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# Short-term Exposure to Air Pollution and Incidence of Stroke in the Women's Health Initiative

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## Abstract

**Background:** Evidence of the association between daily variation in air pollution and risk of stroke is inconsistent, potentially due to the heterogeneity in stroke etiology.

**Objectives:** To estimate the associations between daily variation in ambient air pollution and risk of stroke and its subtypes among participants of the Women's Health Initiative, a large prospective cohort study in the United States.

**Methods:** We used national-scale, log-normal ordinary kriging models to estimate daily concentrations of fine particulate matter ($PM_{2.5}$), respirable particulate matter ($PM_{10}$), nitrogen dioxide ($NO_2$), nitrogen oxides (NOx), sulphur dioxide, and ozone at participant addresses. Stroke was adjudicated by trained neurologists and classified as ischemic or hemorrhagic. Ischemic strokes were further classified according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification. We used a time-stratified case-crossover approach to estimate the odds ratio (OR) of the risk of stroke associated with an interquartile range (IQR) increase in concentrations of each air pollutant. We performed stratified analysis to examine whether associations varied across subgroups defined by age at stroke onset, US census region, smoking status, body mass index, and prior history of diabetes mellitus, hypertension, heart or circulation problems, or arterial fibrillation at enrollment.

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**Results:** Among 5,417 confirmed strokes between 1993 and 2012, 4,300 (79.4%) were classified as ischemic and 924 (17.1%) as hemorrhagic. No association was observed between day-to-day variation in any pollutant and risk of total stroke, ischemic stroke, or specific etiologies of ischemic stroke. We observed a positive association between risk of hemorrhagic stroke and $NO_2$ and $NO_x$ in the 3 days prior to stroke with OR of 1.24 (95% CI: 1.01, 1.52) and 1.18 (95% CI: 1.03, 1.34) per IQR increase, respectively. The observed associations with hemorrhagic stroke were more pronounced among non-obese participants.

**Conclusions:** In this large cohort of post-menopausal US women, daily $NO_2$ and NOx were associated with higher risk of hemorrhagic stroke, but ambient levels of four other air pollutants were not associated with higher risk of total stroke, ischemic stroke, or ischemic stroke subtypes.

**Keywords**

Air pollution; Hemorrhagic stroke; Ischemic stroke; Case-crossover; United States

## 1. Background

In 2017 stroke was a leading cause of long-term disability and the second leading cause of death worldwide (James et al., 2018; Roth et al., 2018). Globally, it is estimated that stroke claimed approximately 6 million lives (over 10% of all deaths) and 102 million disability-adjusted life years lost (about 4% of total) per year (James et al., 2018; Roth et al., 2018). In the United States (US), about 800,000 Americans experience a new or recurrent stroke, resulting in more than 130,000 deaths and 1 million hospital admissions each year (Benjamin et al., 2017). Stroke imposes a considerable economic burden with an estimated $105.2 billion in direct and indirect costs in 2012, projected to increase to $240.67 billion by 2030 (Ovbiagele et al., 2013). When considering the diminished productivity and reduced quality of life among disabled stroke survivors, the true cost could be even greater. Therefore, it is of significant public health interest to identify modifiable risk factors for stroke.

It is estimated that modifiable risk factors (e.g., smoking, poor diet, and air pollution) contribute to over 90% of the stroke burden globally, and air pollution alone accounted for an estimated one third (Feigin et al., 2016). Despite numerous studies (Shah et al., 2015; Wang et al., 2014; Yang et al., 2014), the evidence linking transient variation in air pollution with the risk of cerebrovascular events remains equivocal with some (Andersen et al., 2010; Chan et al., 2006; Dominici et al., 2006; Fisher et al., 2019; Wellenius et al., 2012), but not all studies (Barnett et al., 2006; Butland et al., 2017; Halonen et al., 2009; O'Donnell et al., 2011; Villeneuve et al., 2006; Vivanco-Hidalgo et al., 2018) finding a positive association.

Some of the heterogeneity observed across prior studies may be due, at least in part, to heterogeneity in stroke etiology. Many prior studies have examined the relation between air pollutants and the risk of hospitalizations for the composite endpoint of cerebrovascular diseases (Barnett et al., 2006; Chan et al., 2006; Dominici et al., 2006; Halonen et al., 2009), with relatively fewer studies focusing specifically on the risk of ischemic or hemorrhagic stroke (Andersen et al., 2010; Fisher et al., 2019; Mechtouff et al., 2012; O'Donnell et al., 2011; Wellenius et al., 2005). Ischemic stroke itself is an etiologically diverse disease and

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even fewer studies have assessed whether the association of ischemic stroke with air pollutants may differ according to presumed ischemic stroke etiology (Andersen et al., 2010; Henrotin et al., 2007; O'Donnell et al., 2011; Vivanco-Hidalgo et al., 2018; Wellenius et al., 2012). Moreover, many prior studies have been based on strokes identified from administrative claims data, which may be susceptible to misclassification of the outcome (Heckbert et al., 2004; Jones et al., 2014) potentially leading to biased health effects estimates.

