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http://dx.doi.org/10.1289/ehp.1307301
Received: 1 July 2013
Accepted: 15 May 2014
Advance Publication: 16 May 2014

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Running title: Long-term exposure to air pollution and stroke

Acknowledgments: The research leading to these results has received funding from the European Community's Seventh Framework Program (FP7/2007-2011) under grant agreement number: 211250. For the Finnish part, additional funding came from the Academy of Finland (project number 129317). The four Swedish cohorts (SNAC-K, SALT, 60y, SDPP) were partially funded by the Swedish Environmental Protection Agency, the Swedish Council for Working Life and Social Research and the Swedish Heart-Lung Foundation. The SALT cohort was additionally supported by NIH grant AG-08724. The 60y cohort was additionally funded by the Stockholm County Council and the Swedish Research Council (longitudinal research and 0593). The SDPP cohort was additionally funded by the Stockholm County Council; the Swedish Research Council; the Swedish Diabetes Association; and the Novo Nordisk Scandinavia. We thank the Heinz Nixdorf Foundation, the German Ministry of Education and Science (BMBF), the German Aerospace Center (Deutsches Zentrum für Luft- und Raumfahrt (DLR)), and the German Research Foundation (DFG HO 3314/2-1 and JO170/8-1), Bonn, Germany, for their generous support of this study. The KORA research platform and the MONICA Augsburg studies were initiated and financed by the Helmholtz Zentrum München, German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education and Research and by the State of Bavaria. The SIDRIA cohort study was partially funded by the Italian Ministry of Health. We thank Simone Bucci, Marloes Eeftens, and Pekka Tiittanen for their help with exposure assessment and data management. For the Finnish part, exposure

assessment was performed by Tarja Yli-Tuomi, Pekka Taimisto, and Arto Pennanen. Mortality, area-level SES, and building data were provided by Statistics Finland. Giuseppe Costa and Roberta Onorato provided data from the Turin Longitudinal Study. Exposure assessment in Turin was performed by Daniela Raffaele and Marco Gilardetti. Noise assessment in Turin was performed by Daniele Grasso and Jacopo Fogola, from the Regional Agency for the Protection of the Environment of Piedmont.

Competing financial interests: No competing financial interest.

Abstract

Background: Few studies have investigated effects of air pollution on the incidence of cerebrovascular events.

Objectives: We assessed the association between long-term exposure to multiple air pollutants and the incidence of stroke in European cohorts.

Methods: Data from 11 cohorts were collected and occurrence of a first stroke was evaluated. Individual air pollution exposures were predicted from land-use regression models developed within the "European Study of Cohorts for Air Pollution Effects" (ESCAPE). The exposures were: $PM_{2.5}$ (particulate matter [PM] below 2.5 μm in diameter), coarse PM (PM between 2.5 and 10 μm), PM_{10} (PM below 10 μm), $PM_{2.5}$ absorbance, nitrogen oxides, and two traffic indicators. Cohort-specific analyses were conducted using Cox proportional hazards models. Random-effects meta-analysis was used for pooled effect estimation.

Results: 99,446 subjects were included, 3,086 of whom developed stroke. A 5-$\mu g/m^3$ increase in annual $PM_{2.5}$ exposure was associated with 19% increased risk of incident stroke (hazard ratio [HR] = 1.19, 95% confidence interval [CI]: 0.88, 1.62). Similar findings were obtained for PM_{10}. The results were robust to adjustment for an extensive list of cardiovascular risk factors and noise co-exposure. The association with $PM_{2.5}$ was apparent among those aged 60+ years (HR = 1.40, 95% CI: 1.05, 1.87), among never-smokers (HR = 1.74, 95% CI: 1.06, 2.88), and among subjects with $PM_{2.5}$ exposure below 25 $\mu g/m^3$ (HR = 1.33, 95% CI: 1.01, 1.77).

Conclusions: We found suggestive evidence of an association between fine particles and incidence of cerebrovascular events in Europe, even at lower concentrations than set by the current air quality limit value.

Introduction

Air quality standards are under revision in Europe, and a new policy is due by the European Parliament. As part of this process, the EU has indicated several specific issues of concern when considering the chronic effects of long-term exposure to ambient air pollution, especially the effects of fine particulate matter (PM with aerodynamic diameter less than 2.5 microns, $PM_{2.5}$) on cardiovascular and respiratory health in Europe.

Substantial evidence from large studies conducted in the United States (Krewski et al. 2009; Laden et al. 2006; Miller et al. 2007) and Canada (Crouse et al. 2012) has documented effects of fine particles on natural and cardiopulmonary mortality as the primary endpoints. Only a limited number of studies have been conducted in Europe (Andersen et al. 2012; Atkinson et al. 2013; Brunekreef et al. 2009; Filleul et al. 2005; Gehring et al. 2006), mostly including only one cohort from a single country, and focusing on the intra-cohort spatial contrasts rather than on differences across study areas. It is therefore uncertain to what degree the results can be generalized to other areas in Europe. In recent years, some attempts have also been made to investigate the relationship between long-term air pollution exposure and incidence of cerebrovascular disease, providing conflicting evidence (Andersen et al. 2012; Atkinson et al. 2013; Krewski et al. 2009; Miller et al. 2007). Recently, Maaten and Brook (2011) indicated that the relationship "merits further attention on global research and public policy agendas".

Biological mechanisms linking long-term air pollution exposure to chronic damage of the cardiovascular system may include endothelial dysfunction and vasoconstriction, increased blood pressure, prothrombotic and coagulant changes, systemic inflammatory and oxidative stress responses, autonomic imbalance and arrhythmias, and the progression of atherosclerosis. On these bases, the American Heart Association delivered a scientific statement concluding that the

overall evidence is consistent with PM playing a causal role in cardiac morbidity and mortality (Brook et al. 2010). For cerebrovascular diseases, several studies have indicated the effects of short-term exposures potentially leading to ischemic stroke (O'Donnell et al. 2011; Wellenius et al. 2012). However, the evidence of a link between long-term exposure to air pollution and cerebrovascular events is less developed.

