Thrombosis Research 225 (2023) 116–125

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Air pollution impacts on in-hospital case-fatality rate of ischemic stroke patients

Karsten Keller [a,b,c,*,1], Seyed Hamed Rastguye Haghi [a,1], Omar Hahad [a,d], Irene Schmidtmann [e], Sourangsu Chowdhury [f,g], Jos Lelieveld [f], Thomas Münzel [a,d], Lukas Hobohm [a,b]

[a] Department of Cardiology, University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany
[b] Center for Thrombosis and Hemostasis (CTH), University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany
[c] Medical Clinic VII, Department of Sports Medicine, University Hospital Heidelberg, Heidelberg, Germany
[d] German Center for Cardiovascular Research (DZHK), Partner Site Rhine Main, Mainz, Germany
[e] Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI), University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany
[f] Max Planck Institute for Chemistry, Mainz, Germany
[g] CICERO Center for International Climate Research, Oslo, Norway

ARTICLE INFO

Keywords:
Cardiovascular diseases
Stroke
Air pollution
Carbon monoxide
Benzene
PM_{10}
$PM_{2.5}$
Ozone
Nitric oxide
Nitrogen dioxide
Sulphur dioxide

ABSTRACT

Background: A growing body of evidence suggests that air pollution exposure is associated with an increased risk for cardiovascular diseases. Data regarding the impact of long-term air pollution exposure on ischemic stroke mortality are sparse.

Methods: The German nationwide inpatient sample was used to analyse all cases of hospitalized patients with ischemic stroke in Germany 2015–2019, which were stratified according to their residency. Data of the German Federal Environmental Agency regarding average values of air pollutants were assessed from 2015 to 2019 at district-level. Data were combined and the impact of different air pollution parameters on in-hospital case-fatality was analyzed.

Results: Overall, 1,505,496 hospitalizations of patients with ischemic stroke (47.7% females; 67.4 % ≥70 years old) were counted in Germany 2015–2019, of whom 8.2 % died during hospitalization. When comparing patients with residency in federal districts with high vs. low long-term air pollution, enhanced levels of benzene (OR 1.082 [95%CI 1.034–1.132],$P = 0.001$), ozone (O_3, OR 1.123 [95%CI 1.070–1.178],$P < 0.001$), nitric oxide (NO, OR 1.076 [95%CI 1.027–1.127],$P = 0.002$) and $PM_{2.5}$ fine particulate matter concentrations (OR 1.126 [95%CI 1.074–1.180],$P < 0.001$) were significantly associated with increased case-fatality independent from age, sex, cardiovascular risk-factors, comorbidities, and revascularization treatments. Conversely, enhanced carbon monoxide, nitrogen dioxide, PM_{10}, and sulphur dioxide (SO_2) concentrations were not significantly associated with stroke mortality. However, SO_2 concentrations were significantly associated with stroke-case-fatality rate of >8 % independent of residence area-type and area use (OR 1.518 [95%CI 1.012–2.278],$P = 0.044$).

Conclusion: Elevated long-term air pollution levels in residential areas in Germany, notably of benzene, O_3, NO, SO_2, and $PM_{2.5}$, were associated with increased stroke mortality of patients.

Research in context: Evidence before this study:

Besides typical, established risk factors, increasing evidence suggests that air pollution is an important and growing risk factor for stroke events, estimated to be responsible for approximately 14 % of all stroke-associated deaths. However, real-world data regarding the impact of long-term exposure to air pollution on stroke mortality are sparse.

Added value of this study:

The present study demonstrates that the long-term exposure to the air pollutants benzene, O_3, NO, SO_2 and $PM_{2.5}$ are independently associated with increased case-fatality of hospitalized patients with ischemic stroke in Germany.

Implications of all the available evidence:

* Corresponding author at: Department of Cardiology, Cardiology I, University Medical Center Mainz, Johannes Gutenberg-University Mainz, Langenbeckstrasse 1, 55131 Mainz, Germany.
E-mail address: Karsten.Keller@unimedizin-mainz.de (K. Keller).
[1] K.K. and S.H.R.H. contributed equally and share first authorship

https://doi.org/10.1016/j.thromres.2023.03.006
Received 23 October 2022; Received in revised form 15 March 2023; Accepted 17 March 2023
Available online 22 March 2023

The results of our study support the urgent need to reduce the exposure to air pollution by tightening emission controls to reduce the stroke burden and stroke mortality.

1. Introduction

The United Nations (UN) have called upon all governments worldwide to regulate air pollution emissions more strictly and develop plans to improve air quality [1,2], based on strong evidence that air pollution exposure is associated with the development of cardiovascular disease including stroke [2–9].

