

Long-term exposure to low-level ambient air pollution and incidence of stroke and coronary heart disease: a pooled analysis of six European cohorts within the ELAPSE project



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Summary

Background Long-term exposure to outdoor air pollution increases the risk of cardiovascular disease, but evidence is unclear on the health effects of exposure to pollutant concentrations lower than current EU and US standards and WHO guideline limits. Within the multicentre study Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE), we investigated the associations of long-term exposures to fine particulate matter (PM_{2.5}), nitrogen dioxide (NO₂), black carbon, and warm-season ozone (O₃) with the incidence of stroke and acute coronary heart disease.

Methods We did a pooled analysis of individual data from six population-based cohort studies within ELAPSE, from Sweden, Denmark, the Netherlands, and Germany (recruited 1992–2004), and harmonised individual and area-level variables between cohorts. Participants (all adults) were followed up until migration from the study area, death, or incident stroke or coronary heart disease, or end of follow-up (2011–15). Mean 2010 air pollution concentrations from centrally developed European-wide land use regression models were assigned to participants' baseline residential addresses. We used Cox proportional hazards models with increasing levels of covariate adjustment to investigate the association of air pollution exposure with incidence of stroke and coronary heart disease. We assessed the shape of the concentration-response function and did subset analyses of participants living at pollutant concentrations lower than predefined values.

Findings From the pooled ELAPSE cohorts, data on 137 148 participants were analysed in our fully adjusted model. During a median follow-up of 17·2 years (IQR 13·8–19·5), we observed 6950 incident events of stroke and 10 071 incident events of coronary heart disease. Incidence of stroke was associated with PM_{2.5} (hazard ratio 1·10 [95% CI 1·01–1·21] per 5 µg/m³ increase), NO₂ (1·08 [1·04–1·12] per 10 µg/m³ increase), and black carbon (1·06 [1·02–1·10] per 0·5 10⁻⁵/m increase), whereas coronary heart disease incidence was only associated with NO₂ (1·04 [1·01–1·07]). Warm-season O₃ was not associated with an increase in either outcome. Concentration-response curves indicated no evidence of a threshold below which air pollutant concentrations are not harmful for cardiovascular health. Effect estimates for PM_{2.5} and NO₂ remained elevated even when restricting analyses to participants exposed to pollutant concentrations lower than the EU limit values of 25 µg/m³ for PM_{2.5} and 40 µg/m³ for NO₂.

Interpretation Long-term air pollution exposure was associated with incidence of stroke and coronary heart disease, even at pollutant concentrations lower than current limit values.

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Introduction

Ambient air pollution has decreased in recent decades in Europe and North America, but epidemiological studies in Australia, Canada, and the USA have suggested adverse health effects even at very low concentrations of pollution.^{1–7} However, most of these studies investigated mortality and less evidence is available for incident disease.^{8–12} According to WHO, cardiovascular disease is the leading cause of death worldwide and accountable for a large share of

morbidity and health-care costs.¹³ Thus, assessing the specific air pollution-related health burden of cardiovascular disease is crucial to inform policy makers. Such an assessment is especially important in view of upcoming revisions to the air quality directive in Europe,¹⁴ the US national ambient air quality standard for particulate matter (PM)¹⁵ and the WHO air quality guidelines.

Of all types of cardiovascular disease, coronary heart disease and stroke constitute the most frequent

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Research in context

Evidence before this study

We searched PubMed without language restrictions from database inception up to March 25, 2020, using the search terms “air pollution”, “long-term”, “incidence” and “stroke” or “cerebrovascular” or “ischemic” or “ischaemic” or “coronary” or “cardiovascular”. We then screened abstracts and full texts to select relevant articles. Our literature review showed that epidemiological evidence is inconsistent and scarce, especially for nitrogen dioxide (NO₂), black carbon, and ozone (O₃). Previous studies on low-level air pollution mainly focused on fine matter (PM_{2.5}) and natural and cause-specific mortality, and studies on cardiovascular morbidity endpoints are rare. Furthermore, it remains unclear whether a potential threshold exists below which air pollutants are not harmful for cardiovascular health, as few studies have investigated the shape of the concentration-response function.

Added value of this study

This study provides the first European multicountry analysis, pooling data from six well characterised European cohorts to investigate whether long-term exposure to low

diagnoses. Air pollution has been implicated in multiple biological mechanisms including systemic inflammation, oxidative stress, and autonomic nervous system imbalance affecting the cardiovascular system and the development of atherosclerosis,^{16,17} all of which are known disease mechanisms leading to coronary heart disease or stroke. Several epidemiological cohort studies have reported associations of cardiovascular disease incidence or mortality with long-term exposure to outdoor air pollution.^{9,11,18–22} Although most evidence is available for fine PM (PM_{2.5}), uncertainty remains about the shape of the concentration-response function, particularly in the low-level exposure range. Several studies have suggested a steep slope in the lower range,^{5,6,11} whereas others have reported a linear increase.^{6,9} Only a few studies have evaluated the long-term effects of other regulated pollutants such as nitrogen dioxide (NO₂) and ozone (O₃), and of non-regulated pollutants such as black carbon (an indicator of soot).^{8–11,19–21,23}

In the multicentre project Effects of Low-level Air Pollution: a Study in Europe (ELAPSE), we built on previous work of the European Study of Cohorts for Air Pollution Effects (ESCAPE),^{20,21} by pooling data of several existing cohort studies representing the lower range of air pollutant concentrations in Europe. Compared to the meta-analytical approach in ESCAPE, ELAPSE pooled and harmonised individual participant data, with a uniform exposure assessment via centrally developed European-wide air pollution maps,²⁴ and included a prolonged follow-up period. These updates increased our power to detect associations and enabled an investigation of the concentration-response function at low levels of exposure.

concentrations of outdoor air pollution affects the incidence of cardiovascular events. In addition to PM_{2.5}, for which some evidence is already available from Canada and the USA, we also assessed the regulated pollutants NO₂ and O₃, and non-regulated black carbon as an indicator for soot, all of which were modelled centrally for western Europe. Exposure concentrations of PM_{2.5}, NO₂, and black carbon had significant associations with stroke, and for NO₂, with coronary heart disease, even after adjustment for road traffic noise. Importantly, we provide novel insights into the shape of the concentration-response function, which did not show evidence for threshold effects.

Implications of all the available evidence

Our study provides evidence on the positive association between long-term exposure to ambient air pollution and cardiovascular events at concentrations lower than the existing EU and WHO guideline limits. Our findings are consistent with previous studies and are of major importance, as they imply that populations might benefit from a lowering of concentrations of PM_{2.5}, NO₂, and black carbon in Europe.

