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Stroke and Long-Term Exposure to Outdoor Air Pollution From Nitrogen Dioxide

A Cohort Study

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Background and Purpose—Years of exposure to tobacco smoke substantially increase the risk for stroke. Whether long-term exposure to outdoor air pollution can lead to stroke is not yet established. We examined the association between long-term exposure to traffic-related air pollution and incident and fatal stroke in a prospective cohort study.

Methods—We followed 57 053 participants of the Danish Diet, Cancer and Health cohort in the Hospital Discharge Register for the first-ever hospital admission for stroke (incident stroke) between baseline (1993–1997) and 2006 and defined fatal strokes as death within 30 days of admission. We associated the estimated mean levels of nitrogen dioxide at residential addresses since 1971 to incident and fatal stroke by Cox regression analyses and examined the effects by stroke subtypes: ischemic, hemorrhagic, and nonspecified stroke.

Results—Over a mean follow-up of 9.8 years of 52 215 eligible subjects, there were 1984 (3.8%) first-ever (incident) hospital admissions for stroke of whom 142 (7.2%) died within 30 days. We detected borderline significant associations between mean nitrogen dioxide levels at residence since 1971 and incident stroke (hazard ratio, 1.05; 95% CI, 0.99–1.11, per interquartile range increase) and stroke hospitalization followed by death within 30 days (1.22; 1.00–1.50). The associations were strongest for nonspecified and ischemic strokes, whereas no association was detected with hemorrhagic stroke.

Conclusions—Long-term exposure to traffic-related air pollution may contribute to the development of ischemic but not hemorrhagic stroke, especially severe ischemic strokes leading to death within 30 days. **(*Stroke*. 2012;43:00-00.)**

Key Words: air pollution ■ hemorrhagic stroke ■ ischemic stroke ■ stroke ■ traffic

Outdoor air pollution is an ubiquitous and amendable exposure, which was linked to ischemic heart disease.[1] Early epidemiological data linking air pollution to stroke morbidity and mortality come from 2 short episodes of extreme high levels of air pollution in London in December 1952[2] and New York City in November 1966.[3] More recently, studies have shown that at also at moderate and low air pollution levels, several days' exposures to elevated air pollution levels can trigger death[4–6] as well as hospitalization[7–14] from stroke, except in 1 study.[15] These studies also offer rather consistent evidence for an effect on ischemic but not hemorrhagic stroke[7,9,10,12–14] with the lack of effect on hemorrhagic stroke observed in hospitalization data during the London 1952 smog episode.[16] However, it is still not clear whether exposure to everyday levels of air pollution over years, decades, or lifetimes promotes the development of stroke in the manner that long-varying exposure to tobacco smoke does. Current evidence is sparse and conflicting,[17–23] in part due to the lack of cohort data with individual-level assessment of air pollution exposure. A cohort of American women showed an association between long-term exposure to air pollution and stroke incidence,[17] whereas American[18] and Norwegian[19] cohorts failed to detect an association with stroke mortality. Survival after stroke was significantly reduced in those living in areas with high levels of traffic-related air pollution in a recent London-based study.[20] An English ecological study showed excess risk of stroke mortality and stroke hospital admissions in areas with high levels of air pollution,[21] but a similar Canadian study failed to link emergency department admissions for stroke to air pollu-

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tion.[22] None of the mentioned studies[17–22] distinguished between ischemic and hemorrhagic stroke. A single study found no significant associations with chronic exposure to air pollution in a case–control study of ischemic stroke hospitalizations in Sweden.[23] Better understanding of the link between air pollution and stroke is imperative for successful targeting of preventive efforts, which may have a significant impact on stroke burden.

We studied the association between traffic-related air pollution levels assessed as modeled levels of nitrogen dioxide (NO_2) at the residence since 1971 and the risk for incident and fatal stroke in a Danish cohort and separately for ischemic and hemorrhagic stroke.

Methods

Design and Health Outcome

The Danish Diet, Cancer, and Health cohort[24] recruited 57 053 people from Copenhagen or Aarhus, free of cancer, and aged 50 to 65 years in 1993 to 1997 who completed a questionnaire on diet, health, education, occupation, and lifestyle. We linked the cohort to the Danish National Hospital Discharge Register to identify hospital admissions using primary discharge diagnoses for stroke (International Classification of Diseases, 10th Revision: I60, I63–64), chronic obstructive pulmonary disease (J40–44), and asthma (J45–46); the Central Population Registry to obtain date of death or emigration and residential address history (1971–2006); and the Danish Address Database to obtain geographical coordinates. The incidence of stroke was defined as the first-ever hospital admission between baseline (1993–1997) and June 27, 2006. Fatal strokes were defined as the subset of hospitalized patients who died within 30 days of hospitalization and not confirmed by death certificates. Intracerebral hemorrhage (I60), ischemic stroke (I63), and unspecified stroke (I64) were considered separately. Comorbidity with respiratory disease was defined as a hospital admission for chronic obstructive pulmonary disease or asthma before stroke admission.

