OPEN

Journal of Exposure Science and Environmental Epidemiology (2015) 25, 517–523

www.nature.com/jes

ORIGINAL ARTICLE

Traffic-related air pollution exposure and incidence of stroke in four cohorts from Stockholm

Michal J. Korek[1], Tom D. Bellander[1,2], Tomas Lind[2], Matteo Bottai[3], Kristina M. Eneroth[4], Barbara Caracciolo[5], Ulf H. de Faire[1], Laura Fratiglioni[5,6,7], Agneta Hilding[8], Karin Leander[1], Patrik K. E. Magnusson[9], Nancy L. Pedersen[9], Claes-Göran Östenson[8], Göran Pershagen[1] and Johanna C. Penell[1]

We investigated the risk of stroke related to long-term ambient air pollution exposure, in particular the role of various exposure time windows, using four cohorts from Stockholm County, Sweden. In total, 22,587 individuals were recruited from 1992 to 2004 and followed until 2011. Yearly air pollution levels resulting from local road traffic emissions were assessed at participant residences using dispersion models for particulate matter (PM_{10}) and nitrogen oxides (NO_X). Cohort-specific hazard ratios were estimated for time-weighted air pollution exposure during different time windows and the incidence of stroke, adjusted for common risk factors, and then meta-analysed. Overall, 868 subjects suffered a non-fatal or fatal stroke during 238,731 person-years of follow-up. An increment of 20 $\mu g/m^3$ in estimated annual mean of road-traffic related NO_X exposure at recruitment was associated with a hazard ratio of 1.16 (95% CI 0.83–1.61), with evidence of heterogeneity between the cohorts. For PM_{10}, an increment of 10 $\mu g/m^3$ corresponded to a hazard ratio of 1.14 (95% CI 0.68–1.90). Time-window analyses did not reveal any clear induction-latency pattern. In conclusion, we found suggestive evidence of an association between long-term exposure to NO_X and PM_{10} from local traffic and stroke at comparatively low levels of air pollution.

Journal of Exposure Science and Environmental Epidemiology (2015) **25,** 517–523; doi:10.1038/jes.2015.22; published online 1 April 2015

Keywords: epidemiology; exposure modeling; particulate matter; personal exposure

INTRODUCTION

Stroke is a leading cause of disease and death in the Western world although the incidence has decreased in recent decades.[1] The body of evidence regarding long-term air pollution exposure, especially to respirable particles, and various cardiovascular risk factors and diseases is growing.[2] For example, associations have been reported with the development of atherosclerosis, hyper tension, ischemic heart disease and cardiovascular mortality. Proposed pathophysiological mechanisms include systemic inflammation and oxidative stress, imbalance in the autonomic nervous system, endothelial dysfunction, vasoconstriction and thrombosis. Although some studies show associations with cerebrovascular incidence or mortality in relation to long-term air pollution exposure, evidence is limited and conflicting.[3–6] Data regarding the role of air pollution exposure for ischemic *vs* hemorrhagic stroke and the influence of potential effect modifiers are sparse and ambiguous.

In understanding the mechanisms behind effects of long-term exposure to ambient air pollution on cardiovascular disease, as well as to predict consequences of preventive measures, it is important to assess the role of timing of exposure in relation to occurrence of the adverse outcomes. It has been shown, that cardiovascular and other mortality decreased within a year after a coal ban in Dublin, Ireland, which drastically lowered the black smoke levels.[7] A follow-up of the Harvard Six City study and a study of myocardial infarction survivors, suggested that the relevant exposure period for mortality was the past few years[8,9] Studies of air pollution effects on cardiovascular disease or mortality have generally not detected marked associations with timing of exposure during follow-up periods of up to two decades.[3,10,11] Most of the studies on cerebrovascular effects of air pollution, however, did not address this issue.

The aim of the current study was to assess individual long-term exposure to air pollution from road traffic in relation to stroke incidence, in an area with relatively low air pollution levels. We took changes in residence and in annual exposure levels during follow-up into account and investigated different types of stroke, in a combined analysis of four cohorts from Stockholm County, Sweden.

METHODS

Study Population

The study included four cohorts based in Stockholm County, Sweden. The Stockholm Diabetes Preventive Program (SDPP),[12] a population-based prospective study, recruited 3128 men in 1992–1994 and 4821 women in 1996–1998 from five municipalities in Stockholm County. The study participants were 35–56 years old at recruitment. None had previously

[1]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; [2]Centre for Occupational and Environmental Medicine, Stockholm County Council, Stockholm, Sweden; [3]Division of Biostatistics, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; [4]Environment and Health Administration, Stockholm, Sweden; [5]Department of Neurobiology, Care Sciences and Society, Aging Research Center, Karolinska Institutet, Stockholm, Sweden; [6]Stockholm Gerontology Research Center, Stockholm, Sweden; [7]Division of Clinical Geriatrics, Karolinska University Hospital, Stockholm, Sweden; [8]Department of Molecular Medicine and Surgery, Karolinska University Hospital, Stockholm, Sweden and [9]Department of Medical Epidemiology and Biostatistcs, Karolinska Institutet, Stockholm, Sweden. Correspondence: Michal Korek, Karolinska Institutet, Institute of Environmental Medicine, Nobels väg 13 Box 210, Stockholm, SE-171 77, Sweden.
Tel.: +46 8 524 87457. Fax: +46 8 304571.
E-mail: michal.korek@ki.se
Received 5 August 2014; revised 23 February 2015; accepted 23 February 2015; published online 1 April 2015

diagnosed diabetes and half of the cohort (53%) had a family history of diabetes (one first degree relative or two second degree relatives), while the other half was selected to match on age and sex of the first half. The cohort study of 60 year olds (SIXTY)[13] invited a random population sample consisting of one-third of all men and women who were living in Stockholm County and turned 60 years of age between August 1997 and March 1999. The SIXTY study included 4232 subjects. The Screening Across the Lifespan Twin Study (SALT)[14] screened all twins born in Sweden before 1958 for the most common complex diseases with a focus on cardiovascular diseases. Recruitment took place during 1998–2002. In the present study, the SALT participants residing in Stockholm County at recruitment were included, resulting in 7043 subjects with an age range of 42–100 years of age at recruitment. The Swedish National study of Aging and Care in Kungsholmen (SNAC-K)[15] included randomly sampled individuals $>=60$ years of age between March 2001 and June 2004 from a central area in Stockholm City. A total of 3363 subjects of 60–104 years of age were recruited.

