

## Long-Term Exposure to Fine Particulate Matter, Residential Proximity to Major Roads and Measures of Brain Structure

Elissa H. Wilker, ScD; Sarah R. Preis, ScD; Alexa S. Beiser, PhD; Philip A. Wolf, MD; Rhoda Au, PhD; Itai Kloog, PhD; Wenyuan Li, MS; Joel Schwartz, PhD; Petros Koutrakis, PhD; Charles DeCarli, MD; Sudha Seshadri, MD; Murray A. Mittleman, MD, DrPH

**Background and Purpose**—Long-term exposure to ambient air pollution is associated with cerebrovascular disease and cognitive impairment, but whether it is related to structural changes in the brain is not clear. We examined the associations between residential long-term exposure to ambient air pollution and markers of brain aging using magnetic resonance imaging.

**Methods**—Framingham Offspring Study participants who attended the seventh examination were at least 60 years old and free of dementia and stroke were included. We evaluated associations between exposures (fine particulate matter [PM<sub>2.5</sub>] and residential proximity to major roadways) and measures of total cerebral brain volume, hippocampal volume, white matter hyperintensity volume (log-transformed and extensive white matter hyperintensity volume for age), and covert brain infarcts. Models were adjusted for age, clinical covariates, indicators of socioeconomic position, and temporal trends.

**Results**—A 2- $\mu\text{g}/\text{m}^3$  increase in PM<sub>2.5</sub> was associated with  $-0.32\%$  (95% confidence interval,  $-0.59$  to  $-0.05$ ) smaller total cerebral brain volume and 1.46 (95% confidence interval, 1.10 to 1.94) higher odds of covert brain infarcts. Living further away from a major roadway was associated with 0.10 (95% confidence interval, 0.01 to 0.19) greater log-transformed white matter hyperintensity volume for an interquartile range difference in distance, but no clear pattern of association was observed for extensive white matter.

**Conclusions**—Exposure to elevated levels of PM<sub>2.5</sub> was associated with smaller total cerebral brain volume, a marker of age-associated brain atrophy, and with higher odds of covert brain infarcts. These findings suggest that air pollution is associated with insidious effects on structural brain aging even in dementia- and stroke-free persons. (*Stroke*. 2015;46:00-00. DOI: 10.1161/STROKEAHA.114.008348.)

**Key Words:** air pollution ■ brain infarcts ■ neuroimaging

Long-term exposure to particulate air pollution has been associated with higher incidence of stroke<sup>1</sup> and impaired cognitive function in older adults.<sup>2,3</sup> Long-term exposures have also been associated with changes in cerebral hemodynamics,<sup>4</sup> impaired microvascular reactivity,<sup>5</sup> and greater carotid atherosclerotic burden.<sup>6</sup> Air pollution has been hypothesized to affect the central nervous system through activation of systemic inflammatory pathways and vascular dysfunction.<sup>7</sup> Particulate air pollution is a pervasive component of urban and suburban ambient air pollution. Animal models have shown that particles can translocate from the nose via the olfactory nerve into the brain, and evidence of these particles has been found in the striatum, frontal cortex, and cerebellum.<sup>8</sup> However, it

is not known whether long-term exposures to air pollution at urban background levels are related to measures of structural integrity and atrophy in the brains of older adults.

Magnetic resonance imaging (MRI) of the brain can detect early vascular impairment<sup>9</sup> that is associated with subsequent risk of dementia and stroke.<sup>10</sup> Therefore, we investigated the associations between exposure to fine particulate matter (PM<sub>2.5</sub>) and residential proximity to major roadways with measures of total cerebral brain volume (TCBV), hippocampal volume (HV), white matter hyperintensity volume (WMHV), and covert brain infarcts (CBI) in the Framingham Offspring Study. We hypothesized that higher long-term exposure to ambient air pollution would be associated with

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From the Cardiovascular Epidemiology Research Unit, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA (E.H.W., M.A.M.); Exposure, Epidemiology and Risk Program, Department of Environmental Health (E.H.W., J.S., P.K.) and Department of Epidemiology (W.L., J.S., M.A.M.), Harvard T.H. Chan School of Public Health, Boston, MA; Department of Biostatistics, School of Public Health (S.R.P., A.S.B., R.A.) and Department of Neurology, School of Medicine (A.S.B., P.A.W., S.S.), Boston University, MA; Framingham Heart Study, MA (S.R.P., A.S.B., P.A.W., S.S.); Department of Geography and Environmental Development, Ben-Gurion University of the Negev, Beer Sheva, Israel (I.K.); and Department of Neurology and Center for Neuroscience, University of California, Davis (C.D.).

