Associations of Fine and Ultrafine Particulate Air Pollution With Stroke Mortality in an Area of Low Air Pollution Levels

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Background and Purpose—Daily variation in outdoor concentrations of inhalable particles (PM$_{10}$ <10 µm in diameter) has been associated with fatal and nonfatal stroke. Toxicological and epidemiological studies suggest that smaller, combustion-related particles are especially harmful. We therefore evaluated the effects of several particle measures including, for the first time to our knowledge, ultrafine particles (<0.1 µm) on stroke.

Methods—Levels of particulate and gaseous air pollution were measured in 1998 to 2004 at central outdoor monitoring sites in Helsinki. Associations between daily levels of air pollutants and deaths caused by stroke among persons aged 65 years or older were evaluated in warm and cold seasons using Poisson regression.

Results—There was a total of 1304 and 1961 deaths from stroke in warm and cold seasons, respectively. During the warm season, there were positive associations of stroke mortality with current- and previous-day levels of fine particles (<2.5 µm, PM$_{2.5}$) (6.9%; 95% CI, 0.8% to 13.8%; and 7.4%; 95% CI, 1.3% to 13.8% for an interquartile increase in PM$_{2.5}$) and previous-day levels of ultrafine particles (8.5%; 95% CI, −1.2% to 19.1%) and carbon monoxide (8.3; 95% CI, 0.6 to 16.6%). Associations for fine particles were mostly independent of other pollutants. There were no associations in the cold season.

Conclusions—Our results suggest that especially PM$_{2.5}$, but also ultrafine particles and carbon monoxide, are associated with increased risk of fatal stroke, but only during the warm season. The effect of season might be attributable to seasonal differences in exposure or air pollution mixture. (Stroke. 2007;38:918-922.)

Key Words: air pollution ■ epidemiology ■ mortality ■ particulate matter ■ stroke

A

association between daily variation in ambient particulate matter and all-cause mortality has been demonstrated in epidemiological studies.1–3 Several studies also suggest that fine particles (<2.5 µm in diameter; PM$_{2.5}$) are more strongly associated with mortality than inhalable particles (<10 µm; PM$_{10}$) or total suspended particles.4–6 Only a single short-term study has analyzed associations between ultrafine particles (<0.1 µm) and mortality.5 Finer-size fractions of particulate air pollution originate mostly from combustion, and it has been suggested that these particles are especially harmful.7,8 Particularly ultrafine particles have been found capable of inducing harmful cellular changes in toxicological studies.9 Compared with other particle fractions, ultrafine particles have better deposition efficiency and higher number and area concentration.10 They also have ability to enter directly from lungs into systemic circulation.11

It has been hypothesized that the harmful effects of particulate air pollution on cardiovascular morbidity and mortality proceed through inflammation.12 Levels of ambient particulate matter have been associated with increased blood pressure and plasma viscosity,13–15 which are indicators of hemodynamic disturbances, and increased circulatory levels of inflammatory markers.14 These are also known risk factors for stroke.16 Stroke patients may also form a susceptible subgroup for other effects of air pollution, including pneumonia.5,17

In previous studies, total suspended particles and PM$_{10}$ have been associated with increased mortality and hospital admissions for stroke.18–22 However, there is no information on the effects of ultrafine particles on stroke, and only 2 studies on the effects of PM$_{15}$ on cerebrovascular diseases.23,24 The earlier studies on the associations between particulate air pollution and stroke mortality mainly have been conducted in Asia, where concentrations are relatively high.18,19 We therefore investigated whether fine and ultrafine particles are associated with increased stroke mortality among the elderly in Helsinki, Finland, an area with relatively low levels of air pollution.
Materials and Methods

We obtained mortality data for the residents of Helsinki metropolitan area (~1 million inhabitants) from Statistics Finland. The annual death rate for all strokes is 5700/100 000 inhabitants. Deaths with ICD-10 codes I60-I61 and I63-I64 as the underlying cause of death were considered as fatal strokes, and code I63 was considered as fatal ischemic stroke. We limited our data to persons aged 65 years or older, because there were only 569 deaths in the younger age group. In preliminary analyses, there were no associations between air pollutants and stroke in the younger age group.

Particle size distribution was measured with a differential mobility particle sizer of the University of Helsinki as described earlier.\textsuperscript{25} Particles <0.1 μm in diameter were counted as ultrafine particles. In the beginning of the study period, ultrafine particles were measured at a bank hill Siltavuori, a 20-meter-high peninsula surrounded by urban areas, including downtown Helsinki, at the distance of few hundred meters. In March 2001, the measurements started on a hilltop in Kumpula, located ~3 km northeast of Siltavuori. The measurements were conducted on the fourth floor of an office building (20 meters high). At a distance of 100 m, there is a major highway.