Accordingly, we sought to estimate the associations between transient exposure to air pollution (including both particulate and gaseous pollutants) and risk of stroke and its subtypes among participants of the Women's Health Initiative, a large prospective cohort of post-menopausal US women. To identify potential susceptible subpopulations, we also examined whether the association varied across subgroups defined by participant characteristics.

## 2. Methods

### 2.1. Study Population

The Women's Health Initiative (WHI) is a nationwide prospective cohort of postmenopausal women that included three clinical trials from 1993–2005, as has been described in detail elsewhere (The WHI Study Group, 1998). We used data from both the observational study (OS) and clinical trial (CT) components of the WHI, which together enrolled 161,808 postmenopausal women aged 50 to 79 years between 1993 and 1998 at baseline from 40 clinical centers in the US (The WHI Study Group, 1998). We restricted our analyses to those participants who experienced a stroke event between enrollment and September 14, 2012, had no history of stroke upon enrollment, had a known address at the time of stroke, and for who the date of stroke hospitalization was documented. The WHI protocols were approved by institutional review boards at all participating institutes.

### 2.2. Exposure Assessment

We estimated geocoded participant address-specific daily mean concentrations of fine particulate matter ($PM_{2.5}$) 32.5 ($\mu g/m^3$), respirable particulate matter ($PM_{10}$) ($\mu g/m^3$), nitrogen dioxide ($NO_2$) (ppb), nitrogen oxides ($NO_x$) (ppb), sulfur dioxide ($SO_2$) (ppb), and ozone ($O_3$) (ppb) between 1993 and 2012 for each participant using a log-normal ordinary kriging model as previously described (Liao et al., 2006). This model estimates daily air pollutants at each address based on weighted average of measurement from nearby monitors (Legendre and Fortin, 1989). The performance of these models has been assessed using cross-validation parameters including standardized prediction error (SPE), prediction error (PE), and root mean square standardized (RMSS) (Liao et al., 2006). The PEs and SPEs of the six air pollutants in 2000, 2005, and 2010 are very close to 0 with a range from 0 to 0.27 for PE and −0.11 to 0.04 for SPE, and the RMSSs are all close to 1 (Table S1).

We estimated daily mean ambient temperature (°C), dew point temperature (°C), and relative humidity (%) by averaging the daily means across all National Climatic Data Center stations < 50km from each participant's geocoded address in the contiguous US (National Climatic

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Data Center, 2019). These exposure estimates have been used in previous health studies (Fisher et al., 2019; Shih et al., 2010; Zhang et al., 2009).

### 2.3. Outcome Assessment

Cerebrovascular events during follow-up were self-reported on the questionnaires by participants. All potential strokes were then centrally adjudicated by trained neurologists using a standardized approach (Curb et al., 2003). Stroke was defined as the rapid onset of a persistent neurologic deficit attributed to an obstruction or rupture lasting >24 hour without evidence for other causes, unless death supervened or there was a demonstrable lesion compatible with acute stroke on brain imaging studies. Trained adjudicators classified strokes as ischemic, hemorrhagic, or of undetermined subtype based on results of brain imaging studies. Presumed ischemic stroke etiology was evaluated according to the scheme developed for the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) and classified as: large artery atherosclerosis, small vessel occlusion, cardioembolism, and stroke of other determined or undetermined etiology.

### 2.4. Statistical Analysis

We used a case-crossover study design to estimate the association between day-to-day variation in ambient air pollutants and the relative risk of stroke events. The case-crossover design is widely used to study the acute effects of transient exposures on the relative risk of acute events (Carracedo-Martínez et al., 2010; Levy et al., 2001). With this design, each participant experiencing an event of interest serves as his/her own control, and the inference is based on comparing exposures over time within the same person (Carracedo-Martínez et al., 2010; Levy et al., 2001). In the present study, the concentrations of air pollutants on the event day or prior days (i.e., case period) are compared to pollutant concentrations on other days when participants did not experience the event (i.e., control periods). We used a time-stratified approach to select the control periods such that pollutant concentrations during the case period were compared to concentrations on other days of the same year, month, and day of the week as the case day. This approach to control selection has been shown to control for confounding by season, long-term time trends, and other potential measured or unmeasured confounders that vary relatively slowly over time (Levy et al., 2001). We adjusted for time-varying confounders including daily mean ambient temperature, dew point temperature, and relative humidity using natural cubic splines with three degrees of freedom each.

We used conditional logistic regression to estimate odds ratios (OR) and 95% confidence intervals per an interquartile range (IQR) increase in each air pollutant. We estimated the association of stroke with air pollution on the stroke event day (1-day moving average), 2-day moving average, and 3-day moving average, adjusting for mean ambient temperature and dew point temperature over the same time period. In sensitivity analyses, we also examined the ORs for air pollution over 4-, 5-, and 6-day moving averages.