In all four cohorts, individual data collected at enrolment on socio-demographic characteristics such as occupation status and education were obtained from questionnaires that also provided information on lifestyle factors, including smoking status, levels of physical activity and alcohol consumption. Information on diabetes and hypertension was obtained either from questionnaires or clinical data. Socio-economic variables aggregated at neighborhood level were retrieved from Statistics Sweden. Neighborhoods consisted of small geographical units with an average population of 1000–2000 subjects considered to be homogenous with regard to socio-economic characteristics. The study was approved by the Ethical Review Board Stockholm, Sweden.

Outcome Data

Data on individual stroke events were retrieved from the National Hospital Discharge Registry and the National Cause of Death Registry, including data from February 1964 to December 2011. A stroke event was defined based on the International Classification of Diseases (ICD) version 9 and 10: hospitalizations with principal diagnosis of ischemic stroke (ICD9: 433; 434; ICD10: I63), hemorrhagic stroke (ICD9: 431; ICD10: I61), unspecified stroke (ICD9: 436; ICD10: I64) and out-of-hospital deaths from cerebrovascular diseases (ICD9: 431–436; ICD10: I61-I64). If the person passed away within 28 days after a stroke event, the event was classified as fatal. Only stroke events after recruitment of the respective cohort were included in analyses, whereas earlier events were used to classify later events as non-incident.

Exposure Assessment

Long-term exposure to ambient air pollution from road traffic was estimated based on a methodology described in detail elsewhere.[16] Briefly, residential histories retrieved from the Swedish tax authorities were available for all cohort participants from 1991 until 2010, including data on all residential addresses and the date from which the person resided at each particular address. The residential address was known also earlier than 1991 for those moving in before this year. In case of emigration from Sweden or Stockholm County, this was recorded with a specific date used for censoring (see below). The residential addresses within Stockholm County were geocoded, 90% by automatic matching against the Swedish Mapping Cadastral and Land Registration Authority Databases, and an additional 9% manually. One percent of the addresses could not be geocoded, mainly because of insufficient address details.

Annual mean concentrations of nitrogen oxides (NO_x) and particulate matter with an aerodynamic diameter of less than 10 micrograms (PM_{10}) were calculated using a wind model and a Gaussian air quality dispersion model, both part of the Airviro Air Quality Management System (SMHI, Norrköping, Sweden; http://airviro.smhi.se). The emission inventory of the Stockholm and Uppsala County Air Quality Management Association supplied the input to the model. Information in this database has been updated yearly by the municipalities in the region since 1993. It is a geographic information system and contains detailed information about emissions from, for example, road and ferry traffic, petrol stations, industrial areas and households.[17] For the present study, only emissions from local road traffic were included as it is the dominating source of both NO_x and PM_{10}.[18,19] NO_x was used as a marker of road traffic-derived combustion pollutants, while PM_{10} was used as a marker for road wear. Emission factors for NO_x and exhaust particles from road traffic were obtained from the EVA model of the Swedish Transport Administration. Emission factors for non-exhaust PM (mainly road wear but including some contributions from brake and tyre wear) were obtained using NO_x as tracer for traffic emissions.[20] In Stockholm, road wear increases drastically because of the use of studded tyres and traction sand on streets during winter; up to 90% of the locally emitted PM_{10} may be due to road abrasion.[19,21] The contributions from road, tyre and brake wear in Stockholm is further analysed in a modelling study which clearly shows the dominance of road wear and that the surface moisture, and subsequent retention and suppression of suspension, also influences the PM_{10} levels.[22]

The model resolution for inner Stockholm and the urban parts of the municipalities of Solna, Järfälla and Södertälje was 25 m grid cells. The rest of Stockholm County had a resolution of 100 m or 500 m, respectively, in urban and rural areas. The model estimates air pollution concentrations 2 m above ground level and handles buildings by using a roughness parameter.[23] This results in underestimated concentrations in street canyons with heavy traffic. Therefore, a street canyon contribution was calculated using the SMHI-Airviro street canyon model (http://airviro.smhi.se). This contribution was added to all addresses with multistory houses on both sides within 30 m of the most polluted street segments in the inner city of Stockholm, and corresponded to air pollution levels at half the building height at those addresses.

The SMHI-Airviro Gaussian model has been validated in a number of previous studies, for example, Johansson *et al.*[24] and Eneroth *et al.*[25] The comparison between time series calculations of annual mean NO_x concentrations and urban background measurements from a continuous monitoring station in Stockholm during the period 1998–2005 provided R^2 of 0.74–0.80 for different years.[26] Within the European Study of Cohorts for Air Pollution Effects (ESCAPE), differences between dispersion model estimates and monitoring results were explored.[27] In Stockholm, SMHI-Airviro Gaussian model calculations were compared with measured concentrations of NO_2 and PM_{10}, respectively, at 39 and 19 monitoring sites, providing Spearman rank correlations of 0.755 for NO_2 and 0.580 for PM_{10}.