The ESCAPE project was designed to assess the long-term exposure of the population to air pollution and to investigate exposure-response relationships and thresholds for a number of adverse health outcomes (ESCAPE 2007). The objective of this paper was to estimate the association between long-term exposure to ambient air pollution, especially PM mass, black carbon and nitrogen oxides, and the incidence of stroke in 11 European cohorts. A companion paper focusing on incident coronary events has been recently published (Cesaroni et al. 2014).

Methods

Study population

Individual data were collected for 11 existing cohort studies from Finland, Sweden, Denmark, Germany, and Italy. Individuals had been enrolled at different periods, ranging from 1992 to 2007, and were followed until migration, death, or the occurrence of the study outcome until 2006-2010. Baseline individual data included: socio-demographic characteristics (age, gender, marital status, education, occupation), lifestyle variables (smoking status, smoking intensity and duration, physical activity, alcohol consumption), physiological parameters (body mass index [BMI], cholesterol level), chronic conditions (diabetes, hypertension), and modeled road traffic noise exposure at the residential address. In addition, different area-level socio-economic variables were collected for each cohort. Finally, if the study area included different degrees of

urbanization, a binary "rural" indicator was used to characterize each residential address. Further details are reported in the Supplemental Material, Table S1.

The original cohort studies were approved by appropriate institutional medical ethics committees and undertaken in accordance with the Declaration of Helsinki. Each cohort study followed the rules for ethics and data protection set up in the country in which they were based.

Outcome definition

The identification of first cerebrovascular events during follow-up was accomplished by interview, inspection of medical records and death certificates, or by record-linkage with mortality registries and hospital discharge databases. Prevalent cases of either coronary or cerebrovascular disease at baseline were excluded. Methods to define and ascertain prevalent cases differed between the cohorts, as reported in the Supplemental Material, Methods.

Exposure assessment

Long-term exposure to ambient air pollutants at the residential address of each individual was estimated following a three-step procedure. First, $PM_{2.5}$, $PM_{2.5}$ absorbance, PM_{10}, nitrogen dioxide (NO_2) and nitrogen oxides (NO_x) were measured between October 2008 and April 2011 using standardized protocols (Cyrys et al. 2012; Eeftens et al. 2012b). Coarse PM was calculated as the difference between PM_{10} and $PM_{2.5}$. Second, land-use regression (LUR) models were developed for each study area and pollutant (Beelen et al. 2013a; Eeftens et al. 2012a). Third, individual annual exposures were predicted using these models. In addition, traffic intensity on the nearest road (vehicles/day), and traffic load on major roads within a 100m buffer (product of traffic intensity and length of roads intersecting the buffer) were computed. Noise exposure was

assessed locally, by calculating the day-evening-night equivalent noise level (Lden) for the most exposed façade of dwellings (see Supplemental Material, Methods).

Statistical analysis

We carried out the analyses using a two-stage approach, with cohort-specific analyses in the first stage and random-effects meta-analysis in the second.

At the first stage, we fitted Cox proportional hazards regression models in each cohort, with age as the underlying time variable. All analyses were conducted using a common statistical protocol and STATA script. We defined adjustment models a priori. We defined three degrees of adjustment: 1) estimates adjusted only for gender and calendar year of enrolment (model 1); 2) adjustment for the shared set of potential individual-level confounders: gender, calendar year, marital status, education, occupational status, smoking status, smoking duration among ever smokers, and smoking intensity among current smokers (model 2); 3) adjustment for the shared set of individual-level confounders (model 2) plus one cohort-specific area-level socio-economic variable (model 3, also referred to as the "main" model). All confounders were baseline characteristics and were included as fixed covariates in the regression models. Only subjects with no missing information from any of the exposures and confounders in the "main" model were included in all analyses.

We performed a number of additional analyses within each cohort. First, we addressed the potential effect due to lack of adjustment for relevant cardiovascular risk factors. With this aim, we first adjusted for intermediate variables only (diabetes and hypertension, available in all the cohorts); then we adjusted for cardiovascular confounders available in most cohorts (physical activity, alcohol consumption and body mass index, available in eight cohorts); finally we added

to previously mentioned factors the cholesterol level (available in four cohorts). Second, we added the "rural" indicator to the "main" model to better account for different degrees of urbanization within the study areas. Third, we evaluated potential confounding by noise. Fourth, we restricted the analyses to people who never changed address during follow-up. Fifth, we performed diagnostic tools to check the proportionality-hazard (PH) assumption for the categorical predictors in the "main" model, and stratified the Cox model for the predictors that did not meet the PH assumption. Sixth, we evaluated the potential for spatial clustering by running "frailty" models (Jerrett et al. 2003). Finally, we evaluated the robustness of the results by excluding the most influential cohort (Diet, Cancer and Health - DCH), and by stratifying the cohorts by performance of the LUR model, choosing a cut-off point of 0.6 for the leave-one-out cross-validation (LOOCV) R-squared coefficient (Eeftens et al. 2012a).

Next, we evaluated a number of individual characteristics considered a priori as potential effect modifiers: gender, age during follow-up (< 60 years, 60-74 years, 75+ years), education, smoking status, BMI (< 25 kg/m^2, 25-29 kg/m^2, 30+ kg/m^2), previous diabetes or hypertension, residence in rural/urban area.

Finally, we examined in each cohort the shape of the relationship between each exposure and the study outcome by: 1) inputting the exposure term as a natural cubic spline with three equally-spaced inner knots, and comparing the model fit of the linear and the spline models, via likelihood-ratio test; 2) implementing "threshold models", in which threshold concentrations were defined a priori for each exposure, and cohort-specific models were run only on observations with predicted exposures below each threshold in turn.