The specific objective of this study was to investigate the association of long-term ambient air pollution exposure (to PM_{2.5}, NO₂, black carbon, and warm-season O₃) and the incidence of stroke and acute coronary heart disease, with assessment of the shape of the concentration-response function at concentrations lower than current limit values set by the EU (PM_{2.5} 25 µg/m³, NO₂ 40 µg/m³), the US Environmental Protection Agency (PM_{2.5} 12 µg/m³), and WHO air quality guidelines (PM_{2.5} 10 µg/m³, NO₂ 40 µg/m³).²⁵

Methods

Study population

We did a pooled analysis of individual data from six existing population-based cohort studies (12 subcohorts) within ELAPSE. The cohorts enrolled adults from four northwestern European countries: Sweden (Cardiovascular Effects of Air Pollution and Noise in Stockholm [CEANS] study), Denmark (Diet, Cancer and Health [DCH] cohort and Danish Nurse Cohort [DNC]), the Netherlands (European Prospective Investigation into Cancer and Nutrition, the Netherlands [EPIC-NL]), and Germany (Heinz Nixdorf Recall [HNR] study and Cooperative Health Research in the Region of Augsburg [KORA]; appendix pp 2–9). Recruitment and baseline examinations took place between 1992 and 2004, and participants were followed up until migration or emigration from the study area, death, or incident stroke or coronary heart disease, or end of follow-up in 2011–15, whichever came first. All cohorts extracted and recoded their data according to a shared codebook for the ELAPSE project, and transferred their data to the Institute for Risk Assessment Sciences at Utrecht University (Utrecht,

Netherlands), where the data were checked, pooled, and stored on a secure server. For the purposes of this analysis, participants with their residential address missing at baseline were excluded. The present analysis and wider ELAPSE project was done in accordance with the Declaration of Helsinki. The original cohort studies were approved by the relevant authorities complying with all relevant national, state, and local regulations, and written informed consent was obtained from all participants before enrolment.

Outcome definitions

We analysed incident events of stroke and coronary heart disease that occurred during follow-up. Events were derived by record-linkage of hospital discharge and mortality registries for all cohorts except those from Germany. Stroke was defined according to the criteria of relevant International Classification of Diseases (ICD) codes, comprising hospitalisation with principal diagnosis of ischaemic, haemorrhagic, or unspecified stroke, and out-of-hospital deaths from cerebrovascular diseases. Acute coronary heart disease was defined (per ICD codes) as hospitalisation with a principal diagnosis of acute myocardial infarction or other acute or subacute forms of coronary heart disease, or out-of-hospital death from coronary heart disease. The specific ICD codes are provided in the appendix (p 10). For the German cohorts, outcome identification was accomplished by interview and inspection of medical records and death certificates. To derive incident events, we excluded participants with a history of either stroke or coronary heart disease at least 3 years before enrolment.

Exposure assessment

Annual mean concentrations of PM_{2.5}, NO₂, black carbon, and warm-season O₃ (from April to September inclusive) were centrally modelled for western Europe for the year 2010 by land use regression (LUR) models.²⁴ We regressed routine monitoring data from the AirBase network of the European Environmental Agency (PM_{2.5}, NO₂, and O₃) or measurements from ESCAPE monitoring sites (black carbon) on satellite observations, chemical transport model estimates, land use, and road data (appendix p 11). Models were validated with 5-fold cross-validation; all models performed well with an R² value (ie, spatial variability of the measured concentrations that can be explained by the model) of 66% for PM_{2.5}, 58% for NO₂, 51% for black carbon, and 60% for O₃. We then applied the models to 100 m grids to produce concentration surfaces and assigned the respective exposures of these grids to the residential addresses of our cohort participants at recruitment, as spatial variation of the pollutant concentrations has been shown to be reasonably stable during periods of about 10 years (appendix p 12). In addition, we estimated pollutant concentrations for each year from recruitment to end of follow-up via back-extrapolation using both the absolute difference and the ratio between

annual average concentrations and 2010 exposures from our main model, and assigned these concentrations to participant addresses during follow-up when available (appendix p 12). Spearman correlation coefficients were calculated separately for each subcohort to assess and compare correlations between air pollutants.

Statistical analysis

We used Cox proportional hazards models with age as an underlying time variable, following each cohort member from start of follow-up to time of first occurrence of stroke or coronary heart disease, or censoring at the date of death, migration, loss to follow-up, or end of follow-up. We stratified models by subcohort, thus allowing the baseline hazard to vary by subcohort, to address heterogeneity of participant characteristics and outcome diagnosis coding across cohorts.²⁶ We specified a priori three models with increasing strengths of confounder adjustment on the basis of previous studies^{20,21} and availability of data in the participating cohorts. Model 1 included age (time scale, in years), sex and subcohort (both as strata variables), and the cohort baseline year. Model 2 further adjusted for individual lifestyle and socioeconomic information at baseline: marital status (single, married or living with partner, divorced or separated, or widowed), body-mass index (BMI; following the WHO categorisation of underweight [<18.5 kg/m²], normal weight [18.5 – 24.9 kg/m²], overweight [25.0 – 29.9 kg/m²], and obese [≥ 30.0 kg/m²]), smoking status (never, former, or current) and smoking duration (years), intensity of smoking among current and former smokers (cigarettes per day) and smoking intensity squared, employment status (yes or no), and education level (primary or less, secondary, or tertiary, as per country-specific definitions). Model 3 additionally included neighbourhood-level socioeconomic status (mean income in 2001)²⁷. The spatial scale of neighbourhoods varied from small neighbourhoods and city districts (in the CEANS, EPIC-NL, and HNR studies) to municipalities (in the DCH, DNC, and KORA studies). Participants with missing information in model 3 covariates were excluded from most analyses, although to examine potential selection bias, we also ran model 1 and model 2 with the eligible populations for each model. Each pollutant was first included separately as a linear term. To assess the shape of the concentration-response function, we applied natural cubic splines with three degrees of freedom and a 2016 modelling framework called the shape-constrained health impact function (SCHIF; appendix p 17).²⁸ We investigated if associations persisted at low concentrations by excluding participants living at concentrations higher than a priori defined cutoff values, which were partly based on existing EU and US limit values and WHO guidelines (cutoff values in the ranges 10–25 µg/m³ for PM_{2.5} and 20–40 µg/m³ for NO₂) and expected ranges (0.5–3.0 10⁻⁵/m for black carbon and 60–100 µg/m³ for warm-season O₃). Black

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For more on ELAPSE see <http://www.elapseproject.eu/>

For the EU air quality standards see <https://ec.europa.eu/environment/air/quality/standards.htm>

For the US air quality standards see <https://www.epa.gov/criteria-air-pollutants/naaqs-table>

See Online for appendix

carbon was measured by the reflectance of PM_{2.5} filters and expressed in absorbance units. We further used two-pollutant models to test the independence of the pollutant effect estimates. Hazard ratios (HRs) and 95% CIs (calculated with a normal approximation) are presented for fixed increments in each exposure (approximately the IQR after rounding), defined a priori to cover the range in concentrations within the different cohorts while maintaining increments broadly comparable between pollutants in terms of variability.

