ORIGINAL ARTICLE

Air Quality, Stroke, and Coronary Events

Results of the Heinz Nixdorf Recall Study From the Ruhr Region

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SUMMARY

Background: Studies have shown that air pollution is associated with cardio-pulmonary mortality, but there has been less research of the possible effect of air pollution on stroke and non-fatal coronary events. The Heinz Nixdorf Recall (HNR) study addressed the question of the effect of long-term air pollution on stroke and coronary events. Ambient acoustic noise was also considered as a risk factor.

Methods: The HNR study, initiated in 2000, is a prospective, population-based cohort study in the Ruhr region of Germany. Long-term exposure to fine-particle dust (PM₁₀, PM_{2.5} and PM_{2.5abs} [carbon black content]) and traffic noise at the subjects' home addresses were determined using land-use regression and dispersion models, respectively. Strokes and coronary events were ascertained from patient records by an independent end-point committee on the basis of predefined study criteria. The adjusted hazard ratio (HR) was calculated using Cox regression analysis for an increase in concentration from the 5th to the 95th percentile for each exposure.

Results: Data from 4433 subjects were evaluated. The incidence of stroke was 2.03 per 1000 person-years (PY), and that of coronary events was 3.87 per 1000 PY. The highest hazard ratios for stroke were seen for PM₁₀ (HR 2.61, 95% confidence interval [CI] 1.13–6.00) and PM_{2.5} (HR 3.20, 95% CI 1.26–8.09). The highest hazard ratios for coronary events were found for PM₁₀ (HR 1.07, 95% CI 0.56–2.04) and for PM_{2.5abs} (HR 1.37, 95% CI 0.80–2.36).

Conclusion: Long-term exposure to fine-particle dust is associated with a higher risk of stroke, regardless of the subject's exposure to noise at his or her home address. The results for coronary events are less clear, but still suggest increased risk.

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In Germany, the times of great smog episodes are largely things of the past. But even today, air quality thresholds are frequently exceeded and discussions of solutions range from low emission zones, bypass roads, industrial restrictions, etc., to personal lifestyle interventions. In addition, the quality of air pollution has changed significantly due to a number of factors including effective filtering of larger particles, which has led to a relative increase of smaller, respirable particles. The rapidly increasing body of evidence for the adverse health effects of particulate matter that has emerged in recent years (*Box*) (1) prompted the U.S. Environmental Protection Agency to revise its standards in 2013. Thus, the long-term threshold for respirable particulate matter with an aerodynamic diameter of under 2.5 µm (PM_{2.5}) was lowered from 15 µg/m³ to 12 µg/m³ (2). In the European Union (EU), the roughly comparable value is currently 25 µg/m³ (3).

Although in recent years numerous studies have reported correlations between air pollution and total mortality as well as cardiovascular and respiratory mortality (4–12), the association with stroke incidence has been less frequently studied and with conflicting results (13–16). In addition, several studies have shown an association between cardiovascular disease and chronic noise exposure, which often coexists with high levels of air pollution (17). Studies examining both environmental stressors simultaneously remain uncommon (18).

Because of its substantial relevance at the population level, this topic deserves worldwide attention from the research and public health communities (19). To investigate the health impact of long-term exposure to the concentrations of air pollutants currently found in Europe, the EU, through its Framework Programme 7, funded a large, multicenter study: the European Study of Cohorts on Air Pollution Effects (ESCAPE). One particular goal of the ESCAPE study was to provide epidemiological evidence for the modification of European thresholds. The incidences of stroke and coronary events were examined as two key endpoints of the ESCAPE study (20, 21).

The German Heinz Nixdorf Recall (HNR) study is one of the cohort studies making a substantial contribution to this European project. Because of the location of the study in the Ruhr region, a densely populated and

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BOX

Particulate matter

- Particulate matter with aerodynamic diameters less than 10 or 2.5 μm (PM_{10} and $\text{PM}_{2.5}$) are considered air pollutants for which adverse health effects have been proven.
- The main sources of particulate matter are traffic, industry, agriculture, heating, and earth crust material.
- Short-term increases in daily exposure to particulate matter already lead to an increased mortality rate.
- Long-term residential exposure to particulate matter is associated with increased mortality. Decreased particulate matter exposure extends life expectancy.
- Oxidative stress, pulmonary and systemic inflammation, autonomic nervous system imbalance, as well as direct effects from absorbed pollutants are suspected biological etiologies.
- Pulmonary and systemic markers of inflammation as well as blood pressure increases are early subclinical effects. In addition, pulmonary function is impaired, glucose metabolism is worsened, and atherosclerotic progression is accelerated (1).

still recently highly industrialized area, the studied cohort is highly suitable to evaluate the effects of long-term air pollution. The goal of the current study is to extend the HNR-specific results regarding stroke and coronary events by accounting for concomitant chronic noise pollution.