In the second stage of the analysis, we pooled the cohort-specific results by random-effects meta-analysis (DerSimonian and Laird 1986). We evaluated the presence of heterogeneity in the cohort-specific results by applying the X^2 test from Cochran's Q statistic, which was then quantified by calculating the I^2 statistic (Higgins and Thompson 2002). We considered cohort-specific effect estimates to be significantly heterogeneous when I^2 was greater than 50% or the p-value of the X^2 test was lesser than 0.05. Finally, we checked the presence of effect modification across strata of each modifier by meta-analyzing the pooled estimates from the different strata, and by performing the X^2 test of heterogeneity. We considered pooled strata-specific effect estimates to be significantly different when the p-value of X^2 test was below 0.10.

We expressed all results as hazard ratios (HR), and 95% confidence intervals (CI), relative to fixed increments in each exposure, defined a priori: 5 $\mu g/m^3$ for $PM_{2.5}$ and coarse PM, 10 $\mu g/m^3$ for PM_{10} and NO_2, 20 $\mu g/m^3$ for NO_x, 10^{-5}/m for $PM_{2.5}$ absorbance, 5000 motor vehicles/day for traffic intensity on the nearest road, and 4,000,000 motor vehicles*m/day for the total traffic load on all major roads within a 100 m buffer.

All first-stage and meta-analyses were fit using the Stata software, version 11 (StataCorp, College Station, TX, USA). The frailty and spline models were fit with the R software, version 2.15.0 (R development Core Team (2011), ISNB 3-90005107-0, URL http://R-project.org).

Results

A total of 111,931 subjects were under study. After the exclusion of the prevalent cases and of subjects with missing exposure, a total of 105,025 subjects remained. However, 5,579 subjects had missing information on any of the variables in the "main" model, therefore 99,446 subjects (88.8% of the original study population, and 92.4% of the original cohorts after exclusion of

prevalent cases) were included in the analyses, providing more than one million person-years of observation. 3,086 incident stroke events were registered during the follow-up. The majority of the stroke cases with defined etiology were coded as ischemic stroke, however 43% of all cases were undefined, thus precluding the possibility of analyzing different types of stroke separately. The baseline age distribution was heterogeneous across cohorts, with mean values ranging from 44 (two Italian cohorts) to 74 (a Swedish cohort) years while gender, education, and occupation had less variability. The percentage of current smokers at baseline was the highest in southern Europe and the lowest in Sweden and Germany (Table 1). The comparison of the studied population before and after the exclusion of the subjects with missing data on the confounders did not show differences in relation to air pollution exposure (i.e. $PM_{2.5}$) and occurrence of the study outcome.

A map of the study areas and further details on individual and area-level characteristics can be found in Supplemental Material, Figure S1 and Table S1. Exposure levels and ranges were generally higher in Italy than in the other areas (Table 2). More details on air pollution exposures are reported in the Tables S2 and S3 of the Supplemental Material.

Table 3 shows the HR, and 95% CI, from models 1, 2 and 3 (the "main" model) for all pollutants and traffic variables. Estimates were the highest in the first model, and significantly heterogeneous for most exposures. Estimates and heterogeneity decreased when adjusting for the common set of individual-level and area-level confounders, however heterogeneity remained in the "main" model for $PM_{2.5}$. None of the associations was statistically significant. The highest estimate was found with $PM_{2.5}$: a 5-$\mu g/m^3$ increase in $PM_{2.5}$ was associated with a 19% increased risk of incident stroke (HR = 1.19, 95% CI: 0.88, 1.62, I^2 = 49%). $PM_{2.5}$ and PM_{10} cohort-specific and pooled results are reported in Supplemental Material, Figure S2.

The main $PM_{2.5}$ results were robust to confounding adjustment and to model specification as found in extensive sensitivity analyses (Table 4). There were no relevant departures from the results of the "main" model when intermediate variables, additional cardiovascular risk factors, "rural" indicator or noise co-exposure were adjusted for, or when stratified Cox models were implemented on the predictors that did not meet the PH assumption. Also, the results did not change when spatial autocorrelation was accounted for with "frailty" models (not shown). We found marked differences in the $PM_{2.5}$ associations with incident stroke depending on the precision of the cohort-specific land-use regression models in predicting individual $PM_{2.5}$, with a significant estimate in the 6 cohorts with LOOCV R-squared coefficients above 0.6 (HR = 1.75, 95% CI: 1.30, 2.35), and no association in the other 5 cohorts (HR = 0.89, 95% CI: 0.70, 1.13).

The results of the effect modification analysis are reported in Figure 1, together with the p-values for heterogeneity across the pooled strata-specific estimates. There was a suggestion of effect modification by age (p-value 0.09), with a null effect below 60 years (563 cases, HR = 0.81, 95% CI: 0.81, 1.18) and higher effects in the 60-74 years (1,960 cases, HR = 1.22, 95% CI: 0.93, 1.61) and 75+ years (563 cases, HR = 1.62, 95% CI: 0.91, 2.90) categories. The hazard ratio for those 60+ years was 1.40 (95% CI: 1.05, 1.87) with little evidence of heterogeneity in the cohort-specific estimates (I^2 = 25.8%, p-value of heterogeneity 0.20, results not shown). Never-smokers had a significantly higher estimate of $PM_{2.5}$ on the risk of incident stroke, with an increased risk of 74% (HR = 1.74, 95% CI: 1.06, 2.88).

