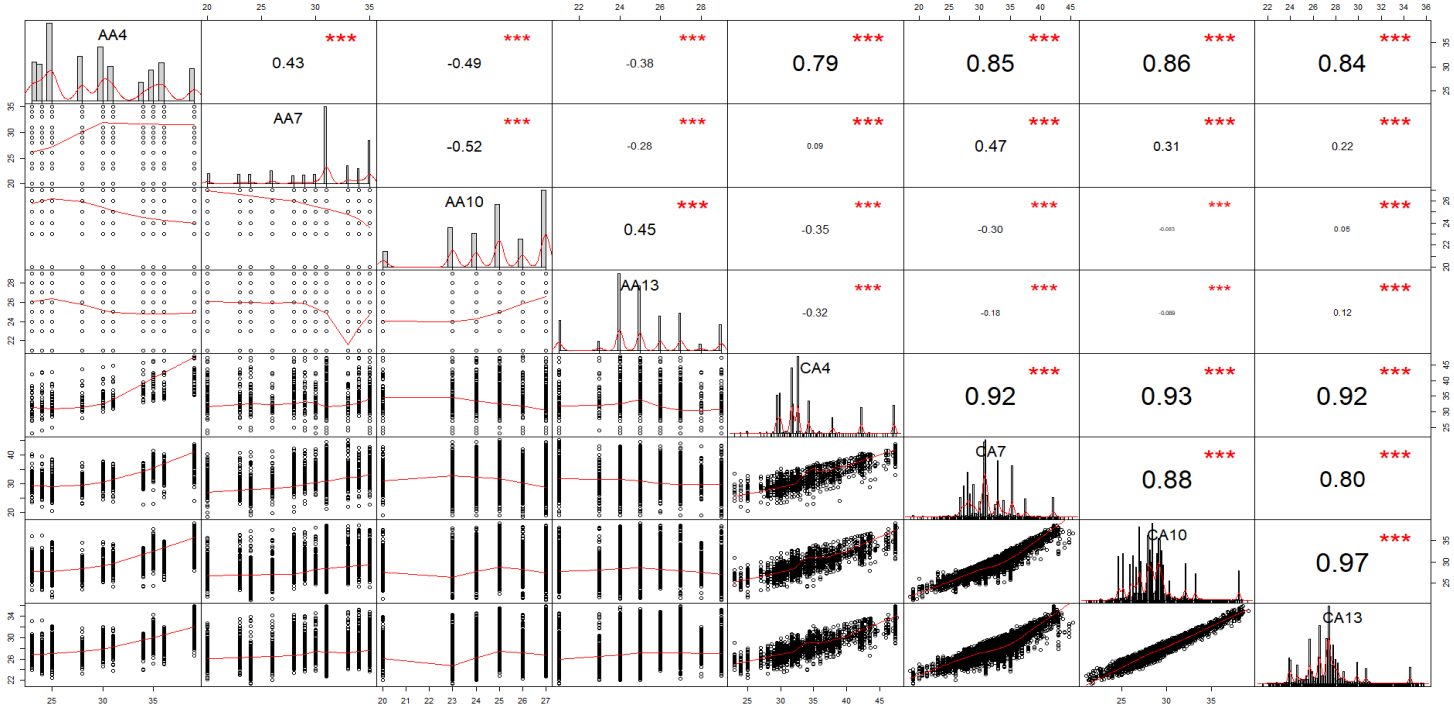


Figure 13. Histograms and scatter plots for annual average $PM_{2.5}$ concentrations and cumulative average $PM_{2.5}$ concentrations; AA4: annual average in 2004 (μg/m^3), CA4: cumulative average in 2004 (μg/m^3), $PM_{2.5}$: particulate matter with an aerodynamic diameter of <2.5 μm.

$PM_{2.5}$ concentrations ranged from 16.0 to 27.8 μg/m^3, from 27.9 to 30.6 μg/m^3, and from 30.7 to 55.0 μg/m^3 in tertiles 1, 2, and 3, respectively. The risk of HS was higher in the highest tertile than the lowest tertile (Table 2). The HS risk was also associated with the increase in tertile (HR: 1.27, 95% CI: 1.04-1.22, p-value: 0.006)

Table 2. Risk of hemorrhagic stroke among tertiles of cumulative average $PM_{2.5}$ levels using the time-dependent Cox model with individual-level time-varying covariates

	Cumulative average $PM_{2.5}$ Tertile 1	Cumulative average $PM_{2.5}$ Tertile 2	Cumulative average $PM_{2.5}$ Tertile 3
Mean ± SD (μg/m^3)	26.3 ± 1.3	29.2 ± 0.9	35.4 ± 4.8
Median ± IQR (μg/m^3)	26.7 ± 1.8	29.0 ± 1.6	34.0 ± 4.7
HR (95% CI)	Reference	1.12 (0.97-1.28)	1.26 (1.07-1.48)
P for trend		0.006	

CI: confidence interval; HR: hazard ratio; IQR: Inter-quartile range; $PM_{2.5}$: particulate matter with an aerodynamic diameter of <2.5 μm; SD: Standard deviation. Model adjusted for age group and sex, insurance type, income decile, and medical histories of hypertension, diabetes, and congestive heart failure.

The estimated HRs for HS based on 10-μg/m^3 increments of $PM_{2.5}$ are presented in Table 3. The multivariable adjusted HR for 10-μg/m^3 increments in cumulative average $PM_{2.5}$ exposure was 1.43 (95% CI: 1.11–1.84). A non-linear association was observed for $PM_{2.5}$ exposure. When we analyzed the association between $PM_{2.5}$ and HS incidence by spline regression, the HR (95% CI) of $PM_{2.5}$ exposure was higher (HR: 2.52, 95% CI: 1.92–3.30) than that by the linear regression model.

Table 3. Hazard ratios for hemorrhagic stroke per 10-μg/m^3 increment in updated cumulative average $PM_{2.5}$ levels using the time-dependent Cox model with individual-level time-varying covariates

Models	HR (95% CI)	
Unadjusted model	1.16	(1.01-1.34)
Model 1	1.20	(1.05-1.38)
Model 2	1.16	(1.01-1.34)
Model 3	1.43	(1.10-1.84)
Model 4	1.43	(1.11-1.84)
Model 5	1.43	(1.09-1.88)

CI: confidence interval; HR: hazard ratio; $PM_{2.5}$: particulate matter with an aerodynamic diameter of <2.5 μm.

Model 1: adjusted for age group and sex

Model 2: Model 1 + insurance type, income decile, and medical histories

Model 3: Model 2 + body mass index, smoking status, and family histories

Model 4: Model 3 + number of moves

Model 5: Model 3 + moves with change in exposure level

Long-term $PM_{2.5}$ exposure was also associated with a higher risk of HS in the concentration-response curve analysis. When $PM_{2.5}$ was fitted as a spline with 25.1 $\mu g/m^3$ as the reference, an almost linear association was observed (Figure 14). A multivariable Cox regression model with a penalized spline (df = 3) was fit for $PM_{2.5}$ and the concentration-response curve was estimated. The adjusted variables included age group, sex, insurance type, income decile, medical history, family history, smoking status, and body mass index.

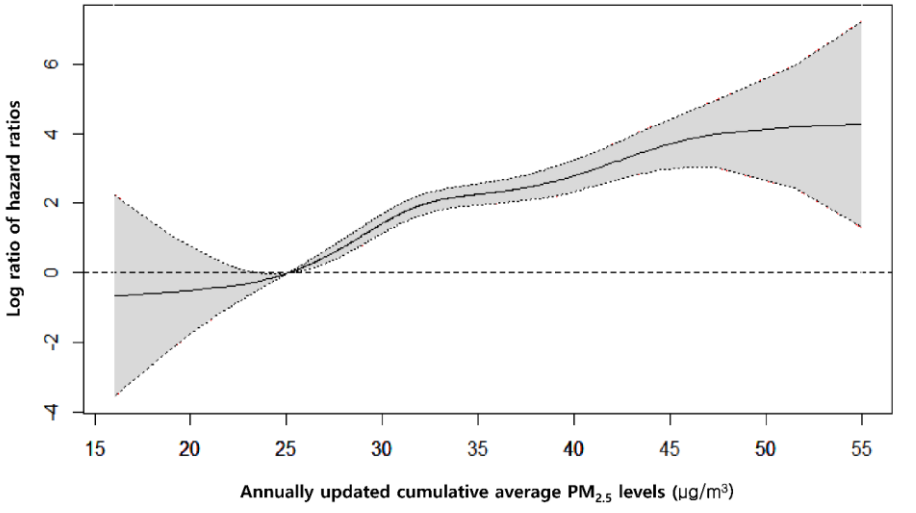


Figure 14. Concentration response curve of exposure to $PM_{2.5}$ levels on the incidence of hemorrhagic stroke. Model adjusted for age group, sex, insurance type, income decile, medical histories, body mass index, smoking status, and family

histories.

Subgroup analyses revealed that the association between HS with $PM_{2.5}$ exposure remained among individuals with middle income level (HR: 2.11, 95% CI: 1.26–3.54), with hypertension (HR: 1.67, 95% CI: 1.22–2.28), of female sex (HR: 1.55, 95% CI: 1.09–2.22), who never moved during the follow-up period (HR: 1.5, 95% CI: 1.13–1.99), who had never smoked (HR: 1.40, 95% CI: 1.05–1.88), with no family history of ischemic heart disease (HR: 1.46, 95% CI: 1.09–1.85) or stroke (HR 1.42, 95% CI: 1.09–1.85), and in individuals without aortic plaque (HR: 1.42, 95% CI: 1.10–1.83) or congestive heart failure (HR: 1.4, 95% CI: 1.06–1.83), or diabetes (HR: 1.39, 95% CI: 1.01–1.91). In the test for effect modification, some subgroups were more susceptible to the adverse effects of cumulative average $PM_{2.5}$ exposure (Figure 15). The risk of HS associated with $PM_{2.5}$ exposure was higher among individuals who were elderly (≥65 years, HR: 2.00, 95% CI: 1.33−3.02) and obese (BMI 25.0−29.9 kg/m^2, HR: 1.91, 95% CI: 1.28−2.84) than that among individuals 45-64 years of age and not obese (BMI <23.0 kg/m^2).