In sensitivity analyses, we examined the robustness of findings by reiterating the main linear model with either annual mean concentrations back-extrapolated to the year of baseline examination, or time-varying concentrations linking back-extrapolated annual mean concentrations per year to each participant address from baseline to an incident event or censoring for those cohorts with complete residential history (CEANS, DCH, and EPIC-NL). For the second approach, we incorporated 1-year or 5-year strata of follow-up time in the Cox model to account for time trends in incidence (appendix p 18). In addition, we inspected natural splines with three degrees of freedom in time-varying analysis (with the ratio back-extrapolation and 1-year strata to adjust for time trends) to test the sensitivity of our findings with respect to the strength of associations. Because traffic noise has been reported as an important environmental risk factor for cardiovascular disease,^{22,29} we additionally adjusted for locally assessed road traffic noise at the baseline address (appendix p 19). Furthermore, since air pollution has also been related to obesity^{30,31} and, therefore, BMI might be a factor in the causal pathway from air pollution to cardiovascular disease, we excluded BMI from the main adjustment set in model 3 to examine potential overadjustment. We also did stratified analyses by subcohort with subsequent pooling of cohort-specific effect estimates using random-effects meta-analyses with the DerSimonian and Laird method.³²

We evaluated violation of the proportional hazards assumption of the Cox models for all covariates by investigating the scaled Schoenfeld residuals against time, and applying the global test from the R survival package. All statistical analyses were done in R, version 3.4.0, according to centrally developed analysis scripts run via secure remote access to the Utrecht University server.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The pooled ELAPSE cohorts with available data on stroke or coronary heart disease provided information on 157265 participants, of whom 151981 (96.6%) had complete air pollution exposure information (based on

residential address at baseline) and no stroke or coronary heart disease diagnosis in the past three years (appendix pp 4–9, 20). After exclusion of participants with missing information on the main model 3 covariates (14833 [9.8%]), ranging from 71 (1.6%) of 4446 in the HNR study, to 1734 (46.3%) of 3747 in the KORA-S4 subcohort (for which neighbourhood mean income was not available for the city of study, Augsburg), a total of 137148 participants contributing 2168806 person-years at risk were included in the main analyses (table 1). Of these participants, 6950 had an incident event of stroke and 10071 had an incident event of coronary heart disease during a median follow-up of 17.2 years (IQR 13.8–19.5). Cohorts were heterogeneous in terms of participant number and characteristics, and distribution of covariates. The mean age at baseline was 54 years (SD 5), 92427 participants (67.4%) were women, 17470 (12.7%) had obesity, and 43137 (31.5%) were current smokers (table 1). A map of the study areas and further details on individual cohort characteristics are provided in the appendix (pp 4–9, 20, 26).

Air pollution concentrations varied between studies and within the study areas of subcohorts (figure 1). All participants were exposed to PM_{2.5} concentrations markedly lower than the EU limit value of 25 µg/m³, and most participants in Sweden were at concentrations lower than the WHO guideline limit of 10 µg/m³. For NO₂, 127305 (92.8%) participants (ranging from all 7488 participants in the CEANS-Stockholm Diabetes Prevention Program subcohort, to 3324 [76.0%] in the HNR study) resided in areas at concentrations lower than the EU limit value and WHO guideline limit of 40 µg/m³. The correlations (Spearman) between different pollutants were heterogeneous across subcohorts, although overall were positive for PM_{2.5}, NO₂, and black carbon, with the highest coefficients between NO₂ and black carbon (0.64 to 0.93, except 0.38 in the CEANS-Swedish National Study on Aging and Care in Kungsholmen subcohort; appendix p 27), and mostly moderate correlations between PM_{2.5} and NO₂ (0.20 to 0.75). Warm-season O₃ mostly showed negative correlations with all other pollutants (eg, –0.85 to –0.15 for NO₂).

In linear analyses, HR point estimates indicated positive associations for all pollutants with stroke or coronary heart disease incidence except warm-season O₃ (table 2). The magnitude of the associations decreased with stricter covariate adjustment, although most of the significant associations remained significant in our main model 3. Hazard ratios for the incidence of stroke and coronary heart disease per 10 µg/m³ increase in NO₂ were 1.08 (95% CI 1.04–1.12) and 1.04 (1.01–1.07), respectively, indicating significant associations. The reduction in HR was primarily due to adjustments for smoking when excluding each variable separately (data not shown). PM_{2.5} was significantly associated with incident events of stroke (HR 1.10 [1.01–1.21] per 5 µg/m³ increase) but not with coronary heart disease incidence (1.02 [0.95–1.10]). Black carbon was significantly

Cohort details	Sweden: CEANS*										Pooled	
	1992-1998	1997-99	1998-2002	2001-04	1993-97	1993	Denmark: DNCT†	Netherlands: EPIC-NL‡	Germany: HNR	Germany: KORAS		1999-2001
Recruitment	1992-98	1997-99	1998-2002	2001-04	1993-97	1993	Denmark: DNCT†	Netherlands: EPIC-NL‡	Germany: HNR	Germany: KORAS	1999-2001	1992-2004
End of follow-up	2011	2014	2011	2011	2015	2013	2013	2013	2015	2011	2013-14	2011-15
Participants¶	7488	3814	5929	2547	52088	16810	8055	17643	4375	2182	2013	137148
Person-years at risk	116 698	56 351	60 058	18 426	894 170	297 060	114 071	287 420	51 666	25 582	24 138	2 168 806
Stroke events	132	199	241	203	4116	1009	101	280	129	53	43	6950
Coronary heart disease events	238	298	303	210	4374	1802	335	1127	193	66	70	10 071
Participant baseline characteristics												
Age, years	47 (5)	60 (0)	57 (10)	72 (10)	57 (4)	56 (8)	48 (4)	43 (11)	59 (8)	49 (13)	49 (13)	54 (9)
Women	4582 (61.2%)	2023 (53.0%)	3326 (56.1%)	1580 (62.0%)	27 657 (53.1%)	16 810 (100%)	8055 (100%)	9718 (55.1%)	2280 (52.1%)	1124 (51.5%)	1068 (53.1%)	92 427 (67.4%)
Married or living with partner	6259 (83.6%)	2820 (73.9%)	4026 (67.9%)	1194 (46.9%)	37 288 (71.6%)	11 406 (67.9%)	6114 (75.9%)	11 552 (65.5%)	3277 (74.9%)	1784 (81.8%)	1608 (79.9%)	98 236 (71.6%)
BMI, kg/m²	26 (4)	27 (4)	25 (3)	26 (4)	26 (4)	24 (3)	24 (4)	25 (4)	28 (5)	27 (4)	27 (5)	26 (4)
Obesity, BMI ≥30.0 kg/m²	936 (12.5%)	721 (18.9%)	379 (6.4%)	326 (12.8%)	7442 (14.3%)	864 (5.1%)	533 (6.6%)	2020 (11.4%)	1177 (26.9%)	475 (21.8%)	478 (23.7%)	17 470 (12.7%)
Current smokers	1973 (26.3%)	804 (21.1%)	1260 (21.3%)	374 (14.7%)	18 785 (36.1%)	6304 (37.5%)	2309 (28.7%)	6121 (34.7%)	1037 (23.7%)	438 (20.1%)	459 (22.8%)	43 137 (31.5%)
Education level of primary school or lower	2354 (31.4%)	1510 (39.6%)	1556 (26.2%)	629 (24.7%)	7664 (14.7%)	0	0	1985 (11.3%)	494 (11.3%)	307 (14.1%)	209 (10.4%)	19 854 (14.5%)
Employed	6794 (90.7%)	2622 (68.7%)	3902 (65.8%)	617 (24.2%)	41 063 (78.8%)	11 856 (70.5%)	7655 (95.0%)	12 179 (69.0%)	1830 (41.8%)	1286 (58.9%)	1241 (61.6%)	98 309 (71.7%)
Neighbourhood mean income, €1000	24 (4)	25 (7)	25 (7)	29 (2)	20 (3)	19 (3)	19 (2)	12 (2)	25 (8)	37 (4)	38 (7)	20 (6)
Noise (day-evening-night noise level), dB**	46 (3)	50 (6)	50 (6)	59 (7)	58 (7)	53 (6)	53 (6)	NA	55 (9)	54 (6)	54 (6)	55 (7)