Exposure Assessment

The Danish geographic information system-based air pollution and human exposure modeling system (AirGIS)[25] (described in an online Supplement; http://stroke.ahajournals.org) was used to model outdoor concentrations of NO_2 at the residential addresses of cohort participants since 1971 of the cohort members with an ≥80% residential history (97.6% of the cohort). Missing values due to missing address or missing geographical coordinates were substituted by the levels calculated for the preceding address or, when the first address was missing, for the subsequent address. We thus obtained a complete series of annual mean NO_2 concentrations at the residential addresses of each cohort member since 1971 with a time-weighted mean of NO_2 levels since 1971 until censoring/event date as the main exposure proxy.

We defined several alternative proxies of long-term exposure to air pollution at the baseline address (1993–1997; online Supplemental material): 1-year mean modeled NO_2 concentration, the presence of a major road (density ≥10 000 vehicles/day) within a 50-m radius of the residence, and traffic load (total kilometers driven by vehicles) within a 100-m radius.

Statistical Methods

We used a Cox proportional hazards model to study the association between stroke incidence and exposure to NO_2 with age as the underlying time, left truncation at age at recruitment, event defined at age of stroke admission, and right censoring at age at stroke admission, death, emigration, or June 27, 2006, whichever came first. The effects of exposure to NO_2 on different types of stroke were evaluated in separate models with adjustment for a priori-defined confounders: (1) age; (2) also including gender, smoking status (current/previous/never), smoking duration (years), smoking intensity (g/day), indicator for environmental tobacco smoke at home or work for minimum 4 hours/day, body mass index, educational level (<8/8–10/≥10 years), indicator of sports activity in leisure time, intensity of sports activity (hours/week), indicator of alcohol consumption, alcohol consumption (g/day), fruit and vegetable intake (g/day), and fat intake (g/day); and (3) also including an indicator of having diagnoses or taking medication for hypertension, hypercholesterolemia, or diabetes. Information on the prevalence of vascular risk factors (hypertension, hypercholesterolemia, and diabetes) as well as other confounders at baseline was self-reported through the questionnaire administered at the recruitment into the cohort. Smoking intensity was calculated by equating a cigarette to 1 g, a cheroot or a pipe 3 g, and a cigar 5 g of tobacco. Mean of NO_2 levels since 1971 was log-transformed and modeled as time-dependent variables with estimates reported per interquartile range increase corresponding to a 43% increase in exposure. The potential effect modifiers of an association between NO_2 and stroke incidence were evaluated by introducing interaction terms into the model and tested by the Wald test. The results are presented as hazard ratios with 95% CIs estimated in R statistical software 2.9.0 (library Survival), whereas exposure–response curves were estimated and visualized using restricted cubic splines (library Design).

Results

Of the 57 053 cohort members, we excluded 571 with cancer before baseline, 496 admitted to the hospital for stroke before baseline, 449 with self-reported stroke at baseline, 2050 with missing information on covariates, and 1272 with <80% of residential address history available (1971 to end of follow-up). Of the 52 215 participants, 1984 (3.8%) were admitted to the hospital for stroke for the first time between baseline and June 27, 2006, over an average follow-up of 9.8 years with an incidence rate of 3.9 cases per 1000 person-years. Of 1984 incident strokes, 1010 (50.9%) were nonspecified, 629 (31.7%) ischemic, and 345 (17.4%) hemorrhagic, whereas 142 (7.2%) participants died within 30 days of admission. Of these, 29 (20.4%) had nonspecified, 23 (16.2%) ischemic, and 90 (63.4%) hemorrhagic stroke.

Patients with stroke were more likely to be men; obese; current or previous smokers; exposed to environmental tobacco smoke; have hypertension, hypercholesterolemia, or diabetes; drink more alcohol; consume more fat and less fruit; and have <10 years of education (Table 1; Supplemental Table I); and had higher air pollution levels (Supplemental Table II) than the whole cohort. Patients with fatal strokes (Supplemental Table II) had similar prevalence of vascular risk factors as all patients with stroke (Table 1), but were older, less educated, and smoked and drank more. Consistent for all 4 proxies of exposure to air pollution, patients with incident stroke had higher levels of air pollution than the whole cohort, and patients with fatal stroke had the highest levels (Supplemental Table II).