Worldwide, ischemic stroke is one of the leading causes of death [2,10–12]. More than 6 million people die from stroke events each year, and a similar number of patients suffer from permanent disabilities [10,11,13]. More than 12 million (95 % CI 11·0–13·6) incident cases of stroke, 101 million (93.2–111.0) prevalent cases of stroke, and 143 million (133–153) disability-adjusted life-years (DALYs) due to strokes were recorded worldwide [13]. Ischemic stroke events represent devastating health conditions with a significant burden of neurologic disability and associated excess mortality [14–19]. The enormous morbidity of stroke survivors is based on a strong interplay between the neurological impairment accompanied by emotional and social consequences and a high risk for stroke recurrence and complications [11,20,21].

Typical, established risk factors for ischemic stroke can be categorized as modifiable or nonmodifiable factors [22–24]. While the age, sex, and race/ethnicity of individuals are non-modifiable risk factors for ischemic stroke, arterial hypertension, smoking, poor nutrition, as well as physical in-activity are important known modifiable risk factors [22,23,25]. In this context, atrial fibrillation plays an outstanding role as a major risk factor for the development of ischemic stroke and has to be adequately treated in order to prevent stroke events among the comorbid conditions [19,26–33]. Additional important contributing factors of ischemic stroke comprise infection, inflammatory disorders, cardiac atrial disorders independent of atrial fibrillation, and environmental risk factors, in particular air pollution [22,23]. Mounting evidence suggests that air pollution is an important risk factor for stroke events [2,3,5,34]. Previous studies estimated that health-hazardous air pollution levels over the past decades were responsible for approximately 14 % of all stroke-associated deaths [2] including 64,000 excess deaths due to ischemic and hemorrhagic strokes in Europe, i.e., about 38,000 and 26,000 per year, respectively [6]. Studies analyzing the impact of the societal lockdowns during the COVID-19 pandemic demonstrated that these interventions led to substantial reductions in air pollution exposure, which has avoided excess deaths [35–38].

Current data for the impact of air pollution exposure on the incidence and mortality of stroke in mid-west Europe and Germany are limited. The objective of the present work has been to investigate the impact of different air pollutants on in-hospital mortality stroke with a focus on ischemic stroke patients.