Methods

Study population

The HNR is a population-based prospective cohort study involving a random sample of 45- to 74-year-old inhabitants of the Ruhr region cities of Bochum, Essen, and Mülheim/Ruhr (22). During the years 2000 to 2003, 4814 people took part in the baseline investigation (participation rate: 55.8%) (23). All subjects provided written informed consent. The study was approved by the Ethics Committee of the University of Duisburg–Essen.

Endpoint assessment

Subsequent to the baseline examination, annual questionnaire-based follow-up was performed. In cases where stroke or coronary events were suspected, the medical records or other sources were investigated (22). For the endpoints of the current analysis, clearly documented incidents of stroke and coronary events (infarction, sudden cardiac death, and fatal coronary heart disease [CHD]) were considered. These endpoints are defined according to a protocol harmonized among the individual European cohorts: diagnoses with

ICD-10 I61, I63, or I64 and cause of death I61 to I64 apply for stroke (21), diagnoses with ICD-10 I21, I23, I20.0, or I24 and cause of death I20 to I25 apply for coronary events (20).

For all end points, the independent endpoint committees of the HNR study evaluated patient records containing laboratory values, ECG, and pathology results. In cases of deceased participants, death certificates were evaluated and interviews with treating physicians, relatives, and witnesses were conducted as needed.

Exposure assessment

As part of the ESCAPE project, exposure to particulate matter was measured using a standardized protocol at 20 locations in the studied region over the time from August 2008 to July 2009 (24, 25). The pollutants measured were PM_{10} (aerodynamic diameter of $\leq 10 \mu\text{m}$), $\text{PM}_{2.5}$ ($\leq 2.5 \mu\text{m}$), $\text{PM}_{2.5-10}$, and $\text{PM}_{2.5\text{abs}}$ (the absorbance [abs] of $\text{PM}_{2.5}$ is a measure of the soot content). Using land-use regression (LUR) models (*eBox*), the levels of pollutants at the home residence were allocated for each participant. Traffic from busy roads (>5000 vehicles/day) within a 100 m radius of the residence was considered as an additional exposure. Chronic noise pollution from road traffic near the home was determined using noise models prepared according to the European guidelines. The results of the noise pollution models were made available by the cities and then assigned to the home addresses of the study participants.

Confounding variables

The following covariates collected during the baseline examination were considered (Table 1):

- Marital status
- Education
- Employment status
- Smoking status, including duration and intensity
- Cholesterol
- Blood pressure
- Type 2 diabetes mellitus
- Categorical variables for body mass index (BMI)
- Physical activity
- Alcohol consumption.

In addition, the unemployment rate for the residential district was considered as an indicator of socioeconomic status. This is because this factor, independent of personal socioeconomic status, affects cardiovascular disease, access to healthcare, and lifestyle factors (26). In the final model, we did not adjust for cholesterol because there was no significant impact on the effect estimates, and there was a significant reduction in sample size when using it, since not all subjects had blood samples, and thus cholesterol values, available.

Statistical analysis

Cox regression analysis was performed with age as a time scale to determine the association between exposure and event incidence. 4433 participants reporting no history of coronary events or stroke at baseline and

offering complete information regarding the confounding variables, were included in the study. We analyzed the most recent complete data set, from February 2012. (Table 1).

A combined endpoint of stroke and coronary events was defined as the main outcome, but each end point was also evaluated independently.

A priori defined sets were used for the adjustment of the confounding variables:

- Model 1: adjustment for sex and recruitment year.
- Model 2: additional adjustment for marital status, education, employment status, smoking status, smoking duration and intensity, and unemployment rate in the residential district.
- Model 3: additional adjustment for BMI, physical activity, and alcohol consumption.
- Model 4: additional adjustment for night traffic noise.

The effects were specified for an increase corresponding to the difference in concentration from the 5th to 95th percentiles of each pollutant exposure within the study region. Thus, it becomes possible to compare effects of different pollutants within the study area.

In a sensitivity analysis based on Model 2, those individuals who had lived at least five years in their residence prior to the baseline examination and who had not changed address during follow up were investigated. All analyses were performed using STATA Software (www.stata.com).