We found significant association between NO_2 and stroke incidence (hazard ratio, 1.12; 95% confidence interval, 1.06–1.18 per interquartile range) and fatal stroke (1.33; 1.09–1.62) in crude models, which attenuated to borderline significant associations (1.05; 0.99–1.11 and 1.22; 1.00–1.50, respectively) in fully adjusted models (Table 2) showing linear exposure–response relationship (Figure). The associations with the ischemic stroke and nonspecified stroke were similar in magnitude to those for all strokes, whereas a negative association was detected with hemorrhagic stroke. Similarly for fatal stroke, the strongest associations were

Table 1. Characteristics of Diet, Cancer and Health Cohort (n=52 215) by Incident Stroke Status at Follow-Up

Baseline Cohort Covariates From Questionnaire	Total (n=52 215)	Stroke (n=1984)
Median (10th–90th percentile) age, y	56.2 (51.2–63.2)	58.5 (51.8–63.9)
Older than 56 y at baseline, no. (%)	26 650 (51.0)	1 297 (65.4)
Males, no. (%)	24 801 (47.5)	1 155 (58.2)
Never smoked, no. (%)	18 652 (35.7)	481 (24.2)
Previously smoked, no. (%)	14 926 (28.6)	496 (25.0)
Currently smoke, no. (%)	18 637 (35.7)	1007 (50.8)
Median (10th–90th percentile) smoking duration, y	32.0 (10.0–44.0)	36.0 (15.0–44.0)
Median (10th–90th percentile) smoking intensity, g/d	15.0 (6.0–30.0)	20.0 (8.0–30.0)
Environmental tobacco smoke, no. (%)	33 397 (64.0)	1470 (74.1)
Consume alcohol, no. (%)	51 041 (97.8)	1924 (97.0)
Median (10th–90th percentile) alcohol use, g/d	13.3 (1.1–47.8)	15.2 (1.9–60.3)
Obese (BMI $\geq$30 kg/m^2, no. (%)	7554 (14.5)	366 (18.4)
Sports active, no. (%)	28 379 (54.4)	827 (41.7)
Median (10th–90th percentile) sports activity, hr/wk	2.0 (0.5–5.0)	2.0 (0.5–5.0)
<8 y of education, no. (%)	17 147 (32.8)	784 (39.5)
8–10 y of education, no. (%)	24 148 (46.2)	844 (42.5)
$\geq$10 y of education, no. (%)	10 920 (20.9)	356 (17.9)
Median (10th–90th percentile) fruit/vegetable intake, g/d	312 (131–617)	278 (76–564)
Median (10th–90th percentile) fat intake, g/d	81 (51–123)	84 (51–129)
Diagnosed or taking medication for hypertension, no. (%)	8332 (16.0)	575 (29.0)
Diagnosed or taking medication for hypercholesterolemia, no. (%)	3779 (7.2)	230 (11.6)
Diagnosed or taking medication for diabetes mellitus, no. (%)	1031 (2.0)	97 (4.9)
Comorbidity with chronic respiratory disease (ICD-10 code*)		
COPD hospitalization before stroke (J40–44), no. (%)	2133 (4.1)	121 (6.1)
Asthma hospitalization before stroke (J45–46), no. (%)	1331 (2.5)	50 (2.5)

BMI indicates body mass index; ICD-10, International Classification of Diseases, 10th Revision; COPD, chronic obstructive pulmonary disease.

*Identified in the Danish Hospital Discharge register.

detected for nonspecified (1.88; 1.23–2.88) and ischemic stroke, respectively, whereas there was no association with hemorrhagic stroke. No significant associations were detected with alternative proxies of long-term exposure to air pollution, except for 1-year mean NO_2 at baseline address and fatal stroke (1.22; 1.00–1.48; Supplemental Table III). The effects of exposure to NO_2 were significantly attenuated in those with >10 years of education, whereas there was no significant effect modification of association between exposure to NO_2 and either incident or fatal stroke by age, gender, smoking status, environmental tobacco smoke, obesity, hypertension, hypercholesterolemia, diabetes, chronic obstructive pulmonary disease, or asthma (Supplemental Table IV).

Discussion

Long-term exposure to traffic-related air pollution may contribute to the development of ischemic but not hemorrhagic stroke, especially severe ischemic strokes leading to death within 30 days.

Our study benefitted from the large prospective cohort with well-defined outcome and risk factor data as well as individual exposure assessment. We adjusted for major risk factors for stroke[26,27] and observed incidence rates and distribution of risk factors agree well with international[26] and Danish[27] data.

Stroke incidence was defined as first-ever hospitalization for stroke, a good marker of stroke onset, because a very high proportion of people having a stroke are hospitalized in Denmark (90%) due to free health care.[27] Subtypes of strokes were determined by a CT scan, and a large proportion (50%) of unspecified strokes reflects lack of routine CT imaging on admission for stroke in Danish hospitals. Fatal strokes do not represent the total stroke mortality because they do not include out-of-hospital stroke deaths. A Danish study with extensive diagnose ascertainment found approximately 10% overestimation of stroke diagnoses in the hospital discharge registry,[28] which implies possibly attenuated and diluted estimates of associations with air pollution in our study. The positive predictive values were high for both strokes coded as ischemic at 97% and hemorrhagic at 74%, whereas the majority (three fourths) of nonspecified strokes were found to be ischemic.[28] This is in agreement with the expected percent of ischemic strokes between 80% and 90% of total stroke[26,27] and implies substantial underestimation of ischemic strokes by the hospital discharge registry.[28] Thus, observed significant positive associations between NO_2 and nonspecified strokes, most of which assumed ischemic, suggest air pollution relevance for ischemic strokes.