Particle mass measurements were performed using β-attenuation method (FH 62 L-R; Eberline Instruments). Measurement site for PM\textsubscript{10}, PM\textsubscript{2.5}, NO\textsubscript{2}, and carbon monoxide (CO) was the same. Monitors were first located (until the end of 2001) in a park 14 meters from the closest road. Later the monitoring was conducted at a sports area, where the nearest busy road was 80 meters away from the site. We obtained mass of coarse particles (PM\textsubscript{10} to PM\textsubscript{1.3}) by subtracting daily levels of PM\textsubscript{2.5} from PM\textsubscript{10}. Ozone was measured at a site representing background concentrations in the metropolitan Helsinki area. Missing values were replaced with data from measurement sites that were most identical with the primary site.

The associations between air pollutants and stroke mortality were examined with Poisson regression. We used penalized thin-plate regression splines in the generalized additive models framework to take into account possible nonlinear confounders.\textsuperscript{26} Modeling was implemented using R software and mgcv 1.3-7 procedure.\textsuperscript{27}

In the analyses, we used 24-hour median concentrations for ultrafine particles because of the rightly skewed distribution. Average 24-hour concentrations were used for other pollutants except for O\textsubscript{3} and CO, for which 8-hour moving averages were used. Lag 0 was defined as the 24-hour period from midnight to midnight of the day of death, lag 1 was defined as the preceding 24-hour period, and so on.

We built first the basic model without air pollution using all the data. We also built separate basic models for the warm (May to September) and cold (October to April) season. The stratification was based on the variation in temperature and ultrafine particle concentration.

We selected potential confounders based on the literature. Time trend was modeled with penalized spline smoothing (always in the model). Dummy variables for weekdays and general holidays were included when necessary (P <0.25). To control for confounding effects of meteorological variables, current day temperature, relative humidity, and barometric pressure were always in the models. The covariates for mean temperature and relative humidity of the previous 3 days were included to represent slower effects of meteorology, when P<0.25. To take into account one measurement site change for ultrafine particles and PM\textsubscript{1.3}, dummy variables were added into models.

Partial autocorrelogram of the residuals and visual inspection of the smoothed curves were checked to avoid over-smoothing and to define the amount of autocorrelation in the residuals.

Because all air pollution monitoring sites were located in the city of Helsinki, but mortality data came from Helsinki metropolitan area, analyses were also performed for the city of Helsinki only. Other sensitivity analyses were also conducted. We used an alternative definition of the warm season (April to July) to find out if the higher O\textsubscript{3} levels during this period had an effect on the results. We controlled temperature with the same lag as the pollutant concentration in the models. We also performed analyses with a month and year dummy variables to control time trend instead of smoothed trend variable. Finally, to exclude the effect of high pollution days, we used the 98th percentile as the cut point for each pollutant.

Results

There were a total of 3265 deaths (0 to 6 per day) from stroke, 1304 in warm and 1961 in cold season. Data of daily pollutant concentrations and meteorological variables and their correlation with PM\textsubscript{2.5} and ultrafine particles by season is shown in Table 1.

No consistent associations were found between mortality and air pollution when analyzing the dataset for the whole year (data not shown) or for the cold season. During the warm season, increases in PM\textsubscript{2.5} were significantly associated with increased stroke mortality at lags 0 and 1, and ultrafine particles borderline significantly at lag 1 (Table 2). For PM\textsubscript{10}, we found a significant association at lag 0. Of gaseous pollutants CO had one significant estimate with stroke at lag 1. We performed also analyses for 5-day mean of lags 0 to 4. The estimates were lower than in the analyses using single-day lags, and there were no significant associations.

When PM\textsubscript{2.5} and ultrafine particles were analyzed in the same model, the associations were slightly reduced. Percent increases in stroke mortality were now 6.6% (95% CI, −0.5% to 14.2%) and 4.8% (95% CI, −1.7% to 11.7%) for lags 0 and 1 of PM\textsubscript{2.5}, and 0.1% (95% CI, −10.1% to 11.4%) and 6.6% (95% CI, −3.8% to 18.1%) for the respective lags of ultrafine particles. When analyzing PM\textsubscript{2.5} and coarse particles in the same model the increase in mortality at lag 0 was 6.5% (95% CI, −0.9 to 14.5) and at lag 1 7.4% (95% CI, 0.5 to 14.9).