Levels of NO_x and PM_{10} resulting from local road traffic emissions were calculated for all geocoded addresses for every year from 1987 until the end of follow-up. Reduced emissions of exhaust particulates and NO_x due to stricter European vehicle regulations are included in the EVA emission model. The emission factors for non-exhaust PM were assumed to be constant as the proportion of cars with studded tyres in Stockholm has been relatively stable during the period of the present study. To compensate for trends in traffic volumes, the calculated levels of NO_x and PM_{10} were re-scaled based on measured traffic flow in and out of the regional centre of Stockholm on an annual basis. Concentrations of NO_2 were calculated based on modelled concentrations of NO_x. An empirical non-linear relationship was derived for each year based on measured concentrations of NO_x and NO_2 in Stockholm and its surroundings.The annual subject-specific exposure estimates were used to construct study entry and time-weighted exposure concentrations during different time windows.

Statistics

Cohort-specific Cox proportional hazard regression analysis was used to estimate hazard ratios (HRs) of stroke associated with long-term ambient air pollution exposure. NO_x and PM_{10} were analysed separately. Person-time at risk was calculated from enrolment into the study until stroke, death from another cause, emigration (i.e., to an address without information on air pollution exposure) or end of study (31 December 2011), whichever event occurred first. Age was used as the underlying time scale in all models. Risk estimates were calculated as HRs with 95% confidence intervals using increments of 20 $\mu g/m^3$ for NO_x and 10 $\mu g/m^3$ for PM_{10}. The data were divided into 6-month periods, allowing us to use exposure to PM_{10} and NO_x as time-varying covariates and to adjust for calendar year in 5-year periods. First, concentrations of NO_x and PM_{10} at the study entry address of each individual were used as exposure variables in cohort-specific analyses. Second, the NO_x and PM_{10} exposures were calculated for each subject for each subject-specific 6-month period during the follow-up. Exposure time windows were then created for 6–10-, 4–6-, 2–4- and 0–2-year intervals prior the end date of every 6-month interval during the follow-up.

Adjustment models were defined *a priori* and covariates were chosen based on the literature and available data from the cohorts. The fully adjusted models had a common set of individual-level covariates including gender, education level, smoking status, smoking intensity among current smokers and socio-economic index. This index was based on current or last (if retired) profession and categorized into low (blue collar worker),

medium (low and intermediate level white collar worker, and self-employed) and high (high-level white-collar worker). Additional variables were included if present for at least two cohorts.

The proportional-hazard assumption for all covariates was investigated. If any variable in the individual cohort models violated this assumption, effect estimates were compared with a stratified Cox analysis for that cohort.[3] In the analyses, we included only individuals with complete data on exposure estimates and confounders. We did not include confounders with missing data for more than 20% of the individuals; hence for SALT, alcohol consumption and occupational status and for SNAC-K physical activity was excluded.

To increase power, we combined the effect estimates of the four cohorts using a random effect meta-analysis model.[28] We investigated heterogeneity between the cohorts using the Higgins I^2 statistics.[29] Furthermore, we investigated a linear trend between subsequent exposure time windows in time and the risk of stroke. We used the time-window-specific effect estimates as a dependent variable and the time-window intervals as a categorical explanatory variable in a meta-regression model.

Potential effect modification by gender, smoking, hypertension (defined as $\geq$ 140 mm Hg systolic or $\geq$ 90 mm Hg diastolic BP, or intake of blood pressure-lowering medication, or in the SALT cohort, on self-reported data on prevalent hypertension) and diabetes were investigated by cohort-specific stratified analysis adjusted for the full set of covariates, and then combined into meta-analysis. When analysing effect modification by diabetes, calendar year was recoded into two periods instead of three periods in the model for SIXTY owing to the lack of model convergence when using 5-year intervals. Furthermore, the impact of family history of diabetes on the association between exposure and risk of stroke was investigated in SDPP and SIXTY by stratified analysis. Such data were lacking for the other two cohorts.

Sensitivity analyses were performed by restricting events to (i) only ischemic stroke, (ii) only non-fatal cases and (iii) only including incident cases after study enrolment. In a separate analysis, we explored the influence of contextual confounding by adding neighborhood mean income as an area-level socio-economic variable to the fully adjusted model

All analyses were performed using Stata version 11.0 (StataCorp LP, College Station, TX, USA).

RESULTS

A total of 22,587 subjects were recruited into the four cohorts (Table 1). After exclusion of the subjects recruited into more than one cohort or with missing data in any of the exposures or covariates, 20,070 subjects remained for the analysis. Overall, 6–13% of the subjects in each cohort were excluded owing to missing data.

At study entry, the mean age of all subjects was 60 years (range 35–104), and varying between cohorts (Table 2). Most participants had education up to secondary school or equivalent and were predominantly working or retired. Across cohorts, 15% to 25% of the participants were current smokers and about half reported regular alcohol consumption (daily/weekly). Diabetes prevalence was low, ranging from 1.6% to 8.6% across cohorts, while the proportion of hypertensive individuals was between 22.2% and 69.8% in the different cohorts. Most participants were either in the high or medium socio-economic category, and the average household income in the neighborhood was similar for three cohorts but higher for the cohort located in Stockholm city.

Air pollution linkage was successfully made for 99% of all individual addresses in Stockholm county ($n = 43{,}344$ addresses). The base-line exposure concentrations of NO_x and PM_{10} were similar for the two cohorts with recruitment in the whole of Stockholm County (SIXTY and SALT), whereas the SNAC-K cohort from Stockholm city had higher exposure levels. The SDPP cohort had the lowest levels and least variability for both PM_{10} and NO_x because of the recruitment of study participants from five suburban and semi-urban municipalities (Figure 1). Average concentrations varied somewhat across the exposure windows and followed the same between-cohort variability as for the study entry exposure data (Supplementary Table 1).

In general, NO_x concentrations were reduced during the observation period, whereas levels of PM_{10} were relatively constant. Modeled NO_x and PM_{10} were highly correlated for all cohorts, where SDPP, SIXTY and SALT had a high Pearson correlation ($r \sim 0.9$), whereas SNAC-K had a slightly lower correlation ($r = 0.75$).