These is the first data on ischemic and hemorrhagic stroke and long-term exposure to air pollution, defined as exposure to NO_2. Our findings contradict those of studies on ischemic stroke admissions,[23] stroke mortality,[18,19] and an ecological data on stroke incidence,[22] which failed to detect associations with air pollution, but agree with 2 studies linking stroke incidence[17,21] to chronic exposures to air pollution. Our results corroborate rather established evidence regarding acute exposure to air pollution, which was linked to ischemic but not hemorrhagic strokes.[1,7,9,10,12] A plausible biological mechanism of air pollution-induced injury leading to ischemic stroke is rather well known from the literature on cardiovascular disease linking air pollution through systemic inflammation to acceleration of atherosclerosis through endothelial dysfunction, vasoconstriction, and thrombus formation.[1] Hypertension, hypercholesterolemia, and diabetes, established risk factors for stroke[26,27] and outcomes linked to air pollution, are hypothesized to be on a biological pathway of the air pollution effects leading to stroke with systemic inflammation providing a common link.[1] A medical history of these risk factors, especially diabetes, has been found to enhance associations between air pollution and ischemic

Table 2. Association Between NO_2 (per Interquartile Range*) and Incident Stroke for Different Types of Stroke Among 52 215 Participants in the Diet, Cancer, and Health Cohort

	No. of Cases	IR‡	Adjusted for Age HR (95% CI)	Fully Adjusted† HR (95% CI)	Fully Adjusted†+Hypertension, Hypercholesterolemia, and Diabetes HR (95% CI)
Incident stroke§					
Any stroke	1984	3.9	1.12 (1.06–1.18)	1.05 (0.99–1.11)	1.05 (0.99–1.11)
Nonspecified	1010	2.0	1.15 (1.06–1.24)	1.08 (1.00–1.17)	1.08 (1.00–1.17)
Ischemic	629	1.2	1.13 (1.03–1.25)	1.06 (0.96–1.17)	1.05 (0.95–1.17)
Hemorrhagic	345	0.7	0.99 (0.86–1.14)	0.93 (0.81–1.07)	0.93 (0.81–1.07)
Fatal stroke‖					
Any stroke	142	0.28	1.33 (1.09–1.62)	1.22 (0.99–1.49)	1.22 (1.00–1.50)
Nonspecified	29	0.06	1.93 (1.09–1.62)	1.79 (1.19–2.70)	1.88 (1.23–2.88)
Ischemic	23	0.04	1.55 (0.91–2.65)	1.47 (0.90–2.38)	1.46 (0.90–2.39)
Hemorrhagic	90	0.18	1.09 (0.84–1.43)	1.00 (0.76–1.31)	1.00 (0.76–1.31)

NO_2, nitrogen dioxide; IR, incidence rate; HR, hazard ratio; CI, confidence interval.

*Corresponding to 43% increase in exposure to NO_2.

†For smoking (status, duration, intensity), environmental tobacco smoke, gender, body mass index, education, sports activity, alcohol consumption, fruit consumption, and fat consumption.

‡Crude hospitalization rate per 1000 person-years.

§First-ever admission for stroke between baseline and June 27, 2006.

‖Death within 30 d of first-ever admission for stroke.

stroke incidence.[29] In our study, hypertension, hypercholesterolemia, and diabetes did not attenuate (Table 2) or modify (Supplemental Table IV) the association between air pollution and stroke. However, prevalence of hypertension, hypercholesterolemia, and diabetes was quite low in our cohort as compared with data from stroke registers,[26,27] an underestimation likely due to a selection bias of more healthy participants into the cohort.[24] This low prevalence of vascular risk factors or a selection bias may have impacted the multivariate analyses[29] and may in part explain the only borderline significant association between NO_2 pollution and stroke incidence.

Associations with fatal stroke were markedly stronger than those with incident ischemic stroke, in agreement with Miller et al[17] and Maheswaran et al,[21] and a study of acute exposures to air pollution showing twice as strong effects with stroke mortality than morbidity.[7] Current explanations suggest that exposure to air pollution is more likely to result in fatal stroke,[21] methodological consideration of reduced misclassification of fatal events,[17] and that the effects of air pollution