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Correspondence to Elissa Wilker, ScD, Cardiovascular Epidemiology Research Unit, Beth Israel Deaconess Medical Center, 375 Longwood Ave WMS/443, Boston, MA 02215. E-mail [ewilker@bidmc.harvard.edu](mailto:ewilker@bidmc.harvard.edu)

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subclinical damage as indicated by smaller TCBV and HV, larger WMHV, and higher odds of CBI.

## Materials and Methods

### Study Participants

The design of the Framingham Offspring Study has been detailed previously.<sup>10,11</sup> Community-dwelling participants living in the New England Region with no history of dementia, stroke, or transient ischemic attack who attended the seventh examination (1998–2001) were aged  $\geq 60$  years at the time of MRI and were eligible for inclusion in this study (n=943). All participants provided written informed consent, and the Institutional Review Boards at Beth Israel Deaconess Medical Center and Boston Medical Center approved the protocol.

### Exposure Assessment

#### *PM<sub>2.5</sub> Satellite Data*

Participant primary addresses at the seventh examination were geocoded using ArcGIS 10 (ESRI, Redlands, CA), and census tract median household income was assigned (US Census 2000). Beginning in the year 2000, Moderate Resolution Imaging Spectroradiometer satellite-derived Aerosol Optical Density measurements were used to predict daily PM<sub>2.5</sub> concentration across New England as previously described.<sup>12,13</sup>

#### *Near Roadway Exposure*

Residential proximity to the nearest A1, A2, or A3 roadway was determined by US Census Features Class in ArcGIS. We categorized proximity based on the following cut points: <50, 50 to <100, 100 to <200, 200 to <400, and 400 to <1000 m. We also evaluated the continuous association between the natural logarithm of proximity to a major roadway and neuroimaging outcomes because we have previously reported that this exposure and mortality were linearly associated.<sup>12</sup> Participants living further than 1000 m from a major road in rural areas were excluded in primary analyses because the exposures of individuals living in exurb areas beyond 1000 m away from a major roadway are likely to be different from those of people living in urban and suburban areas.

#### *Volumetric Brain MRI*

TCBV, HV, and WMHV assessments and inter-rater reliability have been described previously.<sup>14–17</sup> Total cranial volume was determined by manual delineation of the intracranial vault, and total brain parenchymal volume was determined by mathematical modeling. TCBV was then computed as a ratio of brain parenchymal volume:total cranial volume. The T2-weighted double spin-echo coronal sequences were acquired in 4-mm contiguous slices. Extensive WMHV (EXT-WMHV) was determined as a binary outcome by whether the log(WMHV/total cranial volume) was >1 SD above the age-adjusted mean in this cohort.<sup>10,18</sup> The presence of CBI was determined manually on the basis of size (>3 mm), location, and characteristics of the lesions.<sup>19</sup>

#### *Additional Covariates*

History of cardiovascular disease was determined as previously described.<sup>20</sup> Prevalent diabetes mellitus was defined as a fasting glucose  $\geq 126$  mg/dL or oral hypoglycemic or insulin use at an examination or any previous history of diabetes mellitus (excluding gestational diabetes). Smoking status (never, current, and former), pack-years smoked (<10 years,  $\geq 10$  years, and missing), education (no high school, high school, some college, bachelors or higher), and alcohol intake (0, 1–7 drinks/wk, and 7–14,  $\geq 15$ ) were self-reported. Fasting homocysteine was measured in plasma. Systolic and diastolic seated blood pressures were calculated as the mean of 2 measurements taken during the clinical examination.

**Table 1. Population Characteristics (n=943)**

Characteristic	Median [IQR] or n (%)
Age at MRI, y	68 [9]
Systolic blood pressure, mm Hg	129 [25]
Diastolic blood pressure, mm Hg	72 [13]
Men	456 (48%)
Prevalent cardiovascular disease	130 (14%)
Smoking status	
Current	73 (8%)
Former	532 (56%)
Never	337 (36%)
Missing	1 (<1%)
Prevalent heart failure	46 (5%)
Diabetes mellitus	134 (14%)
Hypertension medication use	366 (39%)
Homocysteine	8.3 [3.1]
Education	
Less than high school	51 (5%)
High school	311 (33%)
Some college/associate degree	275 (29%)
Bachelors or higher	298 (32%)
Missing education	8 (<1%)
Median household income	63,479 [29,270]
Total cerebral brain volume	78.41 [4.39]
Hippocampal volume	0.33 [0.07]
Log white matter hyperintensity volume	-2.69 [1.30]
Extensive white matter hyperintensity	135 (14%)
Covert brain infarcts	133 (14%)

IQR indicates interquartile range; and MRI, magnetic resonance imaging.