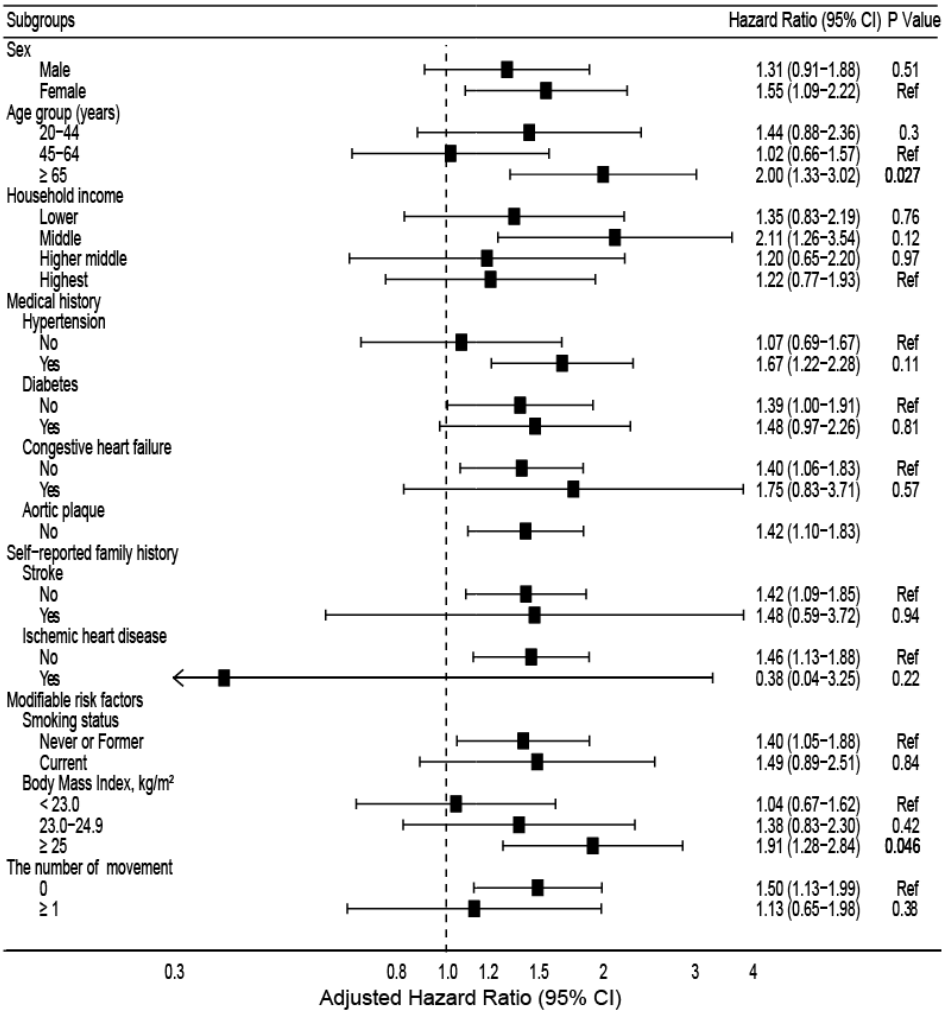


Figure 15. Hazard ratios for hemorrhagic stroke per 10-μg/m^3 increment in $PM_{2.5}$ for each subgroup. CI: confidence interval; $PM_{2.5}$: particulate matter with an aerodynamic diameter of <2.5 μm; Hazard ratios and 95% CIs are shown per increase of 10 μg per cubic meter in $PM_{2.5}$. The P values were calculated from the test of effect modification.

In the sensitivity analyses for examining the validity of wash-out period for pre-existing hemorrhagic stroke, the results were well maintained and the analyses yielded slightly higher risk estimates where wash-out periods were longer than 1 year (Table 4). Consistent results were also observed on performing analyses for testing the differences in the adjusted covariates; the risk increased when body mass index or family history were incorporated in the model.

Results of sensitivity analyses using the last 5-year average $PM_{2.5}$ were consistent with those of the primary analyses, after controlling for the potential district-level residual confounding variables. The risks estimated from the analyses using the annual average $PM_{2.5}$ or last 3-year average $PM_{2.5}$ (Table 5, Table 6) were lower than those estimated from the primary analyses and were not significant.

Table 4. Sensitivity analysis for the wash-out period for potentially pre-existing hemorrhagic stroke

Wash-out period (years)	1		2		3	
Models	HR	95% CI	HR	95% CI	HR	95% CI
Unadjusted model	1.16	(1.01-1.34)	1.18	(1.02-1.37)	1.25	(1.06-1.47)
Model 1	1.20	(1.05-1.38)	1.22	(1.05-1.43)	1.30	(1.10-1.53)
Model 2	1.16	(1.01-1.34)	1.18	(1.01-1.38)	1.25	(1.06-1.48)
Model 3	1.16	(1.01-1.34)	1.18	(1.01-1.38)	1.25	(1.06-1.48)
Model 4	1.25	(1.00-1.57)	1.34	(1.07-1.69)	1.43	(1.13-1.82)
Model 5	1.27	(1.00-1.61)	1.35	(1.06-1.72)	1.42	(1.11-1.83)
Model 6	1.43	(1.10-1.84)	1.53	(1.18-1.99)	1.62	(1.24-2.12)
Model 7	1.43	(1.11-1.84)	1.53	(1.18-1.99)	1.63	(1.24-2.12)
Model 8	1.43	(1.09-1.88)	1.43	(1.09-1.88)	1.43	(1.09-1.88)

HR: hazard ratio; CI: confidence interval.

Model 1: adjusted for age group and sex

Model 2: Model 1 + insurance type and income decile

Model 3: Model 2 + medical histories

Model 4: Model 3 + body mass index

Model 5: Model 4 + smoking status

Model 6: Model 5 + family histories

Model 7: Model 6 + number of moves

Model 8: Model 6 + moves with change in exposure level

Table 5. Sensitivity analysis for exposure assessment and annual average

Exposure assessment	Cumulative average		Annual average	
Models	HR	95% CI	HR	95% CI
Unadjusted model	1.16	(1.01-1.34)	1.04	(0.90-1.19)
Model 1	1.2	(1.05-1.38)	1.05	(0.92-1.21)
Model 2	1.16	(1.01-1.34)	1.04	(0.90-1.19)
Model 3	1.16	(1.01-1.34)	1.03	(0.90-1.19)
Model 4	1.25	(1.00-1.57)	0.93	(0.74-1.18)
Model 5	1.27	(1.00-1.61)	0.94	(0.73-1.20)
Model 6	1.43	(1.10-1.84)	1.00	(0.77-1.31)
Model 7	1.43	(1.11-1.84)	1.00	(0.77-1.31)
Model 8	1.43	(1.09-1.88)	0.94	(0.71-1.26)

HR: hazard ratio; CI: confidence interval.

Model 1: adjusted for age group and sex

Model 2: Model 1 + insurance type and income decile

Model 3: Model 2 + medical histories

Model 4: Model 3 + body mass index

Model 5: Model 4 + smoking status

Model 6: Model 5 + family histories

Model 7: Model 6 + number of moves

Model 8: Model 6 + moves with change in exposure level

Table 6. Sensitivity analysis for district-level confounding variables

Exposure assessment	Cumulative average		Average during last 5 years		Average during last 3 years	
Models	HR	95% CI	HR	95% CI	HR	95% CI
Model 1	1.43	(1.10-1.84)	1.30	(1.00-1.68)	1.09	(0.84-1.42)
Model 2	1.42	(1.11-1.83)	1.30	(1.00-1.68)	1.10	(0.85-1.43)
Model 3	1.40	(1.09-1.81)	1.30	(1.01-1.66)	1.10	(0.85-1.42)

HR: hazard ratio; CI: confidence interval.

Model 1: adjusted for age group and sex, insurance type, income decile, medical histories, body mass index, smoking status, family histories, number of moves

Model 2: Model 1 + Population density, Proportion of married population

Model 3: Model 2 + Deprivation index

IV. DISCUSSION

This study evaluated data from metropolitan city residents who were part of a 12-year follow-up of a nationally representative Korean cohort using district-level cumulative average $PM_{2.5}$ exposures as the time-varying covariates. Furthermore, we improved the spatiotemporal sensitivity of the cumulative exposure accounting for the individuals' intra-city relocation using the time-dependent Cox proportional hazard method. Based on our results, it appears that greater cumulative average $PM_{2.5}$ exposure might increase the long-term risk of HS. Furthermore, obese and older individuals were especially susceptible to the effects of $PM_{2.5}$ exposure. To the best of our knowledge, this is the first study to investigate the association between time-varying cumulative average $PM_{2.5}$ exposure and HS.