### 2.5. Subgroup Analysis

We used stratified analyses to investigate whether air pollution was differentially associated with strokes of different subtypes (ischemic, hemorrhagic, or undetermined) or with ischemic strokes of different TOAST classifications (large artery atherosclerosis, small

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vessel occlusion, cardioembolism, stroke of other determined or undetermined etiology). In secondary analyses of the association between air pollution and each stroke type we additionally examined whether the associations varied across subgroups defined by age at stroke onset (<75 or ≥75 years), US census region (Northeast, South, Midwest, and West) or the following participant characteristics at enrollment: smoking status (ever or never), body mass index (BMI) (<25.0, 25.0–30.0, or ≥30.0 kg/$m^2$), and prior history of diabetes mellitus (yes or no), hypertension (yes or no), heart or circulation problems (yes or no), or atrial fibrillation (yes or no). We implemented a Wald statistic to test whether associations between air pollution and stroke types were statistically significantly different across strata of participant characteristics (Rothman et al., 2008).

We conducted all analyses in R version 3.5.1 with the "survival" package version 2.42–6 for conditional logistic regression. We considered a 2-sided $p$-value < 0.05 as statistically significant.

## 3. Results

Between enrollment and 2012, there were a total of 5,417 confirmed strokes among participants with no prior history of stroke, 4,300 (79.4%) of which were classified as ischemic, 924 (17.1%) of which were classified as hemorrhagic, and 193 (3.6%) of which were classified as of undetermined type (Table 1). At the time of stroke, participants had a mean age of 74.4 (SD: 7.3) years and were likely to have at enrollment a history of diabetes (10.9%), hypertension (50.0%), heart or circulation problems (26.2%), and atrial fibrillation (8.3%). Compared to participants experiencing hemorrhagic strokes, participants with ischemic stroke were more likely to be obese and have a history of diabetes, hypertension, and heart or circulation problems at enrollment (Table 1).

Concentrations of air pollutants were approximately normally distributed (Table S2 and Fig. S1). The IQR of air pollutants on the day of stroke hospitalization were 8.2 μg/$m^3$ for $PM_{2.5}$, 14.3 μg/$m^3$ for $PM_{10}$, 10.2 ppb for $NO_2$, 21.8 ppb for $NO_x$, 2.5 ppb for $SO_2$, and 20.6 ppb for $O_3$ (Table 2). The Pearson correlations among air pollutants were generally moderate or low ($r$<0.50), except for the correlation between $NO_2$ and $NO_x$ ($r$=0.81), and the correlation between $PM_{2.5}$ and $PM_{10}$ ($r$=0.57). Although estimated associations varied depending on the time period prior to stroke and air pollutant being considered, we found little evidence of an association between short-term changes in any of the six air pollutants and relative risks of total stroke, ischemic stroke, or undetermined type of stroke (Table 3). For example, an IQR (8.2 μg/$m^3$) increase in the 3-day moving average of $PM_{2.5}$ was associated with an OR of 0.96 (95% CI: 0.91, 1.02) for total stroke, 0.95 (95% CI: 0.89, 1.01) for ischemic stroke, and 0.93 (95% CI: 0.68, 1.27) for undetermined type of stroke. However, we found that $NO_2$ and $NO_x$ were associated with relative risk of hemorrhagic stroke with ORs of 1.24 (95% CI: 1.01, 1.52) and 1.18 (95% CI: 1.03, 1.34) per IQR increase in 3-day moving average of $NO_2$ and $NO_x$, respectively. We also examined the specific etiologies of ischemic stroke defined by TOAST classification and found no evidence of a positive association for any pollutant (Fig. 1).

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In sensitivity analyses, we estimated the association for air pollutants over 4-, 5-, and 6-day moving averages. Other than a positive association between hemorrhagic stroke and $NO_x$ at 4- and 5-day moving averages, there was no association between any stroke subtypes and longer moving average of any of the six air pollutants (Table S3).

In secondary analyses we evaluated whether the association varied across subgroups defined by participant characteristics and US census region. We observed no evidence of effect modification by age, smoking status, diabetes, hypertension, heart or circulation problems, and atrial fibrillation (Fig. 2). We did find some evidence that the association of total stroke with $PM_{2.5}$ or the association of hemorrhagic stroke with $PM_{2.5}$, $PM_{10}$, $NO_2$, or $NO_x$ was more pronounced among non-obese versus obese participants ($p<0.05$) (Fig. 2, Fig. S2 & Fig. S3). Although the short-term association of air pollutants with stroke varied by US census region ($p<0.05$), there was no consistent pattern of variation in associations (Table S4).