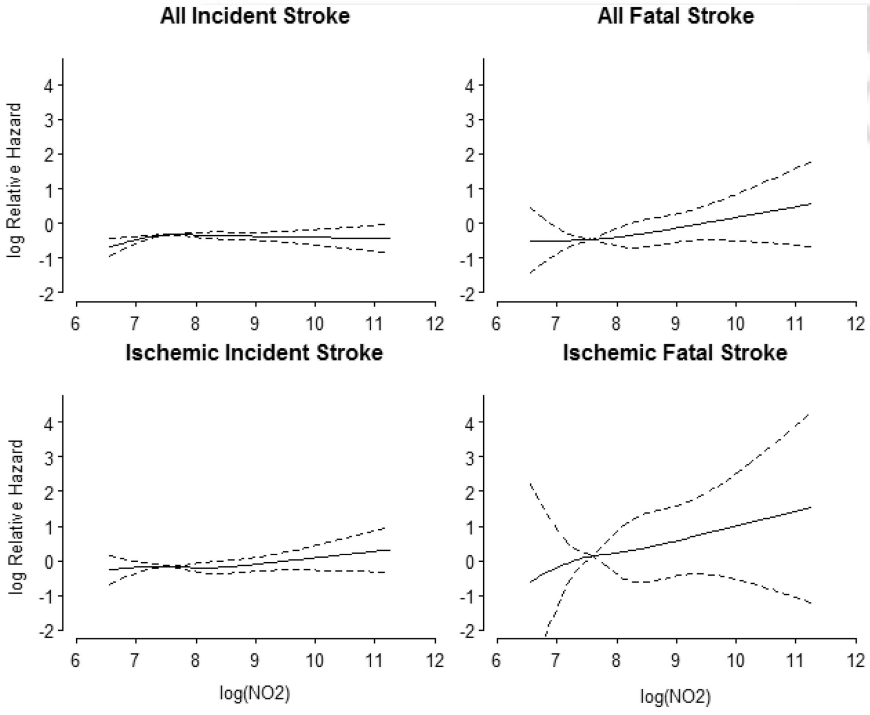

Figure. Exposure–response relationship between NO_2 and incident (left total, n=1984; right ischemic n=629) and fatal (left total n=142; right ischemic, n=23) stroke among 52 215 participants in the Diet, Cancer, and Health cohort members. NO_2 indicates nitrogen dioxide.

disproportionally result in fatal events such as hemorrhagic stroke as compared with nonfatal events.[17] In our data, a substantially higher percent of hemorrhagic stroke was observed among fatal strokes (63.4%) than incident strokes (17.4%), but this was not explained by exposure to NO_2, which was not associated with either incident or fatal hemorrhagic stroke. Stronger effects of exposure to NO_2 in fatal ischemic may be explained by the fact that fatal strokes represent a subgroup of ischemic strokes that were more severe, and stroke severity is the single most important predictor of survival within the first poststroke month.[30] Another possible explanation is that fatal stroke triggered by air pollution has specific mechanisms leading to high severity such as vessel occlusion, arrhythmia, etc. We propose, therefore, that extended exposure to NO_2 leads to development of ischemic strokes and especially of severe ischemic strokes with a poor prognosis.

Assigning individual exposure to air pollution with high spatial (address-specific) and temporal (annual mean) resolution since 1971 is novel, limiting formal comparisons with existing literature, which typically lacked historical air pollution assessment.[17,21,22] Pope et al[18] and Nafstad et al[19] had historical information of air pollution levels but failed to detect an association with stroke mortality assessed from death records. Miller et al[17] applied single-year particulate matter levels measured at the nearest monitor from residence, whereas Oudin et al[23] using modeled NO_x levels (500×500 m) at residence in 1 year before stroke admission. Ecological studies[21,22] linked 5-year mean air pollution levels in small geographical areas to the same 5-year stroke mortality or admission rates. Lack of effects was assigned to low air pollution levels in Sweden[23] and Canada.[22] We observed slightly weaker associations with stroke incidence using single-year NO_2 levels at baseline (1.03; 0.98–1.09; Supplemental Table III) than with mean levels since 1971 (Table 2) and failed to detect an association with single-year NO_2 levels at the year of stroke admission (0.95; 0.89–1.01, results not shown), similarly to Oudin et al.[23] The dynamic assessment of NO_2 levels over many years before stroke onset likely provided for a better proxy of long-term exposure than 1-point-in-time assessment close to the event time and might have been a condition for detecting effects in this study.

Earlier studies suggested that the risk of stroke and cardiovascular disease per unit concentration associated with long-term exposure to air pollution is substantially higher than the risk associated with acute exposures,[17] and this could be related to the accumulated effect of the prolonged exposure. We have observed similar risk estimates (per interquartile range) associating short-term exposure to NO_x to first-ever ischemic stroke admissions in Copenhagen[13] to those observed here. Some of the observed effects in this study could possibly be ascribed to the short-term effects of increases in NO_2 in days before stroke admission,[13] but we could not discern acute from chronic effects of air pollution on stroke due to lack of daily mean of air pollution levels for >60% of the cohort.