A total of 868 subjects suffered a stroke during the 238,731 person-years at risk. Of the subjects, 775 (89%) were first ever cases of stroke after study entry, 755 (87%) were non-fatal and 737 (84%) were ischemic. The occurrence of stroke events were distributed over cohorts accordingly; 130 events in SDPP, 160 events in SIXTY, 314 events in SALT and 264 events in SNAC-K (Table 2).

The cohort-specific HR for total stroke per 20 $\mu g/m^3$ increment of road-traffic-related exposure to NO_x at enrolment address ranged between 0.84 and 1.78 (statistically significant only in the SIXTY cohort) when adjusting for all covariates (Figure 2, Supplementary Table 2). The combined HR was 1.16 (0.83–1.61). Similar risk estimates were seen per 10 $\mu g/m^3$ increase of traffic-related PM_{10}, where the cohort specific HR ranged between 0.59 and 2.21, also significant only in the SIXTY cohort. The combined analysis gave an overall HR of 1.14 (0.68–1.90). Moderate heterogeneity was suggested by the Higgin's I^2 statistic: 53.7% for NO_x and 66.9% for PM_{10}. There were no major or consistent differences in risk estimates between crude and adjusted models, indicating only limited confounding by the risk factors under study (Supplementary Table 2). Furthermore, the cohort specific and combined HRs were very similar using NO_2 and NO_X (Supplementary Figure 1).

In the time-window analysis for the fully adjusted model, no clear trend in the effect estimates could be detected after meta-analysis (Figure 3, Supplementary Table 3), but the confidence intervals were wide. Results were similar for NO_x and PM_{10} exposure, although a close to statistically significant excess risk was seen for NO_x exposure 6–10 years prior to the event. Moderate heterogeneity was also found in all separate time-window meta-analyses, ranging from $I^2 = 35.4\%$ to 67.0% for NO_x and 58.3% to 67.0% for PM_{10}. There was no significant trend between the effect estimates from the meta-analysed exposure time windows and the time interval they covered. The *P*-value for time-window category as an explanatory variable for the meta-analysed

Table 1. Number of individuals included in the analysis of four cohorts from Stockholm County.

Cohort[a]	*SDPP*	*SIXTY*	*SALT*	*SNAC-K*
Number recruited	7949	4232	7043	3363
Reasons for exclusion				
Participation in more than one cohort[a]	0	8	159	78
Missing exposure data for time window	111	47	168	17
Missing data on covariates	387	480	710	352
Total number in analysis (% of number recruited)	7451 (94%)	3697 (87%)	6006 (85%)	2916 (87%)

[a]Subjects are included in the first cohort into which they were selected.

Table 2. Characteristics of the study participants included in the analyses from the four cohorts in Stockholm County.

	SDPP[a]	*SIXTY*[b]	*SALT*[c]	*SNAC-K*[d]
N	7451	3697	6006	2916
Number of stroke events during follow-up	130	160	314	264
Years of enrolment	1992–1998	1997–1999	1998–2002	2001–2004
Age, years: median (minimum—maximum)	48 (35–56)	60 (59–61)	56 (42–97)	72 (60–104)
Male (%)	42.9	46.4	42.3	35.2
Education (%)				
Primary school or less	25.5	27.0	21.3	24.2
Up to secondary school or equivalent	45.5	44.3	42.8	42.5
University degree and more	29.0	28.7	35.9	33.3
Occupation status (%)				
Employed/self-employed	92.6	52.0	N/A[e]	26.5
Unemployed	7.4	9,9	N/A[e]	N/A[e]
Homemaker/housewife	N/A[e]	7.7	N/A[e]	N/A[e]
Retired	N/A[e]	30.3	N/A[e]	73.5
Smoking status (%)				
Current smoker	25.5	19.4	19.9	14.4
Former smoker	36.7	39.4	44.5	36.7
Never smoker	37.9	41.2	35.6	48.9
Number of cigarettes/day for current smokers mean ± SD	13.6 (7.4)	13.2 (7.2)	13.0 (7.5)	10.7 (8.0)
Alcohol consumption (%)				
Daily	7.4	4.4	N/A[e]	20.4
Weekly	37.0	20.4	N/A[e]	24.2
Seldom	51.6	45.1	N/A[e]	46.4
Never	4.1	30.1	N/A[e]	9.0
Diagnosed diabetes[f] *(%)*				
Yes (%)	1.6	3.9	4.1	8.6
No (%)	98.4	96.1	95.9	91.4
Diagnosed hypertension[g] *(%)*				
Yes	24.2	51.9	22.2	69.8
No	75.8	48.1	77.8	30.2
Socio-economic index (%)				
Low	28.3	22.3	29.3	18.2
Medium	26.8	55.2	52.5	30.2
High	44.9	22.6	18.2	51.7
Physical activity (%)				
Once a month or less / < 1 h/week	10.7	68.6	25.6	N/A[e]
About once a week / ~ 1 h/week	81.5	23.8	62.7	N/A[e]
3 times a week or more / > 2 h/week	7.8	7.6	11.7	N/A[e]
Average household income in neighborhood[h] (SEK) mean ± (SD)	288645 (50881)	300990 (85723)	305333 (81989)	351723 (27125)

[a]Stockholm Diabetes Prevention Program study. [b]60-year-old cohort study. [c]Screening Across the Lifespan Twin study. [d]Swedish National Study on Aging and Care in Kungsholmen. [e]Data not available for a sufficient number of individuals. [f]Information on diabetes was based on glucose tolerance test in SDPP and on questionnaire data in remaining cohorts. [g]Information on hypertension was defined by blood pressure measurements or intake of blood pressure lowering medication in three cohorts and through questionnaire in SALT. [h]Individual socio-economic status was based on current or last (if retired) profession and categorized into low (blue collar worker), medium (low and intermediate level white collar worker, and self-employed) and high (high-level white-collar worker).

time-window HRs was not significant ($P = 0.75$). There were rather high correlations in individual exposure between different time windows, that is, 0.7–1 for PM_{10} and 0.5–0.9 for NO_X, which contributes to the similar risk estimates. Only, about half of the study subjects moved during the follow-up period.