### Statistical Methods

Linear and logistic regression models were used to evaluate continuous outcomes (TCBV, HV, and WMHV) and dichotomous outcomes (EXT-WMHV and CBI), respectively. We first adjusted for age at MRI, [age at MRI]<sup>2</sup>, sex, time from examination 7 to MRI, median household income, date of MRI, smoking status, pack-years smoked, education, alcohol intake, and sine and cosine of MRI date to account for seasonal trends (model 1). We then added covariates thought to be potential confounders that could also be mediators of the associations

**Table 2. Exposure Characteristics**

Exposure	Median [IQR] or n (%)	Range
PM <sub>2.5</sub> , $\mu\text{g}/\text{m}^3$ *	11.1 [1.7]	7.7–17.6
Distance to major road, m†	173 [367]	0–993
Distance by category, m		
<50	226 (24%)	...
50 to <100	87 (9%)	...
100 to <200	149 (16%)	...
200 to <400	186 (20%)	...
400 to <1000	226 (24%)	...
$\geq 1000$	69 (7%)	...

IQR indicates interquartile range; and PM<sub>2.5</sub>, particulate matter.

\*Estimates unavailable on 13 participants.

†Sixty-nine participants living  $\geq 1000$  m from a major road excluded.

**Table 3. Associations Between Exposures and Continuous Volumetric Outcomes**

Outcome	Exposure	Model 1*			Model 2†		
		β	95% CI	n	β	95% CI	n
Hippocampal volume	<50	0.004	(−0.005 to 0.014)	865	0.005	(−0.004 to 0.015)	853
	50 to <100	0.003	(−0.011 to 0.016)	...	0.003	(−0.010 to 0.017)	...
	100 to <200	0.005	(−0.006 to 0.016)	...	0.005	(−0.006 to 0.016)	...
	200 to <400	0.003	(−0.007 to 0.013)	...	0.003	(−0.007 to 0.013)	...
	400 to <1000	Ref	...	...	Ref	...	...
	Log(distance)‡	−0.002	(−0.007 to 0.003)	865	−0.003	(−0.008 to 0.002)	853
Log (white matter hyperintensities)	PM <sub>2.5</sub> §	0.0001	(−0.005 to 0.005)	921	0.0004	(−0.005 to 0.005)	909
	<50	−0.17	(−0.35 to 0.01)	873	−0.16	(−0.34 to 0.02)	861
	50 to <100	−0.13	(−0.37 to 0.11)	...	−0.12	(−0.36 to 0.11)	...
	100 to <200	−0.07	(−0.27 to 0.13)	...	−0.06	(−0.26 to 0.13)	...
	200 to <400	0.02	(−0.16 to 0.21)	...	0.03	(−0.15 to 0.22)	...
	400 to <1000	Ref	...	...	Ref	...	...
Total cerebral brain volume	Log(distance)‡	0.10	(0.01 to 0.19)	873	0.09	(−0.0004 to 0.18)	861
	PM <sub>2.5</sub> §	−0.06	(−0.16 to 0.03)	929	−0.08	(−0.17 to 0.01)	917
	<50	0.23	(−0.29 to 0.75)	873	0.09	(−0.42 to 0.60)	861
	50 to <100	0.45	(−0.24 to 1.14)	...	0.47	(−0.21 to 1.16)	...
	100 to <200	−0.02	(−0.60 to 0.56)	...	−0.14	(−0.71 to 0.43)	...
	200 to <400	−0.19	(−0.73 to 0.35)	...	−0.30	(−0.84 to 0.23)	...
Total cerebral brain volume	400 to <1000	Ref	...	...	Ref	...	...
	Log(distance)‡	−0.15	(−0.41 to 0.11)	873	−0.10	(−0.36 to 0.16)	861
	PM <sub>2.5</sub> §	−0.32	(−0.59 to −0.05)	929	−0.26	(−0.53 to 0.004)	917

CI indicates confidence interval; MRI, magnetic resonance imaging; and PM<sub>2.5</sub>, particulate matter.

\*Model 1 adjusted for age, age2, sex, time from examination 7 to MRI, median household income, date of MRI, smoking status, pack-years smoked, education (no high school, high school, some college, bachelors or higher), drinking categories and sine and cosine of MRI date to account for seasonal trends.

†Model 2 adjusted for model 1 covariates+log (homocysteine), systolic blood pressure, diabetes mellitus, cardiovascular disease, history of atrial fibrillation, hypertension medications, and obesity.

‡Scaled to difference between 25th and 75th percentile of distance (367 m).