Data are mean (SD) or n (%). Detailed numbers for individual cohorts are provided in the appendix (pp 3-9, 20). CEANS=Cardiovascular Effects of Air Pollution and Noise in Stockholm study. DGH=Diet, Cancer and Health cohort. DNC=Danish Nurses Cohort. EPIC-NL=European Prospective Investigation into Cancer and Nutrition, the Netherlands. HNR=Heinz Nixdorf Recall study. KORAS=Cooperative Health Research in the Augsburg Region. BMI=body-mass index. NA=not available. *Four subcohorts (left to right in the table): Stockholm 60 years old study, the Stockholm Screening Across the Lifespan Twin study and TwinGenes study (subset living in Stockholm), and the Swedish National Study on Aging and Care in Kungsholmen. †Two subcohorts (left to right in the table): Monitoring Project on Risk Factors for Chronic Diseases and PROSPECT. ‡Two subcohorts (left to right in the table): Survey 3 and Survey 4. ¶Participants included in the main analysis of the present study. ||Neighbourhood spatial scale: smaller neighbourhoods and city districts for CEANS, EPIC-NL, and HNR; municipalities for DGH, DNC, and KORAS. **Lower cutoff value 45 dB (all values <45 dB were set to 45 dB).

Table 1: Description of the six European cohorts (12 subcohorts) and individual baseline characteristics of participants in the present analysis

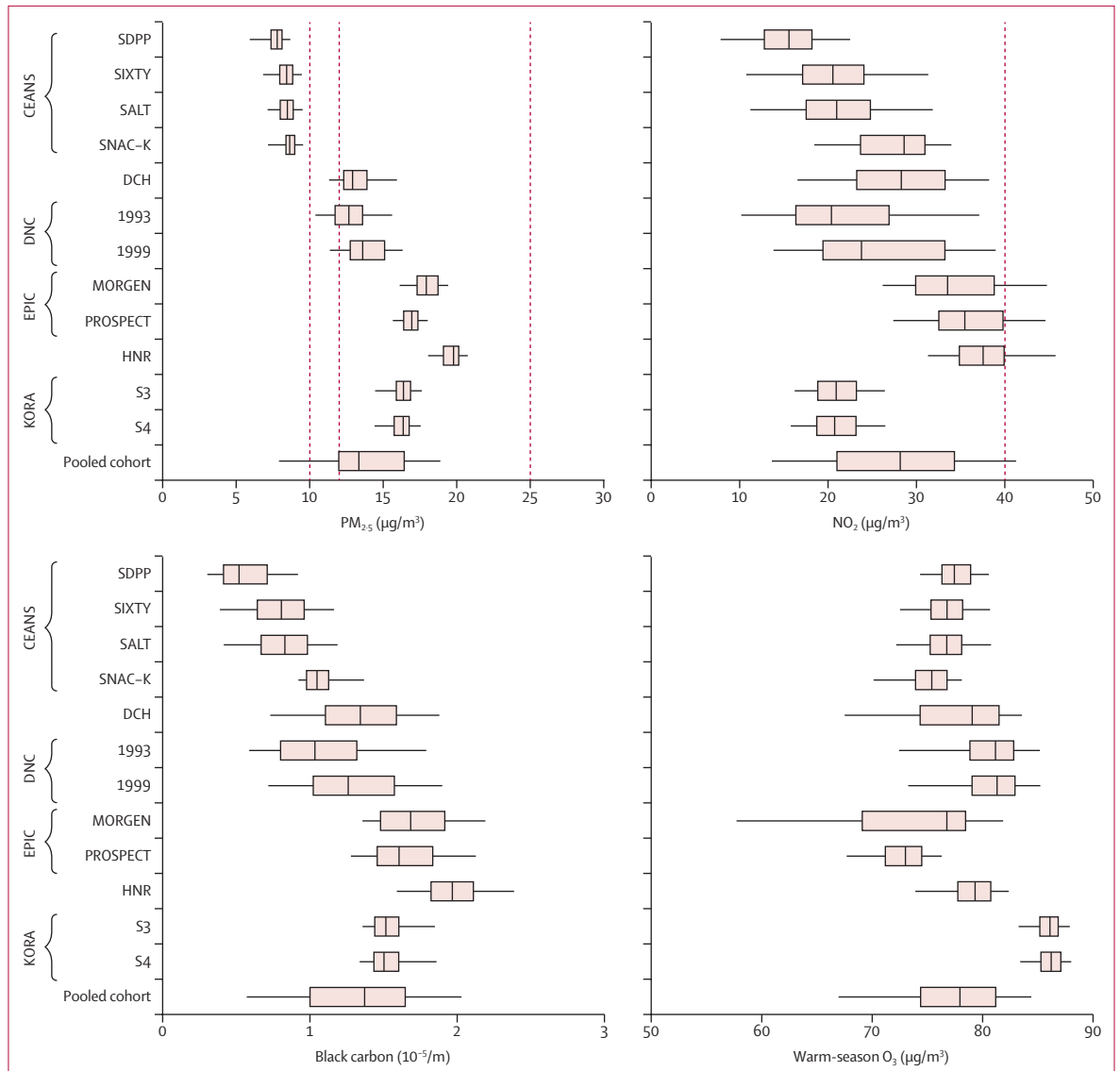


Figure 1: Residential air pollution exposure as 2010 annual mean concentrations

Vertical red lines indicate the limit values set by the EU ($PM_{2.5}$ 25 $\mu g/m^3$, NO_2 40 $\mu g/m^3$), US Environmental Protection Agency ($PM_{2.5}$ 12 $\mu g/m^3$), and WHO guidelines ($PM_{2.5}$ 10 $\mu g/m^3$, NO_2 40 $\mu g/m^3$). Bold lines in the middle of the boxes indicate median values (50th percentiles); lower and upper hinges correspond to 25th and 75th percentiles; lower and upper whiskers to 5th and 95th percentiles. CEANS=Cardiovascular Effects of Air Pollution and Noise in Stockholm study. SDPP=Stockholm Diabetes Prevention Program. SIXTY=the Stockholm 60 years old study. SALT=the Stockholm Screening Across the Lifespan Twin study and TwinGene study. SNAC-K=the Swedish National Study on Aging and Care in Kungsholmen. DCH=Diet, Cancer, and Health cohort. DNC=Danish Nurses Cohort. EPIC-NL=European Prospective Investigation into Cancer and Nutrition, the Netherlands. MORGEN= Monitoring Project on Risk Factors for Chronic Diseases. HNR=Heinz Nixdorf Recall study. KORA=Cooperative Health Research in the Augsburg Region. S3=Survey 3. S4=Survey 4. NO_2 =nitrogen dioxide. O_3 =ozone.

associated with stroke (1.06 [1.02–1.10]) per 0.5 $10^{-5}/m$ but not with coronary heart disease (1.02 [0.99–1.06]). Similar (sometimes identical) effect estimates were obtained from models 1 and 2 when analysing the main model 3 population or the eligible populations for those models, suggesting that low selection bias was introduced by excluding participants with missing covariates.