Our findings corroborate the results from previous studies regarding the statistically robust associations of $PM_{2.5}$ exposure with cerebrovascular events. In the California Teachers Study,[42] 10-$\mu g/m^3$ increments of long-term residential $PM_{2.5}$ exposure was associated with the risk of incident stroke (HR: 1.19, 95% CI: 1.02–1.38). The prospective Women's Health Initiative study also revealed that 10-$\mu g/m^3$ increments in the 1-year average $PM_{2.5}$ levels exhibited a strong association with the risk of stroke (HR: 1.28, 95% CI: 1.02–1.61).[40] However, other studies have revealed conflicting results. For example, one UK study did not detect a positive association between long-term air pollution exposure and the incidence of stroke.[54] Furthermore, a recent study in Hong Kong observed that the association between

long-term $PM_{2.5}$ exposure and incident HS was less clear regarding the higher risk of incident ischemic stroke.[107] Canadian Census Health and Environment Cohort studies have also reported a protective association between time-varying exposures of $PM_{2.5}$ and cerebrovascular mortality.[108]

Herein, we also evaluated the modifying effects of various risk factors on the association between long-term $PM_{2.5}$ exposure and HS. Increased risks of HS were still observed among individuals who had hypertension, were female, had not moved during the follow-up period, had never smoked, had no family history of ischemic heart disease or stroke, and who did not have aortic plaque, congestive heart failure, or diabetes, although the risks did not differ from those in the other groups. This finding might be due to the relatively small sample size of each group. Subgroup analyses revealed effect modifications for some traditional risk factors;[95] individuals aged $\geq$65 years and obese individuals with a BMI $\geq$25 kg/m^2 were especially susceptible to the effects of high cumulative average $PM_{2.5}$ exposure. These findings are consistent with those of a meta-analysis that evaluated 11 European cohorts and with suggestions of stronger associations among women aged $\geq$70 years and obese individuals in the Nurses' Health Study.[85,96] A few studies have also evaluated susceptible population subgroups and have reported higher risks among older individuals or individuals with several cardiovascular risk factors, a history of stroke, and diabetes mellitus.[109-111]

Our findings cannot explain the mechanisms behind the association of $PM_{2.5}$ exposure with incident HS. However, $PM_{2.5}$ exposure may trigger acute vascular

dysfunction (e.g., acute endothelial dysfunction, vasoconstriction, and direct ischemic damage) and HS events.[112,113] Other reviews of epidemiological studies have also stated that, despite the numerous confounding variables and methodological differences, $PM_{2.5}$ may promote hypertensive hemodynamic responses, increase blood pressure, and help trigger acute cardiovascular events, especially among high-risk individuals.[114,115] The mechanisms for this subacute pathophysiology may include promoting and maintaining high oxidative stress after an increase in the levels of systemic inflammatory cytokines and changes in the levels and functions of factors in the coagulation pathway (e.g., fibrinogen and tissue factor).[116-119] Furthermore, $PM_{2.5}$ exposure is associated with higher resting cerebrovascular resistance and lower cerebral blood flow velocity,[120] while long-term $PM_{2.5}$ exposure might induce atherosclerosis or alterations in autonomic nervous system control, which could result in heart rate variability or brain atrophy.[121-126] Long-term exposure might also compromise blood pressure management in patients with hypertension, or aggravate the risk of future stroke that is related to chronic disorders. In this context, $PM_{2.5}$ exposure-related changes in methylation (an epigenetic modification mechanism that involves gene-environment interactions) through novel pathways could negatively affect health.[127,128] Thus, long-term $PM_{2.5}$ exposure may exert chronic effects on the cardiovascular system through various biological mechanisms such as direct ischemic damage, endothelial dysfunction, vasoconstriction, increased blood pressure, prothrombotic and coagulant changes, systemic inflammatory and

oxidative stress responses, autonomic imbalance and arrhythmia, and/or the progression of atherosclerosis (Figure 16).[81,129,130]

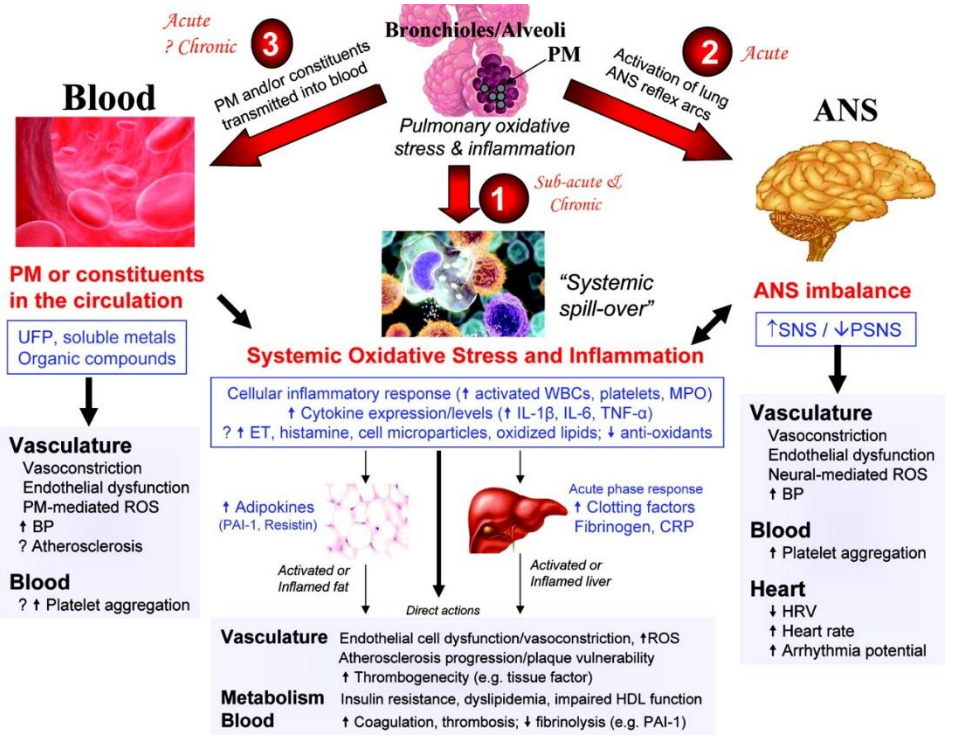


Figure 16. Biological mechanisms linking PM exposure with cardiovascular and cerebrovascular diseases. Source: Brook RD, Rajagopalan S, Pope CA, 3rd, Brook JR, Bhatnagar A, Diez-Roux AV, et al. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. Circulation 2010;121:2331-78.

The present study had several strengths. First, we used data from metropolitan city residents who were part of a large and well-characterized nationally

representative cohort, which included 12-year follow-up data regarding demographic characteristics, lifestyle factors, medical history, and stroke events. In addition, the repeated surveys regarding lifestyle factors and medical history allowed for record updating, which minimized the risk of misclassification. Furthermore, we used cumulatively updated $PM_{2.5}$ exposures that reflected the individuals' intra-city relocation, which provides the most robust estimation of exposure.[131] Moreover, not considering the relevance of cumulative effects may limit interpretation. However, because only a few long-term studies have focused on cumulative air pollution exposure in relation to stroke, we might be underestimating the associations and long-term effects.[92] Another point of merit is the extensive list of potential confounders that we adjusted for, and the use of time-varying covariates to adjust for time-dependent confounding. Several studies have adjusted for socioeconomic status using a variety of indicators, such as household income[132,133] and a modified Index of Multiple Deprivation,[54] at an ecological rather than individual level. The HRs in the present study were adjusted annually for each individuals' updated socioeconomic status (household income decile and type of insurance). We believe that this adjustment is important, as it can control for important unmeasured confounders such as food security, nutritional status, and occupational status.

The present study also had several limitations. First, exposure data were obtained from outdoor, automated fixed-site monitoring stations in each district; and we could not calculate any indoor exposure. However, a recent study has demonstrated

that measurement error biases the estimated effects toward the null hypothesis.[24] Second, we defined the outcome as the first diagnosis of HS and misclassification might be present, although the resulting bias would also likely be toward the null hypothesis. This is because we applied a washout period and the computed tomography-based diagnosis of HS is relatively accurate in this population.[102] Third, the study population might not be nationally representative. In order to adjust for lifestyle and physical examination covariates, we only evaluated individuals who lived in Seoul and underwent at least one health examination among a nationwide randomly sampled NHIS cohort. Thus, individuals with a relatively healthy status might be overrepresented in our results, which would limit the extrapolation of our findings to less health-oriented subgroups. Nevertheless, these individuals might be more open to targeted education and behavioral interventions to prevent HS. Fourth, the NHIS data do not include education data, which might influence our results, as education is correlated with $PM_{2.5}$ exposure and cardiovascular disease.[134,135] However, we adjusted for household income and occupation to control for the effects of socioeconomic status. Fifth, most of the included individuals were Asian, and racial differences are known to be correlated with both exposure and cardiovascular disease.[134] Although we could not investigate differences in genetic background, and although ethnic or genetic heterogeneity is possible, our adjustment for family history of stroke and ischemic heart disease might help address any genetic differences. Moreover, most reported associations from genome-wide studies are weak, difficult to replicate, and inconsistent with

ethnicity,[52] which makes it unlikely that these associations would affect our findings.

V. CONCLUSION

In conclusion, our findings indicate that cumulative average $PM_{2.5}$ exposure might increase the risk of HS, which would have implications for interventions that aim to prevent cerebrovascular events and improve public health. These findings may also help identify susceptible population subgroups, which could be educated to reduce their modifiable risk factors (including $PM_{2.5}$ exposure).

REFERENCES

1. U.S. EPA. Particulate matter basics. Available at: https://www.epa.gov/pm-pollution/particulate-matter-pm-basics [Accessed 30 June 2019]
2. Park SS, Kim YJ. Source contributions to fine particulate matter in an urban atmosphere. Chemosphere 2005;59:217-26.
3. Dockery DW, Pope CA, 3rd, Xu X, Spengler JD, Ware JH, Fay ME, et al. An association between air pollution and mortality in six U.S. cities. N Engl J Med 1993;329:1753-9.
4. World Health Organization. Regional Office for Europe. Air quality guidelines for Europe, 2nd ed. Copenhagen: WHO Regional Office for Europe.; 2000.
5. Gamble JF, Nicolich MJ. Comments on the updated Harvard Six Cities study. Am J Respir Crit Care Med 2006;174:722; author reply -4.
6. Pope CA, 3rd, Thun MJ, Namboodiri MM, Dockery DW, Evans JS, Speizer FE, et al. Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. Am J Respir Crit Care Med 1995;151:669-74.
7. Lipfert F. Commentary on the HEI reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality. J Toxicol Environ Health A 2003;66:1705-14; discussion 15-22.

8. Krewski D, Burnett RT, Goldberg MS, Hoover BK, Siemiatycki J, Jerrett M, et al. Overview of the reanalysis of the Harvard Six Cities Study and American Cancer Society Study of Particulate Air Pollution and Mortality. J Toxicol Environ Health A 2003;66:1507-51.

9. United States Environmental Protection Agency. Table of Historical Particulate Matter (PM) National Ambient Air Quality Standards (NAAQS). Available at: https://www.epa.gov/pm-pollution/table-historical-particulate-matter-pm-national-ambient-air-quality-standards-naaqs [Accessed 30 June 2019]

10. World Health Organization. Occupational and Environmental Health Team. WHO Air quality guidelines for particulate matter, ozone, nitrogen dioxide and sulfur dioxide : global update 2005 : summary of risk assessment. World Health Organization; 2006.

11. National Research Council. Research Priorities for Airborne Particulate Matter: I. Immediate Priorities and a Long-Range Research Portfolio. Washington, DC: The National Academies Press; 1998.