No strong effect modification of the association between NO_x or PM_{10} and stroke was observed by gender, smoking, hypertension or diabetes (Supplementary Figure 2). The HRs for NO_x and stroke for individuals with heredity for diabetes in SDPP and SIXTY were 2.07 (0.72–5.96) and 1.27 (0.38–4.29), respectively, compared with 1.36 (0.33–5.64) and 1.63 (1.10–2.40) for individuals without heredity for diabetes. Corresponding results for PM_{10} were 4.10 (0.98–17.11)) and 1.73 (0.39–7.71) for those with heredity for diabetes, respectively, compared with 0.8 (0.10–7.13) and 1.84 (1.10–3.09) for those without (data not shown). Restricting stroke events to non-fatal, ischemic or incident cases as well as adjusting the main model for mean income as area-level socio-economic indicator did not have any major impact on the risk estimates (Supplementary Figure 3). Further sensitivity analyses assessed the potential effect modification by age in the SALT and SNACK cohorts, which included a sizable fraction of older subjects. When individuals older than 75 or 85 years of age were excluded, there was no clear or consistent pattern of changes in the HRs (data not shown).

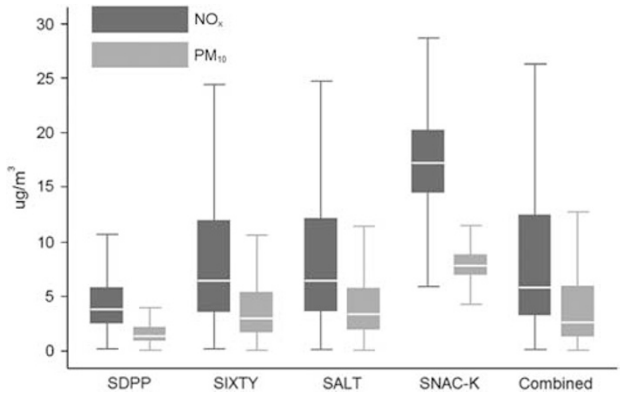

Figure 1. Modeled exposure levels of traffic-generated NO_x and PM_{10} ($\mu g/m^3$) at study entry addresses in four cohorts from Stockholm. Notes: Box layers describe the 75, 50, 25th percentile while outliers are not shown.

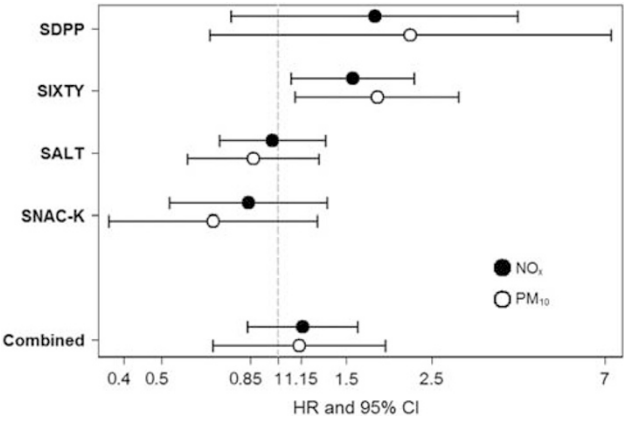

Figure 2. Exposure at recruitment from road traffic NO_x (per 20 $\mu g/m^3$) and PM_{10} (per 10 $\mu g/m^3$) and adjusted hazard ratio (HR) of stroke, in four cohorts in Stockholm County, separately and combined.

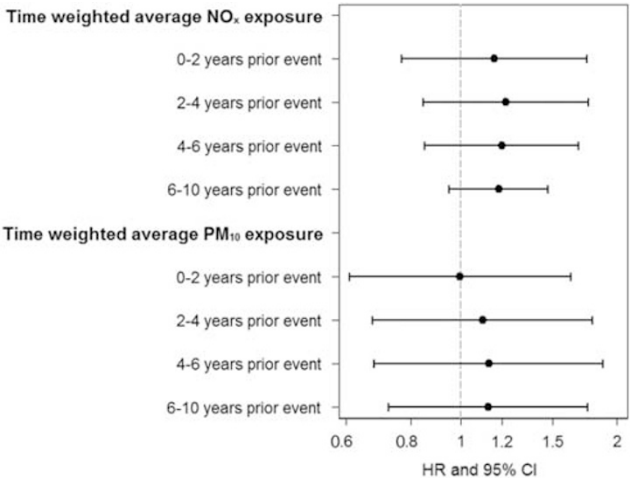

Figure 3. Adjusted hazard ratios (HR) of stroke, in relation to time-window exposure to NO_x (per 20 $\mu g/m^3$) and PM_{10} (per 10 $\mu g/m^3$) from road traffic in a meta-analysis of four cohorts from Stockholm County.

DISCUSSION

We found suggestive evidence of an association between air pollution from local road traffic, using NO_x and PM_{10} as indicators, and incidence of stroke in a region with comparatively low air pollution levels. No clear differences were indicated in effect estimates between various exposure time windows, but the power was limited in these analyses.

Some heterogeneity between cohorts in risk estimates for stroke related to long-term air pollution exposure was observed. Other studies have shown mixed results with borderline significant associations primarily for fatal stroke, with NO_2 (from dispersion modelling with high spatial detail) in Denmark,[5] and statistically significant associations for both ischemic and hemorrhagic stroke and NO_2 (exposure based on land-use regression models) in Japan.[30] The ESCAPE study on incidence of cerebrovascular events found suggestive evidence of an association for stroke and $PM_{2.5}$, PM $_{10}$ and Coarse PM but not for NO_2 or NO_x (exposure based on land-use regression models).[6] On the contrary, studies from England,[31] Oslo[3] and North America[4,10,32] did not see any elevated stroke risks associated with air pollution (mainly based on exposure assessment with less geographic detail). A study on women in USA, based on vicinity to urban background monitors, found larger effect estimates for $PM_{2.5}$ on cerebrovascular events (and death) for within-city exposure differences than for between-city differences, but no effects of NO_2.[33] These differences indicate that high spatial resolution is needed to describe the air pollution contrasts that may be associated with stroke risk.