Results

The profile of this at-risk study population, with no history of stroke nor coronary events at baseline, is listed in Table 1. The analysis population for whom information regarding covariates are available (N = 4433) represent 90% of the total population of the HNR study (N = 4814), and 97% of the study participants who at the time of the baseline examination reported neither stroke nor coronary event (N = 4465). Over an average observation period of 7.9 ± 1.5 years, there were 206 events in a total of 34 644 at-risk person-years (PY), of these 135 coronary events in 34 909 PY and 71 strokes in 34 941 PY. Thus, the incidence was 5.95/1000 PY for all events, 3.87/1000 PY for coronary events, and 2.03/1000 PY for stroke. A detailed description of the study population including risk scores is given in the study by Erbel et al. (27). The individual pollutant exposure was on average $27.8 \mu\text{g}/\text{m}^3$ for PM_{10} and $18.4 \mu\text{g}/\text{m}^3$ for $\text{PM}_{2.5}$ (Table 2).

An analysis of the combined endpoint of stroke and coronary events yielded increased point estimates for all investigated exposures in the fully adjusted model (Model 4), particularly for PM_{10} (hazard ratio [HR] = 1.41; 95% confidence interval [CI]: 0.85 to 2.36), $\text{PM}_{2.5}$ (HR = 1.45; 95% CI: 0.84 to 2.52), and with soot content of the particulate matter $\text{PM}_{2.5\text{abs}}$ (HR = 1.51; 95% CI: 0.99 to 2.31) (Table 3). When subjects who had moved within five years prior to the baseline study were excluded, the HR increased for $\text{PM}_{2.5\text{abs}}$ to 1.65

TABLE 1

Profile of the study population at risk at baseline

		n or MV	% or SD
Total		4433	100
Age (Years; MV $\pm$ SD)		59.3	7.8
Sex (n, %)	Male	2124	47.9
BMI in kg/m^2 (MV $\pm$ SD)		27.8	4.6
Cholesterol (mg/dL; MV $\pm$ SD)		230.8	39.0
Systolic blood pressure (mm Hg; MV $\pm$ SD)		132.8	20.8
Education (n, %)	≤ 10 years	499	11.3
	11–13 years	2466	55.6
	>13 years	1468	33.1
Employment status (n, %)	Employed	1859	41.9
	Unemployed	280	6.3
	Homemaker	630	14.2
	Retired	1664	37.5
Marital status (n, %)	Single	256	5.8
	Married	3319	74.9
	Divorced	444	10
	Widowed	414	9.3
Unemployment rate (%; MV $\pm$ SD)		12.5	3.5
Smoking status (n, %)	Smoker	1040	23.5
	Ex-smoker	1482	33.4
	Never smoker	1911	43.1
Smoking duration (years; MV $\pm$ SD) ^{*1}		36.2	8.6
Smoking intensity (Cig./day; MV $\pm$ SD) ^{*1}		17.3	11.8
Alcohol intake (n, %)	Never	2127	48.0
	1–6 glasses ^{*2} /week	1190	26.8
	> 6 glasses ^{*2} /week	1015	22.9
Physical activity (n, %)	≤ 1 hr./wk	2263	51.2
	1–3 hr./wk	490	11.1
	>3 hr./wk	1667	37.7
Diabetes mellitus type 2 (n, %)	Yes	556	12.5
Events during Follow Up			
Stroke (n, %)	Yes	71	1.6
Coronary event (n, %)	Yes	135	3.1
Combined (stroke or coronary event) (n, %)	Yes	206	4.6

BMI, body mass index;
MV, mean value;
SD, standard deviation;
Cig., cigarettes;

^{*1} For smokers only (N = 1040)

^{*2} One glass is 0.25 L beer, 0.1 L wine or 0.02 L liquor.

The percentages are based on the study population of 4433. In the base population, certain covariates like alcohol intake were sometimes unavailable and not individually accounted for. Thus, the sum of percentages does not always equal 100%

TABLE 2

Exposure to air pollutants PM₁₀, PM_{2.5-10}, PM_{2.5} and PM_{2.5abs}, traffic and chronic noise exposure at baseline, 2000–2003. Heinz Nixdorf Recall Study

Exposure		Distribution		
		Mean	Standard deviation	5 th –95 th percentile
PM ₁₀	µg/m ³	27.78	1.86	6.32
PM _{2.5-10}	µg/m ³	9.99	1.83	5.26
PM _{2.5}	µg/m ³	18.41	1.06	3.51
PM _{2.5abs}	10 ⁻⁵ /m	1.59	0.35	0.98
Traffic* ¹	km × veh/d	1017	2236	4302
Night noise* ²	dB(A)	45.32	8.64	26

Veh., vehicles

*¹ Traffic exposure through busy streets in vicinity of 100 m/1000 (traffic intensity multiplied by length of road)

*² for participants with modelled noise values >35 dB(A); noise values under 35 dB(A) were not modelled

(95% CI: 1.07 to 2.55) and for a high traffic load to 1.27 (95% CI: 0.97 to 1.66).