12. National Center for Environmental Assessment. Integrated science assessment for particulate matter. Research Triangle Park, N.C.: U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment; 2009.

13. National Center for Environmental Assessment. Preamble to the Integrated Science Assessments. Research Triangle Park, NC; 2015.

14. Health Effects Institute Accountability Working Group. Assessing health impact of air quality regulations : concepts and methods for accountability research. Boston, MA: Health Effects Institute; 2003.

15. Steinle S, Reis S, Sabel CE, Semple S, Twigg MM, Braban CF, et al. Personal exposure monitoring of PM2.5 in indoor and outdoor microenvironments. Sci Total Environ 2015;508:383-94.

16. Wilson WE, Mage DT, Grant LD. Estimating separately personal exposure to ambient and nonambient particulate matter for epidemiology and risk assessment: why and how. J Air Waste Manag Assoc 2000;50:1167-83.

17. Sarnat JA, Koutrakis P, Suh HH. Assessing the relationship between personal particulate and gaseous exposures of senior citizens living in Baltimore, MD. J Air Waste Manag Assoc 2000;50:1184-98.

18. Ozkaynak H, Baxter LK, Dionisio KL, Burke J. Air pollution exposure prediction approaches used in air pollution epidemiology studies. J Expo Sci Environ Epidemiol 2013;23:566-72.

19. Zeger SL, Thomas D, Dominici F, Samet JM, Schwartz J, Dockery D, et al. Exposure measurement error in time-series studies of air pollution: concepts and consequences. Environ Health Perspect 2000;108:419-26.

20. Lane KJ, Kangsen Scammell M, Levy JI, Fuller CH, Parambi R, Zamore W, et al. Positional error and time-activity patterns in near-highway proximity studies: an exposure misclassification analysis. Environ

Health 2013;12:75.

21. Sheppard L, Burnett RT, Szpiro AA, Kim SY, Jerrett M, Pope CA, 3rd, et al. Confounding and exposure measurement error in air pollution epidemiology. Air Qual Atmos Health 2012;5:203-16.

22. Goldman GT, Mulholland JA, Russell AG, Strickland MJ, Klein M, Waller LA, et al. Impact of exposure measurement error in air pollution epidemiology: effect of error type in time-series studies. Environ Health 2011;10:61.

23. Pope CA, 3rd, Ezzati M, Dockery DW. Fine-particulate air pollution and life expectancy in the United States. N Engl J Med 2009;360:376-86.

24. Kioumourtzoglou MA, Spiegelman D, Szpiro AA, Sheppard L, Kaufman JD, Yanosky JD, et al. Exposure measurement error in PM2.5 health effects studies: a pooled analysis of eight personal exposure validation studies. Environ Health 2014;13:2.

25. Jerrett M, Turner MC, Beckerman BS, Pope CA, van Donkelaar A, Martin RV, et al. Comparing the Health Effects of Ambient Particulate Matter Estimated Using Ground-Based versus Remote Sensing Exposure Estimates. Environ Health Perspect 2017;125:552-9.

26. Baxter LK, Wright RJ, Paciorek CJ, Laden F, Suh HH, Levy JI. Effects of exposure measurement error in the analysis of health effects from traffic-related air pollution. J Expo Sci Environ Epidemiol 2010;20:101-11.

27. Sheppard L, Slaughter JC, Schildcrout J, Liu LJ, Lumley T. Exposure and measurement contributions to estimates of acute air pollution effects. J Expo Anal Environ Epidemiol 2005;15:366-76.

28. Kim SY, Sheppard L, Kaufman JD, Bergen S, Szpiro AA, Larson TV, et al. Individual-level concentrations of fine particulate matter chemical components and subclinical atherosclerosis: a cross-sectional analysis based on 2 advanced exposure prediction models in the multi-ethnic study of atherosclerosis. Am J Epidemiol 2014;180:718-28.

29. Alexeeff SE, Schwartz J, Kloog I, Chudnovsky A, Koutrakis P, Coull BA. Consequences of kriging and land use regression for PM2.5 predictions in epidemiologic analyses: insights into spatial variability using high-resolution satellite data. J Expo Sci Environ Epidemiol 2015;25:138-44.

30. Hart JE, Liao X, Hong B, Puett RC, Yanosky JD, Suh H, et al. The association of long-term exposure to PM2.5 on all-cause mortality in the Nurses' Health Study and the impact of measurement-error correction. Environ Health 2015;14:38.

31. Hart JE, Spiegelman D, Beelen R, Hoek G, Brunekreef B, Schouten LJ, et al. Long-Term Ambient Residential Traffic-Related Exposures and Measurement Error-Adjusted Risk of Incident Lung Cancer in the Netherlands Cohort Study on Diet and Cancer. Environ Health Perspect 2015;123:860-6.

32. Willis A, Jerrett M, Burnett RT, Krewski D. The association between sulfate air pollution and mortality at the county scale: an exploration of the impact of scale on a long-term exposure study. J Toxicol Environ Health A 2003;66:1605-24.

33. Kloog I, Koutrakis P, Coull BA, Lee HJ, Schwartz J. Assessing temporally and spatially resolved PM2.5 exposures for epidemiological studies using satellite aerosol optical depth measurements. Atmos Environ 2011;45:6267-75.

34. Kloog I, Ridgway B, Koutrakis P, Coull BA, Schwartz JD. Long- and short-term exposure to PM2.5 and mortality: using novel exposure models. Epidemiology 2013;24:555-61.

35. Cefalu M, Dominici F. Does exposure prediction bias health-effect estimation?: The relationship between confounding adjustment and exposure prediction. Epidemiology 2014;25:583-90.

36. Laden F, Schwartz J, Speizer FE, Dockery DW. Reduction in fine particulate air pollution and mortality: Extended follow-up of the Harvard Six Cities study. Am J Respir Crit Care Med 2006;173:667-72.

37. Lepeule J, Laden F, Dockery D, Schwartz J. Chronic exposure to fine particles and mortality: an extended follow-up of the Harvard Six Cities study from 1974 to 2009. Environ Health Perspect 2012;120:965-70.

38. Pope CA, 3rd, Burnett RT, Thun MJ, Calle EE, Krewski D, Ito K, et al. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine

particulate air pollution. JAMA 2002;287:1132-41.

39. Krewski D, Jerrett M, Burnett RT, Ma R, Hughes E, Shi Y, et al. Extended follow-up and spatial analysis of the American Cancer Society study linking particulate air pollution and mortality. Res Rep Health Eff Inst 2009:5-114; discussion 5-36.

40. Miller KA, Siscovick DS, Sheppard L, Shepherd K, Sullivan JH, Anderson GL, et al. Long-term exposure to air pollution and incidence of cardiovascular events in women. N Engl J Med 2007;356:447-58.

41. Cesaroni G, Forastiere F, Stafoggia M, Andersen ZJ, Badaloni C, Beelen R, et al. Long term exposure to ambient air pollution and incidence of acute coronary events: prospective cohort study and meta-analysis in 11 European cohorts from the ESCAPE Project. BMJ 2014;348:f7412.

42. Lipsett MJ, Ostro BD, Reynolds P, Goldberg D, Hertz A, Jerrett M, et al. Long-term exposure to air pollution and cardiorespiratory disease in the California teachers study cohort. Am J Respir Crit Care Med 2011;184:828-35.

43. Hoffmann B, Weinmayr G, Hennig F, Fuks K, Moebus S, Weimar C, et al. Air quality, stroke, and coronary events: results of the Heinz Nixdorf Recall Study from the Ruhr Region. Dtsch Arztebl Int 2015;112:195-201.

44. Adar SD, Sheppard L, Vedal S, Polak JF, Sampson PD, Diez Roux AV, et al. Fine particulate air pollution and the progression of carotid intima-medial thickness: a prospective cohort study from the multi-ethnic study

of atherosclerosis and air pollution. PLoS Med 2013;10:e1001430.

45. Sun M, Kaufman JD, Kim SY, Larson TV, Gould TR, Polak JF, et al. Particulate matter components and subclinical atherosclerosis: common approaches to estimating exposure in a Multi-Ethnic Study of Atherosclerosis cross-sectional study. Environ Health 2013;12:39.

46. Hart JE, Puett RC, Rexrode KM, Albert CM, Laden F. Effect Modification of Long-Term Air Pollution Exposures and the Risk of Incident Cardiovascular Disease in US Women. J Am Heart Assoc 2015;4.

47. Hartiala J, Breton CV, Tang WH, Lurmann F, Hazen SL, Gilliland FD, et al. Ambient Air Pollution Is Associated With the Severity of Coronary Atherosclerosis and Incident Myocardial Infarction in Patients Undergoing Elective Cardiac Evaluation. J Am Heart Assoc 2016;5.

48. Koton S, Molshatzki N, Yuval, Myers V, Broday DM, Drory Y, et al. Cumulative exposure to particulate matter air pollution and long-term post-myocardial infarction outcomes. Prev Med 2013;57:339-44.

49. Chi GC, Hajat A, Bird CE, Cullen MR, Griffin BA, Miller KA, et al. Individual and Neighborhood Socioeconomic Status and the Association between Air Pollution and Cardiovascular Disease. Environ Health Perspect 2016;124:1840-7.

50. Gan WQ, Allen RW, Brauer M, Davies HW, Mancini GB, Lear SA. Long-term exposure to traffic-related air pollution and progression of

carotid artery atherosclerosis: a prospective cohort study. BMJ Open 2014;4:e004743.

51. Kunzli N, Jerrett M, Garcia-Esteban R, Basagana X, Beckermann B, Gilliland F, et al. Ambient air pollution and the progression of atherosclerosis in adults. PLoS One 2010;5:e9096.

52. Kaufman JD, Adar SD, Barr RG, Budoff M, Burke GL, Curl CL, et al. Association between air pollution and coronary artery calcification within six metropolitan areas in the USA (the Multi-Ethnic Study of Atherosclerosis and Air Pollution): a longitudinal cohort study. Lancet 2016;388:696-704.

53. Dorans KS, Wilker EH, Li W, Rice MB, Ljungman PL, Schwartz J, et al. Residential Proximity to Major Roads, Exposure to Fine Particulate Matter, and Coronary Artery Calcium: The Framingham Heart Study. Arterioscler Thromb Vasc Biol 2016;36:1679-85.