The results from threshold models are reported in Table 5. We chose three exposure thresholds a priori: 25 $\mu g/m^3$ (the current air quality limit value for annual average $PM_{2.5}$ concentration in Europe), 20 $\mu g/m^3$, and 15 $\mu g/m^3$. The association between $PM_{2.5}$ below 20 $\mu g/m^3$ and incident

stroke was high and borderline significant (HR = 1.29, 95% CI: 1.00, 1.68) for the 9 cohorts with individuals below such concentrations. For the 7 cohorts with $PM_{2.5}$ concentrations below all the chosen thresholds, there was a 33% increased risk of incident stroke (HR = 1.33, 95% CI: 1.01, 1.77) for each 5-$\mu g/m^3$ increase in $PM_{2.5}$. The comparison of the linear and spline models suggested the linear shape of the concentration-response function as a good approximation for most of the cohorts (data not shown).

Discussion

This first multi-center European study on long-term exposure to ambient air pollution and stroke incidence found suggestive evidence of an association between $PM_{2.5}$ exposure and stroke incidence although the main estimate did not reach statistical significance. The results were robust to confounding adjustment and model specification. Stronger associations were estimated among subjects 60+ years old, never-smokers and when all subjects exposed to $PM_{2.5}$ concentrations above 20 $\mu g/m^3$ were removed from the analysis.

Most of the evidence on the effects of air pollution on stroke comes from time series studies of cerebrovascular or stroke mortality (Maynard et al. 2007; O'Donnell et al. 2011; Wellenius et al. 2012). Evidence from previous studies on long-term effects is conflicting (Maaten and Brook 2011). The Women's Health Initiative cohort study (Miller et al. 2007) found a 28% increased risk of stroke incidence in women (HR = 1.28, 95% CI: 1.02, 1.61) per 10 $\mu g/m^3$ increase in $PM_{2.5}$, which is similar to the estimate of the present study, 38% excess risk for 10 $\mu g/m^3$ $PM_{2.5}$ increments. In contrast, previous analyses of the American Cancer Society cohort (Krewski et al. 2009) and on a Norwegian cohort (Nafstad et al. 2004) failed to identify effects of air pollution on stroke mortality. More recently, a large prospective study conducted within the Danish Diet,

Cancer and Health (DCH) cohort (which also contributes to the present analysis) detected a borderline significant associations between NO_2 and incident stroke (HR = 1.05, 95% CI: 0.99, 1.11, per 5.7 $\mu g/m^3$ increase in NO_2) (Andersen et al. 2012). In the present study, there was no association between long-term NO_2 exposure and incident stroke in the DCH cohort. It should be considered that there are differences in the results reported from the DCH cohort: first, the whole cohort including the two largest cities in Denmark, Aarhus and Copenhagen, contributed to the previous analysis, for a total of 52,215 subjects, whereas only the Copenhagen part of the cohort was included in the present study (36,215 subjects); second, the exposure assessment was different, because a dispersion model was used in the first analysis, with NO_2 exposure assessed all the way back to 1971 and the mean from 1971 until the end of follow-up was used. A recent study in the UK found no relationship between long-term air pollution exposure and stroke incidence (Atkinson et al. 2013).

We noted significant heterogeneity in association estimates for most exposures. With the exception of the KORA cohort, all of the younger cohorts have point estimates for HRs, though non-significant, at or below 1. When we restricted the study population to those over the age of 60, in the light of the results of effect modification analyses suggesting the lowest risk is for those <60 and the highest for those > 74 years of age, we found that the heterogeneity was reduced (from $I^2 = 49.2\%$, p-value of heterogeneity = 0.032 for all ages, to $I^2 = 25.8\%$, p-value heterogeneity = 0.20) and the increased relative risk was borderline statistically significant. Therefore, the different age composition of the cohorts seems to be the most plausible interpretation for the heterogeneity. However, it should be considered that a correlation was present between age and various characteristics of the cohorts (prevalence of smoking, quality of the LUR models, levels of air pollution exposures, and quality of the outcome assessment) with

older cohorts having lower smoking rates, higher LUR LOOCV R-squared coefficients, lower $PM_{2.5}$ levels, and stroke ascertainment based on expert medical record review in addition to mortality and hospitalization databases. It is therefore likely that any combination of these factors, not only age, might have been responsible for the heterogeneity in the associations across cohorts that we found. In addition, this is the most likely explanation for the stronger associations at lower exposure levels (below 20 $\mu g/m^3$ $PM_{2.5}$), for the cohorts with the highest LOOCV R-squared coefficients, better case ascertainment, and for the result among never smokers.

In any case, the result for never smokers is relevant as it indicates limited possibility of residual confounding from smoking and that the relative effect of ambient air pollution on stroke incidence is more easily detectable in the absence of a strong risk factor for stroke such as active smoking.

A few limitations of the present study should be mentioned. First, air pollution measurement campaigns were implemented between 2008 and 2011, after the follow-up period of most cohorts (Cyrys et al. 2012; Eeftens et al. 2012b). As a consequence, this study relies on the assumption that the intra-cohort spatial distribution of air pollution has not dramatically changed in the last 10-15 years, and that the land-use model predictions are thus representative of the baseline spatial contrasts for all the cohorts investigated. Several studies in the literature support this assumption over periods of about 10 years (Cesaroni et al. 2012; Eeftens et al. 2011). In addition, within the ESCAPE project many efforts were made to back-extrapolate air pollution concentrations, taking into account long-term time trends (see Supplemental Material, Methods), and analyses relating back-extrapolated data to the health outcomes showed no clear differences in the results compared with original data (results not shown). We also performed an exploratory