High education was associated with attenuated effects of air pollution (Supplemental Table IV), as reported earlier,[18] whereas no other significant interactions were detected (Supplemental Table IV). The effect of exposure to NO_2 seemed limited to previous and current smokers, as observed earlier,[17,18] implying that exposure to air pollution imposes additional negative effects on the risk for stroke that are additive or synergistic with smoking. This is in agreement with earlier findings of larger risks of cardiovascular mortality associated with exposure to both air pollution and active smoking than the expected risk associated with smoking alone.[31]

The literature is rather consistent with respect to traffic as the responsible pollution source.[6–23] Levels of NO_2 used here are a proxy of traffic-related air pollution and are closely related to traffic-generated particles, which more likely represent the responsible agent.[1] We did not have available modeled concentrations of particles, PM_{10} and $PM_{2.5}$, or ozone and could not examine whether adjustment for these pollutants would modify observed associations. Overall stroke incidence in this cohort has been recently associated with traffic-related noise levels at the year of stroke admission when adjusting for the same year levels of NO_x.[32] Modeled levels of traffic-related noise and NO_x at the year of stroke were highly correlated with a Spearman correlation of 0.6.[32] There was no association between NO_2 levels at the year of stroke admission (0.95; 0.89–1.01, results not shown) in this study. Because we did not have available data on noise levels dating back to 1971, adjustment for long-term exposure to noise assessed in the same manner as air pollution data could not be done here but cannot exclude the possibility that the association between stroke and NO_2 was confounded by noise.

The dispersion models used to assess NO_2 levels have been successfully validated against measured values[33] (see details in an online Supplemental material) and applied earlier in studies of chronic obstructive pulmonary disease[34] and lung cancer[35] in this cohort. A limitation of the exposure assessment method is that we assessed only outdoor concentrations and lacked information on work address, commuting habits, and personal activities. However, resulting exposure misclassification is likely to be nondifferential with respect to stroke hospitalization. Furthermore, this misclassification was found to be a Berkson-type error, which is not expected to bias the estimates but likely decreases their precision, as discussed in more detail elsewhere.[35]

Our study offers new evidence that long-term exposure to traffic-related air pollution in adult life may be a risk factor for ischemic stroke but not hemorrhagic stroke. Fatal ischemic strokes, likely denoting admissions for more severe strokes, were most strongly associated with NO_2. Our study adds to the existing evidence that reductions in NO_2 levels might mitigate the stroke burden.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Supplemental Methods - AirGIS Model

The Danish air pollution and human exposure modelling system (AirGIS model)[1] is based on a geographical information system (GIS), and used for estimating traffic-related air pollution with high temporal (an hour) and spatial (individual address) resolution. AirGIS calculates air pollution at a location as the sum of three contributors: (1) local air pollution from street traffic, calculated with the Operational Street Pollution Model[2,3] (OSPM) from data on traffic (intensity and type), emission factors for each vehicle type and EURO class, street and building geometry, and meteorology; (2) urban background, calculated from a simplified urban background (SUB) procedure[3] that takes into account urban vehicle emission density, city dimensions (transport distance), and average building height (initial dispersion height); and (3) regional background, estimated from trends at rural monitoring stations and from national vehicle emissions.[4] Input data for the AirGIS system come from various sources: a GIS-based national street and traffic database, including construction year and traffic data for the period 1960–2005,[5] and a database on emission factors for the Danish car fleet,[6,7] with data on light- and heavy-duty vehicles dating back to 1960, built and entered into the emission module of the OSPM. A national GIS database with building footprints supplemented with construction year and building height from the national building and dwelling register, national survey and cadastre data-bases, and a national terrain-evaluation model, provided the correct street geometry for a given year at a given address. The geocode of an address refers to the location of the front door with a precision within 5 m for most addresses. With a geocoded address and a year, the starting point is specified in place and time, and the AirGIS system automatically generates street configuration data for the OSPM, including street orientation, street width, building heights in wind sectors, traffic intensity and type, and the other data required for the model. Air pollution is calculated in 2 m height at the façade of the address building.

The AirGIS system has been validated and applied in several studies[3, 8-13] and the correlation between modeled and measured ½-year mean NO_2 concentrations at 204 positions in the greater Copenhagen area showed a correlation coefficient (r) of 0.90 with measured concentrations being on average 11% lower than the modeled[3]. We also compared modeled and measured one-month mean concentrations of NO_x and NO_2 over a 12-year period (1995-2006) in a busy street in Copenhagen (Jagtvej, 25 000 vehicles per day, street canyon), which showed correlation coefficients (r) of 0.88 for NO_x and 0.67 for NO_2. The modeled mean NO_x concentration over the whole 12-year period was 6% lower than the measured[12]. Thus, the model predicted both geographical and temporal variation well.

Supplemental Tables

Table S1. Characteristics of Diet, Cancer and Health cohort (*n* = 52 215) by fatal stroke status at follow-up.