54. Atkinson RW, Carey IM, Kent AJ, van Staa TP, Anderson HR, Cook DG. Long-term exposure to outdoor air pollution and incidence of cardiovascular diseases. Epidemiology 2013;24:44-53.

55. Liao D, Whitsel EA, Duan Y, Lin HM, Quibrera PM, Smith R, et al. Ambient particulate air pollution and ectopy--the environmental epidemiology of arrhythmogenesis in Women's Health Initiative Study, 1999-2004. J Toxicol Environ Health A 2009;72:30-8.

56. Fuks KB, Weinmayr G, Foraster M, Dratva J, Hampel R, Houthuijs D, et

al. Arterial blood pressure and long-term exposure to traffic-related air pollution: an analysis in the European Study of Cohorts for Air Pollution Effects (ESCAPE). Environ Health Perspect 2014;122:896-905.

57. Coogan PF, White LF, Jerrett M, Brook RD, Su JG, Seto E, et al. Air pollution and incidence of hypertension and diabetes mellitus in black women living in Los Angeles. Circulation 2012;125:767-72.

58. Coogan PF, White LF, Yu J, Burnett RT, Seto E, Brook RD, et al. PM2.5 and Diabetes and Hypertension Incidence in the Black Women's Health Study. Epidemiology 2016;27:202-10.

59. Shih RA, Griffin BA, Salkowski N, Jewell A, Eibner C, Bird CE, et al. Ambient particulate matter air pollution and venous thromboembolism in the Women's Health Initiative Hormone Therapy trials. Environ Health Perspect 2011;119:326-31.

60. Pun VC, Hart JE, Kabrhel C, Camargo CA, Jr., Baccarelli AA, Laden F. Prospective Study of Ambient Particulate Matter Exposure and Risk of Pulmonary Embolism in the Nurses' Health Study Cohort. Environ Health Perspect 2015;123:1265-70.

61. Madrigano J, Kloog I, Goldberg R, Coull BA, Mittleman MA, Schwartz J. Long-term exposure to PM2.5 and incidence of acute myocardial infarction. Environ Health Perspect 2013;121:192-6.

62. Di Q, Wang Y, Zanobetti A, Wang Y, Koutrakis P, Choirat C, et al. Air Pollution and Mortality in the Medicare Population. N Engl J Med

2017;376:2513-22.

63. Puett RC, Hart JE, Suh H, Mittleman M, Laden F. Particulate matter exposures, mortality, and cardiovascular disease in the health professionals follow-up study. Environ Health Perspect 2011;119:1130-5.

64. Wolf K, Stafoggia M, Cesaroni G, Andersen ZJ, Beelen R, Galassi C, et al. Long-term Exposure to Particulate Matter Constituents and the Incidence of Coronary Events in 11 European Cohorts. Epidemiology 2015;26:565-74.

65. Gan WQ, Koehoorn M, Davies HW, Demers PA, Tamburic L, Brauer M. Long-term exposure to traffic-related air pollution and the risk of coronary heart disease hospitalization and mortality. Environ Health Perspect 2011;119:501-7.

66. Pope CA, 3rd, Dockery DW. Health effects of fine particulate air pollution: lines that connect. J Air Waste Manag Assoc 2006;56:709-42.

67. Hajat A, Allison M, Diez-Roux AV, Jenny NS, Jorgensen NW, Szpiro AA, et al. Long-term exposure to air pollution and markers of inflammation, coagulation, and endothelial activation: a repeat-measures analysis in the Multi-Ethnic Study of Atherosclerosis (MESA). Epidemiology 2015;26:310-20.

68. Viehmann A, Hertel S, Fuks K, Eisele L, Moebus S, Mohlenkamp S, et al. Long-term residential exposure to urban air pollution, and repeated

measures of systemic blood markers of inflammation and coagulation. Occup Environ Med 2015;72:656-63.

69. Hennig F, Fuks K, Moebus S, Weinmayr G, Memmesheimer M, Jakobs H, et al. Association between source-specific particulate matter air pollution and hs-CRP: local traffic and industrial emissions. Environ Health Perspect 2014;122:703-10.

70. Liu Q, Gu X, Deng F, Mu L, Baccarelli AA, Guo X, et al. Ambient particulate air pollution and circulating C-reactive protein level: A systematic review and meta-analysis. Int J Hyg Environ Health 2019;222:756-64.

71. Zhang Z, Chang LY, Lau AKH, Chan TC, Chieh Chuang Y, Chan J, et al. Satellite-based estimates of long-term exposure to fine particulate matter are associated with C-reactive protein in 30 034 Taiwanese adults. Int J Epidemiol 2017;46:1126-36.

72. Ostro B, Malig B, Broadwin R, Basu R, Gold EB, Bromberger JT, et al. Chronic PM2.5 exposure and inflammation: determining sensitive subgroups in mid-life women. Environ Res 2014;132:168-75.

73. Kampfrath T, Maiseyeu A, Ying Z, Shah Z, Deiuliis JA, Xu X, et al. Chronic fine particulate matter exposure induces systemic vascular dysfunction via NADPH oxidase and TLR4 pathways. Circ Res 2011;108:716-26.

74. Ying Z, Xie X, Bai Y, Chen M, Wang X, Zhang X, et al. Exposure to

concentrated ambient particulate matter induces reversible increase of heart weight in spontaneously hypertensive rats. Part Fibre Toxicol 2015;12:15.

75. Rao X, Zhong J, Maiseyeu A, Gopalakrishnan B, Villamena FA, Chen LC, et al. CD36-dependent 7-ketocholesterol accumulation in macrophages mediates progression of atherosclerosis in response to chronic air pollution exposure. Circ Res 2014;115:770-80.

76. Hicken MT, Adar SD, Diez Roux AV, O'Neill MS, Magzamen S, Auchincloss AH, et al. Do psychosocial stress and social disadvantage modify the association between air pollution and blood pressure?: the multi-ethnic study of atherosclerosis. Am J Epidemiol 2013;178:1550-62.

77. Chan SH, Van Hee VC, Bergen S, Szpiro AA, DeRoo LA, London SJ, et al. Long-Term Air Pollution Exposure and Blood Pressure in the Sister Study. Environ Health Perspect 2015;123:951-8.

78. Chen H, Burnett RT, Kwong JC, Villeneuve PJ, Goldberg MS, Brook RD, et al. Spatial association between ambient fine particulate matter and incident hypertension. Circulation 2014;129:562-9.

79. Ying Z, Xu X, Bai Y, Zhong J, Chen M, Liang Y, et al. Long-term exposure to concentrated ambient PM2.5 increases mouse blood pressure through abnormal activation of the sympathetic nervous system: a role for hypothalamic inflammation. Environ Health Perspect 2014;122:79-

86.

80. Wold LE, Ying Z, Hutchinson KR, Velten M, Gorr MW, Velten C, et al. Cardiovascular remodeling in response to long-term exposure to fine particulate matter air pollution. Circ Heart Fail 2012;5:452-61.

81. Brook RD, Rajagopalan S, Pope CA, 3rd, Brook JR, Bhatnagar A, Diez-Roux AV, et al. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. Circulation 2010;121:2331-78.

82. Cascio WE. Proposed pathophysiologic framework to explain some excess cardiovascular death associated with ambient air particle pollution: Insights for public health translation. Biochim Biophys Acta 2016;1860:2869-79.

83. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet 2010;376:112-23.

84. Leiva GM, Santibanez DA, Ibarra ES, Matus CP, Seguel R. A five-year study of particulate matter (PM2.5) and cerebrovascular diseases. Environ Pollut 2013;181:1-6.

85. Stafoggia M, Cesaroni G, Peters A, Andersen ZJ, Badaloni C, Beelen R, et al. Long-term exposure to ambient air pollution and incidence of cerebrovascular events: results from 11 European cohorts within the

ESCAPE project. Environ Health Perspect 2014;122:919-25.

86. Crouse DL, Peters PA, van Donkelaar A, Goldberg MS, Villeneuve PJ, Brion O, et al. Risk of nonaccidental and cardiovascular mortality in relation to long-term exposure to low concentrations of fine particulate matter: a Canadian national-level cohort study. Environ Health Perspect 2012;120:708-14.

87. Villeneuve PJ, Weichenthal SA, Crouse D, Miller AB, To T, Martin RV, et al. Long-term Exposure to Fine Particulate Matter Air Pollution and Mortality Among Canadian Women. Epidemiology 2015;26:536-45.

88. Di Q, Dai L, Wang Y, Zanobetti A, Choirat C, Schwartz JD, et al. Association of Short-term Exposure to Air Pollution With Mortality in Older Adults. JAMA 2017;318:2446-56.

89. Anderson JO, Thundiyil JG, Stolbach A. Clearing the air: a review of the effects of particulate matter air pollution on human health. J Med Toxicol 2012;8:166-75.

90. Newby DE, Mannucci PM, Tell GS, Baccarelli AA, Brook RD, Donaldson K, et al. Expert position paper on air pollution and cardiovascular disease. Eur Heart J 2015;36:83-93b.

91. Wang Y, Eliot MN, Wellenius GA. Short-term changes in ambient particulate matter and risk of stroke: a systematic review and meta-analysis. J Am Heart Assoc 2014;3:e000983.

92. Yang WS, Wang X, Deng Q, Fan WY, Wang WY. An evidence-based

appraisal of global association between air pollution and risk of stroke. Int J Cardiol 2014;175:307-13.

93. Shah AS, Lee KK, McAllister DA, Hunter A, Nair H, Whiteley W, et al. Short term exposure to air pollution and stroke: systematic review and meta-analysis. BMJ 2015;350:h1295.

94. Lin H, Guo Y, Di Q, Zheng Y, Kowal P, Xiao J, et al. Ambient PM2.5 and Stroke: Effect Modifiers and Population Attributable Risk in Six Low- and Middle-Income Countries. Stroke 2017;48:1191-7.

95. Wolf PA. Stroke risk profiles. Stroke 2009;40:S73-4.

96. Hart JE, Puett RC, Rexrode KM, Albert CM, Laden F. Effect Modification of Long-Term Air Pollution Exposures and the Risk of Incident Cardiovascular Disease in US Women. J Am Heart Assoc 2015;4:e002301.