§Scaled to 2 μg/m<sup>3</sup> difference in PM<sub>2.5</sub>.

between particulate air pollution and brain structure, including natural logarithm of homocysteine, systolic blood pressure, diabetes mellitus, cardiovascular disease, history of atrial fibrillation, hypertension medications, and obesity (body mass index ≥30 kg/m<sup>2</sup>) (model 2).

We tested whether observed associations differed by factors related to biological susceptibility and socioeconomic position as an evaluation of effect modification using cross-product terms for sex, diabetes mellitus, obesity, current and former smoking (versus never smoking), and median household income <25th percentile (≤\$44 901).

In sensitivity analyses, we accounted for clustering by census tract to further control confounding by socioeconomic position using generalized estimating equations with exchangeable working correlation matrix. Nonlinearity was evaluated using restricted cubic splines with knots at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles. We evaluated associations with PM<sub>2.5</sub> restricting to participants living within 1000 m of a major road. We also considered whether adjusting for CBI altered findings for associations between exposures of interest and TCBV.<sup>16</sup>

Models of PM<sub>2.5</sub> were scaled to 2 μg/m<sup>3</sup>, which approximates the interquartile range (1.7 μg/m<sup>3</sup>). We present the results of log-linear residential proximity to major roadway within 1000 m analyses for an interquartile range. All analyses were performed in SAS version 9.3 or STATA version 12. Plots were created using the POSTRCSPLINE package in Stata.<sup>21</sup>

### Results

Table 1 shows population characteristics. The median (interquartile range) of PM<sub>2.5</sub> exposure was 11.1 (1.7) μg/m<sup>3</sup>.

Participants lived a median distance (25th to 75th percentile) from a major road of 173 (48–415) m (Table 2). The Spearman rank correlation between the natural logarithm of residential distance from a major road and PM<sub>2.5</sub> was −0.15.

Higher PM<sub>2.5</sub> was associated with smaller TCBV and 1.46 times (95% confidence interval [CI], 1.10 to 1.94) higher odds of CBI (Tables 3 and 4). A 2-μg/m<sup>3</sup> increase in PM<sub>2.5</sub> was associated with a 0.32 U difference in TCBV (95% CI, −0.59 to −0.05). There was no clear pattern of association between PM<sub>2.5</sub> and HV, WMHV, or EXT-WMHV.

An interquartile range difference in residential proximity to a major road was associated with 0.10 (95% CI, 0.01 to 0.19) higher WMHV. A similar pattern was observed with categories of distance. However, there was no evidence of an association between proximity to a major road and EXT-WMHV, or was it associated with TCBV, HV, or CBI.

There was no evidence of effect modification for the observed associations by sex, diabetes mellitus diagnosis, obesity, smoking, or median income below the 25th percentile.

Only the association between PM<sub>2.5</sub> and TCBV met criteria for significant deviation from linearity, suggesting a stronger association at lower exposure levels and wide CIs at high levels (Figure I in the online-only Data Supplement). We found

**Table 4. Associations Between Exposures and Binary Outcome**

Outcome	Exposure	Model 1*			Model 2†		
		OR	95% CI	n	OR	95% CI	n
Extensive white matter hyperintensity volume for age	<50	0.88	(0.51–1.52)	873	0.94	(0.53–1.67)	861
	50 to <100	0.56	(0.25–1.29)	...	0.59	(0.25–1.38)	...
	100 to <200	0.86	(0.46–1.60)	...	0.96	(0.51–1.83)	...
	200 to <400	1.05	(0.60–1.84)	...	1.16	(0.65–2.06)	...
	400 to <1000	Ref	...	...	Ref	...	...
	Log(distance)‡	1.11	(0.84–1.48)	873	1.09	(0.81–1.47)	861
Covert brain infarcts	PM <sub>2.5</sub> §	1.00	(0.76–1.32)	929	0.94	(0.70–1.26)	917
	<50	1.21	(0.67–2.17)	870	1.29	(0.70–2.36)	861
	50 to <100	1.25	(0.58–2.67)	...	1.16	(0.53–2.56)	...
	100 to <200	1.17	(0.61–2.23)	...	1.10	(0.56–2.15)	...
	200 to <400	1.69	(0.95–3.00)	...	1.72	(0.95–3.11)	...
	400 to <1000	Ref	...	...	Ref	...	...
	Log(distance)‡	1.05	(0.79–1.40)	870	1.02	(0.75–1.37)	861
	PM <sub>2.5</sub> §	1.46	(1.10–1.94)	926	1.37	(1.02–1.85)	917

CI indicates confidence interval; MRI, magnetic resonance imaging; OR, odds ratio; and PM<sub>2.5</sub>, particulate matter.

\*Model 1 adjusted for age, age<sup>2</sup>, sex, time from examination to MRI, median household income, date of MRI, smoking status, pack-years smoked, education (no high school, high school, some college, bachelors or higher), drinking categories and sine and cosine of MRI date to account for seasonal trends.