Our investigation of concentration-response relationships with natural cubic splines suggested steeper slopes at low exposures versus high exposures with no evidence

of a threshold (focusing on the 5th and 95th percentiles of the concentration distribution) for the association of $PM_{2.5}$, NO_2 , and black carbon with stroke, and $PM_{2.5}$ with coronary heart disease (figure 2). For NO_2 and coronary heart disease, we found little evidence of an association at concentrations lower than 20 $\mu g/m^3$. These findings were supported by the SCHIF model analysis, which showed slightly steeper slopes at low exposures for the association of $PM_{2.5}$, NO_2 , and black carbon with stroke, an increase in slope at concentrations higher than 20 $\mu g/m^3$ for NO_2 and

	Increment	Main model 3 population			Other model populations	
		Model 1* (n=137 148)	Model 2† (n=137 148)	Model 3‡ (n=137 148)	Model 1* (n=151 981)	Model 2† (n=141 965)
Stroke						
PM _{2.5} , µg/m ³	5	1.20 (1.09–1.31)	1.10 (1.01–1.21)	1.10 (1.01–1.21)	1.20 (1.10–1.31)	1.11 (1.02–1.22)
NO ₂ , µg/m ³	10	1.10 (1.06–1.14)	1.07 (1.03–1.11)	1.08 (1.04–1.12)	1.11 (1.08–1.15)	1.08 (1.04–1.12)
Black carbon, 10 ³ /m	0.5	1.09 (1.05–1.13)	1.06 (1.02–1.10)	1.06 (1.02–1.10)	1.10 (1.06–1.14)	1.07 (1.03–1.10)
Warm-season O ₃ , µg/m ³	10	0.90 (0.86–0.95)	0.96 (0.91–1.01)	0.96 (0.91–1.01)	0.89 (0.85–0.93)	0.95 (0.90–1.00)
Coronary heart disease						
PM _{2.5} , µg/m ³	5	1.09 (1.01–1.18)	1.02 (0.95–1.11)	1.02 (0.95–1.10)	1.10 (1.03–1.19)	1.02 (0.95–1.10)
NO ₂ , µg/m ³	10	1.06 (1.03–1.09)	1.03 (1.00–1.06)	1.04 (1.01–1.07)	1.07 (1.04–1.10)	1.04 (1.01–1.07)
Black carbon, 10 ³ /m	0.5	1.05 (1.01–1.08)	1.02 (0.99–1.05)	1.02 (0.99–1.06)	1.05 (1.02–1.08)	1.02 (0.99–1.05)
Warm-season O ₃ , µg/m ³	10	0.90 (0.86–0.93)	0.94 (0.90–0.98)	0.94 (0.90–0.98)	0.89 (0.86–0.93)	0.94 (0.90–0.98)

Models 1–3 provide increasing control for covariates (greatest in the main model 3 population). NO₂=nitrogen dioxide. O₃=ozone. *Model 1: adjusted for subcohort (strata), age (timescale), sex (strata), and year of baseline visit. †Model 2 further adjusted for marital status, body-mass index, smoking (status, duration, intensity, intensity squared), employment status, and education. ‡Model 3 further adjusted for 2001 mean income on a neighbourhood level.

Table 2: Hazard ratios and 95% CIs for linear associations between air pollution exposures and incidence of stroke or coronary heart disease

coronary heart disease, and decreasing curves for warm-season O₃ (appendix p 28). Corresponding with the concentration-response curves, effect estimates were mostly unchanged or slightly increased in subset analyses at low air pollution concentrations (table 3), but the precision of the estimates decreased with smaller numbers of cohorts and participants remaining in the analysis at successively low cutoff concentrations (eg, for stroke, HR of 1.18 [95% CI 1.04–1.33] at <15 µg/m³ PM_{2.5} and 1.12 [1.06–1.18] at <30 µg/m³ NO₂).

In two-pollutant models, effect estimates for NO₂ and black carbon were robust to PM_{2.5} adjustment, whereas PM_{2.5} estimates decreased on adjustment for NO₂ and black carbon (appendix p 21). O₃ was not robust to adjustment for NO₂, resulting in a positive association, although non-significant, with stroke and a weakened, non-significant inverse association with coronary heart disease.

In our sensitivity analyses, effect estimates of air pollutants back-extrapolated to the year of baseline examination were similar to or slightly smaller than our main exposures, except for the association of PM_{2.5} with stroke, for which the effect was almost halved (appendix p 22). Restriction to cohorts with complete residential history (CEANS, DCH, and EPIC-NL) had minimal effect on the results of the main model and time-varying concentrations for this subset caused only slight differences in the magnitude of the HRs (appendix p 23). Time-varying exposure natural splines also indicated associations at low pollution concentrations, specifically for the association of NO₂ and black carbon with stroke (appendix p 29). Noise was only moderately correlated with all air pollutants (positive correlations with PM_{2.5}, NO₂, and black carbon, negative correlations with O₃; appendix p 27) and adjustment for noise did not affect the

estimates except for PM_{2.5} in relation to stroke (slightly reduced effect estimate; appendix p 24). The exclusion of adjustment for BMI in model 3 resulted in almost identical estimates compared with those in our main linear model (appendix p 25). Stratified analysis by subcohort and subsequent meta-analysis indicated similar pooled estimates to those in our main model, with little evidence of heterogeneity ($I^2 \leq 50\%$ for all combinations and χ^2 p value ≥ 0.05 for all combinations except NO₂ and coronary heart disease) in the cohort-specific estimates (appendix 30–31).

We detected deviation from the proportional hazards assumption for BMI and smoking status. A sensitivity analysis incorporating these in strata did not show results deviating from the main analysis (appendix p 32).

Discussion

In this pooled analysis of more than 130 000 participants from six European cohorts, we observed increased HRs for stroke incidence with long-term exposure to PM_{2.5}, NO₂, and black carbon. For coronary heart disease, we observed an increased HR with NO₂ exposure only. Warm-season O₃ exposure was not related to stroke or coronary heart disease. The concentration-response functions indicated no threshold values for these associations, and visible associations were maintained when restricting analyses to participants living at pollutant concentrations lower than the EU annual mean limits of 40 µg/m³ for NO₂ and 25 µg/m³ for PM_{2.5}, the US standard of 12 µg/m³ for PM_{2.5}, and the WHO air quality guideline limit of 40 µg/m³ for NO₂ and 10 µg/m³ for PM_{2.5}.