Coarse particles were not significantly associated with mortality. Estimates of PM\textsubscript{2.5} reduced slightly when CO was analyzed in the same model. Now percent increases in mortality at lags 0 and 1 were 6.3% (95% CI, −0.3% to 13.4%) and 6.1% (95% CI, −0.1% to 12.7%) for PM\textsubscript{2.5}, and 2.9% (95% CI, −5.4% to 12.0%) and 6.5% (95% CI, −2.0% to 15.8%) for CO, respectively. Analyzing ultrafine particles with CO together the observed effect estimates at lag 1 were 6.2% (95% CI, −3.6 to 17) and 5.9% (95% CI, −2.3 to 14.8).

There were 897 and 1373 deaths from ischemic stroke in the warm and cold seasons, respectively. The associations of PM\textsubscript{2.5} and ultrafine particles with ischemic stroke mortality during the warm season were stronger than for total stroke mortality. At lags 0 and 1, percent increases in mortality were now 11.0% (95% CI, 2.9 to 19.7) and 9.9% (95% CI, 2.7 to 17.7) for an interquartile increase in PM\textsubscript{2.5}, and 6.5% (95% CI, −5.6 to 20.1) and 16.6% (95% CI, 3.8 to 31.1) for ultrafine particles, respectively. Coarse particles had significant association at lag 1 (16.2%; 95% CI, 0.6 to 34.1) and CO at lag 3 (10.7%; 95% CI, 1.5 to 20.9).

The use of month and year dummy variables instead of trend variable increased the estimate for PM\textsubscript{2.5} at lag 0. The percent increase of stroke mortality at lag 0 was now 8.9% (95% CI, 1.5 to 11.8) for an interquartile increase in PM\textsubscript{2.5}, and 7.1% (95% CI, 0.4 to 14.3) at lag 1. There was an increase also in the estimates for ultrafine particles, the percent increases in mortality at lag 0 was 0.9% (95% CI, −9.2 to 12.2) and at lag 1 11.0% (95% CI, 0.1 to 23.1). For CO, the percent increase in mortality at lag 1 decreased and was nonsignificant (6.4%; 95% CI, −2.7 to 20.2).

In further sensitivity analyses, when using the 98th percentile cut point for PM\textsubscript{2.5}, an interquartile increase in PM\textsubscript{2.5} was associated with 1.8% (95% CI, −6.3 to 10.3) and 11.2%
Discussion

In the present study, daily variations in the levels of fine, but not coarse, particles were significantly associated with fatal stroke among persons older than 65 years in Helsinki, Finland. There was also some evidence of an association for ultrafine particles. Associations of PM$_{2.5}$ were robust and independent of other pollutants. Associations of ultrafine particles and CO were less consistent and depended on each other. This is the first study to examine the association between stroke and ultrafine particles.

Particulate air pollution may increase stroke mortality through different mechanisms. Fine and ultrafine particles cause pulmonary inflammation and oxidative stress. Local inflammation contributes to a systemic inflammatory state, which in turn is capable of activating hemostatic pathways, deteriorating vascular function, and possibly promoting rupture of atherosclerotic plaques.$^{12,28}$ Known risk factors for stroke, such as elevated blood pressure, blood fibrinogen concentration, and plasma viscosity, have been associated with particulate air pollution.$^{13,15,29}$

Patients who have experienced a stroke may also form a susceptible subgroup to other effects of particulate air pollution, including increased risk of pneumonia.$^{17}$ Particulate air pollution appears to be able to trigger new cerebrovascular events, but it may also increase the risk of death among stroke patients through recurrent cerebrovascular events or other complications. It should be noted that a major fraction of strokes are not fatal. Studies combining fatal and nonfatal outcomes are needed to increase the understanding on the mechanisms of action of particulate matter on stroke.

Positive associations occurred only during the warm season. The difference cannot be explained by particle concentration variations, because outdoor concentrations were slightly lower during the warm season. A possible explanation is greater exposure to particles indoors during the warm season due to higher ventilation rates,$^{30}$ especially people living in houses with no air conditioning who have lower exposure to air pollutants in winter than in summer.$^{31}$ There is also greater exposure outdoors during the warm season because of more active lifestyle. This may also increase the accuracy of exposure assessment during the warm season because the data are based on outdoor measure-

(95% CI, 3.2 to 19.8) increase in mortality at lags 0 and 1, respectively, and for ultrafine particles 1.1% (95% CI, −9.3 to 12.8) and 10.7% (95% CI, −0.3 to 22.9) at lags 0 and 1, respectively. The effect estimates for other pollutants did not change. When the same day lag was used for temperature and PM$_{2.5}$, the increase in stroke mortality at lags 0 and 1 was 6.9% (95% CI, 0.4 to 13.8) and 6.1% (95% CI, 0.0 to 12.6), respectively, for an interquartile increase in PM$_{2.5}$. In the analyses for the city of Helsinki alone, the effect estimates for pollutants did not change. Ozone did not have effect on mortality even though the season stratification was changed.