## 4. Discussion

Among clinically recognized strokes occurring in this nationwide prospective cohort of postmenopausal US women, we found no evidence of a positive association between day-to-day variation in air pollution and the relative risk of total stroke, ischemic stroke, or specific etiologies of ischemic stroke, but found that $NO_2$ and $NO_x$ were associated with higher relative risk of hemorrhagic stroke. We found the association between air pollution and hemorrhagic stroke was generally more pronounced among non-obese versus obese participants, but did not vary by other participant characteristics.

Our findings of no association between particulate pollutants ($PM_{2.5}$ and $PM_{10}$) and total stroke or stroke subtypes was consistent with a recent meta-analysis reporting that evidence of the association of $PM_{2.5}$ and $PM_{10}$ with hospital admission for total cerebrovascular diseases or ischemic or hemorrhagic stroke was heterogeneous and not statistically significant overall (Wang et al., 2014). The overall meta-analytic estimates per 10 $\mu g/m^3$ increase in $PM_{2.5}$ were 1.003 (95% CI: 0.995, 1.012) for total cerebrovascular disease, 1.013 (95% CI: 0.958, 1.070) for ischemic and 0.990 (95% CI: 0.955, 1.026) for hemorrhagic strokes. However, a number of studies have reported a positive association between $PM_{2.5}$ or $PM_{10}$ and relative risk of total stroke or ischemic stroke (Andersen et al., 2010; Dominici et al., 2006; Fisher et al., 2019; Wellenius et al., 2012; Wellenius et al., 2005). For example, Dominici et al (2006) used administrative data on 11.5 million Medicare enrollees aged ≥65 years reported that a 10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with 1.008 (95% CI: 1.003, 1.013) higher risk of hospitalization rate for total cerebrovascular disease (Dominici et al., 2006). In the context of the Health Professionals Follow-Up Study (HPFS), a nationwide prospective cohort study of US men, Fisher et al (2019) found that an IQR (14.46 $\mu g/m^3$) increase in $PM_{10}$ was associated with a relative risk of ischemic stroke of 1.26 (95% CI: 1.03, 1.55) among 727 strokes (Fisher et al., 2019). On the other hand, they observed negative associations between particulate pollutants and hemorrhagic stroke, although the associations were not statistically significant (Fisher et al., 2019).

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We also found no evidence of an association between gaseous pollutants and the relative risk of total stroke or ischemic stroke. On the other hand, we observed a positive association between $NO_2$ and $NO_x$ and hemorrhagic stroke. These findings were partially in agreement with a meta-analysis of 94 studies across 28 countries, which found $NO_2$, $SO_2$, and $O_3$ were all linked with higher risk of total stroke hospitalizations, but only $NO_2$ was positively associated with ischemic and hemorrhagic stroke (Shah et al., 2015). Our findings are also in line with a multi-city study by Ren et al (2013) (Chen et al., 2013), which showed that $NO_2$ was positively associated with higher risk of stroke mortality in China, where hemorrhagic stroke accounted for approximately 30% of the total stroke (Zhang et al., 2003), compared with 17% of all recognized strokes in this study. Our findings are also consistent with a large body of prior studies that failed to find a positive association between gaseous pollutants and total stroke or ischemic stroke (Butland et al., 2017; Chan et al., 2006; Mechtouff et al., 2012; Villeneuve et al., 2006). For example, a study in London, UK, found daily variation in levels of $NO_2$, $NO_x$, and $O_3$ were not associated with risk of total stroke or ischemic stroke using stroke register data with a total of 1,758 strokes (Butland et al., 2017). Likewise, analyses of data in Taipei, Taiwan (Chan et al., 2006), Edmonton, Canada (Villeneuve et al., 2006), and Lyon, France (Mechtouff et al., 2012) did not find any associations between $NO_2$, $NO_x$, or $O_3$ and relative risk of emergency hospital admissions for total stroke or ischemic stroke. Ischemic stroke itself is an etiologically diverse disease, and we further examined whether the association varied by ischemic stroke subtypes defined by the TOAST classification. We found no evidence of a positive association for any pollutant. Prior evidence of the association between ischemic stroke subtypes and air pollution is limited and inconsistent with some reporting a positive association between non-cardioembolic ischemic stroke (large artery atherosclerosis or small vessel occlusion) and $PM_{2.5}$, $NO_2$, or $O_3$ (Andersen et al., 2010; Henrotin et al., 2007; Wellenius et al., 2012), but not other studies (O'Donnell et al., 2011; Vivanco-Hidalgo et al., 2018). For example, Wellenius et al. (2012) performed a time-stratified case-crossover study among 1,750 Boston area stroke patients whose ischemic stroke events were confirmed by neurologists and estimated that an IQR ($6.4 \mu g/m^3$) increase in $PM_{2.5}$ was associated with a 1.24-fold (95% CI: 1.04, 1.48) higher risk of large artery ischemic stroke and 1.19-fold (95% CI: 1.02, 1.37) higher risk of small vessel stroke, but not with cardioembolic or other or undetermined ischemic stroke (Wellenius et al., 2012).