Most evidence on low-level air pollution is available for PM_{2.5} and our results for stroke are generally in line with previous studies. A study in the USA¹¹ on hospital

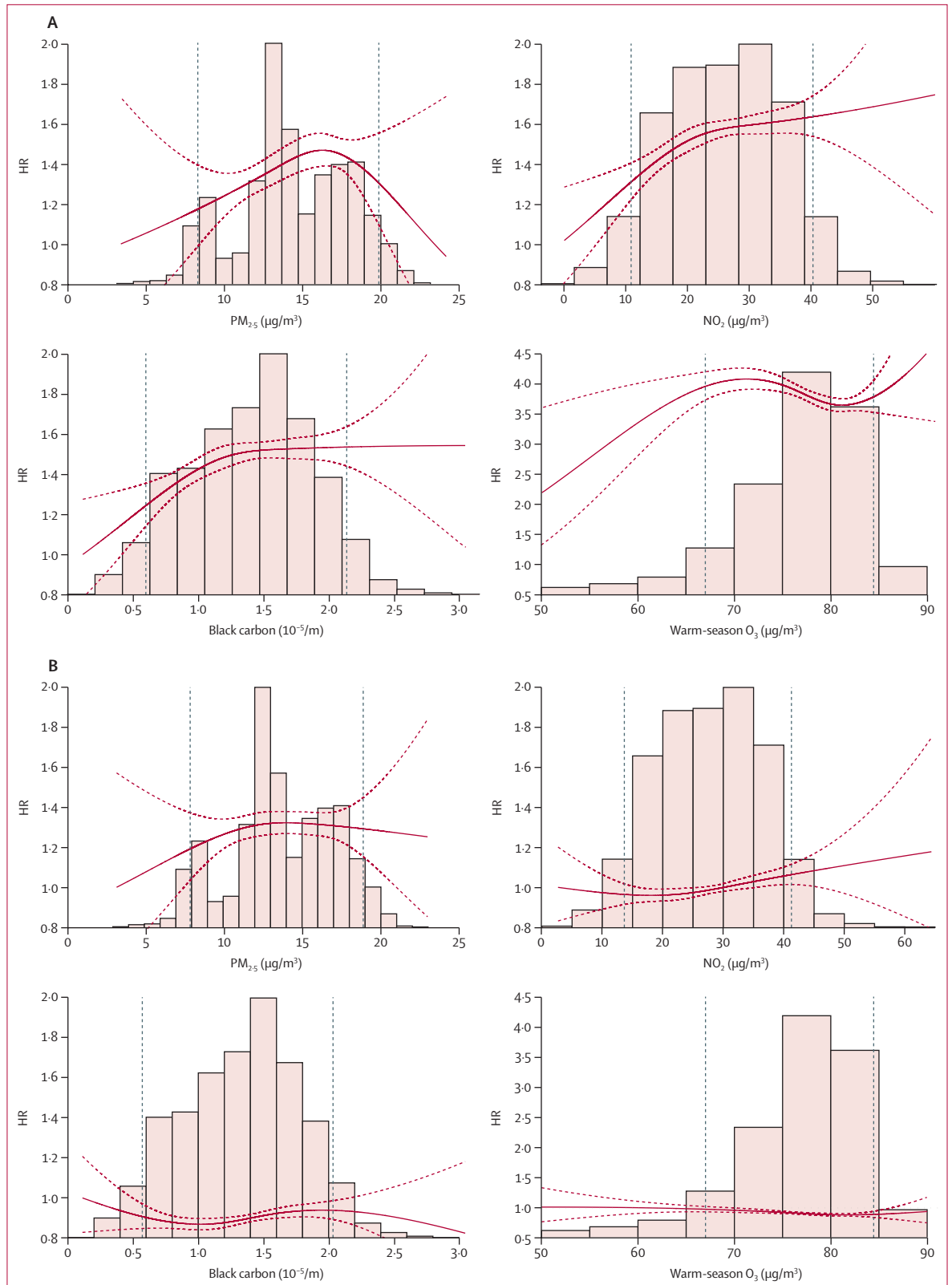


Figure 2: Natural cubic splines for stroke (A) and coronary heart disease (B)

The solid line is at three degrees of freedom; red dashed lines show 95% CIs. The model adjusted for subcohort (strata), age (timescale), sex (strata), year of baseline visit, marital status, body-mass index, smoking (status, duration, intensity, intensity squared), employment status, education, and neighbourhood mean income. The bars are histograms (independent of the y axis) and indicate distribution of the air pollutant data, and dashed vertical lines the 5th and 95th percentiles. The HR is 1 for minimum pollution exposure. HR=hazard ratio. NO₂=nitrogen dioxide. O₃=ozone.

	Cohorts	Participants	Participants with incident event		Hazard ratio (95% CI)	
			Stroke	Coronary heart disease	Stroke incidence	Coronary heart disease incidence
PM_{2.5}, µg/m³						
Full dataset	12	137 148	6950	10 071	1.10 (1.01–1.21)	1.02 (0.95–1.10)
<25	12	137 148	6950	10 071	1.10 (1.01–1.21)	1.02 (0.95–1.10)
<20	12	135 537	6904	9990	1.10 (1.01–1.21)	1.02 (0.94–1.10)
<15	12	85 498	5181	6607	1.20 (1.04–1.38)	1.06 (0.94–1.20)
<12	9	34 848	1690	2356	1.25 (0.90–1.72)	1.15 (0.88–1.50)
<10	7	20 241	799	1095	1.91 (0.60–1.38)	1.15 (0.80–1.65)
NO_x, µg/m³						
Full dataset	12	137 148	6950	10 071	1.08 (1.04–1.12)	1.04 (1.01–1.07)
<40	12	127 305	6603	9355	1.08 (1.04–1.13)	1.04 (1.00–1.07)
<30	12	79 157	4117	5662	1.17 (1.09–1.25)	1.01 (0.95–1.07)
<20	11	29 451	1255	2072	1.16 (0.97–1.40)	1.05 (0.92–1.21)
Black carbon, 10⁻⁵/m						
Full dataset	12	137 148	6950	10 071	1.06 (1.02–1.10)	1.02 (0.99–1.06)
<3.0	12	137 114	6948	10 068	1.06 (1.02–1.10)	1.02 (0.99–1.06)
<2.5	12	136 696	6932	10 036	1.06 (1.02–1.10)	1.02 (0.99–1.05)
<2.0	12	128 825	6689	9536	1.06 (1.02–1.11)	1.02 (0.99–1.06)
<1.5	12	84 602	4497	6230	1.11 (1.04–1.19)	1.02 (0.97–1.08)
<1.0	8	34 153	1579	2382	1.17 (0.98–1.40)	0.88 (0.76–1.01)
<0.5	7	4844	117	230	1.73 (0.48–6.23)	0.76 (0.32–1.79)
Warm-season O₃, µg/m³						
Full dataset	12	137 148	6950	10 071	0.96 (0.91–1.01)	0.94 (0.90–0.98)
<100	12	137 148	6950	10 071	0.96 (0.91–1.01)	0.94 (0.90–0.98)
<80	12	89 251	4466	6548	0.98 (0.91–1.05)	0.93 (0.88–0.98)
<60	8	1602	23	125	0.29 (0.09–0.96)	1.64 (0.81–3.31)

Participants living at concentrations higher than the specified cutoff values were excluded. The model adjusted for subcohort (strata), age (timescale), sex (strata), year of baseline visit, marital status, body-mass index, smoking (status, duration, intensity, intensity squared), employment status, education, and neighbourhood mean income. Increments for the hazard ratio were 5 µg/m³ for PM_{2.5}, 10 µg/m³ for NO_x, 0.5 10⁻⁵/m for black carbon, and 10 µg/m³ for O₃. HR=hazard ratio. NO_x=nitrogen dioxide. O₃=ozone.