97. Lee J, Lee JS, Park SH, Shin SA, Kim K. Cohort Profile: The National Health Insurance Service-National Sample Cohort (NHIS-NSC), South Korea. Int J Epidemiol 2016; doi:10.1093/ije/dyv319.

98. The Statistics Korea. Causes of Death Statistics. Available at: http://kostat.go.kr/portal/eng/index.action [Accessed 1 April 2019]

99. Lim YR, Bae HJ, Lim YH, Yu S, Kim GB, Cho YS. Spatial analysis of PM10 and cardiovascular mortality in the Seoul metropolitan area. Environ Health Toxicol 2014;29:e2014005.

100. Leem JH, Kim ST, Kim HC. Public-health impact of outdoor air

pollution for 2(nd) air pollution management policy in Seoul metropolitan area, Korea. Ann Occup Environ Med 2015;27:7.

101. Yi O, Hong YC, Kim H. Seasonal effect of PM(10) concentrations on mortality and morbidity in Seoul, Korea: a temperature-matched case-crossover analysis. Environ Res 2010;110:89-95.

102. Kim HC, Kang DR, Nam CM, Hur NW, Shim JS, Jee SH, et al. Elevated serum aminotransferase level as a predictor of intracerebral hemorrhage: Korea medical insurance corporation study. Stroke 2005;36:1642-7.

103. Park TH, Choi JC. Validation of Stroke and Thrombolytic Therapy in Korean National Health Insurance Claim Data. J Clin Neurol 2016;12:42-8.

104. Seoul Solution. Air Pollution Monitoring Network. Available at: https://seoulsolution.kr/en/node/6540 [Accessed 25 June 2019]

105. Li R HE, Louie M, Chen L, Spiegelman D. The SAS LGTPHCURV9 Macro. Available at: https://www.hsph.harvard.edu/donna-spiegelman/software/lgtphcurv9/ [Accessed 1 April 2019]

106. Meira-Machado L, Cadarso-Suarez C, Gude F, Araujo A. smoothHR: an R package for pointwise nonparametric estimation of hazard ratio curves of continuous predictors. Comput Math Methods Med 2013;2013:745742.

107. Qiu H, Sun S, Tsang H, Wong CM, Lee RS, Schooling CM, et al. Fine particulate matter exposure and incidence of stroke: A cohort study in

Hong Kong. Neurology 2017;88:1709-17.

108. Crouse DL, Peters PA, Hystad P, Brook JR, van Donkelaar A, Martin RV, et al. Ambient PM2.5, O(3), and NO(2) Exposures and Associations with Mortality over 16 Years of Follow-Up in the Canadian Census Health and Environment Cohort (CanCHEC). Environ Health Perspect 2015;123:1180-6.

109. Jerrett M, Burnett RT, Beckerman BS, Turner MC, Krewski D, Thurston G, et al. Spatial analysis of air pollution and mortality in California. Am J Respir Crit Care Med 2013;188:593-9.

110. O'Donnell MJ, Fang J, Mittleman MA, Kapral MK, Wellenius GA. Fine particulate air pollution (PM2.5) and the risk of acute ischemic stroke. Epidemiology 2011;22:422-31.

111. Maheswaran R, Pearson T, Smeeton NC, Beevers SD, Campbell MJ, Wolfe CD. Outdoor air pollution and incidence of ischemic and hemorrhagic stroke: a small-area level ecological study. Stroke 2012;43:22-7.

112. Chiu HF, Chang CC, Yang CY. Relationship between hemorrhagic stroke hospitalization and exposure to fine particulate air pollution in Taipei, Taiwan. J Toxicol Environ Health A 2014;77:1154-63.

113. Krishnan RM, Adar SD, Szpiro AA, Jorgensen NW, Van Hee VC, Barr RG, et al. Vascular responses to long- and short-term exposure to fine particulate matter: MESA Air (Multi-Ethnic Study of Atherosclerosis

and Air Pollution). J Am Coll Cardiol 2012;60:2158-66.

114. Giorgini P, Di Giosia P, Grassi D, Rubenfire M, Brook RD, Ferri C. Air Pollution Exposure and Blood Pressure: An Updated Review of the Literature. Curr Pharm Des 2016;22:28-51.

115. Xu MM, Jia YP, Li GX, Liu LQ, Mo YZ, Jin XB, et al. Relationship between ambient fine particles and ventricular repolarization changes and heart rate variability of elderly people with heart disease in Beijing, China. Biomed Environ Sci 2013;26:629-37.

116. Lane KJ, Levy JI, Scammell MK, Peters JL, Patton AP, Reisner E, et al. Association of modeled long-term personal exposure to ultrafine particles with inflammatory and coagulation biomarkers. Environ Int 2016;92-93:173-82.

117. Ghio AJ, Carraway MS, Madden MC. Composition of air pollution particles and oxidative stress in cells, tissues, and living systems. J Toxicol Environ Health B Crit Rev 2012;15:1-21.

118. Neri T, Pergoli L, Petrini S, Gravendonk L, Balia C, Scalise V, et al. Particulate matter induces prothrombotic microparticle shedding by human mononuclear and endothelial cells. Toxicol In Vitro 2016;32:333-8.

119. Li W, Wilker EH, Dorans KS, Rice MB, Schwartz J, Coull BA, et al. Short-Term Exposure to Air Pollution and Biomarkers of Oxidative Stress: The Framingham Heart Study. J Am Heart Assoc 2016;5:e002742.

120. Wellenius GA, Boyle LD, Wilker EH, Sorond FA, Coull BA, Koutrakis P, et al. Ambient fine particulate matter alters cerebral hemodynamics in the elderly. Stroke 2013;44:1532-6.

121. Mills NL, Tornqvist H, Robinson SD, Gonzalez MC, Soderberg S, Sandstrom T, et al. Air pollution and atherothrombosis. Inhal Toxicol 2007;19 Suppl 1:81-9.

122. Wilker EH, Preis SR, Beiser AS, Wolf PA, Au R, Kloog I, et al. Long-term exposure to fine particulate matter, residential proximity to major roads and measures of brain structure. Stroke 2015;46:1161-6.

123. Akintoye E, Shi L, Obaitan I, Olusunmade M, Wang Y, Newman JD, et al. Association between fine particulate matter exposure and subclinical atherosclerosis: A meta-analysis. Eur J Prev Cardiol 2016;23:602-12.

124. Rhoden CR, Wellenius GA, Ghelfi E, Lawrence J, Gonzalez-Flecha B. PM-induced cardiac oxidative stress and dysfunction are mediated by autonomic stimulation. Biochim Biophys Acta 2005;1725:305-13.

125. Pieters N, Plusquin M, Cox B, Kicinski M, Vangronsveld J, Nawrot TS. An epidemiological appraisal of the association between heart rate variability and particulate air pollution: a meta-analysis. Heart 2012;98:1127-35.

126. Genc S, Zadeoglulari Z, Fuss SH, Genc K. The adverse effects of air pollution on the nervous system. J Toxicol 2012;2012:782462.

127. Byun HM, Colicino E, Trevisi L, Fan T, Christiani DC, Baccarelli AA.

Effects of Air Pollution and Blood Mitochondrial DNA Methylation on Markers of Heart Rate Variability. J Am Heart Assoc 2016;5:e003218.

128. Panni T, Mehta AJ, Schwartz JD, Baccarelli AA, Just AC, Wolf K, et al. A Genome-Wide Analysis of DNA Methylation and Fine Particulate Matter Air Pollution in Three Study Populations: KORA F3, KORA F4, and the Normative Aging Study. Environ Health Perspect 2016;124:983-90.

129. Claeys MJ, Rajagopalan S, Nawrot TS, Brook RD. Climate and environmental triggers of acute myocardial infarction. Eur Heart J 2016; doi:10.1093/eurheartj/ehw151.ehw151.

130. Chin MT. Basic mechanisms for adverse cardiovascular events associated with air pollution. Heart 2015;101:253-6.

131. White LF, Yu J, Jerrett M, Coogan P. Temporal aspects of air pollutant measures in epidemiologic analysis: a simulation study. Sci Rep 2016;6:19691.

132. Puett RC, Schwartz J, Hart JE, Yanosky JD, Speizer FE, Suh H, et al. Chronic particulate exposure, mortality, and coronary heart disease in the nurses' health study. Am J Epidemiol 2008;168:1161-8.

133. Puett RC, Hart JE, Yanosky JD, Paciorek C, Schwartz J, Suh H, et al. Chronic fine and coarse particulate exposure, mortality, and coronary heart disease in the Nurses' Health Study. Environ Health Perspect 2009;117:1697-701.

134. Bell ML, Ebisu K. Environmental inequality in exposures to airborne particulate matter components in the United States. Environ Health Perspect 2012;120:1699-704.

135. Zeka A, Zanobetti A, Schwartz J. Individual-level modifiers of the effects of particulate matter on daily mortality. Am J Epidemiol 2006;163:849-59.

APPENDICES

Appendix table 1. Hazard ratios (HRs) and 95% confidence intervals (CIs) for hemorrhagic stroke per 10-μg/m^3 increment in updated cumulative average $PM_{2.5}$ levels using the time-dependent Cox model with individual-level time-varying covariates.