analysis to evaluate whether the association between $PM_{2.5}$ and stroke incidence differed according to accrual time, under the hypothesis that the assumption of stable spatial distribution of air pollution over time could be more valid for more recent cohorts: we did not find meaningful differences in the association estimates across cohorts according to accrual time (results not shown). Second, our approach exploited only within-study area contrasts, which has limited the exposure contrast, but decreased the risk of potential confounding when comparing diverse cohorts from different countries. Third, the data available to adjust for confounding were somewhat different from cohort to cohort, allowing the possibility of different degrees of residual confounding in the cohort-specific results. However, the most relevant cardiovascular risk factors (smoking, diabetes or hypertension, BMI, physical activity) were available in almost all the cohorts, and thus severe bias in the effect estimates due to residual confounding is unlikely. Finally, we did not consider the possible impact of loss to follow-up (drop out or death) on the findings. Air pollution exposure is an established cause of mortality, so that older participants are likely to represent a population that is "selected" such that those who sustained higher exposures are more likely to have characteristics (genetic or otherwise) that place them at lower risk for stroke, resulting in underestimation of the causal relation of exposure with stroke risk. However, given the small relative risk of the air pollution-mortality association (i.e. HR < 1.10 for 5 $\mu g/m^3$ increase in $PM_{2.5}$ or 10 $\mu g/m^3$ increase in PM_{10} or NO_2 as reported in Beelen et al. 2013b), this underestimation is likely to be small.

This study has several strengths. The exposure assessment, one of the most critical aspects of this kind of study, was performed in a rigorous way with standardized procedures across all study areas (Cyrys et al. 2012; Eeftens et al. 2012b). The LOOCV R-squared coefficients from the $PM_{2.5}$ land-use regression models ranged from 0.53 in Finland to 0.79 in Germany (Ruhr Area),

denoting strong discriminatory power of the spatial attributes used in these models to capture the spatial contrasts of exposures within the study areas (Eeftens et al. 2012a). An additional point of merit is the extensive list of variables available for confounding adjustment, including cardiovascular mediators and confounders, road traffic noise exposure at each residence and the urban/rural indicator used to characterize the degree of urbanization of each study area. Also, the statistical modeling was rigorously standardized between cohorts and addressed several methodological issues, including the potential for spatial autocorrelation of the study outcomes, and the linearity of the relationship between long-term air pollution exposure and stroke incidence.

Conclusions

In summary, we found suggestive evidence of an association between long-term exposure to fine particles and stroke incidence in 11 European cohorts, especially among subjects aged 60+ years and never-smokers. The association was also observed below current European limit values, which indicates harmful effects of fine particles even at low concentrations.

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Table 1. Study population: individual baseline characteristics, 11 cohorts.

Variables	FINRISK	SNAC-K	SALT	60y	SDPP	DCH	HNR	KORA	EPIC Turin	SIDRIA Turin	SIDRIA Rome
n subjects	9,995	2,684	6,084	3,686	7,723	35,693	4,433	7,581	7,230	5,137	9,200
Person-years at risk	105,060	16,256	51,756	39,978	106,995	464,055	34,941	76,027	91,490	56,366	102,894
% of the original cohort[a]	89.3	79.8	86.4	87.1	97.2	90.5	92.1	83.2	82.4	95.1	86.8
n cases	184	164	216	125	107	1,848	71	210	55	37	69
Years of enrollment	1992, 1997, 2002, 2007	2001-2004	1998-2002	1997-1999	1992-1998	1993-1997	2000-2003	1994-1995, 1999-2001	1993-1998	1999	1999
Individual characteristics											
Age, years: mean (minimum - maximum)	48 (25-74)	74 (60-102)	59 (42-97)	60 (59-61)	47 (35-56)	57 (50-66)	59 (45-75)	50 (25-82)	50 (35-67)	44 (27-76)	44 (28-63)
Gender: % females	55	65	58	53	61	54	52	51	48	52	53
Marital status											
% single	16	15	14	5	17[b]	7	6	10	6	2	0
% married/living with partner	70	47	67	71	83	69	75	77	86	95	100
% divorced/separated	11	13	11	17	-	18	10	7	5	1	0
% widowed	3	25	8	7	-	6	9	6	3	2	0
Education											
% primary school or less	30	27	21	28	26	30	11	12	44	17	45
% up to secondary school or equivalent	52	42	43	44	45	47	56	75	43	71	40
% university degree and more	17	31	36	28	29	23	33	13	14	11	15
Occupation status											
% employed/self-employed	71	75	-	51	92	80	42	60	-	73	71
% unemployed	6	25[c]	-	10	8[c]	20[c]	6	3	-	7	4
% homemaker/housewife	4	-	-	8	-	-	14	14	-	21	25
% retired	19	-	-	31	-	-	38	23	-	0	0
Smoking status											
% current smoker	26	15	23	21	26	36	23	25	24	41	42
% former smoker	28	34	43	38	36	28	33	31	33	21	23
% never smoker	46	51	35	40	37	36	43	44	43	38	34
Years of smoking, among ever smokers: mean ± SD	15 ± 12	30 ± 17	-	26 ± 13	20 ± 10	29 ± 10	36 ± 9[d]	21 ± 12	23 ± 10	18 ± 8	18 ± 7
Number of cigarettes/day, among current smokers: mean ± SD	15 ± 9	11 ± 8	13 ± 8	13 ± 7	14 ± 7	17 ± 10	17 ± 12	15 ± 11	14 ± 9	15 ± 9	15 ± 9

Abbreviations: SNAC-K, Swedish National Study on Aging and Care in Kungsholmen; SALT, Screening Across the Lifespan Twin study; 60y, 60-year-olds study; SDPP, Stockholm Diabetes Prevention Program study; DCH, Danish Diet, Cancer and Health cohort study; HNR, Heinz Nixdorf Recall Study; KORA, Cooperative Health Research in the Augsburg Region; EPIC, European Prospective Investigation into Cancer and Nutrition; SIDRIA, International Study on Asthma and Allergies in Childhood.