### Table 1

<table>
<thead>
<tr>
<th>Days (N)</th>
<th>Min</th>
<th>25%</th>
<th>50%</th>
<th>75%</th>
<th>Max</th>
<th>Correlation With PM$_{2.5}$</th>
<th>Correlation With UFP</th>
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<td>1116</td>
<td>6640</td>
<td>8986</td>
<td>13 970</td>
<td>52 800</td>
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<td>PM$_{2.5}$, μg/m$^3$</td>
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<td>1.1</td>
<td>5.6</td>
<td>8.2</td>
<td>12.3</td>
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<td>1454</td>
<td>3.1</td>
<td>11.5</td>
<td>16.3</td>
<td>25.3</td>
<td>136.7</td>
<td>0.70</td>
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<td>PM$_{2.5-10}$, μg/m$^3$</td>
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<td>0.0</td>
<td>4.2</td>
<td>6.7</td>
<td>12.5</td>
<td>101.4</td>
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<td>CO, mg/m$^3$ 8-hour mean</td>
<td>1482</td>
<td>0.1</td>
<td>0.4</td>
<td>0.5</td>
<td>0.6</td>
<td>2.4</td>
<td>0.32</td>
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<td>O$_3$, μg/m$^3$, 8-hour mean</td>
<td>1485</td>
<td>1.6</td>
<td>44.0</td>
<td>55.8</td>
<td>68.8</td>
<td>130.6</td>
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<td>5.9</td>
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<td>35.6</td>
<td>95.6</td>
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<td>0.7</td>
<td>3.9</td>
<td>14.7</td>
<td>−0.07</td>
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<td>Relative humidity, %</td>
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<td>41.0</td>
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<td>87.0</td>
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<td>99.0</td>
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<td>1002</td>
<td>1011</td>
<td>1 020</td>
<td>1 052</td>
<td>0.20</td>
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<td>UFP, 1/cm$^3$</td>
<td>1048</td>
<td>2240</td>
<td>6121</td>
<td>7587</td>
<td>11 100</td>
<td>23 070</td>
<td>0.30</td>
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<td>PM$_{2.5}$, μg/m$^3$</td>
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<td>1.1</td>
<td>5.3</td>
<td>7.8</td>
<td>11</td>
<td>41.5</td>
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<td>PM$_{10}$, μg/m$^3$</td>
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<td>3.3</td>
<td>12.3</td>
<td>16.5</td>
<td>22.1</td>
<td>67.4</td>
<td>0.81</td>
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<td>PM$_{2.5-10}$, μg/m$^3$</td>
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<td>0.0</td>
<td>6.1</td>
<td>8.4</td>
<td>11.8</td>
<td>42.0</td>
<td>0.42</td>
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<tr>
<td>CO, mg/m$^3$ 8-hour mean</td>
<td>1071</td>
<td>0.1</td>
<td>0.3</td>
<td>0.4</td>
<td>0.5</td>
<td>1.1</td>
<td>0.24</td>
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<tr>
<td>O$_3$, μg/m$^3$, 8-hour mean</td>
<td>1068</td>
<td>16.3</td>
<td>58.6</td>
<td>71.5</td>
<td>84.1</td>
<td>159.1</td>
<td>0.44</td>
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<tr>
<td>NO$_2$, μg/m$^3$</td>
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<td>3.4</td>
<td>19.3</td>
<td>25.2</td>
<td>32.7</td>
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<td>0.47</td>
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<td>Temperature, °C</td>
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<td>14.5</td>
<td>17.2</td>
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<td>84.0</td>
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<td>1007</td>
<td>1012</td>
<td>1 018</td>
<td>1 036</td>
<td>0.10</td>
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</tbody>
</table>

Min indicates minimal value; 25%, the first quartile value; 50%, median value; 75%, third quartile value; Max, maximum value; UFP, ultrafine particles.
Stronger associations between PM10 and mortality may explain our results. For PM2.5, clear seasonal patterns. It is unclear, what is the role of seasonal differences in the urban air pollution mixture, mainly from traffic. In contrast, the longitudinal correlation between outdoor and personal PM2.5 has been shown to be high in Helsinki.

Third, we had rather small number of cases for seasonal analyses, which widened the confidence intervals and calls for caution when interpreting the magnitudes of estimates.

In conclusion, we found an increase in stroke mortality among the elderly in association with daily variations in PM2.5, and to a lesser extent with ultrafine particles and CO. The associations for fine particles were independent of other pollutants. Our results suggest that the levels of combustion originating particles rather than coarse particles explain the association between particulate matter and stroke. Thus, regulatory efforts should be focused on reducing of emissions of combustion particles. The monitoring of outdoor concentrations of the smaller size fractions should also be considered.

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**Disclosures**

None.

**References**


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