Covariates	HR	95% CI
$PM_{2.5}$	1.43	(1.09-1.88)
Sex		
Male (vs. female)	0.99	(0.79-1.24)
Age group, years		
20-39 (reference)	1.00	
40-49	1.34	(0.90-1.99)
50-59	1.6	(1.09-2.34)
60-69	2.46	(1.66-3.65)
≥70	2.9	(1.90-4.42)
Type of health insurance		
Employee	0.93	(0.76-1.13)
Community	1.00	
Income decile (%)		
Lowest	0.98	(0.73-1.31)

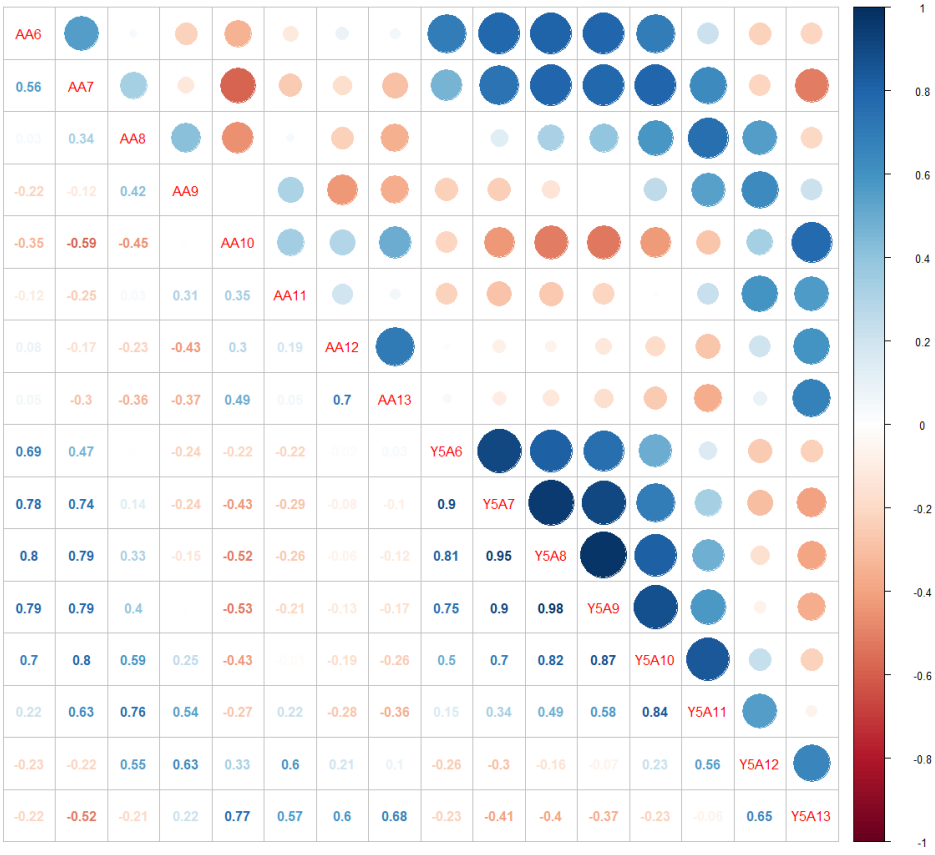
Lower middle	1.09	(0.82-1.46)
Middle	1.35	(1.04-1.75)
Higher middle	0.97	(0.74-1.25)
Highest	1.00	
Family history		
Stroke	0.99	(0.72-1.38)
Ischemic heart disease	0.67	(0.40-1.13)
Past medical history		
Hypertension	1.91	(1.45-2.54)
Diabetes	3.91	(3.07-4.97)
Congestive heart failure	1.72	(1.40-2.11)
Aortic plaque	0.95	(0.24-3.83)
Smoking status		
Never	1.00	
Former	0.79	(0.56-1.12)
Current	1.29	(0.99-1.67)
Body mass index, kg/m^2	0.97	(0.94-1.00)
Moves with change in exposure level		
0 moves and residing in an area with a lower level of $PM_{2.5}$	1.00	
0 moves and residing in an area with the same or	1.35	(1.07-1.70)

higher level of $PM_{2.5}$		
≥1 move to an area with a lower level of $PM_{2.5}$	1.19	(0.90-1.58)
≥1 move to an area with the same or higher level of $PM_{2.5}$	0.96	(0.68-1.36)

Appendix table 2. The characteristics and annual PM2.5 in each Seoul district (2007)

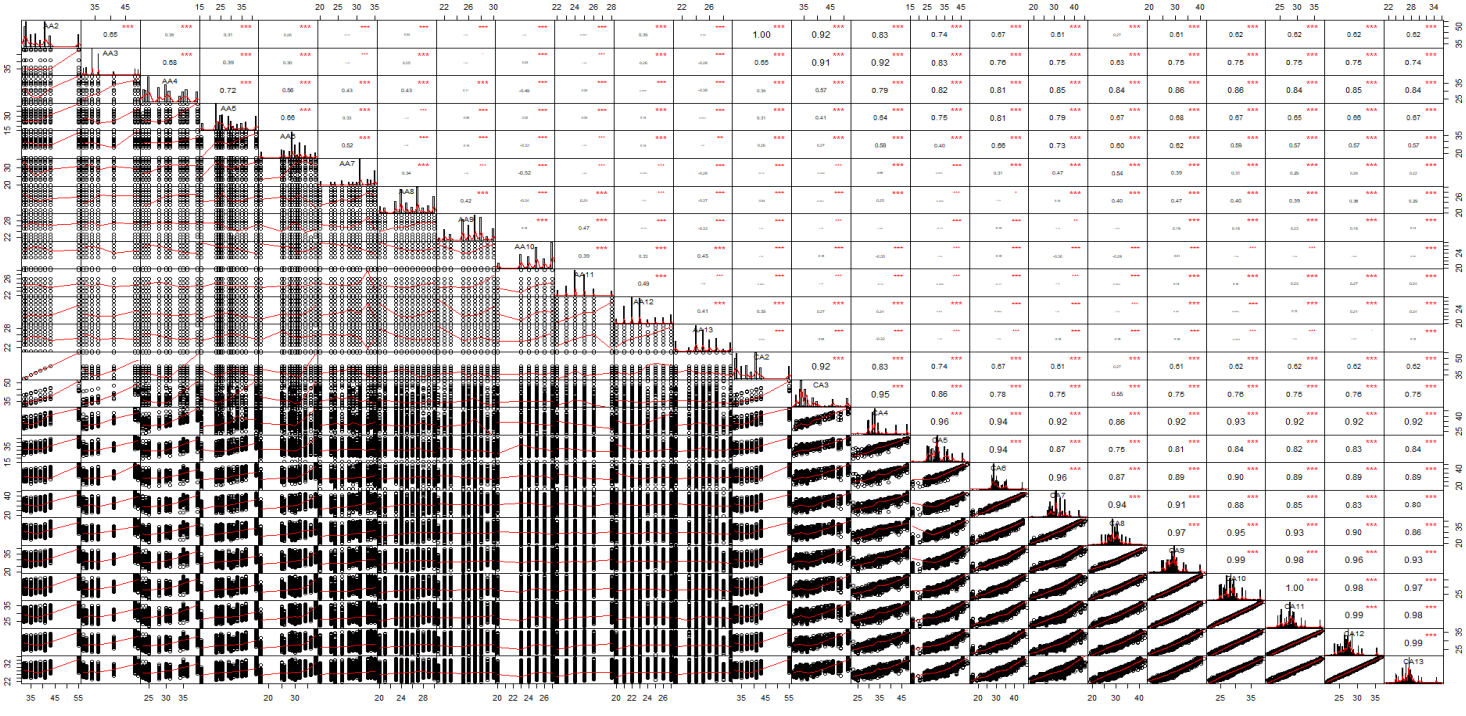
District	Populat-ion (N)	Density (N/km^2)	Area (km^2)	Deprivati-on Index	Married populat-ion (%)
Jongno	173,843	7,271	23.9	1.6	51.5
Jung	137,435	13,799	10.0	4.6	51.5
Yongsan	248,362	11,356	21.9	-1.2	54.3
Seongdong	341,620	20,274	16.9	1.3	55.7
Gwangjin	386,367	22,661	17.1	0.1	53.8
Dongdaemun	385,825	27,171	14.2	3.3	52.6
Jungnang	431,406	23,319	18.5	5.7	55.7
Seongbuk	477,358	19,428	24.6	0.5	55.5
Gangbuk	348,702	14,769	23.6	5.3	55.4
Dobong	378,559	18,288	20.7	1.0	59.1
Nowon	621,192	17,538	35.4	-1.1	58.9

Eunpyeong	463,473	15,600	29.7	2.2	56.4
Seodaemun	357,174	20,282	17.6	0.8	53.5
Mapo	400,392	16,774	23.9	-0.7	53.8
Yangcheon	508,566	29,228	17.4	-3.1	59.8
Gangseo	566,495	13,677	41.4	0.03	56.5
Guro	445,095	22,133	20.1	-0.8	58.4
Gumcheon	264,323	20,317	13.0	4.9	56.3
Yeongdeungpo	439,151	17,873	24.6	-0.9	57.2
Dongjak	414,839	25,372	16.4	-1.6	53.5
Gwanak	550,766	18,626	29.6	1.3	50.1
Seocho	411,951	8,765	47.0	-9.4	56.7
Gangnam	569,176	14,395	39.5	-7.5	52.8
Songpa	630,691	18,615	33.9	-5.1	57.2
Gangdong	469,021	19,081	24.6	-1.2	57.1