Baseline cohort covariates	**Total** *n* = 52 215	**Fatal Stroke** *n* = 142
Median (10-90th percentile) age (years)	56.2 (51.2-63.2)	60.5 (52.2-64.4)
Older than 56 years at baseline *n* (%)	26 650 (51.0)	106 (74.6)
Males *n* (%)	24 801 (47.5)	79 (55.6)
Never smoked *n* (%)	18 652 (35.7)	24 (16.9)
Previously smoked *n* (%)	14 926 (28.6)	32 (22.5)
Currently smoke *n* (%)	18 637 (35.7)	86 (60.6)
Median (10-90th percentile) smoking duration (years)	32.0 (10.0-44.0)	41.0 (32.0-49.0)
Median (10-90th percentile) smoking intensity (g/day)	15.0 (6.0-30.0)	20.0 (9.0-30.0)
Environmental tobacco smoke *n* (%)	33 397 (64.0)	114 (80.3)
Consume alcohol *n* (%)	51 041 (97.8)	137 (96.5)
Median (10-90th percentile) alcohol use (g/day)	13.3 (1.1-47.8)	16.6 (30.0)
Obese (BMI ≥ 30 kg/m^2) *n* (%)	7 554 (14.5)	19 (13.4)
Physically active *n* (%)	28 379 (54.4)	57 (40.1)
Median (10-90th percentile) physical activity (hr/week)	2.0 (0.5-5.0)	0.0 (1.0)
< 8 years of education *n* (%)	17 147 (32.8)	55 (38.7)
8–10 years of education *n* (%)	24 148 (46.2)	55 (38.7)
≥ 10 years of education *n* (%)	10 920 (20.9)	32 (22.5)
Median (10-90th percentile) fruit /vegetable intake† (g/day)	312 (131-617)	259 (93-559)
Median (10-90th percentile) fat intake† (g/day)	81 (51-123)	84 (51-130)
Hypertension *n* (%)	8 332 (16.0)	38 (26.8)
Hypercholesterolemia *n* (%)	3 779 (7.2)	19 (13.4)
Diabetes mellitus *n* (%)	1 031 (2.0)	9 (6.3)
Co-morbid conditions (ICD-10 code‡)		
COPD (J40-44) *n* (%)	2 133 (4.1)	6 (4.2)
Asthma (J45-46) *n* (%)	1 331 (2.5)	3 (2.1)

BMI, body mass index; COPD, chronic obstructive pulmonary disease; ‡For co-morbid conditions identified in Danish Hospital Discharge register·

Table S2. Distribution of proxies of long-term exposure to traffic-related air pollution at the residential address at baseline (1993-1997) in the Diet, Cancer, and Health cohort (*n* = 52 215), total and by incident stroke status at follow-up.

	Total *n = 52 215*		Incident stroke* *n = 1 984*		Fatal stroke† *n = 142*	
	Median (IQR)	10-90th percentile	Median (IQR)	10-90th percentile	Median (IQR)	10-90th percentile
NO_2 (µg/m^3) (1971-event/censoring)	15.2 (5.7)	11.8-23.3	16.2 (6.2)	12.3-24.5	17.7 (7.5)	12.8-25.2
NO_2 (µg/m^3)1-year mean	16.6 (6.7)	12.9-26.2	17.1 (7.0)	13.5-28.0	18.9 (8.9)	13.8-30.5
Traffic Load‡ 100m (10^3 vehicle km/day)	0.4 (0.7)	0.1-3.2	0.47 (1.7)	0.07-3.6	0.8 (1.7)	0.1-3.0
Major road** within 50m *n*(%)	4 244 (8.1%)		200 (10.1%)		16 (11.3%)	

NO_2, nitrogen dioxide; IQR, interquartile range (difference between 75th and 25th percentile); * first-ever admission for stroke; †death within 30 days of admission for stroke; ‡total number of kilometers traveled within 100m (sum of product of street length and traffic density for each road); **road with annual traffic density of 10 000 vehicles or more.

Table S3. Association (per interquartile range increase) between proxies of long-term exposure to traffic-related air pollution at the residential address at baseline (1993-1997) and hospital admissions for stroke among Diet, Cancer, and Health cohort subjects.

	Adjusted for age	Fully adjusted*	Fully adjusted* + hypertension, hypercholesterolemia, & diabetes
	HR (95%CI)	**HR (95%CI)**	**HR (95%CI)**
Air Pollution Proxy			
Stroke incidence† (*n* = 1 984)			
Model NO_2($\mu g/m^3$) 1-year mean	1.08 (1.02-1.14)	1.03 (0.98-1.09)	1.03 (0.98-1.09)
Traffic Load‡ $100m10^4$	1.03 (1.01-1.06)	1.02 (0.99-1.04)	1.02 (0.99-1.04)
Major road** 50m	1.19 (1.03-1.38)	1.09 (0.94-1.26)	1.08 (0.94-1.25)
Fatal stroke†† (*n* = 142)			
Model NO_2($\mu g/m^3$) 1-year mean	1.30 (1.08-1.58)	1.22 (1.00-1.48)	1.22 (1.00-1.48)
Traffic Load‡ $100m10^4$	1.02 (0.94-1.11)	0.99 (0.91-1.09)	0.99 (0.91-1.09)
Major road** 50m	1.33 (0.79-2.23)	1.17 (0.70-1.98)	1.17 (0.69-1.97)

HR, hazard ratio; CI, confidence interval; NO_2, nitrogen dioxide; * for smoking (status, duration, intensity), environmental tobacco smoke, gender, body mass index, education, sports activity, alcohol consumption, fruit consumption, and fat consumption; † first-ever admission for stroke; ‡ defined as a total number of km traveled within 200m (sum of product of street length and traffic density for each road); ** road with annual traffic density of 10 000 vehicles or more; ††death within 30 days of admission for stroke;

Table S4. Modification of associations[*] between NO_2 (per interquartile range[†]) and incident and fatal stroke by baseline characteristics and co-morbid conditions among 52 215 participants in the Diet, Cancer, and Health cohort.