The heterogeneity in results across this and prior studies may be partly explained by differences in methods used for stroke ascertainment, exposure assessment, or statistical, approaches, as well as differences in the relative proportions of strokes of differing etiology or severity, differing population characteristics, and/or differing sources or levels of air pollution. For example, Andersen et al (2010) conducted a case-crossover design in Copenhagen, Denmark, and reported that ultrafine particles and $NO_x$ were strongly associated with mild strokes but not severe strokes, suggesting that the association may vary by stroke severity (Andersen et al., 2010). We found that the magnitude of some associations varied by US census region, suggesting that population characteristics, pollution profiles, or other characteristics that vary geographically may contribute to the heterogeneity of results of studies in the US or from across the globe. Similarly, Shah et al (2015), reported that the short-term association between air pollution and incident stroke were more pronounced in

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low- to middle-income countries versus high-income countries (Shah et al., 2015). We found no evidence that the association between air pollutants and stroke risk varied across subgroups defined by age, smoking status, and the presence of diabetes, hypertension, heart or circulation problems, and atrial fibrillation. However, we did find some suggestion that associations were more pronounced among non-obese participants. Future studies may further identify the individual, community, or geographic factors that confer particular susceptibility to air pollution and stroke.

Although the biological mechanisms are not yet clear, it is biologically plausible that transient increases in $NO_2$ or $NO_x$ could trigger hemorrhagic stroke. $NO_2$ (a component of $NO_x$) and $NO_x$ are both indicators of traffic-related air pollution, which represents a mixture of numerous diverse pollutants, such as particulate pollutants (Brook et al., 2007). $NO_2$ and other traffic-related air pollutants have been associated with endothelial dysfunction through increasing inflammation and oxidative stress (Brook et al., 2010; Münzel et al., 2018), which may increase susceptibility of brain vessels to rupture (Suwa et al., 2002). Traffic-related air pollutants have also been linked with acute vasoconstriction or hypertension (Brook et al., 2010; Yang et al., 2018), which might lead to hemorrhagic stroke. The associations observed for $NO_2$ and $NO_x$ may be also related to smaller relative error of exposure estimates for $NO_2$ and $NO_x$, which is supported by higher monitor-to-monitor temporal correlation for $NO_2$ than other air pollutants ($PM_{10}$, $SO_2$, and CO) in the contiguous US (Ito et al., 2005).

Our study has some important limitations related to exposure assessment. First, we used estimates of ambient air pollution at the address to represent participants' exposure. Although older individuals in the US tend to spend a majority of their time at or near their homes (Klepeis et al., 2001), the lack of information on individual time-activity patterns, housing characteristics, and penetration of ambient pollutants to indoor spaces suggest some degree of exposure misclassification. In addition, the lack of information on indoor pollution sources and exposure to traffic noise may result in residual confounding. However, the case-crossover design controls for all factors that are approximately stable over time, whether measured or unmeasured. Thus, under the assumption that indoor pollution levels, traffic noise, housing characteristics, and time-activity patterns vary only slowly over time (conditional on day of week, holidays, and month/year) or are unrelated to daily variation in ambient air pollution levels, the lack of information on these factors should not have led to biased effect estimates. Second, differences between the day of stroke symptom onset and day of hospitalization may have introduced some degrees of exposure misclassification, which may tend to bias the risk estimates toward the null. Third, the ordinary kriging method we used to estimate daily air pollutants likely reflects urban scale variation in pollutant levels, but may not fully capture microscale spatial gradients typical of urban environments. This limitation is somewhat mitigated by the use of the case-crossover study design to study the acute effects of transient changes in exposure within individuals. Under the assumption that this misclassification of exposure is nondifferential with respect to the outcome, our results may be biased towards the null hypothesis of no association.

Several additional potential limitations are worthy of mention. First, given the number of analyses we conducted, the positive findings for $NO_2$ and $NO_x$ with hemorrhagic stroke may reflect a chance finding. Second, our sample size of ~5,500 stroke cases, while large for a

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study with such detailed information on participants, may have limited our statistical power to detect small associations between air pollution and stroke, especially within stroke subtypes or TOAST classification of ischemic stroke. Third, the associations between air pollution and stroke may vary by age and sex (Dong et al., 2018), menopausal status, and other individual-level or community-level factors. Thus, our findings from this cohort of older women in the US may not be generalizable to younger women, men, other subgroups of the population, or populations in other countries. On the other hand, our study has several notable strengths, including a well-characterized study population, comprehensive characterization of daily levels of ambient air pollutants, updated participant addresses over time, a national scope, and adjudicated outcomes classified by stroke etiology.