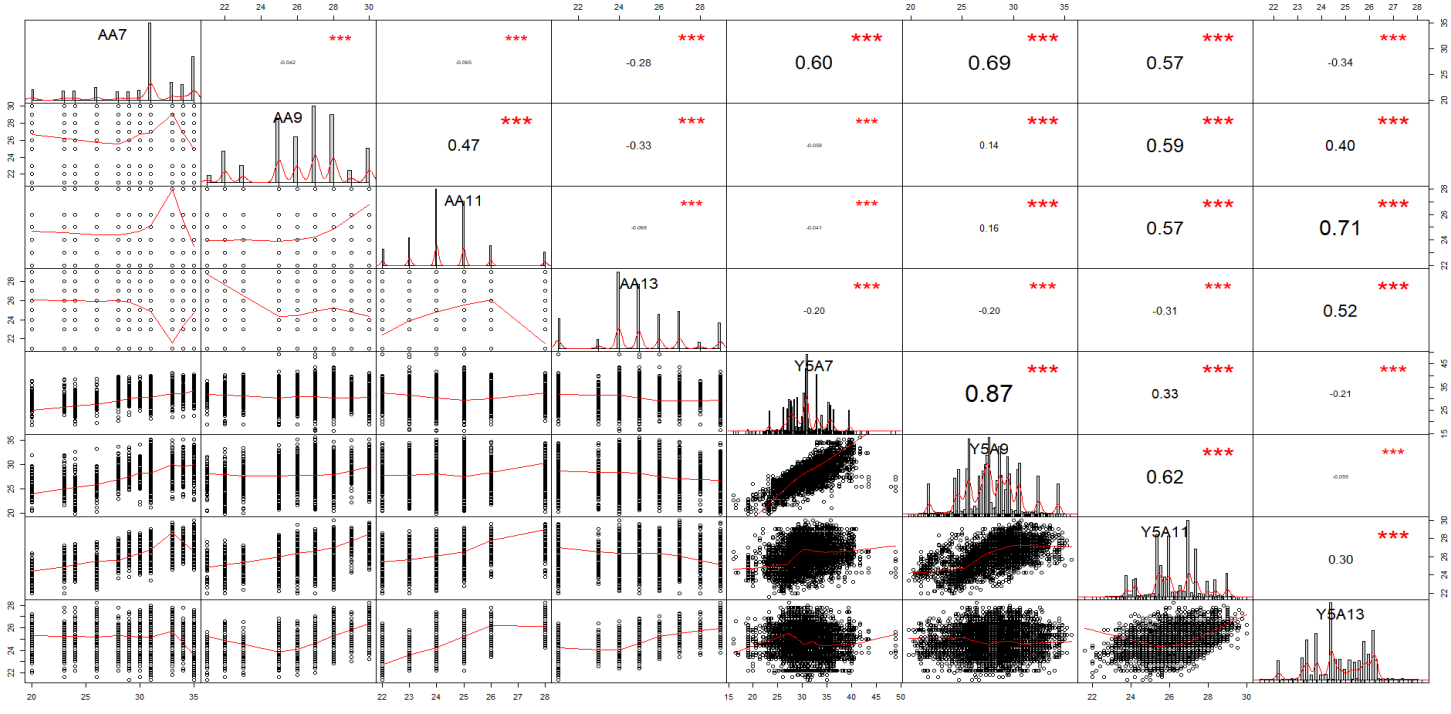


Appendix figure 1. Correlation between annual average $PM_{2.5}$ concentrations and the last 5-year average $PM_{2.5}$ concentrations, AA6: annual average $PM_{2.5}$ concentrations in 2006, Y5A6: the last 5-year average $PM_{2.5}$ concentrations during 2002-2006, $PM_{2.5}$: particulate matter with an aerodynamic diameter of <2.5 μm.

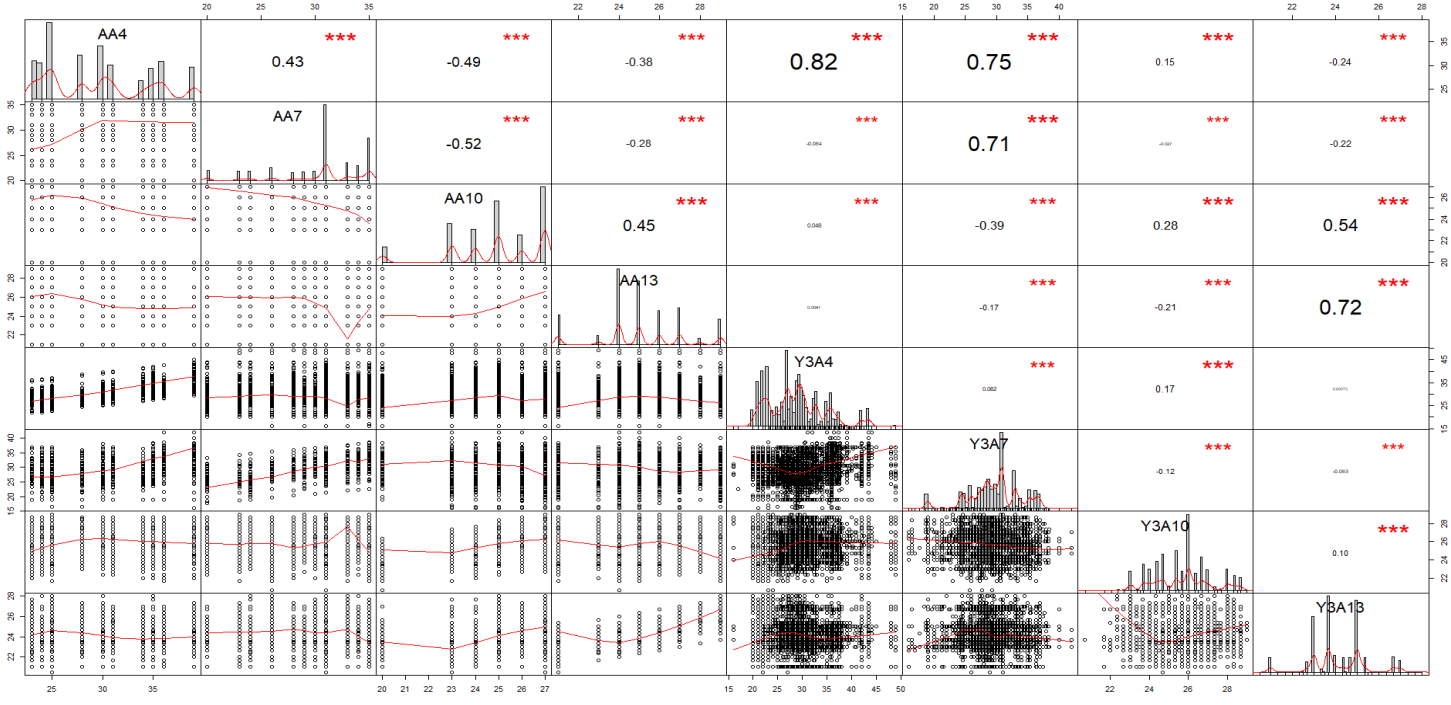
Appendix figure 2. Correlation between annual average $PM_{2.5}$ concentrations and the last 3-year average $PM_{2.5}$ concentrations; AA4: annual average $PM_{2.5}$ concentrations in 2004, Y3A4: the last 3-year average $PM_{2.5}$ concentrations during 2002-2004, $PM_{2.5}$: particulate matter with an aerodynamic diameter of <2.5 μm.



Appendix figure 3. Histograms and scatter plots for annual average $PM_{2.5}$ concentrations and cumulative average $PM_{2.5}$ concentrations; AA2: annual average $PM_{2.5}$ concentrations in 2002 ($\mu g/m^3$), CA2: cumulative average $PM_{2.5}$ concentrations in 2002 ($\mu g/m^3$), $PM_{2.5}$: particulate matter with an aerodynamic diameter of <2.5 μm.



Appendix figure 4. Histograms and scatter plots for annual average $PM_{2.5}$ concentrations and the last 5-year average $PM_{2.5}$ concentrations; AA7: annual average $PM_{2.5}$ concentrations in 2007 (μg/m^3), Y5A7: the last 5-year average $PM_{2.5}$ concentrations during 2003-2007 (μg/m^3), $PM_{2.5}$: particulate matter with an aerodynamic diameter of <2.5 μm.



Appendix figure 5. Histograms and scatter plots for annual average $PM_{2.5}$ concentrations and the last 3-year average $PM_{2.5}$ concentrations; AA2: annual average $PM_{2.5}$ concentrations in 2002 ($\mu g/m^3$), Y3A4: the last 3-year average $PM_{2.5}$ concentrations during 2002-2004 ($\mu g/m^3$), $PM_{2.5}$: particulate matter with an aerodynamic diameter of <2.5 μm.

ABSTRACT (IN KOREAN)

출혈성 뇌졸중 발생 위험에 대한 초미세먼지 ($PM_{2.5}$) 누적 평균값의 만성 영향

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노주환

서론: 여러 역학 연구에서 초미세먼지 ($PM_{2.5}$; 입자의 직경이 2.5μm 미만인 미세먼지)와 심혈관계 질환과의 연관성을 보고하였다. 최근에는 장기적인 초미세먼지 노출과 출혈성 뇌졸중과의 연관성 여부, 나아가 초미세먼지 노출에 더 민감한 인구집단을 찾기 위한 연구가 활발히 진행되고 있다. 장기적인 $PM_{2.5}$ 누적평균 노출정도는 출혈성 뇌졸중의 위험에 영향을 줄 수 있고, 다양한 위험요인들에 따라서 효과 정도가 다를 수 있다.

연구방법: 본 후향적 연구는 2002-2013 국민건강보험공단 가입자 1,025,340 명으로 구성된 표본코호트를 활용하였다. 그 중 서울에 거주하는 62,676명을 총 670, 431 인년 간 추적하여 출혈성 뇌졸중의 첫 진단 시점에 대한 $PM_{2.5}$의 영향을 평가하였다. 시간의존 Cox 비례위험 모형을 활용하여 연령,

성별, 가구소득, 보험가입유형, 체질량지수, 흡연상태, 과거력, 가족력을 보정하였다. 서울시 25개 구(區)의 연평균 $PM_{2.5}$ 농도는 시간의존 변수로 활용하였다. 잠재적인 효과변경인자를 평가하기 위하여 세부집단 분석을 시행하였다.

결과: 장기적으로 $PM_{2.5}$ 누적평균 기준 10-$\mu g/m^3$ 만큼 더 노출될 경우 통계적으로 유의하게 출혈성 뇌졸중의 위험이 높았다 (위험비: 1.43, 95% 신뢰구간: 1.09–1.88). 노출로 인한 건강영향은 특정 그룹에서 더 높은 경향이 있었다: 65세 이상 노인 (위험비: 2.00, 95% 신뢰구간: 1.32–3.02), 체질량지수가 ≥25 kg/m^2 인 군(群) (위험비: 1.91, 95% 신뢰구간: 1.28–2.84).

결론: 결론적으로 장기적으로 높은 농도의 $PM_{2.5}$ 누적평균에 노출된 사람들은 출혈성 뇌졸중 위험이 높아질 가능성이 있다. 특히 65세 이상 노인이나 체질량지수 기준 비만인 사람들이 $PM_{2.5}$ 노출 시 더 민감한 반응을 보일 수 있다.

핵심되는 말: 미세먼지, 만성 영향, 누적평균 노출, 출혈성 뇌졸중

PUBLICATION LIST

1. Noh J, Sohn J, Han M, Kang DR, Choi YJ, Kim HC et al. Long-term Effects of Cumulative Average $PM_{2.5}$ Exposure on the Risk of Hemorrhagic Stroke. Epidemiology. 2019 Jul;30 Suppl 1:S90-S98.