[a]After exclusion of prevalent cases and observations with missing information on any of the variables in the "base" model. [b]All except married/living with partner. [c]All except employed. [d]Only among current smokers.

Table 2. Study population: environmental exposures at residential address, 11 cohorts.

Exposure	FINRISK	SNAC-K	SALT	60y	SDPP	DCH	HNR	KORA	EPIC-Turin	SIDRIA-Turin	SIDRIA-Rome
Environmental exposures at residential address											
$PM_{2.5}$, mg/m^3: mean (5-95 pct. range)	8 (6-9)	8 (6-10)	7 (5-9)	7 (5-9)	7 (5-8)	11 (10-13)	18 (17-20)	14 (12-15)	30 (27-33)	31 (29-34)	19 (17-23)
Coarse PM, mg/m^3: mean (5-95 pct. range)	7 (4-11)	8 (1-19)	7 (2-12)	7 (1-12)	6 (1-9)	6 (4-7)	10 (7-12)	6 (5-8)	16 (12-20)	17 (13-20)	17 (12-24)
PM_{10}, mg/m^3: mean (5-95 pct. range)	14 (10-20)	16 (6-29)	15 (7-21)	15 (7-21)	14 (6-17)	17 (14-20)	28 (25-32)	20 (16-24)	46 (39-52)	48 (41-54)	36 (31-47)
$PM_{2.5}$ absorbance, units: mean (5-95 pct. range)	0.9 (0.5-1.2)	0.8 (0.5-1.2)	0.6 (0.4-0.9)	0.6 (0.4-0.9)	0.5 (0.4-0.7)	1.2 (0.8-1.5)	1.6 (1.2-2.2)	1.7 (1.5-2.0)	3.1 (2.3-3.6)	3.2 (2.6-3.8)	2.7 (2.2-4.0)
NO_2, mg/m^3: mean (5-95 pct. range)	15 (9-24)	17 (9-25)	11 (7-20)	11 (6-20)	8 (6-11)	16 (8-30)	30 (23-39)	19 (14-26)	53 (34-68)	60 (42-77)	39 (26-56)
NO_x, mg/m^3: mean (5-95 pct. range)	24 (14-41)	33 (15-58)	19 (12-40)	19 (12-39)	14 (12-20)	27 (7-66)	51 (33-72)	32 (24-47)	96 (62-132)	107 (79-162)	82 (39-122)
Background NO_2, mg/m^3: mean (5-95 pct. range)	15 (10-19)	16 (12-19)	11 (6-17)	10 (5-17)	7 (4-10)	14 (8-20)	26 (24-30)	18 (14-24)	39 (27-45)	40 (33-45)	41 (29-53)
Daily number of vehicles on the nearest road: mean (5-95 pct. range)	1,670 (50-9,011)	3,726 (500-21,828)	1,454 (500-6,000)	1,455 (500-6,300)	864 (500-2,575)	2,994 (200-16,145)	-	1,613 (500-8,367)	3,907 (0-23,951)	4,290 (0-24,379)	2,966 (500-15,312)
Total traffic load (intensity*length) on major roads in a 100m buffer: mean (5-95 pct. range), thousand	633 (0-3,711)	2,307 (0-6,572)	578 (0-3,437)	521 (0-3,048)	109 (0-986)	1,274 (51-4,719)	1,017 (0-4,302)	438 (0-2,790)	466 (0-2,340)	804 (0-4,197)	1,417 (0-6,947)
Pearson correlations between $PM_{2.5}$ and:											
PM_{10}	0.67	0.70	0.49	0.50	0.31	0.74	0.90	0.42	0.62	0.56	0.92
Coarse PM	0.10	0.71	0.50	0.50	0.32	0.60	0.51	0.38	0.51	0.32	0.90
$PM_{2.5}$ absorbance	0.98	0.98	0.84	0.84	0.90	0.49	0.76	0.50	0.77	0.73	0.78
NO_2	0.41	0.82	0.60	0.61	0.61	0.57	0.63	0.45	0.72	0.67	0.69

Abbreviations: SNAC-K, Swedish National Study on Aging and Care in Kungsholmen; SALT, Screening Across the Lifespan Twin study; 60y, 60-year-olds study; SDPP, Stockholm Diabetes Prevention Program study; DCH, Danish Diet, Cancer and Health cohort study; HNR, Heinz Nixdorf Recall Study; KORA, Cooperative Health Research in the Augsburg Region; EPIC, European Prospective Investigation into Cancer and Nutrition; SIDRIA, International Study on Asthma and Allergies in Childhood; $PM_{2.5}$, particulate matter < 2.5 μm; PM_{10}, particulate matter < 10 μm; NO_2: nitrogen dioxide; NO_x: nitrogen oxides

Table 3. Association between air pollution exposures and stroke incidence in the 11 cohorts under study.

Exposure	Fixed increase	*n* cohorts	*n* subjects	Model 1: Adjusted for age, year of enrolment and gender HR (95% CI)	Model 2: Model 1 + common set of individual-level confounders[a] HR (95% CI)	Model 3: Model 2 + area-level variable[b] ("main" model) HR (95% CI)
$PM_{2.5}$	5 mg/m^3	11	99,446	1.26 (0.92, 1.71)*	1.16 (0.88, 1.53)	1.19 (0.88, 1.62)*
Coarse PM	5 mg/m^3	11	99,446	1.07 (0.92, 1.24)	1.02 (0.89, 1.18)	1.02 (0.90, 1.16)
PM_{10}	10 mg/m^3	11	99,446	1.15 (0.91, 1.46)*	1.11 (0.90, 1.36)	1.11 (0.90, 1.36)
$PM_{2.5}$ absorbance	10^{-5}/m	11	99,446	1.17 (0.86, 1.59)*	1.08 (0.82, 1.42)	1.08 (0.83, 1.41)
NO_2	10 mg/m^3	11	99,446	1.04 (0.91, 1.19)*	1.00 (0.88, 1.14)*	0.99 (0.89, 1.11)
NO_x	20 mg/m^3	11	99,446	1.04 (0.94, 1.16)	1.01 (0.91, 1.12)	0.98 (0.89, 1.07)
Traffic intensity on the nearest road	5,000 mv/day	10[c]	95,013	1.00 (0.97, 1.02)	0.99 (0.97, 1.02)	0.99 (0.97, 1.02)
Traffic load on major roads in a 100m buffer	4,000,000 mv/day*m	11	99,446	1.05 (0.97, 1.13)	1.02 (0.95, 1.10)	1.02 (0.95, 1.10)