The fully adjusted risk for stroke in all particulate matter fractions was markedly increased, particularly for PM₁₀ (HR = 2.61; 95% CI: 1.13 to 6.00) and PM_{2.5} (HR = 3.20; 95% CI: 1.26 to 8.09). The effect estimate for PM_{2.5abs} was 1.86 (95% CI: 0.94 to 3.66). Traffic exposure in proximity to the home was not clearly linked to the risk of stroke. When subjects who had moved within five years prior to the baseline survey were excluded, the risks did not significantly change.

The fully adjusted risks for coronary events were less markedly increased. Only for PM_{2.5abs} was there a not significantly increased effect estimate with HR of 1.37 (95% CI: 0.80 to 2.36), which increased to 1.61 (95% CI: 0.93 to 2.78) when the people who had moved were excluded. The estimate for high traffic load in the home vicinity was also increased (HR = 1.35; 95% CI: 0.98 to 1.86) after the participants who had moved within five years prior to the baseline study were excluded.

Discussion

The concentration of air pollution today is only about a quarter of the value common during the 1970s. The present study shows an association between long-term air pollution and stroke regardless of the presence of noise pollution, and this even at current, lower pollution concentrations. The results of the HNR study indicate that the occurrence of stroke is associated with PM₁₀ and PM_{2.5}, the two currently EU wide regulated PM fractions. In addition, the soot content of the particulate dust, which is currently not legally regulated in the EU, appears to be associated with risk for both stroke and coronary events. These results were robust to changes in various model assumptions and adjustment variables.

The present analysis of the HNR study is based on the multi-center European ESCAPE project that used data from approximately 100 000 test subjects and calculated that a concentration change of 5 µg/m³ PM_{2.5} led to an increased risk for stroke of 19%, and for coronary events of 13% (20, 21). In addition to the main results of the ESCAPE study, our analysis considered chronic noise exposure, which is known as a potentially important variable influencing the effects of air pollution. When noise is considered during the analysis for stroke, there is a trend towards an increase in the effect estimate for particulate matter. By contrast, the effect estimate decreases slightly when evaluating coronary events. Further results from the HNR study indicate a correlation between long-term concentrations of particulate matter at the home and high-sensitivity C-reactive protein (CRP) levels in serum (28, 29), arterial blood pressure (30), and the degree and progression of intima-media thickness of the common carotid artery (a measure for subclinical atherosclerosis) (31, 32). In addition, proximity to busy streets was associated with the degree of coronary artery calcification as measured with electron beam computed tomography (32).

There is no clear explanation for the markedly higher HR for stroke compared to coronary events in the HNR study. It is possible that the selected endpoint of coronary events incompletely reflects the presence of CHD, thanks to the increasingly improved and earlier treatments for the disease. Thus, interventions such as dilatation or stents that prevent events from manifesting should also be considered as endpoints when appropriate. This will be performed in further analyses.

The results of the ESCAPE and HNR studies show linear exposure–effect relationships (20, 21, 29, 31). Also, the associations between particulate matter and the health sequelae listed above also occur beneath the currently valid European thresholds for particulate matter concentrations (20, 21). Thus, if the long-term exposure to particulate matter is reduced, health improvements in the population may be expected, regardless of current levels of exposure. A large U.S. study has already demonstrated that life expectancy increases by 0.6 years when long-term PM₁₀ concentration is decreased by 10 µg/m³ (33).

Possible biological mechanisms whereby the particulate matter may affect the cardiovascular system include (1, 34):

- Endothelial dysfunction and vasoconstriction
- Increased blood pressure
- Prothrombotic changes
- Systemic inflammatory processes and oxidative stress
- Autonomic disequilibrium and arrhythmias
- Progression of atherosclerosis.

The effects of short-term increases in particulate matter concentrations—causing acute events for example through the induction of arrhythmias and atrial fibrillation as well as triggering of inflammatory and procoagulative processes (1)—are differentiated from

TABLE 3

Associations (hazard ratios) with incidence of events in the Heinz Nixdorf Recall Study^{*1}