One technical difference between our study and others' is that we have estimated the partial contribution to air pollution levels from road traffic only, whereas most other studies have estimated total levels. Within the Stockholm region, however, the local spatial differences in residential levels of both PM_{10} and NO_x are dominated by the emissions from road traffic.[34] Adding a regional background effect to all estimated values would not have changed our results, which were based on absolute rather than relative differences in exposure.

It is of particular interest to compare our results with those of the recently published study on cerebrovascular events from the ESCAPE project in which 20% of the stroke cases were in the four cohorts in the present study. Our exposure assessment was based on dispersion modeling, whereas ESCAPE used land use regression and our region constituted the lowest exposed area in ESCAPE, particularly for NO_x. We found suggestive evidence of associations for both NO_x and $PM_{10,}$ whereas no association was observed for NO_x in ESCAPE based on exposure at residential address at study enrolment. Furthermore, the magnitude of the effect was similar for PM_{10} in the two studies (14% and 11% per 10 $\mu g/m^3$). Notably, the cohort-specific effect estimates for long-term air pollution exposure and stroke in this study differed somewhat from the estimates presented for the same cohorts in the ESCAPE study (ESCAPE data retrieved through author correspondence). These variations could to some extent be explained by slightly diverse model adjustments, but a more probable explanation is the choice of exposure modeling technique. A major uncertainty with employment of both exposure assessment methodologies in most epidemiological studies is the failure to consider exposure contributions from occupational locations and commuting.[35] This generally would be expected to contribute to dilution of the associations.

Consistently with other European studies on long-term effects of air pollution on stroke, we did not find a difference between associating ischemic stroke and all stroke cases to PM_{10} and NO_x. Although short-term studies generally suggest a stronger association with ischemic stroke,[5,36–40] the literature on chronic effects of air pollution and types of stroke is sparse and results are mixed. A case–control study of ischemic stroke hospitalization in southern

Sweden and yearly mean NO_x averages prior to events showed no significant association.[41] In a Danish study using address-specific NO_2 concentrations weighted over 9.8 years, the strongest associations were found for non-specified and ischemic strokes whereas no association was found for hemorrhagic stroke.[5] A US study did not find a significant association between stroke type and the interquartile range (4 $\mu g/m^3$) change in average $PM_{2.5}$, $PM_{10-2.5}$ or PM_{10} exposure in the 12 months prior event in a cohort including only men.[10] Studies from Asia have linked air pollution to both ischemic and hemorrhagic stroke[30,42] where one long-term study found a significant association of yearly mean NO_2 levels from 1, 2 and 3 fiscal years prior a ischemic stroke and 2–3 years prior a hemorrhagic event.[30] In general, hemorrhagic stroke is less common than ischemic stroke, which leads to lower statistical precision and power in detecting risks for this type of stroke.

A recent review of epidemiological evidence on long-term exposure to air pollution and cardio-respiratory mortality found significant heterogeneity in $PM_{2.5}$ effect estimates across studies.[43] It was suggested that this was related to differences in particle composition, infiltration of particles indoors, population characteristics and methodological differences in exposure assessment and confounder control. In the ESCAPE study on cerebrovascular events based on 11 cohorts from 7 European countries,[6] heterogeneity was found for all exposure metrics but NO_x and the coarse PM fraction. Age was proposed as a major heterogeneity source but was suggested to correlate with other cohort characteristics.

On the other hand, studies within the ESCAPE project on acute coronary events[44] using the same cohorts, and on mortality adding 11 cohorts,[45] failed to detect such heterogeneity. In our study, we detected between-cohort heterogeneity in the effect estimates for long-term exposure to NO_X and PM_{10} on stroke incidence, even though the cohorts were based in only one region. The two cohorts in our study not showing associations differed from the other in certain aspects. One (SALT) lacked information on occupation status and alcohol consumption, available in all or most other cohorts, which probably led to poorer confounding control. The other (SNAC-K) was considerably older, with ages up to 105 years at recruitment, where less susceptible "survivors" may have been enriched

SNAC-K also differed considerably from the other cohorts in regard to prevalence of hypertension. On the other hand, the SDPP cohort (where associations were suggested) was selected so that diabetes heredity was more common, and those with such heredity appeared at higher risk of stroke associated with air pollution exposure. This cohort also had a longer observation period than the other because of earlier recruitment. However, taken together, we cannot find explanations that fully account for the observed heterogeneity.

A strength of our study consisted in the detailed assessment of air pollution for each subject, which took changes in residential address and calendar time into account. In addition, individual data on many cardiovascular risk factors were available along with information on potential contextual confounders. National health registries that are validated, for example regarding stroke,[46] were used to obtain the outcome data which minimized the risk of misclassification, although the quality of differentiation between ischemic and hemorrhagic stroke was lower during the earlier years of follow-up. Furthermore, the individual cohorts were rather small limiting the statistical power to detect associations, particularly in analyses of subgroups and interactions.

In conclusion, our findings indicated a possible association between local air pollution from road traffic and incidence of stroke in a combined analysis of four cohorts from Stockholm County. No clear differences in risk related to time windows of exposure were seen, but the interpretation was hampered by a limited statistical power in these analyses.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

ACKNOWLEDGMENTS

This project was funded by the Swedish Environmental Protection Agency, the Swedish Council for Working Life and Social Research, and the Swedish Heart-Lung Foundation. The SDPP cohort was additionally funded by the Stockholm County Council, the Swedish Research Council, the Swedish Diabetes Association and the Novo Nordisk Scandinavia. The SIXTY cohort was additionally funded by the Stockholm County Council and the Swedish Research Council (longitudinal research and 0593). The SALT cohort was additionally supported by NIH grant AG-08724. We acknowledge the Stockholm and Uppsala County Air Quality Management Association for enabling use of their emission inventory.