Abbreviations: $PM_{2.5}$, particulate matter < 2.5 μm; PM_{10}, particulate matter < 10 μm; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; mv, motor vehicles; HR, hazard ratio; CI, confidence interval.

[a]Adjusted for: age, year of enrolment, gender, marital status, education level, occupation status, smoking status, years of smoking (among ever smokers), cigarettes/day (among current smokers). [b]FINRISK: median income rate in a 3x3 km grid; SNAC-K: mean income in tertiles, at small neighborhoods level (Small Areas for Market Statistics (SAMS) based on election districts or similar, from Statistics Sweden); SALT and SDPP: mean income in 4 categories, at municipality levels (area widths ranging from 9 km2 to 5,870 km2); 60y: mean income in quartiles, at small neighborhoods level (Small Areas for Market Statistics (SAMS) based on election districts or similar, from Statistics Sweden); DCH: mean income at municipality level (16 units, median population ~1500 inhabitants), per/100,000; HNR: unemployment rate, neighborhood level; KORA: percentage of low income in 5x5 km grid; EPIC-Turin, SIDRIA-Turin and SIDRIA-Rome: deprivation index, census-block level (average population ~ 500 inhabitants). [c]All except HNR.

*Statistically significant heterogeneity, as indicated by $p<0.05$ from Cochran's Q or I^2 >50%.

Table 4. Association between $PM_{2.5}$ exposure and stroke incidence in the 11 cohorts under study. Results of the sensitivity analyses.

Model	*n* cohorts	*n* subjects	HR (95% CI)
"Main" model	11	99,446	1.19 (0.88, 1.62)*
Role of cardiovascular risk factors			
Intermediate variables: diabetes and hypertension			
+ diabetes and hypertension	11	99,446	1.15 (0.84, 1.56)*
Physical activity, alcohol consumption and BMI			
"Main" model, on subset of subjects with additional information	8[a]	76,599	1.32 (0.87, 2.00)*
+ additional information	8[a]	76,599	1.30 (0.86, 1.97)*
All cardiovascular risk factors (diabetes, hypertension, physical activity, alcohol, BMI, cholesterol)[b]			
"Main" model, on subset of subjects with additional information	4[b]	24,948	1.91 (0.96, 3.82)*
+ additional information	4[b]	24,948	1.88 (0.99, 3.57)*
Urban/rural			
+ rural indicator	11	99,446	1.18 (0.87, 1.59)
Noise			
"Main" model, on subset of subjects with additional information	9[c]	73,121	1.25 (0.92, 1.71)
+ noise variable	9[c]	73,121	1.26 (0.89, 1.78)
Change of address during follow-up			
"Main" model, on cohorts with change of address data	10[d]	92,216	1.26 (0.93, 1.72)
no change of address during follow-up	10[d]	62,799	1.19 (0.81, 1.76)
Proportionality-hazards assumption			
Variables which don't meet PH put as strata	11	99,446	1.20 (0.89, 1.62)
Exclusion of DCH cohort			
10 cohorts (all except DCH)	10	63,753	1.22 (0.86, 1.75)[f]
Performance of the LUR model			
LOOCV R2 coefficient > 0.6	6[e]	32,191	1.75 (1.30, 2.35)
LOOCV R2 coefficient ≤ 0.6	5[f]	67,255	0.89 (0.70, 1.13)

Abbreviations: $PM_{2.5}$, particulate matter < 2.5 μm; HR, hazard ratio; CI, confidence interval; DCH, Danish Diet, Cancer and Health cohort study; LUR, land-use regression; LOOCV, leave-one-out cross-validation; BMI, body-mass index.

[a]All cohorts except SALT, SIDRIA-Turin and SIDRIA-Rome. [b]Include FINRISK, 60y, HNR and KORA. [c]All cohorts except SDPP and SIDRIA-Rome. [d]All cohorts except EPIC-Turin. [e]Include: SNAC-K (LOOCV R-squared=0.78), SALT (0.78), 60y (0.78), SDPP (0.78), HNR (0.79) and KORA (0.62). [f]Include: FINRISK (LOOCV= R-squared 0.53), DCH (0.55), EPIC-Turin (0.59), SIDRIA-Turin (0.59) and SIDRIA-Rome (0.60).

*Statistically significant heterogeneity, as indicated by $p<0.05$ from Cochran's Q or I^2 >50%.

Table 5. Association between $PM_{2.5}$ exposure and stroke incidence in subsets of the 11 cohorts under study. Results of the threshold analyses.

Threshold	*n* cohorts	*n* subjects	HR (95% CI)
Cohorts with $PM_{2.5}$ concentrations for the respective threshold			
Below 15 mg/m^3	7[a]	72,769	1.24 (0.98, 1.58)
Below 20 mg/m^3	9[b]	84,496	1.29 (1.00, 1.68)
Below 25 mg/m^3	9[b]	86,812	1.29 (0.84, 1.98)*
Cohorts with $PM_{2.5}$ concentrations available for all thresholds			
Full range of exposure	7[a]	73,446	1.33 (1.01, 1.77)
Below 15 mg/m^3	7[a]	72,769	1.24 (0.98, 1.58)
Below 20 mg/m^3	7[a]	73,446	1.33 (1.01, 1.77)
Below 25 mg/m^3	7[a]	73,446	1.33 (1.01, 1.77)

Abbreviations: $PM_{2.5}$, particulate matter < 2.5 μm; HR, hazard ratio; CI, confidence interval.