†Model 2 adjusted for model 1 covariates+log (homocysteine), systolic blood pressure, diabetes mellitus, cardiovascular disease, history of atrial fibrillation, hypertension medications, and obesity.

‡Scaled to difference between 25th and 75th percentile of distance (367 m).

§Scaled to 2 μg/m<sup>3</sup> difference in PM<sub>2.5</sub>.

no material differences when we considered restricting PM<sub>2.5</sub> analyses to regions within 1000 m of a major road or clustering by socioeconomic position. Adjustment for covert brain injury did not alter the association between PM<sub>2.5</sub> and TCBV.

## Discussion

In this study, we observed that an increase in PM<sub>2.5</sub> within the range of exposures observed at urban and suburban background levels in New England was associated with smaller –0.32 (95% CI, –0.59 to –0.05) TCBV and with 1.46 times (95% CI, 1.10 to 1.94) higher odds of CBI. These findings support the hypothesis that higher long-term exposures to ambient air pollution are associated with structural changes in the brain that could precede cognitive impairment and overt cerebrovascular damage.<sup>22–24</sup>

To our knowledge, there are no published studies of associations between air pollution and brain volume or CBI in older adults. Although CBI may appear asymptomatic, these small infarcts typically located in deep regions of the brain have been associated with neurological abnormalities, poorer cognitive function,<sup>25</sup> onset of dementia,<sup>24</sup> and are thought to reflect small-vessel disease.<sup>26</sup> Smaller TCBV has been associated subsequent stroke among Framingham Offspring participants<sup>27</sup> and also with poorer performance on tests of attention, executive, and visuospatial function.<sup>16</sup> The magnitude of association that we observed for a 2-μg/m<sup>3</sup> increase in PM<sub>2.5</sub> was similar to ≈1 year of brain aging computed as the ratio of the coefficients for PM<sub>2.5</sub> and age in the model. Adjustment for CBI did not alter this association, suggesting that atrophy was

independent of the presence of asymptomatic injury and not merely a direct result of the presence of cerebral infarction.

The mechanisms through which air pollution may affect brain aging remain unclear, but systemic inflammation resulting from deposition of fine particles in alveoli is likely important. Upregulation of a proinflammatory state has been associated both with elevated risk of stroke<sup>7,28</sup> and cognitive decline.<sup>29</sup> Circulating levels of biomarkers indicative of systemic inflammation have been associated with lower brain volume.<sup>30</sup>

Our findings are largely consistent with previous studies showing that long-term exposure to ambient air pollution is associated with vascular impairment.<sup>4,5,12</sup> Several previous studies have reported associations between long-term pollution exposure and living close to major roads with incident stroke<sup>1,31,32</sup> and poorer cognitive function in older adults.<sup>2,3,33</sup> Living in a high air pollution region in Mexico City was associated with greater accumulation of 42-amino acid form of β-amyloid in the frontal cortex and hippocampus than living in a nonpolluted area.<sup>34</sup>

Although evidence on the associations between long-term air pollution exposures and white matter damage is limited, an ecological study in Mexico reported associations between higher levels of air pollution and white matter damage in children and dogs.<sup>35</sup> Our findings of a positive association between WMHV and living further from a major road but no association with EXT-WMHV were unexpected. However, among Framingham Offspring Study participants, EXT-WMHV was associated with poorer cognitive function<sup>18</sup> and elevated risk of stroke<sup>10</sup> but WMHV was not, suggesting a threshold for these associations. Different findings may have distinct underlying pathophysiologic mechanisms. To evaluate this, it will



require additional studies in experimental models designed to address these questions.

There were some differences in associations we observed for PM<sub>2.5</sub> and residential proximity to a major roadway. Although both capture features of long-term exposure to ambient air pollution, proximity is an integrated measure of exposure to traffic, which includes vehicle emissions, noise, ultrafine particles, road dust, and gaseous pollutants such as nitrogen dioxide, carbon monoxide, and volatile organic compounds but does not specifically account for the intensity of traffic or meteorologic conditions at a given location. In contrast, modeled PM<sub>2.5</sub> incorporates both locally and regionally generated air pollution. Hence, they represent different aspects of ambient pollutant exposures.