	Exposure	HR (95% CI) for an increase from 5 th –95 th percentile of exposure					
		Model 1 N = 4433	Model 2 N = 4433	Model 2b ^{*4} N = 4302	Model 3 N = 4302	Model 3b ^{*6} N = 4222	Model 4 N = 4222
Combined endpoint ^{*2}	PM ₁₀	1.50 (0.97–2.31)	1.42 (0.87–2.30)	1.47 (0.90–2.40)	1.48 (0.90–2.42)	1.43 (0.87–2.34)	1.41 (0.85–2.36)
	PM _{2.5–10}	1.07 (0.70–1.61)	1.02 (0.66–1.57)	1.07 (0.69–1.68)	1.10 (0.70–1.72)	1.10 (0.67–1.81)	1.07 (0.65–1.78)
	PM _{2.5}	1.49 (0.96–2.32)	1.47 (0.87–2.48)	1.54 (0.91–2.62)	1.52 (0.90–2.59)	1.47 (0.86–2.51)	1.45 (0.84–2.52)
	PM _{2.5abs}	1.48 (1.06–2.07)	1.49 (1.03–2.16)	1.51 (1.04–2.19)	1.48 (1.02–2.15)	1.46 (1.00–2.12)	1.51 (0.99–2.31)
	Traffic ^{*3}	1.20 (0.95–1.50)	1.19 (0.94–1.50)	1.20 (0.95–1.51)	1.18 (0.93–1.49)	1.16 (0.91–1.47)	1.17 (0.89–1.54)
	Night noise ^{*5}	1.35 (0.86–2.13)	1.26 (0.79–2.00)	1.17 (0.73–1.89)	1.12 (0.70–1.80)	1.12 (0.70–1.80)	/
Stroke	PM ₁₀	1.97 (0.97–4.00)	2.23 (1.01–4.93)	2.36 (1.06–5.24)	2.39 (1.07–5.32)	2.38 (1.06–5.35)	2.61 (1.13–6.00)
	PM _{2.5–10}	1.38 (0.66–2.85)	1.39 (0.64–3.04)	1.47 (0.66–3.29)	1.52 (0.68–3.42)	1.79 (0.72–4.46)	1.92 (0.74–4.98)
	PM _{2.5}	2.11 (1.01–4.43)	2.61 (1.09–6.29)	2.83 (1.17–6.87)	2.89 (1.19–7.04)	2.90 (1.18–7.12)	3.20 (1.26–8.09)
	PM _{2.5abs}	1.53 (0.88–2.69)	1.53 (0.84–2.79)	1.57 (0.87–2.86)	1.57 (0.86–2.85)	1.57 (0.86–2.86)	1.86 (0.94–3.66)
	Traffic ^{*3}	1.08 (0.71–1.65)	1.10 (0.72–1.67)	1.08 (0.71–1.66)	1.07 (0.70–1.64)	1.06 (0.69–1.64)	1.13 (0.69–1.84)
	Night noise ^{*5}	1.06 (0.48–2.33)	1.01 (0.45–2.24)	0.94 (0.41–2.13)	0.91 (0.40–2.06)	0.91 (0.40–2.06)	/
Coronary event	PM ₁₀	1.30 (0.75–2.25)	1.16 (0.63–2.13)	1.17 (0.63–2.19)	1.18 (0.63–2.20)	1.12 (0.60–2.11)	1.07 (0.56–2.04)
	PM _{2.5–10}	0.94 (0.57–1.55)	0.88 (0.52–1.48)	0.93 (0.54–1.58)	0.95 (0.56–1.62)	0.88 (0.49–1.5)	0.84 (0.46–1.52)
	PM _{2.5}	1.25 (0.72–2.17)	1.13 (0.59–2.16)	1.15 (0.59–2.22)	1.12 (0.58–2.18)	1.06 (0.55–2.07)	1.00 (0.51–1.99)
	PM _{2.5abs}	1.46 (0.96–2.21)	1.49 (0.93–2.37)	1.48 (0.92–2.37)	1.44 (0.90–2.32)	1.40 (0.87–2.27)	1.37 (0.80–2.36)
	Traffic ^{*3}	1.26 (0.96–1.65)	1.24 (0.93–1.65)	1.26 (0.95–1.67)	1.23 (0.93–1.64)	1.21 (0.91–1.62)	1.19 (0.85–1.68)
	Night noise ^{*5}	1.54 (0.88–2.69)	1.40 (0.79–2.49)	1.31 (0.73–2.34)	1.25 (0.70–2.23)	1.25 (0.70–2.23)	/

Model 1: adjusted for sex and recruitment year; Model 2: additionally adjusted for marital status, education, employment status, smoking status, duration, and intensity, and neighborhood unemployment; Model 3: additionally adjusted for physical activity, body mass index (BMI), and alcohol intake; Model 4: additionally adjusted for nighttime traffic noise; because cholesterol had no significant influence on the effect estimator but significantly decreased case number (cases without blood results), the adjustment for cholesterol was waived in the final Model 4.