Table 3: Subset analyses at low air pollution concentrations for associations with stroke and coronary heart disease incidence

admissions among Medicare beneficiaries, a study combining two UK cohorts,¹⁰ and our previous study within the ESCAPE project²¹ with partly overlapping cohorts all indicated increased HRs for stroke in linear analyses. Two other large studies in the USA⁴ and Canada⁶ on stroke and cerebrovascular disease mortality reported slightly lower estimates compared with our results (table 4). Compared with our observations, all of these previous studies, and a large Canadian study⁹ on myocardial infarction incidence, reported stronger associations of PM_{2.5} exposure with coronary heart disease (incidence or mortality; HR ranging between 1.06–1.16, all estimates converted to a 5 µg/m³ increase). Most of these studies assessed the shape of the concentration-response functions with splines¹¹, SCHIF modelling,^{6,9} or subset analyses,^{11,20,21} with similar results to our study. The Medicare study¹¹ reported a steep slope of the concentration-response function in the low range, plateauing or slightly decreasing at PM_{2.5} concentrations higher than 12 µg/m³ (stroke) and 14 µg/m³ (myocardial infarction), whereas our curves changed at about 15 µg/m³ (stroke) and 12 µg/m³ (coronary

heart disease). The Canadian mortality study also reported a steep increase in the low range of PM_{2.5} exposure for coronary heart disease mortality, but a linear association with cerebrovascular disease mortality.⁶ A linear increase was also described by the Canadian study for myocardial infarction incidence.⁹ Interestingly, restricting analyses to observations with PM_{2.5} concentrations lower than the US standard of 12 µg/m³ in the Medicare study also increased the HRs. The HR values were 1.29 (95% CI 1.27–1.31) for stroke and 1.18 (1.16–1.21) for myocardial infarction,¹¹ compared with 1.18 (0.97–1.43) and 1.15 (0.88–1.50), respectively, in our subset analyses. Similarly, results of the meta-analysis in ESCAPE^{20,21} indicated increased HRs for the incidence of stroke and coronary heart disease when restricting analyses to participants living at PM_{2.5} concentrations lower than the EU limit value of 25 µg/m³, but also 20 µg/m³ and 15 µg/m³. As a whole, our study results combined with previous studies provide consistent evidence to support associations between long-term PM_{2.5} exposure with incident stroke at exposure concentrations lower than currently used or recommended limits.

	Region	Outcome	Participants	Stroke		Coronary heart disease	
				HR (95% CI)*	Shape of concentration-response function†	HR (95% CI)*	Shape of concentration-response function†
PM_{2.5}, µg/m³							
ELAPSE (current study)	Europe	Incidence	137 148	1.10 (1.01–1.21)	Increase up to ~15 µg/m ³ ; plateau at higher concentrations	1.02 (0.95–1.10)	Increase up to ~12 µg/m ³ ; plateau at higher concentrations
Medicare members (Danesh Yazdi et al, 2019 ²¹)	USA	Incidence	11 084 660
Overall	1.165 (1.159–1.171)†	Increase between ~7.5–12 µg/m ³ ; plateau at concentrations higher than ~12 µg/m ³	1.137 (1.126–1.148)†	Increase between ~7.5–14 µg/m ³ ; decrease at concentrations higher than ~14 µg/m ³
<12 µg/m ³	1.29 (1.27–1.31)	NA	1.18 (1.16–1.21)	NA
ONPHEC (Bai et al, 2019 ⁹)	Canada	Incidence	5 141 172	NA	NA	1.07 (1.06–1.09)	Linear increase
EPIC-Oxford, UK Biobank (Cai et al, 2018 ¹⁰)	UK	Incidence	289 128	1.14 (0.65–1.99)	NA	1.06 (0.76–1.48)	NA
ESCAPE (Cesaroni et al, 2014; ²⁰ Stafoggia et al, 2014 ²¹)	Europe	Incidence	111 931‡
Overall	1.19 (0.88–1.62)	NA	1.13 (0.98–1.30)	NA
<25 µg/m ³	1.29 (0.84–1.98)	NA	1.18 (1.01–1.39)	NA
<20 µg/m ³	1.29 (1.00–1.68)	NA	1.17 (0.91–1.50)	NA
<15 µg/m ³	1.24 (0.98–1.58)	NA	1.19 (1.00–1.42)	NA
NIH-AARP Diet and Health (Hayes et al, 2019 ⁴)	USA	Mortality	565 477	1.07 (1.01–1.13)	NA	1.08 (1.04–1.11)	NA
CANCHEC (Pinault et al, 2017 ⁵)	Canada	Mortality	2 448 500	1.05 (1.00–1.11)	Linear increase	1.16 (1.13–1.20)	Steep increase up to ~7 µg/m ³ ; increase at higher concentrations
NO₂, µg/m³							
ELAPSE (current study)	Europe	Incidence	137 148	1.08 (1.04–1.12)	Steep increase up to ~20 µg/m ³ ; slight increase at higher concentrations	1.04 (1.01–1.07)	Increase higher than ~20 µg/m ³
ONPHEC (Bai et al, 2019 ⁹)	Canada	Incidence	5 141 172	NA	NA	1.004 (0.996–1.012)†	Steep increase up to ~20 µg/m ³ ; slight increase at higher concentrations
Oakland KPNC members (Alexeef et al, 2018 ⁸)	USA	Incidence	41 869	0.99 (0.83–1.18)	Cardiovascular disease incidence only: increase with plateau at ~5–10 µg/m ³	1.07 (0.92–1.24)	Cardiovascular disease incidence only: increase with plateau at ~5–10 µg/m ³
HUNT2, EPIC-Oxford, UK Biobank (Cai et al, 2018 ¹⁰)	Norway, UK	Incidence	355 732	1.03 (0.94–1.12)	NA	0.98 (0.93–1.04)	NA
ESCAPE (Cesaroni et al, 2014; ²⁰ Stafoggia et al, 2014 ²¹)	Europe	Incidence	111 931‡	0.99 (0.89–1.11)	NA	1.03 (0.97–1.08)	NA

HR=hazard ratio. ELAPSE=Effects of Low-Level Air Pollution: A Study in Europe. NA=not available. ONPHEC=Ontario Population Health Environment Cohort. EPIC-Oxford=European Prospective Investigation into Cancer and Nutrition-Oxford. ESCAPE=European Study of Cohorts for Air Pollution Effects. NIH-AARP=National Institutes of Health–American Association of Retired Persons. CANCHEC=Canadian Census Health and Environment Cohort. NO₂=nitrogen dioxide. KPNC=Kaiser Permanente Northern California. HUNT=Helseundersøkelsen i Nord-Trøndelag. * All HRs were transformed to the ELAPSE increments of 5 µg/m³ for PM_{2.5} and 10 µg/m³ for NO₂. †Presented with three decimal places as two were not informative. ‡99 446 participants included in main analysis for stroke and 100 166 for coronary heart disease.

Table 4: Comparison with previous large studies on low-level air pollution and incidence of stroke and coronary heart disease (single-pollutant results)

Concentration-response functions indicate no threshold for association at low concentrations. For stroke, our HR of 1.10 (1.01–1.21) per 5 µg/m³ increase in PM_{2.5} was slightly higher than that reported in a 2019 meta-analysis (1.07 [1.05–1.10] for Europe).¹⁸ Although our study does not confirm an association of PM_{2.5} with incident coronary heart disease, other studies provide evidence of this. In addition to the aforementioned studies of low-level exposure, other studies have provided substantial evidence supporting a positive association between PM_{2.5} and stroke^{18,33–38} or coronary heart disease.^{33,34,36–38}

In contrast to our results, previous studies investigating long-term low-level NO₂ exposure in relation to incident stroke or coronary heart disease have reported no association or only weak associations by linear modelling of exposure (table 4). For stroke, our concentration-response function showed a steep increase up to about 20 µg/m³. Consistently, when restricting our analyses to NO₂ concentrations lower than 30 µg/m³ and 20 µg/m³, the HR showed slight increases, implicating the possibility of associations at concentrations less than half the current EU and WHO guideline limit (40 µg/m³).