Our study is not without limitations. Although we accounted for individual-level and area-level characteristics of socioeconomic position, there may be residual confounding. However, the results from our analysis taking spatial clustering into account were similar to our primary results, and previous literature using modeled PM<sub>2.5</sub> has also shown that correlations between socioeconomic position and PM<sub>2.5</sub> are low within urban areas.<sup>36</sup> The Framingham Offspring population comprised mostly white participants. Therefore, these results may not be generalizable to other populations. Recent addresses were stable, with 91% of participants reporting the same address at the sixth and seventh examination cycles. Our PM<sub>2.5</sub> data are based on an average for the year 2001 similar to other large epidemiological studies.<sup>12,31</sup> This approach limits the influence of secular trends in exposure, while capturing the spatial distribution of average PM<sub>2.5</sub>. This study also has several strengths, including a relatively large, community-based sample, inclusion of both men and women, quantitative brain MRI, and individual-level estimates of exposures.

## Conclusions

We observed evidence suggesting that long-term exposure to PM<sub>2.5</sub> is associated with lower TCBV and more CBI among a community-based sample of participants free of dementia and stroke. These findings suggest that relatively low urban background levels of particulate air pollution may contribute to the acceleration of atrophic changes and small-vessel disease in older adults. Additional studies will be necessary to confirm or refute these findings, extend the work to include longitudinal assessments, and to determine factors that mediate this association.

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## Disclosures

None.

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# Stroke

## Long-Term Exposure to Fine Particulate Matter, Residential Proximity to Major Roads and Measures of Brain Structure

Elissa H. Wilker, Sarah R. Preis, Alexa S. Beiser, Philip A. Wolf, Rhoda Au, Itai Kloog, Wenyan Li, Joel Schwartz, Petros Koutrakis, Charles DeCarli, Sudha Seshadri and Murray A. Mittleman

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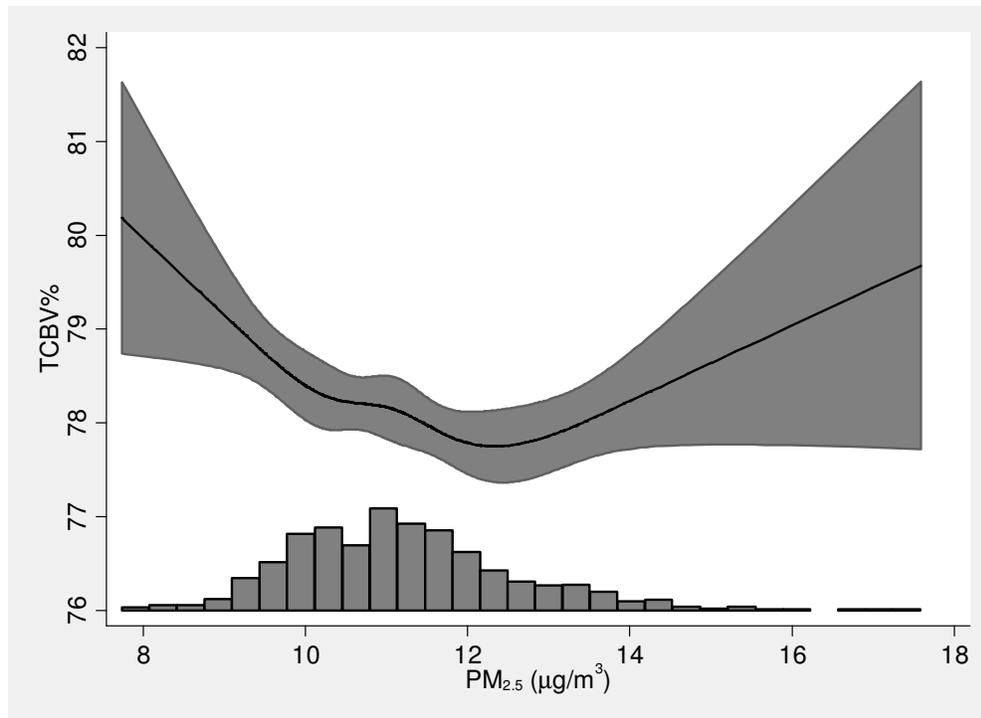
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## SUPPLEMENTAL MATERIAL

Supplemental Figure I: Non-linear association between  $PM_{2.5}$  and total cerebral brain volume



Model 1 adjusted results for association between  $PM_{2.5}$  (5 knots) and total cerebral brain volume. The spline indicates a steeper slope at lower levels of exposures. High levels of exposure were associated with higher brain volume, though confidence intervals in this range of the data were wide. Whether this pattern is due to a leveling off in the exposure-response relationship, the influence of outliers, or residual confounding remains unclear.

5년까지 추적관찰 하였다. 각 추적관찰 기간 동안 허혈뇌졸중의 발생률을 조사하였다.