## 5. Conclusions

In this cohort of post-menopausal women across the US we found little evidence to support the hypothesis that transient elevations in ambient $PM_{2.5}$, $PM_{10}$, $SO_2$, or $O_3$ were associated with higher relative risk of total stroke, ischemic stroke, or hemorrhagic stroke. Daily levels of $NO_2$ and $NO_x$ were likewise not associated with the relative risk of total stroke or ischemic stroke, although we did find that transient changes in $NO_2$ and $NO_x$ were associated with higher risk of hemorrhagic stroke with the strongest association observed with a 3-day moving average prior to stroke hospitalization. Additional studies are still needed to conclusively establish or refute the hypothesis that short-term changes in ambient air pollution levels are associated with higher risk of stroke.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Highlights

- We examined associations between air pollution and stroke subtypes among US women.
- Stroke cases were adjudicated by trained neurologists based on brain imaging.
- We observed no associations between daily air pollution exposures and ischemic stroke and its subtypes.
- We observed a positive association of $NO_2$ and NO with haemorrhagic stroke.

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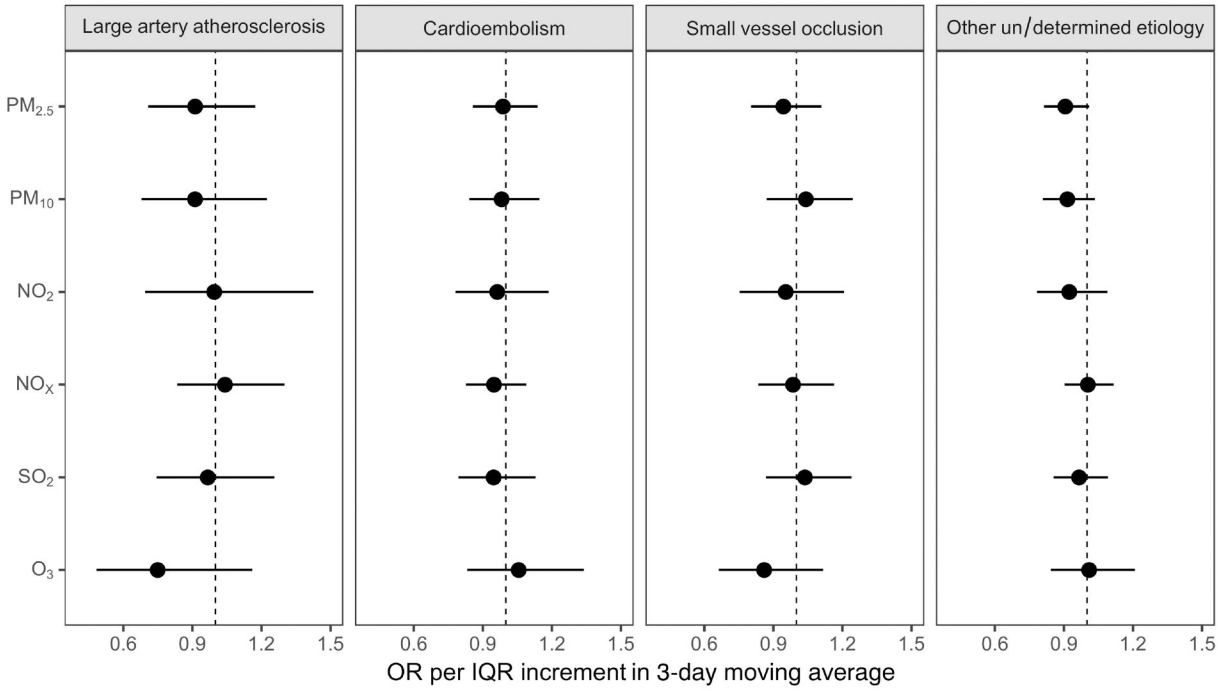


**Fig. 1. Odds ratios and 95% confidence intervals for short-term associations of TOAST classification of ischemic stroke with air pollution per interquartile range (IQR) increase in 3-day moving average in the Women's Health Initiative.**

Abbreviations: OR=odds ratio; IQR=interquartile range; $PM_{2.5}$= particulate matter with aerodynamic diameter ≤ 2.5μm; $PM_{10}$= particulate matter with aerodynamic diameter ≤ 10μm; $NO_2$=nitrogen dioxide; $NO_x$=nitrogen oxides; $SO_2$=sulphur dioxide; $O_3$=ozone.