Additionally, the Canadian incidence study⁹ reported a positive slope in association with myocardial infarction that was steepest below 20 µg/m³. Several other studies on NO₂ and incidence of cardiovascular disease have reported positive associations.^{22,34–36,39}

In our analyses, NO₂ associations were robust on adjustment for PM_{2.5} in two-pollutant models, whereas the HR for PM_{2.5} was reduced to approximately 1 for both outcomes. Because NO₂ was moderately correlated with PM_{2.5} in most of our cohorts and the width of the 95% CIs increased only marginally in two-pollutant models, the reduction of the PM_{2.5} estimate is probably not an artifact of multicollinearity. The NO₂ association might be related to direct NO₂ effects or correlated combustion-related particles such as ultrafine particles or black carbon. Thus, the reduction of the PM_{2.5} HR does not imply that particles in our study are not associated with stroke or coronary heart disease, as adjustment for NO₂ also adjusted for particles from the same sources shared with NO₂, including motorised traffic and other combustion sources. Unlike in a large national study in Switzerland on myocardial infarction mortality,²² we found that NO₂ associations were also stable on adjustment for road traffic noise. The results of the ELAPSE project, therefore, strengthen the role of NO₂ or correlated pollutants as a relevant risk factor for stroke and coronary heart disease. This finding is of major importance, as it convincingly shows that populations might benefit from reduction of NO₂ concentrations to levels substantially lower than the current EU limit and WHO guideline value.

No long-term standards or guidelines exist for black carbon, which is used as an indicator for primary combustion particles. The literature is scarce for black carbon, but in line with our findings, a number of studies have indicated a positive association with incidence of stroke or coronary heart disease (or both).^{8,19–21,23} Similar to NO₂, black carbon was only moderately correlated with PM_{2.5} in most of our cohorts and the associations with black carbon remained robust when adjusted for PM_{2.5}. Black carbon and NO₂ were, however, strongly correlated within most cohorts, resulting in substantially widened 95% CIs in two-pollutant models, which limits interpretation of our results. Nevertheless, for stroke and coronary heart disease incident events, the NO₂ association remained while the HR for black carbon was shifted to less than 1 for both outcomes, potentially indicating a more robust association for NO₂ and, possibly to some extent, a direct effect of NO₂. This finding might also reflect differential measurement error since NO₂ models were based on more sites than the models for black carbon. However, the performance of the NO₂ model was only slightly better than the black carbon model (5-fold cross-validation R² values of 58% for NO₂ and 51% for black carbon).

We did not observe positive associations between warm-season O₃ and incidence of stroke or coronary heart

disease as reported previously.^{3,9,11} Single pollutant HR estimates for O₃ were inverse for both outcomes, but shifted to positive (stroke) or attenuated towards 1 (coronary heart disease) after adjustment for NO₂. Possible reasons might be the small exposure contrast for O₃ in our study regions with most of the estimated concentrations ranging between 70 µg/m³ and 80 µg/m³, whereas ranges of 32–128 µg/m³ were observed in Canada⁹ and 60–120 µg/m³ in the USA.³ Additionally, the correlation of O₃ with PM_{2.5} was low but positive in both North American studies (Pearson's $r=0.2$ in Canada and $r=0.24$ in the USA), while we observed mostly moderate negative correlations with PM_{2.5} (Spearman's r values 0.18 to -0.62) and highly negative correlations with NO₂ (-0.15 to -0.85). Therefore, we do not consider our study to be informative on the health effects of long-term O₃ exposure.

Our study has several limitations. Air pollution concentrations were estimated for the year 2010 and assigned to the baseline addresses of the participants. Because residential histories were not available for all participants, additional exposure misclassification might have been introduced. However, sensitivity analyses with back-extrapolated and time-varying exposures indicated mostly similar associations to those in the main analysis. Exposures were assessed on a 100 m grid scale, which is small compared with other large-scale air pollution studies in Canada and the USA. For NO₂ and black carbon, the 100 m scale cannot fully characterise local variation because the pollutants are highly variable. However, a study across the Netherlands showed high correlations between our ELAPSE exposure model predictions for NO₂ with a national LUR model (Pearson's $r=0.83$) and a dispersion model ($r=0.79$), both of which used exact addresses and models based on the monitoring locations.⁴⁰ Besides area-level socioeconomic status and transportation noise, we did not consider additional contextual factors such as greenness or walkability of areas, which might have been related to both air pollution and cardiovascular disease incidence. Furthermore, we cannot exclude differences in the accuracy of diagnosis for incident stroke and coronary heart disease across the cohorts, considering that hospital discharges, mortality registries, and medical records were used to confirm the diagnosis. To adjust for these potential inconsistencies, we applied Cox models stratified by subcohort, thus allowing the baseline hazard to vary by subcohort. Focusing on low-level air pollution, we did not consider subclassifications of stroke due to concerns over study power and differences in diagnostic procedures both with time and across cohorts. Strengths of this study include the large sample size, pooling and harmonisation of cohort data and subsequent analysis, and availability of a broad range of potential confounders. Furthermore, the centrally developed European-wide exposure surfaces ensured comparable estimates across cohorts. In addition, data on road traffic noise was available for most cohorts, allowing additional adjustment for this

important environmental risk factor for cardiovascular disease. With this robust study design, we were able to examine concentration-response functions at values lower than current regulatory limits.

In conclusion, at concentrations much lower than the current EU annual mean limits, long-term air pollution exposure was associated with incidence of stroke and coronary heart disease in this multicentre European study.

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Contributors

AP, BB, BH, FF, GH, GP, GW, JG, KdH, KK, NAHJ, OH, OR-N, PLSL, PS, RWA, and TB contributed to the concept and design of the study. DF, GH, JB, JC, JG, KdH, MK, MStr, and OH contributed to the development of LUR models for exposure assessment. AL, AP, AT, BH, DR, ES, GP, JJJ, KW, MK, MSø, MStr, WMMV, NLP, OR-N, PLSL, PKEM, SS, Udf, UAH, YTvS, and ZJA provided local cohort data or harmonised the data for pooled analyses. ES, GC, GH, GW, KK, KW, MStA, MStr, RWA, SR, UAH, and ZJA contributed to the development of statistical methods and scripts. JC, MStr, GH, ES, SR, UAH, ZJA, and KW have verified the underlying data. KW did the statistical analysis and drafted the manuscript. MB, JOK, SL, CJMacD, AJM, GN, BO, MR, TS, and DV contributed to intellectual content. All authors had full access to all the data in the study. All authors contributed to the interpretation of results, reviewed the paper, and approved the final draft, and accept responsibility to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

The exposure maps are available on request from Dr Kees de Hoogh (c.dehoogh@swisstph.ch). The cohort data could only be pooled for the ELAPSE framework and is not available for sharing due to strict national data protection regulations and the EU General Data Protection Regulation. The ELAPSE Project protocol is available online. A detailed statistical analysis plan is available from the corresponding author on reasonable request.

For the **ELAPSE protocol** see <http://www.elapseproject.eu>

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