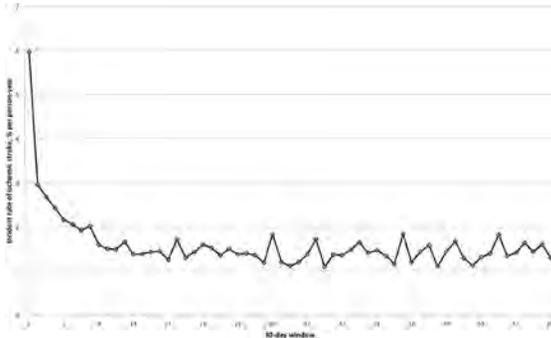
**결과**

5년 경과 후, 새롭게 와파린을 시작한 환자(n=148446) 중 허혈뇌졸중의 누적 발생은 4.0% (n=6006)이었다. 와파린 시작 이후 첫 30일 시점에 뇌졸중 위험이 가장 높았으며(1 인-년 당 6.0%; 95% CI 5.5%-6.4%), 이는 이후 추적관찰 기간 동안의 발생률(1 인-년 당 1.6%; 95% CI 1.5%-1.6%)보다 유의하게 높았다. 또한 뇌졸중 위험은 초기 CHADS<sub>2</sub> 점수(울혈심부전, 고혈압, 75세 이

상의 연령, 당뇨, 이전 뇌졸중 병력)에 비례하였다. 모니터링 빈도가 적은 것도 기여 인자로 관계하였다.

**결론**

심방세동이 있는 고령 환자의 대규모 코호트에서, 와파린 시작 이후 첫 30일 기간 동안에 허혈뇌졸중 발생 위험이 가장 높은 것을 관찰하였다. 본 분석은 관찰 연구로서 그 원인을 밝힐 수는 없었으나, 연구 결과를 통하여 이러한 환자군에서 추가 연구가 필요함을 강조한다



**Figure.** Rate of ischemic stroke among new warfarin users with atrial fibrillation.

**Table 2. Rates of Stroke by Duration of Warfarin Therapy**

	Ischemic Stroke During 5-y Follow-Up, n (%)	Rate of Stroke, % per Person-Year (95% CI)		
		First 30 d	Remainder of 5-y Follow-Up	Overall
Overall	6006	6.0 (5.5-6.4)	1.6 (1.5-1.6)	1.8 (1.7-1.8)
CHADS <sub>2</sub> score				
0	146 (2.4)	2.7 (1.8-4.1)	0.5 (0.5-0.6)	0.6 (0.5-0.7)
1	874 (14.6)	3.8 (3.2-4.6)	0.9 (0.9-1.0)	1.1 (1.0-1.1)
2-3	3609 (60.1)	5.6 (5.1-6.2)	1.6 (1.6-1.7)	1.8 (1.8-1.9)
4-6	1377 (22.9)	14.2 (12.3-16.4)	3.6 (3.4-3.8)	4.2 (4.0-4.4)
Stroke history				
No previous stroke	4900 (81.6)	5.0 (4.6-5.4)	1.4 (1.3-1.4)	1.6 (1.5-1.6)
Previous stroke	1106 (18.4)	19.6 (16.8-23.0)	4.2 (4.0-4.5)	4.9 (4.6-5.2)
Timing of atrial fibrillation diagnosis, d				
≤30	72385 (48.8)	6.1 (5.5-6.8)	1.5 (1.5-1.6)	1.7 (1.7-1.8)
>30	76061 (51.2)	5.8 (5.3-6.5)	1.6 (1.6-1.7)	1.8 (1.8-1.9)

CHADS<sub>2</sub> indicates score comprised of congestive heart failure, hypertension, age ≥75 years, diabetes, previous stroke; and CI, confidence interval.

**Abstract 4**

**미세먼지에의 장기적인 노출, 주거지역의 주요도로 근접여부 및 뇌 구조의 측정**

**Long-Term Exposure to Fine Particulate Matter, Residential Proximity to Major Roads and Measures of Brain Structure**

Elissa H. Wilker, ScD; Sarah R. Preis, ScD; Alexa S. Beiser, PhD; Philip A. Wolf, MD; Rhoda Au, PhD; Itai Kloog, PhD; Wenyuan Li, MS; Joel Schwartz, PhD; Petros Koutrakis, PhD; Charles DeCarli, MD; Sudha Seshadri, MD; Murray A. Mittleman, MD, DrPH

(Stroke. 2015;46:1161-1166.)