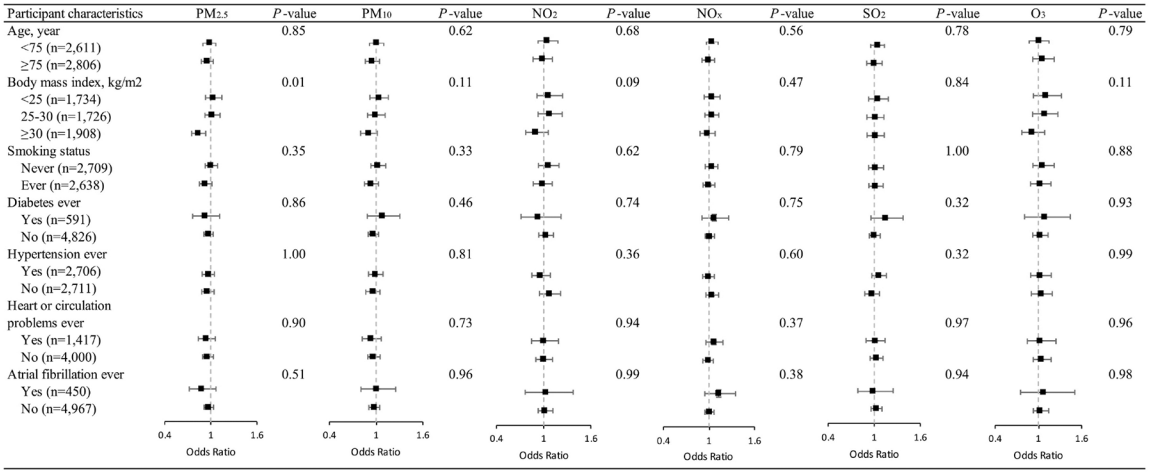


**Fig. 2. Odds ratios of total stroke associated with air pollution per interquartile range (IQR) increase in 3-day moving average stratified by participant characteristics in the Women's Health Initiative.**

Abbreviations: $PM_{2.5}$= particulate matter with aerodynamic diameter ≤ 2.5μm; $PM_{10}$= particulate matter with aerodynamic diameter ≤ 10μm; $NO_2$=nitrogen dioxide; $NO_x$=nitrogen oxides; $SO_2$=sulphur dioxide; $O_3$=ozone.



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**Table 1.**

Descriptive characteristics for women by stroke subtypes in the Women's Health Initiative.

| Characteristics | Total Stroke (n=5,417) | Ischemic Stroke (n=4,300) | Hemorrhagic Stroke (n=924) | Undetermined Type (n=193) |
|---|---|---|---|---|
| Age, year, mean±SD | 74.4±7.3 | 74.7±7.1 | 73.5±7.7 | 70.8±7.1 |
| Smoking status, n (%) | | | | |
| Never | 2,709 (50.0) | 2,152 (50.0) | 465 (50.3) | 92 (47.7) |
| Ever | 2,638 (48.7) | 2,093 (48.7) | 447 (48.4) | 98 (50.8) |
| Missing | 70 (1.3) | 55 (1.3) | 12 (1.3) | 3 (1.6) |
| BMI ($kg/m^2$), n (%) | | | | |
| <25 | 1,734 (32.0) | 1,303 (30.3) | 379 (41.0) | 52 (26.9) |
| 25–30 | 1,726 (31.9) | 1,421 (33.0) | 232 (25.1) | 73 (37.8) |
| ≥30 | 1,908 (35.2) | 1,536 (35.7) | 305 (33.0) | 67 (34.7) |
| Missing | 49 (0.9) | 40 (0.9) | 8 (0.9) | 1 (0.5) |
| Diabetes ever, n (%) | 591 (10.9) | 485 (11.3) | 63 (6.8) | 43 (22.3) |
| Hypertension ever, n (%) | 2,706 (50.0) | 2,214 (51.5) | 379 (41.0) | 113 (58.5) |
| Heart or circulation problems ever, n (%) | 1,417 (26.2) | 1,124 (26.1) | 220 (23.8) | 73 (37.8) |
| Atrial fibrillation ever, n (%) | 450 (8.3) | 352 (8.2) | 74 (8.0) | 24 (12.4) |
| US census region, n (%) | | | | |
| Northeast | 1,267 (23.4) | 1,025 (23.8) | 210 (22.7) | 32 (16.6) |
| South | 1,428 (26.4) | 1,130 (26.3) | 247 (26.7) | 51 (26.4) |
| Midwest | 1,186 (21.9) | 922 (21.4) | 215 (23.3) | 49 (25.4) |
| West | 1,536 (28.4) | 1,223 (28.4) | 252 (27.3) | 61 (31.6) |

Abbreviations: BMI=body mass index; SD=standard deviation.

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**Table 2.**

Air pollutant concentrations on the day of stroke onset, and Pearson correlation coefficients between air pollutants.

| Air pollutants | Mean±SD | IQR | Pearson correlation | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | $PM_{2.5}$ | $PM_{10}$ | $NO_2$ | $NO_x$ | $SO_2$ | $O_3$ |
| $PM_{2.5}$ (μg/$m^3$) | 12.4 ± 7.1 | 8.2 | 1.00 | 0.57 | 0.44 | 0.35 | 0.30 | 0.20 |
| $PM_{10}$ (μg/$m^3$) | 25.3 ± 12.1 | 14.3 | | 1.00 | 0.30 | 0.21 | 0.19 | 0.36 |
| $NO_2$ (ppb) | 15.4 ± 8.0 | 10.2 | | | 1.00 | 0.81 | 0.50 | −0.14 |
| $NO_x$ (ppb) | 27.8 ± 24.6 | 21.8 | | | | 1.00 | 0.50 | −0.14 |
| $SO_2$ (ppb) | 4.0 ± 2.7 | 2.5 | | | | | 1.00 | −0.08 |
| $O_3$ (ppb) | 37.9 ± 15.3 | 20.6 | | | | | | 1.00 |