REFERENCES

1 Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA *et al.* Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet* 2014; **383**: 245–254.
2 Brook RD, Rajagopalan S, Pope CA 3rd, Brook JR, Bhatnagar A, Diez-Roux AV *et al.* Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. *Circulation* 2010; **121**: 2331–2378.
3 Nafstad P, Haheim LL, Wisloff T, Gram F, Oftedal B, Holme I *et al.* Urban air pollution and mortality in a cohort of Norwegian men. *Environ Health Perspect* 2004; **112**: 610–615.
4 Pope CA 3rd, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D *et al.* Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. *Circulation* 2004; **109**: 71–77.
5 Andersen ZJ, Kristiansen LC, Andersen KK, Olsen TS, Hvidberg M, Jensen SS *et al.* Stroke and long-term exposure to outdoor air pollution from nitrogen dioxide: a cohort study. *Stroke* 2012; **43**: 320–325.
6 Stafoggia M, Cesaroni G, Peters A, Andersen ZJ, Badaloni C, Beelen R *et al.* Long-term exposure to ambient air pollution and incidence of cerebrovascular rvents: Results from 11 European cohorts within the ESCAPE Project. *Environ Health Perspect* 2014; **122**: 919–925.
7 Clancy L, Goodman P, Sinclair H, Dockery DW. Effect of air-pollution control on death rates in Dublin, Ireland: an intervention study. *Lancet* 2002; **360**: 1210–1214.
8 Laden F, Schwartz J, Speizer FE, Dockery DW. Reduction in fine particulate air pollution and mortality: Extended follow-up of the Harvard Six Cities study. *Am J Respir Crit Care Med* 2006; **173**: 667–672.
9 Zanobetti A, Schwartz J. Particulate air pollution, progression, and survival after myocardial infarction. *Environ Health Perspect* 2007; **115**: 769–775.
10 Puett RC, Hart JE, Suh H, Mittleman M, Laden F. Particulate matter exposures, mortality, and cardiovascular disease in the health professionals follow-up study. *Environ Health Perspect* 2011; **119**: 1130–1135.
11 Chen R, Zhang Y, Yang C, Zhao Z, Xu X, Kan H. Acute effect of ambient air pollution on stroke mortality in the China air pollution and health effects study. *Stroke* 2013; **44**: 954–960.
12 Eriksson AK, Ekbom A, Granath F, Hilding A, Efendic S, Ostenson CG. Psychological distress and risk of pre-diabetes and Type 2 diabetes in a prospective study of Swedish middle-aged men and women. *Diabet Med* 2008; **25**: 834–842.
13 Wandell PE, Wajngot A, de Faire U, Hellenius ML. Increased prevalence of diabetes among immigrants from non-European countries in 60-year-old men and women in Sweden. *Diabetes Metab* 2007; **33**: 30–36.
14 Lichtenstein P, Sullivan PF, Cnattingius S, Gatz M, Johansson S, Carlstrom E *et al.* The Swedish Twin Registry in the third millennium: an update. *Twin Res Hum Genet* 2006; **9**: 875–882.
15 Meinow B, Kareholt I, Lagergren M. According to need? Predicting the amount of municipal home help allocated to elderly recipients in an urban area of Sweden. *Health Soc Care Community* 2005; **13**: 366–377.
16 Bellander T, Berglind N, Gustavsson P, Jonson T, Nyberg F, Pershagen G *et al.* Using geographic information systems to assess individual historical exposure to air pollution from traffic and house heating in Stockholm. *Environ Health Perspect* 2001; **109**: 633–639.
17 Johansson C, Hadenius A, Johansson P-Å, Jonson T. SHAPE: The Stockholm study on health effects of air pollution and their economic consequences. Part 1: NO2 and particulate matter in Stockholm [Internet] 1999[cited 2015 Jan 23] 1999: 41. Available from http://slb.nu/slb/rapporter/pdf8/lvf1998_006.pdf.
18 Johansson C, Eneroth K. TESS–Traffic Emissions, Socioeconomic valuation and Socioeconomic measures, Part 1: Emissions and exposure of particles and NOx in