		Incident Stroke[‡] (n = 1 984)				**Fatal Stroke[§]** (n = 142)			
Covariates	***Covariate levels***	*n*	*IR*[‖]	**HR (95%CI)**	***p*[#]**	*n*	*IR*	**HR (95%CI)**	***p***
Age	*< 56*	687	2.7	1.02 (0.92-1.12)		36	0.14	0.90 (0.58-1.41)	
	≥ 56	1 297	5.0	1.06 (0.99-1.14)	*0.53*	106	0.41	1.34 (1.06-1.68)	*0.12*
Gender	*Males*	1 155	4.8	1.03 (0.96-1.12)		79	0.33	1.37 (1.05-1.79)	
	Females	829	3.0	1.06 (0.97-1.16)	*0.66*	63	0.23	1.05 (0.77-1.44)	*0.21*
Smoking	*Currently smoke*	1 007	5.6	1.08 (1.00-1.17)	*0.18*	86	0.48	1.35 (1.05-1.74)	*0.42*
status	*Previously smoked*	496	3.4	1.04 (0.92-1.17)	*0.49*	32	0.22	0.98 (0.61-1.57)	*0.83*
	Never smoked	481	2.6	0.98 (0.86-1.11)		24	0.13	1.06 (0.62-1.81)	
ETS	*Yes*	1 470	4.5	1.06 (0.99-1.33)		114	0.35	1.34 (1.07-1.66)	*0.06*
	No	514	2.8	1.01 (0.89-1.13)	*0.47*	28	0.15	0.75 (0.43-1.31)	
Educational level	*< 8 years*	784	4.7	1.08 (0.99-1.18)		55	0.33	1.64 (1.22-2.21)	
	8 - 10 years	844	3.5	1.05 (0.96-1.15)	*0.60*	55	0.23	1.07 (0.77-1.50)	*0.06*
	≥ 10 years	356	3.3	0.94 (0.81-1.08)	*0.09*	32	0.30	0.78 (0.47-1.30)	*0.01*
Obesity	Non-obese (BMI<30)	1 618	3.7	1.06 (0.99-1.13)	*0.43*	123	0.28	1.22 (0.98-1.52)	*0.81*
	Obese (BMI ≥ 30)	366	5.0	0.99 (0.87-1.14)		19	0.26	1.25 (0.73-2.16)	
Hypertension	*Yes*	575	7.2	1.08 (0.97-1.20)		38	0.48	1.17 (0.78-1.76)	
	No	1 409	3.2	1.03 (0.96-1.10)	*0.45*	104	0.24	1.24 (0.98-1.57)	*0.81*
Hypercholesterolemia	*Yes*	230	6.4	1.08 (0.91-1.29)		19	0.53	1.17 (0.66-2.09)	
	No	1 754	3.7	1.05 (0.99-1.11)	*0.90*	123	0.26	1.20 (0.97-1.49)	*0.64*
Diabetes	*Yes*	97	10.4	0.99 (0.76-1.29)		9	0.96	1.12 (0.48-2.61)	
	No	1 887	3.7	1.05 (0.99-1.11)	*0.68*	133	0.26	1.23 (1.00-1.52)	*0.83*
COPD	*Yes*	121	6.0	1.01 (0.80-1.28)		6	0.30	2.24 (0.92-5.43)	
(n = 2 133)	*No*	1 863	3.8	1.05 (0.99-1.11)	*0.78*	136	0.28	1.18 (0.96-1.46)	*0.17*
Asthma	*Yes*	50	3.9	1.23 (0.87-1.74)		3	0.23	3.88 (1.05-14.4)	
(n = 1 331)	*No*	1 934	3.9	1.04 (0.98-1.10)	*0.36*	139	0.28	1.19 (0.97-1.46)	*0.08*

HR, hazard ratio; CI, confidence interval; NO_2, nitrogen dioxide; IR, incidence rate; ETS, environmental tobacco smoke; COPD, chronic obstructive pulmonary disease; [*]for smoking (status, duration, intensity), environmental tobacco smoke, gender, body mass index, education, sports activity, alcohol consumption, fruit consumption, and fat consumption;[†] corresponding to 43% increase in exposure; [‡]first-ever admission for stroke between baseline and 27 June 2006; [§] death within 30 days of first-ever admission for stroke; [‖]crude hospitalization rate per 1 000 person-years; [#]For Wald test for interaction.

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