Abbreviations: SD=standard deviation; IQR=interquartile range; $PM_{2.5}$= particulate matter with aerodynamic diameter ≤ 2.5μm; $PM_{10}$= particulate matter with aerodynamic diameter ≤ 10μm; $NO_2$=nitrogen dioxide; $NO_x$=nitrogen oxides; $SO_2$=sulphur dioxide; $O_3$=ozone.

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**Table 3.**

Odds ratios and 95% confidence intervals for short-term associations between interquartile range increases in air pollutants and relative risk of stroke or stroke subtypes among participants in the Women's Health Initiative.

| Air pollutants | Days of moving average | Total stroke (n=5,417) | Ischemic stroke (n=4,300) | Hemorrhagic stroke (n=924) | Undetermined type (n=193) |
|---|---|---|---|---|---|
| $PM_{2.5}$ | 1 | 0.98 (0.93, 1.02) | 0.97 (0.92, 1.02) | 1.02 (0.92, 1.14) | 0.95 (0.75, 1.21) |
| | 2 | 0.97 (0.92, 1.02) | 0.96 (0.91, 1.02) | 1.04 (0.91, 1.17) | 0.91 (0.68, 1.22) |
| | 3 | 0.96 (0.91, 1.02) | 0.95 (0.89, 1.01) | 1.04 (0.91, 1.20) | 0.93 (0.68, 1.27) |
| $PM_{10}$ | 1 | 0.98 (0.94, 1.03) | 0.98 (0.93, 1.03) | 1.02 (0.90, 1.15) | 0.92 (0.72, 1.18) |
| | 2 | 0.97 (0.92, 1.03) | 0.97 (0.91, 1.04) | 1.02 (0.89, 1.17) | 0.84 (0.62, 1.13) |
| | 3 | 0.98 (0.91, 1.04) | 0.97 (0.90, 1.05) | 0.99 (0.84, 1.16) | 0.96 (0.69, 1.33) |
| $NO_2$ | 1 | 1.00 (0.94, 1.07) | 0.99 (0.92, 1.06) | 1.11 (0.96, 1.30) | 0.89 (0.66, 1.19) |
| | 2 | 1.02 (0.94, 1.10) | 0.99 (0.91, 1.08) | 1.18 (0.98, 1.41) | 0.85 (0.60, 1.22) |
| | 3 | 1.02 (0.93, 1.11) | 0.98 (0.88, 1.08) | **1.24 (1.01, 1.52)** | 0.94 (0.63, 1.39) |
| $NO_x$ | 1 | 1.00 (0.96, 1.05) | 1.00 (0.96, 1.05) | 1.06 (0.96, 1.17) | 0.88 (0.72, 1.06) |
| | 2 | 1.00 (0.96, 1.05) | 1.00 (0.94, 1.05) | 1.11 (0.99, 1.25) | 0.79 (0.62, 1.00) |
| | 3 | 1.02 (0.96, 1.08) | 1.00 (0.94, 1.07) | **1.18 (1.03, 1.34)** | 0.82 (0.63, 1.06) |
| $SO_2$ | 1 | 1.00 (0.95, 1.05) | 1.00 (0.95, 1.06) | 0.96 (0.86, 1.08) | 1.10 (0.90, 1.36) |
| | 2 | 1.01 (0.96, 1.07) | 1.00 (0.94, 1.07) | 1.05 (0.92, 1.20) | 0.97 (0.75, 1.27) |
| | 3 | 1.02 (0.96, 1.09) | 0.99 (0.92, 1.07) | 1.12 (0.96, 1.31) | 1.11 (0.83, 1.49) |
| $O_3$ | 1 | 0.99 (0.92, 1.07) | 1.00 (0.92, 1.09) | 0.96 (0.80, 1.15) | 1.01 (0.68, 1.51) |
| | 2 | 1.03 (0.94, 1.12) | 1.03 (0.93, 1.13) | 0.99 (0.81, 1.21) | 1.24 (0.76, 2.02) |
| | 3 | 1.03 (0.94, 1.14) | 1.03 (0.92, 1.15) | 1.00 (0.80, 1.26) | 1.29 (0.77, 2.18) |

Abbreviations: $PM_{2.5}$= particulate matter with aerodynamic diameter ≤ 2.5μm; $PM_{10}$= particulate matter with aerodynamic diameter ≤ 10μm; $NO_2$=nitrogen dioxide; $NO_x$=nitrogen oxides; $SO_2$=sulphur dioxide; $O_3$=ozone.