HR, hazard ratio; 95% CI, 95% confidence interval

^{*1} Hazard ratio with 95% confidence interval. Results of Models 1–3 for stroke and coronary events according to (20, 21)

^{*2} The combined endpoint summarizes coronary and cerebrovascular events.

^{*3} Traffic exposure from busy streets in vicinity 100 m/1000 [(vehicles × m)/(day × 1000)]

^{*4} only persons with all adjustment variable information for Model 3

^{*5} N for noise analysis 4350

^{*6} only participants with available information regarding noise

the effects of long-term exposure, which accelerate the development of the underlying atherosclerotic disease (31, 32).

The size of the associations found in this study are comparable to known risk factors. For stroke, the HR is approximately 2.0 for smoking, 1.5 for atrial fibrillation, and 1.4 for diabetes mellitus (34). These risk factors, however, are only present for subgroups of the population. On the other hand, the entire population is exposed to greater or lesser concentrations of air pollution. In addition, personal exposure can be only relatively minimally controlled by the individuals themselves. This explains why these findings have such enormous significance for public health.

The American Heart Association (AHA) has produced a comprehensive statement describing the marked effect of air pollution (1, 34). The AHA recommends that practicing physicians should educate pa-

tients regarding the risks of particulate matter. This applies particularly for people at risk, for example because of diabetes mellitus, increased age, or multiple cardiovascular risk factors. Such individuals should restrict extra physical activity on days with higher loads of dust pollution or do so protected in a less polluted indoor area. Overall, the prevention potential for individuals is considered to be very low, so a setting approach for prevention by environmental regulation is necessary. The current recommendations of the World Health Organization (WHO) are annual averages of 20 µg/m³ for PM₁₀ or 10 µg/m³ for PM_{2.5} and are thus markedly lower than the levels measured currently in many urban centers in Germany.

Limitations and strengths of the study

The present study is limited by the fact that disease events had partly already occurred when the air

pollution measurements took place and the resulting exposure models were created. However, studies have confirmed that the procedure used for the land-use regression models does provide valid exposure values for the long-term. Concentration differences within the study region, on which our analyses are based, have been reliably reproduced (35, 36). When exposure values were extrapolated back to the time of the baseline examination, using air pollution concentrations from routine monitoring sites, the risk estimates of the HNR study do not change significantly.

The strength of this study lies in the detailed assessment of exposure, which contrasts to most previous studies, in that the pollutant exposure was assessed with a high spatial resolution and that the noise exposure of each individual residence was taken into account. In addition, the HNR is a large, population-based study, for which an external committee of experts regularly assessed the endpoints of CHD and stroke. Thus, misclassification of events was minimized. A number of potential confounding variables for the investigated correlations were carefully recorded and considered.

Conclusion

The results suggest that long-term home exposure to particulate matter, both PM_{2.5} and PM₁₀, even at current levels as measured in the Ruhr area, increases the risk of stroke. The results for coronary events are less clear, but still indicate—corresponding with findings in the literature and in the European ESCAPE study—increased risk. The role of other dust particles, currently not yet regulated in Europe but possibly also increasing risk, should be investigated in the future. This includes—particularly important in proximity to roads—exposure to soot particles. Concerted action is needed across Europe to further reduce exposure to particulate matter and minimize the health consequences for the population.

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KEY MESSAGES

- Long-term air pollution corresponds to increased stroke risk, regardless of concomitant noise pollution.
- This association is particularly evident for PM₁₀ and PM_{2.5}, the two currently EU-wide regulated fractions of particulate matter.
- Evidence indicates that the soot content of particulate matter, which is not currently regulated in the EU, affects the risk for strokes and coronary events.
- No statistically significant association between PM₁₀ or PM_{2.5} and coronary events was evident. This might be due to low case numbers.
- These results were robust to adjustment of various model assumptions and variables.

Conflict of interest statement

Prof. Hoffmann was remunerated for the review of a related project from the Health Effects Institute. She received research funding from the Volkswagen Foundation (Volkswagenstiftung).