Greater Stockholm. Stockholm and Uppsala County Air Quality Management Association Report LVF [Internet]. 2007:2. [cited 2015 Jan 23] Available from http://slb.nu/slb/rapporter/pdf8/lvf2007_002.pdf.
19 Johansson C, Norman M, Gidhagen L. Spatial & temporal variations of PM10 and particle number concentrations in urban air. *Environ Monit Assess* 2007; **127**: 477–487.
20 Omstedt G, Bringfelt B, Johansson C. A model for vehicle-induced non-tailpipe emissions of particles along Swedish roads. *Atmospheric Environment* 2005; **39**: 6088–6097.
21 Sjödin Å, Ferm M, Björk A, Rahmberg M, Gudmundsson A, Swietlicki E *et al.* Wear particles from road traffic-a field, laboratory, and modelling study. Goteborg. IVL Swedish Environmental Research Institute Ltd.[Internet]: Sweden, 2010 [cited 2015 Jan 23] Available from http://www.ivl.se/webdav/files/B-rapporter/B1830.pdf.
22 Denby B, Sundvor I, Johansson C, Pirjola L, Ketzel M, Norman M *et al.* A coupled road dust and surface moisture model to predict non-exhaust road traffic induced particle emissions (NORTRIP). Part 1: Road dust loading and suspension modelling. *Atmospheric Environment* 2013; **77**: 283–300.
23 Gidhagen L, Johansson C, Langner J, Foltescu V. Urban scale modeling of particle number concentration in Stockholm. *Atmospheric Environment* 2005; **39**: 1711–1725.
24 Johansson C, Hadenius A, Johansson P-Å, Jonson T. SHAPE: The Stockholm study on health effects of air pollution and their economic consequences. Part 1: NO2 and particulate matter in Stockholm VAEGVERKET. PUBLIKATION [Internet]. 1999: 41[cited 2015 Jan 23] 1401-9612 Available from http://www.ivl.se/webdav/files/B-rapporter/B1830.pdf.
25 Eneroth K, Johansson C, Bellander T. Exposure comparison between measurements and calculations based on dispersion modelling (EXPOSE). Stockholm Environment and Health Protection Administration[Internet]. 2006. [cited 2015 Jan 23] Available from http://slb.nu/slb/rapporter/pdf8/lvf2006_012.pdf.
26 Johansson C, Andersson C, Bergström R, Krecl P. Exposure to particles due to local and non-local sources in Stockholm: estimates based on modelling and measurements 1997-2006. *ITM RAPPORT* 2008, Department of Applied Environmental Science, Stockholm University: Stockholm (Sweden). ITM report 175.
27 de Hoogh K, Korek M, Vienneau D, Keuken M, Kukkonen J, Nieuwenhuijsen MJ *et al.* Comparing land use regression and dispersion modelling to assess residential exposure to ambient air pollution for epidemiological studies. *Environ Int* 2014; **73**: 382–392.
28 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**: 177–188.
29 Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21**: 1539–1558.
30 Yorifuji T, Kashima S, Tsuda T, Ishikawa-Takata K, Ohta T, Tsuruta K *et al.* Long-term exposure to traffic-related air pollution and the risk of death from hemorrhagic stroke and lung cancer in Shizuoka, Japan. *Sci Total Environ* 2013; **443**: 397–402.
31 Atkinson RW, Carey IM, Kent AJ, van Staa TP, Anderson HR, Cook DG. Long-term exposure to outdoor air pollution and incidence of cardiovascular diseases. *Epidemiology* 2013; **24**: 44–53.
32 Chen H, Goldberg MS, Burnett RT, Jerrett M, Wheeler AJ, Villeneuve PJ. Long-term exposure to traffic-related air pollution and cardiovascular mortality. *Epidemiology* 2013; **24**: 35–43.
33 Miller KA, Siscovick DS, Sheppard L, Shepherd K, Sullivan JH, Anderson GL *et al.* Long-term exposure to air pollution and incidence of cardiovascular events in women. *N Engl J Med* 2007; **356**: 447–458.
34 Täppefur M. Air pollution in Stockholm and Uppsala Counties, and in Gävle and Sandviken municipalities. Emission data for year 2011. SLB-ANALYS. 2011; APRIL 2013.
35 Ozkaynak H, Baxter LK, Dionisio KL, Burke J. Air pollution exposure prediction approaches used in air pollution epidemiology studies. *J Expo Sci Environ Epidemiol* 2013; **23**: 566–572.
36 Vidale S, Bonanomi A, Guidotti M, Arnaboldi M, Sterzi R. Air pollution positively correlates with daily stroke admission and in hospital mortality: a study in the urban area of Como, Italy. *Neurol Sci* 2010; **31**: 179–182.
37 Wellenius GA, Schwartz J, Mittleman MA. Air pollution and hospital admissions for ischemic and hemorrhagic stroke among medicare beneficiaries. *Stroke* 2005; **36**: 2549–2553.
38 Chan CC, Chuang KJ, Chien LC, Chen WJ, Chang WT. Urban air pollution and emergency admissions for cerebrovascular diseases in Taipei, Taiwan. *Eur Heart J* 2006; **27**: 1238–1244.
39 Andersen ZJ, Olsen TS, Andersen KK, Loft S, Ketzel M, Raaschou-Nielsen O. Association between short-term exposure to ultrafine particles and hospital admissions for stroke in Copenhagen, Denmark. *Eur Heart J* 2010; **31**: 2034–2040.
40 Oudin A, Stromberg U, Jakobsson K, Stroh E, Bjork J. Estimation of short-term effects of air pollution on stroke hospital admissions in southern Sweden. *Neuroepidemiology* 2010; **34**: 131–142.
41 Oudin A, Stroh E, Stromberg U, Jakobsson K, Bjork J. Long-term exposure to air pollution and hospital admissions for ischemic stroke. A register-based case-control study using modelled NO(x) as exposure proxy. *BMC Public Health* 2009; **9**: 301.
42 Yamazaki S, Nitta H, Ono M, Green J, Fukuhara S. Intracerebral haemorrhage associated with hourly concentration of ambient particulate matter: case-crossover analysis. *Occup Environ Med* 2007; **64**: 17–24.
43 Hoek G, Krishnan RM, Beelen R, Peters A, Ostro B, Brunekreef B *et al.* Long-term air pollution exposure and cardio- respiratory mortality: a review. *Environ Health* 2013; **12**: 43.
44 Cesaroni G, Forastiere F, Stafoggia M, Andersen ZJ, Badaloni C, Beelen R *et al.* Long term exposure to ambient air pollution and incidence of acute coronary events: prospective cohort study and meta-analysis in 11 European cohorts from the ESCAPE Project. *BMJ* 2014; **348**: f7412.
45 Beelen R, Raaschou-Nielsen O, Stafoggia M, Andersen ZJ, Weinmayr G, Hoffmann B *et al.* Effects of long-term exposure to air pollution on natural-cause mortality: an analysis of 22 European cohorts within the multicentre ESCAPE project. *Lancet* 2014; **383**: 785–795.
46 Koster M, Asplund K, Johansson A, Stegmayr B. Refinement of Swedish administrative registers to monitor stroke events on the national level. *Neuroepidemiology* 2013; **40**: 240–246.

Supplementary Information accompanies the paper on the Journal of Exposure Science and Environmental Epidemiology website (http://www.nature.com/jes)