**Key Words:** air pollution ■ brain infarcts ■ neuroimaging

**배경과 목적**

오랫동안 주변의 공기 오염에 노출되는 것은 뇌혈관질환과 인지

장애에 영향을 준다. 그러나, 뇌의 구조적인 변화가 관련되는지 여부는 불분명하다. 본 연구에서는 거주지역에서의 주위 공기 오

염에의 장기적인 노출과 MRI를 이용한 뇌의 노화 표지의 관계를 연구하였다

#### 방법

Framingham Offspring Study의 7번째 조사에 참여한 사람 중 60세 이상이며 치매와 뇌졸중 병력이 없는 사람을 연구에 포함하였다. 노출된 정도(미세먼지[PM<sub>2.5</sub>]와 주요 도로에서 얼마나 가까운 곳에 거주하는지)와 총 뇌 용적, 해마 용적, 백색질의 고음영 용적(로그 변환을 하였고, 연령대에 비해 광범위한 백색질 고음영 용적 확인), 무증상 뇌경색 사이의 연관성을 평가하였다. 분석 모형은 나이, 임상적 공변량, 사회경제적 상태 지표, 시간 경향에 대해 보정하였다.

#### 결과

2.5 µm 이하의 미세먼지가 2 µg/m<sup>3</sup> 증가할 때 총 뇌 용적은

0.32%씩 감소했으며(95% CI, -0.59 to -0.05), 무증상 뇌경색은 1.46배의 높은 교차비를 보였다(95% CI, 1.10 to 1.94). 주요 도로에서 멀리 떨어져 사는 것은 거리를 사분위수 범위로 나누었을 때, 한 단계에 대해 로그 변환된 백색질 고음영 용적이 0.1 증가하였다(95% CI, 0.01 to 0.19). 그러나, 광범위한 백색질이 보이는 경우와는 명확한 연관관계가 관찰되지 않았다.

#### 결론

높은 2.5 µm 이하 미세먼지에 노출된 경우에 더 작은 총 뇌 용적, 연령증가와 관련된 뇌 위축, 무증상 뇌경색의 높은 교차비와 연관관계를 보였다. 이러한 결과는 공기 오염이 치매와 뇌졸중을 앓지 않은 사람에서조차 구조적인 뇌의 노화에의 점진적인 영향과 관련되어 있음을 시사한다.

## Abstract 5

### 종합비타민 복용과 뇌졸중 사망 위험

일본 협동 코호트 연구

#### Multivitamin Use and Risk of Stroke Mortality

The Japan Collaborative Cohort Study

Jia-Yi Dong, MMed; Hiroyasu Iso, MD, PhD; Akihiko Kitamura, MD, PhD; Akiko Tamakoshi, MD, PhD; Japan Collaborative Cohort Study Group\*

(Stroke. 2015;46:1167-1172.)

**Key Words:** cohort studies ■ mortality ■ stroke

#### 배경과 목적

뇌졸중 위험에 대한 종합비타민 보충제의 효과는 불확실하다. 이 연구의 목적은 종합비타민 복용과 뇌졸중 및 그 아형별 사망위험 간의 관계를 조사하는 것이다.

#### 방법

1988년에서 1990년 기준 심혈관질환 및 암이 없는 72180명의 일본인 남성 및 여성을 2009년 12월 31일까지 추적관찰 하였다. 종합비타민 복용을 포함한 생활습관을 자가보고식(self-administered) 설문지를 이용하여 수집하였다. 콕스 비례 위험 회귀모형(Cox proportional hazards regression model)이 종합비타민 복용과 관련된 전체 뇌졸중 및 그 아형별 위험도(hazard ratios, HRs)를 추정하는데 사용되었다.

#### 결과

19.1년의 평균(중간값) 추적관찰 기간 동안, 1148건의 허혈뇌졸중

과 877건의 출혈뇌졸중을 포함한 2087건의 사망을 확인하였다. 잠재적 교란요인들을 보정한 이후, 종합비타민 복용은 전체 뇌졸중으로 인한 사망의 위험을 애매하게 유의한 정도로 낮추었는데(HR, 0.87; 95% CI, 0.76-1.01), 주로 허혈뇌졸중(HR, 0.80; 95% CI, 0.63-1.01)에서 그랬고, 출혈뇌졸중(HR, 0.96; 95% CI, 0.78-1.18)에서는 그렇지 않았다. 하위군 분석에서, 하루 3회 미만 과일 및 야채 섭취를 하는 사람들에서 종합비타민 복용은 전체 뇌졸중으로 인한 낮은 사망 위험과 유의한 관련이 있었다(HR, 0.80; 95% CI, 0.65-0.98). 이러한 관련성은 비정기적인 복용자들보다는 정기적인 복용자들 사이에서 더 분명한 것 같다. 유사한 결과가 허혈뇌졸중에 대해서도 발견되었다.

#### 결론

종합비타민 복용, 특히 잦은 빈도의 복용은, 과일과 야채를 잘 먹지 않는 일본 사람들에서 전체 및 허혈뇌졸중 사망률 위험 감소와 관련이 있었다.