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REFERENCES

1. Brook RD, Rajagopalan S, Pope CA III, et al.: Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. *Circulation* 2010; 121: 2331–78.
2. US Environmental Protection Agency: National ambient air quality standards for particulate matter, rules and regulations. *Federal Register* 2013; 78: 10.
3. Europäische Union: Richtlinie 2008/50/EG des Europäischen Parlaments und des Rates vom 21. Mai 2008 über Luftqualität und saubere Luft für Europa. *Amtsblatt der Europäischen Union* 2008; 51: L152: 1.
4. Cesaroni G, Badaloni C, Gariazzo C, et al.: Long-term exposure to urban air pollution and mortality in a cohort of more than a million adults in Rome. *Environ Health Perspect* 2013; 121: 324–31.
5. Chen H, Goldberg MS, Burnett RT, Jerrett M, Wheeler AJ, Villeneuve PJ: Long-term exposure to traffic-related air pollution and cardiovascular mortality. *Epidemiology* 2013; 24: 35–43.
6. Heinrich J, Thiering E, Rzehak P, et al.: Long-term exposure to NO₂ and PM₁₀ and all-cause and cause-specific mortality in a prospective cohort of women. *Occup Environ Med* 2013; 70: 179–86.
7. Raaschou-Nielsen O, Andersen ZJ, Jensen SS, et al.: Traffic air pollution and mortality from cardiovascular disease and all causes: a Danish cohort study. *Environ Health* 2012; 11: 60.
8. Gan WQ, Davies HW, Koehoorn M, Brauer M: Association of long-term exposure to community noise and traffic-related air pollution with coronary heart disease mortality. *Am J Epidemiol* 2012; 175: 898–906.
9. Lepeule J, Laden F, Dockery D, Schwartz J: Chronic exposure to fine particles and mortality: an extended follow-up of the Harvard Six Cities study from 1974 to 2009. *Environ Health Perspect* 2012; 120: 965–70.
10. Dong GH, Zhang P, Sun B, et al.: Long-term exposure to ambient air pollution and respiratory disease mortality in Shenyang, China: a

- 12-year population-based retrospective cohort study. *Respiration* 2012; 84: 360–8.
11. Beelen R, Hoek G, van den Brandt PA, et al.: Long-term exposure to traffic-related air pollution and lung cancer risk. *Epidemiology* 2008; 19: 702–10.
12. Beelen R, Raaschou-Nielsen O, Stafoggia M, et al.: Effects of long-term exposure to air pollution on natural-cause mortality: an analysis of 22 European cohorts within the multicentre ESCAPE project. *Lancet* 2014; 383: 785–95.
13. Miller KA, Siscovick DS, Sheppard L, et al.: Long-term exposure to air pollution and incidence of cardiovascular events in women. *N Engl J Med* 2007; 356: 447–58.
14. Krewski D, Jerrett M, Burnett RT, et al.: Extended follow-up and spatial analysis of the American Cancer Society study linking particulate air pollution and mortality. *Res Rep Health Eff Inst* 2009; 140: 5–114; Discussion 115–36.
15. Atkinson RW, Carey IM, Kent AJ, van Staa TP, Anderson HR, Cook DG: Long-term exposure to outdoor air pollution and incidence of cardiovascular diseases. *Epidemiology* 2013; 24: 44–53.
16. Andersen ZJ, Raaschou-Nielsen O, Ketzel M, et al.: Diabetes incidence and long-term exposure to air pollution: a cohort study. *Diabetes Care* 2012; 35: 92–8.
17. Münzel T, Gori T, Babich W, Basner M: Cardiovascular effects of environmental noise exposure. *Eur Heart J* 2014; 35: 829–36.
18. Foraster M: Is it traffic-related air pollution or road traffic noise, or both? Key questions not yet settled! *Int J Public Health* 2013; 58: 647–8.
19. Mateen FJ, Brook RD: Air pollution as an emerging global risk factor for stroke. *JAMA* 2011; 305: 1240–1.
20. Cesaroni G, Forastiere F, Stafoggia M, et al.: Long term exposure to ambient air pollution and incidence of acute coronary events: prospective cohort study and meta-analysis in 11 European cohorts from the ESCAPE Project. *BMJ* 2014; 348: f7412.
21. Stafoggia M, Cesaroni G, Peters A, et al.: Long-term exposure to ambient air pollution and incidence of cerebrovascular events: results from 11 European cohorts within the ESCAPE Project. *Environ Health Perspect* 2014; 122: 919–25.
22. Schmermund A, Mohlenkamp S, Stang A, et al.: Assessment of clinically silent atherosclerotic disease and established and novel risk factors for predicting myocardial infarction and cardiac death in healthy middle-aged subjects: rationale and design of the Heinz Nixdorf RECALL Study. Risk factors, evaluation of coronary calcium and lifestyle. *Am Heart J* 2002; 144: 212–8.
23. Stang A, Moebus S, Dragano N, et al.: Baseline recruitment and analyses of nonresponse of the Heinz Nixdorf Recall Study: identifiability of phone numbers as the major determinant of response. *Eur J Epidemiol* 2005; 20: 489–96.
24. Eeftens M, Beelen R, de Hoogh K, et al.: Development of land use regression models for PM_{2.5}, PM_{2.5} absorbance, PM₁₀ and PM_{coarse} in 20 European study areas; results of the ESCAPE project. *Environ Sci Technol* 2012; 46: 11195–205.
25. Beelen R, Hoek G, Vienneau D, et al.: Development of NO₂ and NO_x land use regression models for estimating air pollution exposure in 36 study areas in Europe – The ESCAPE project. *Atmos Environ* 2013; 72: 10–23.
26. Diez Roux AV, Merkin SS, Hannan P, Jacobs DR, Kiefe CI: Area characteristics, individual-level socioeconomic indicators, and smoking in young adults: the coronary artery disease risk development in young adults study. *Am J Epidemiol* 2003; 157: 315–26.
27. Erbel R, Möhlenkamp S, Moebus S, et al.: Coronary risk stratification, discrimination, and reclassification improvement based on quantification of subclinical coronary atherosclerosis: the Heinz Nixdorf Recall study. *J Am Coll Cardiol* 2010; 56: 1397–406.
28. Hoffmann B, Moebus S, Dragano N, et al.: Chronic residential exposure to particulate matter air pollution and systemic inflammatory markers. *Environ Health Perspect* 2009; 117: 1302–8.
29. Hennig F, Fuks K, Moebus S, et al.: Association between source-specific particulate matter air pollution and hs-CRP: local traffic and industrial emissions. *Environ Health Perspect* 2014; 122: 703–10.
30. Fuks K, Moebus S, Hertel S, et al.: Long-term urban particulate air pollution, traffic noise and arterial blood pressure. *Environ Health Perspect* 2011; 119: 1706–11.
31. Bauer M, Moebus S, Mohlenkamp S, et al.: Urban particulate matter air pollution is associated with subclinical atherosclerosis: results from the HNR (Heinz Nixdorf Recall) study. *J Am Coll Cardiol* 2010; 56: 1803–8.
32. Hoffmann B, Moebus S, Möhlenkamp S, et al.: Residential exposure to traffic is associated with coronary atherosclerosis. *Circulation* 2007; 116: 489–96.
33. Pope CA 3rd, Ezzati M, Dockery DW: Fine-particulate air pollution and life expectancy in the United States. *N Engl J Med* 2009; 360: 376–86.
34. Gold DR, Mittleman MA: New insights into pollution and the cardiovascular system: 2010 to 2012. *Circulation* 2013; 127: 1903–13.
35. Cesaroni G, Porta D, Badaloni C, et al.: Nitrogen dioxide levels estimated from land use regression models several years apart and association with mortality in a large cohort study. *Environ Health* 2012; 11: 48.
36. Eeftens M, Beelen R, Fischer P, Brunekreef B, Meliefste K, Hoek G: Stability of measured and modelled spatial contrasts in NO₂ over time. *Occup Environ Med* 2011; 68: 765–70.