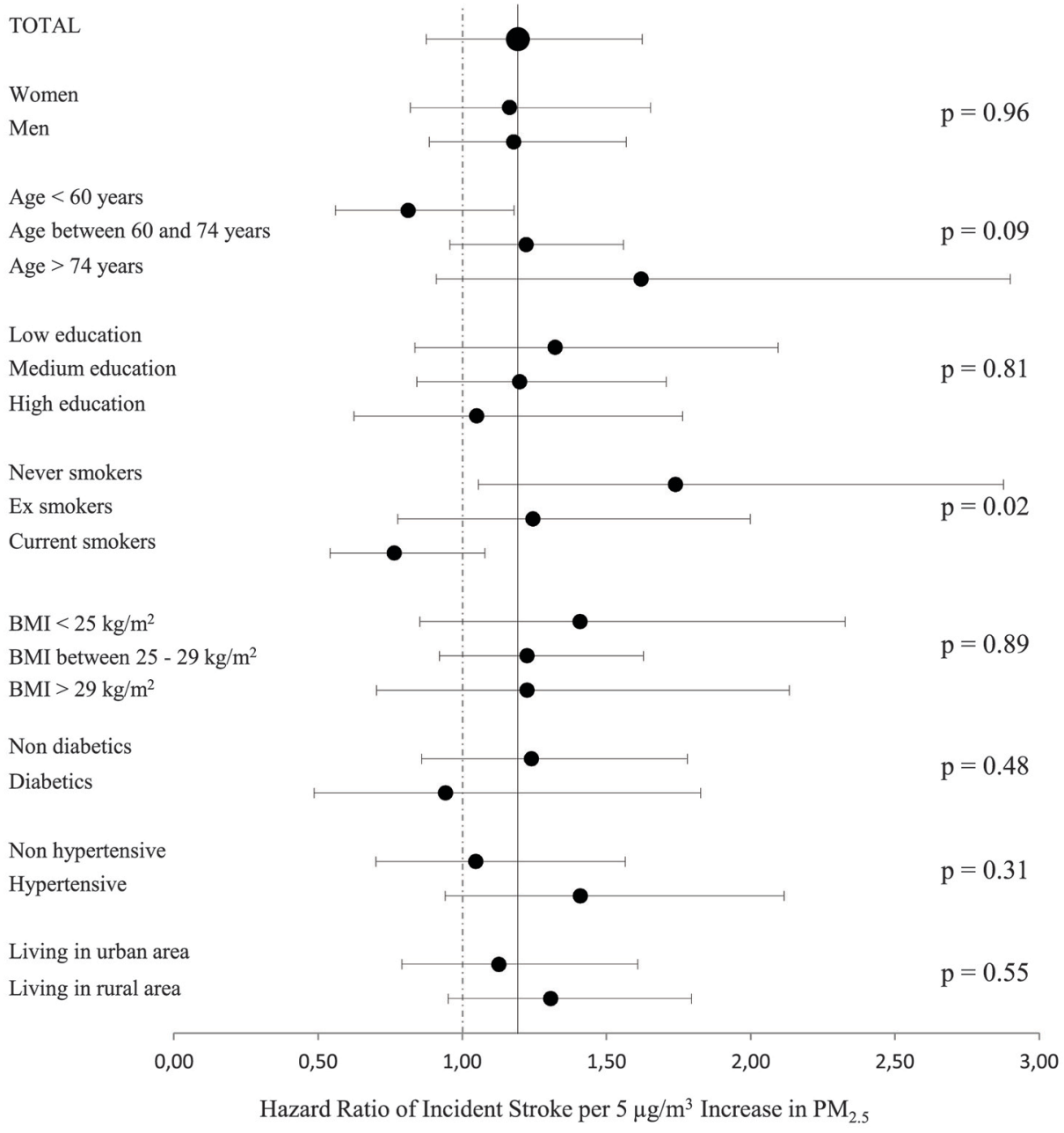
[a]All except HNR, EPIC-Turin, SIDRIA-Turin and SIDRIA-Rome. [b]All except EPIC-Turin and SIDRIA-Turin.

*Statistically significant heterogeneity, as indicated by $p<0.05$ from Cochran's Q or I^2 >50%.

Figure legend

Figure 1. Association between $PM_{2.5}$ exposure and stroke incidence in the 11 cohorts under study: Results of the effect modification analysis. Hazard Ratios, circles, and 95% confidence intervals, error bars, per 5 $\mu g/m^3$ increases in $PM_{2.5}$. P-values of effect modification are reported, calculated as heterogeneity tests among coefficients in different strata of the effect modifiers. Abbreviations: $PM_{2.5}$, particulate matter < 2.5 μm; BMI, body mass index.

Figure 1.


TOTAL
Women
Men
p = 0.96
Age < 60 years
Age between 60 and 74 years
Age > 74 years
p = 0.09
Low education
Medium education
High education
p = 0.81
Never smokers
Ex smokers
Current smokers
p = 0.02
BMI < 25 kg/m²
BMI between 25 - 29 kg/m²
BMI > 29 kg/m²
p = 0.89
Non diabetics
Diabetics
p = 0.48
Non hypertensive
Hypertensive
p = 0.31
Living in urban area
Living in rural area
p = 0.55
0,00
0,50
1,00
1,50
2,00
2,50
3,00
Hazard Ratio of Incident Stroke per 5 µg/m³ Increase in PM2.5