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ORIGINAL ARTICLE

Air Quality, Stroke, and Coronary Events

Results of the Heinz Nixdorf Recall Study From the Ruhr Region

Barbara Hoffmann, Gudrun Weinmayr, Frauke Hennig, Kateryna Fuks, Susanne Moebus, Christian Weimar, Nico Dragano, Dirk M. Hermann, Hagen Kälisch, Amir A. Mahabadi, Raimund Erbel, Karl-Heinz Jöckel

eBOX

Exposure determination

Exposure to particulate matter, i.e. PM_{10} ($\leq 10 \mu m$), $PM_{2.5}$ ($\leq 2.5 \mu m$), $PM_{2.5-10}$, and $PM_{2.5abs}$, was determined using a standardized protocol by the ESCAPE project. First, particulate matter concentrations were measured at 20 locations during three two-week periods over the time from August 2008 to July 2009. One measuring station operated throughout the year. These year-long values were used to extrapolate values for the 20 locations on days where no data was collected. Using these values, the annual mean concentrations of pollutants were calculated for all measuring stations. In a second step, land-use regression (LUR) models were developed. These models use information for land use such as population and traffic densities as predictors for the measured values in a linear regression model. In a third step using the obtained linear model equations, the concentrations of pollutants at the homes of each participant were estimated. For this, the land-use data of the home addresses for the participants was used. Thus, each study participant was assigned an individual exposure value. The research groups of Eeftens (24) and Beelen (25) describe this methodology in greater detail.

Busy road traffic (>5000 vehicles/day) within a 100 m radius of the home was assessed as additional exposure using the regional road map of 2007. For example, if a 200 m long, heavily trafficked street on which 5000 vehicles/day drive runs through this radius, a traffic exposure is calculated as 1 000 000 vehicle exposures x m/day.