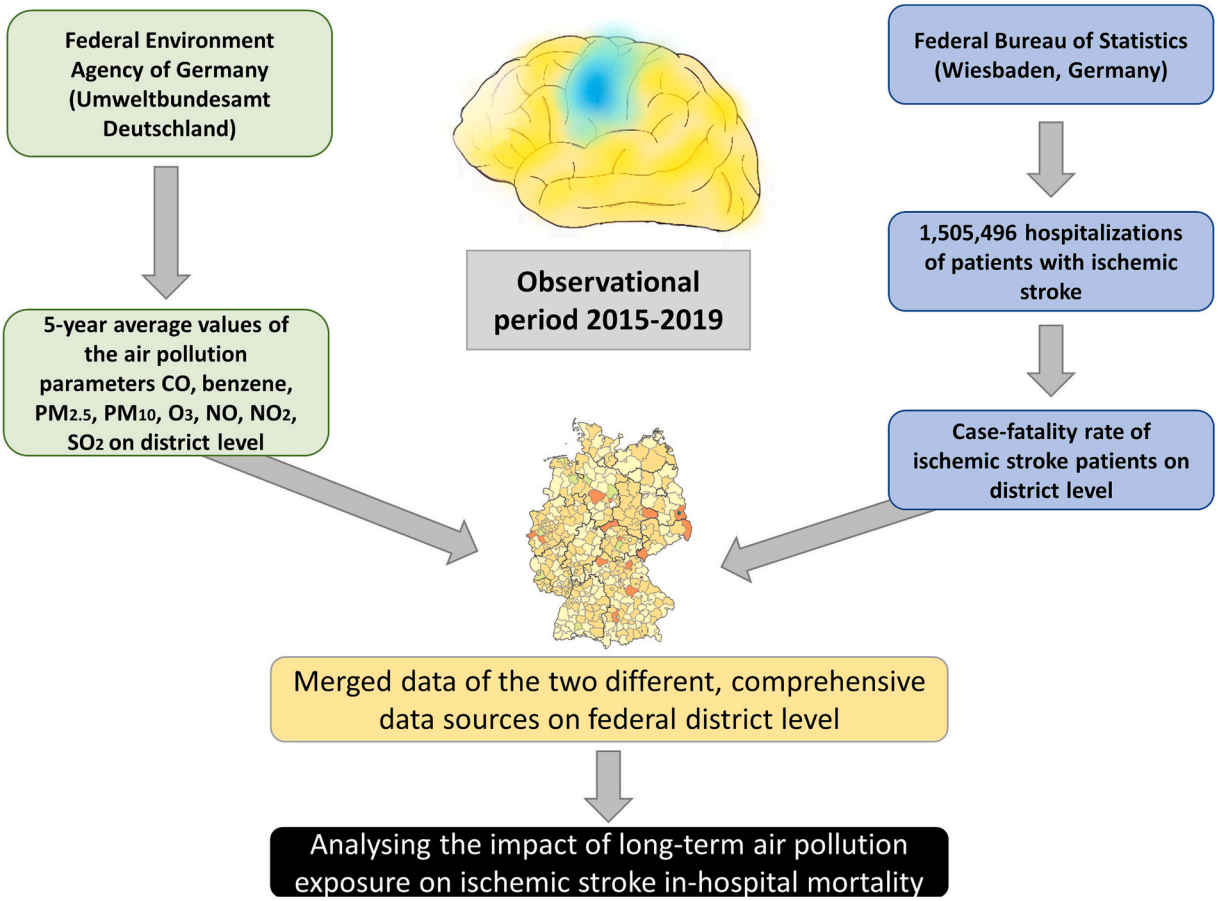

Fig. 1. Flow chart of the study.

2. Methods

2.1. Data sources

We assessed and merged data from two different, comprehensive data sources (Fig. 1). First, we obtained data regarding the annual average values of eight major air pollution parameters from the Federal Environment Agency of Germany (Umweltbundesamt Deutschland). The air pollution parameters comprised carbon monoxide (CO), benzene, $PM_{2.5}$ fine particulate matter (diameter < 2.5 μm), PM_{10} coarse particles (diameter < 10 μm), ozone (O_3), nitric oxide (NO), nitrogen dioxide (NO_2) and sulphur dioxide (SO_2) concentrations in the federal districts of Germany (assessed and allocated by the official [five digits] municipal area code of Germany. We used the 5-year average values for the period 2015–2019 of these air pollution parameters to assess the long-term exposure and linked these values to the in-hospital case-fatality rates of ischemic stroke patients with the corresponding residency districts of Germany (also assessed by the official municipal area code of Germany. Overall, 81 air quality measurement stations for CO, 59 for benzene, 169 for $PM_{2.5}$, 358 for PM_{10}, 243 for O_3, 378 for NO, 378 for NO_2 and 106 for SO_2 with 5-year data values remained for the analysis. An overview of the different air quality stations within the analyzed districts for the eight air pollutants with 5-year average concentrations is shown in Fig. 2. Further, we used the total population numbers of the different federal districts from the Federal Bureau of Statistics (Wiesbaden, Germany). To analyse the hospitalizations of ischemic stroke patients in the corresponding federal districts, we used a second data source. We obtained data from hospitalized patients of the German nationwide inpatient sample at the Federal Bureau of Statistics with the aim of investigating the total numbers of hospitalizations and the in-hospital case-fatality rates of all hospitalized ischemic stroke patients (ICD-code I63) during the observational period between 2015 and 2019 in the different federal districts of Germany where the ischemic stroke patients lived at the time of hospitalization. The statistical analyses by the Federal Bureau of Statistics (Wiesbaden, Germany) regarding this study of the German nationwide inpatient sample were performed on our behalf by the Research Data Center (RDC). The RDC provided aggregate statistics on the basis of our generated SPSS codes (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. IBM Corp: Armonk, NY, USA), which we previously created and made available to the RDC (source: RDC of the Federal Statistical Office and the Statistical Offices of the federal states, DRG Statistics 2015–2019, own calculations) [39,40].

2.2. Coding of diagnoses, procedures and definitions

In the year 2004, a diagnosis- and procedure-related remuneration-system was implemented in the German health care system. A coding according the German Diagnosis Related Groups (G-DRG) system with coding of patient data regarding diagnoses, coexisting conditions, as well as on surgeries/procedures/interventions and the transfer of these data to the Institute for the Hospital Remuneration System are required and mandatory for German hospitals to get their remuneration regarding rendered and provided services [39,40]. In this framework, patients' diagnoses has to be coded according the International Statistical Classification of Diseases and Related Health Problems (of the 10th revision with German modification, ICD-10-GM) and diagnostic, interventional and surgical procedures have to be coded according to special OPS codes (Operationen- und Prozedurenschlüssel) [39,40]. The combination of the data of these two data sources allowed us to analyse the impact of the different air pollution markers on the site-specific case-fatality rate of ischemic stroke patients. The validity of International Classification of Diseases (ICD) codes for identifying stroke in administrative data was corroborated by several studies of main as well as secondary diagnoses. ICD-9/ICD-10 diagnosis codes capture nearly all ischaemic stroke events (positive predictive value ranging between 82.2 % and 94.2 % [41–43], and only one study reported a lower positive predictive value for in-hospital coding [44]). In a larger study, including

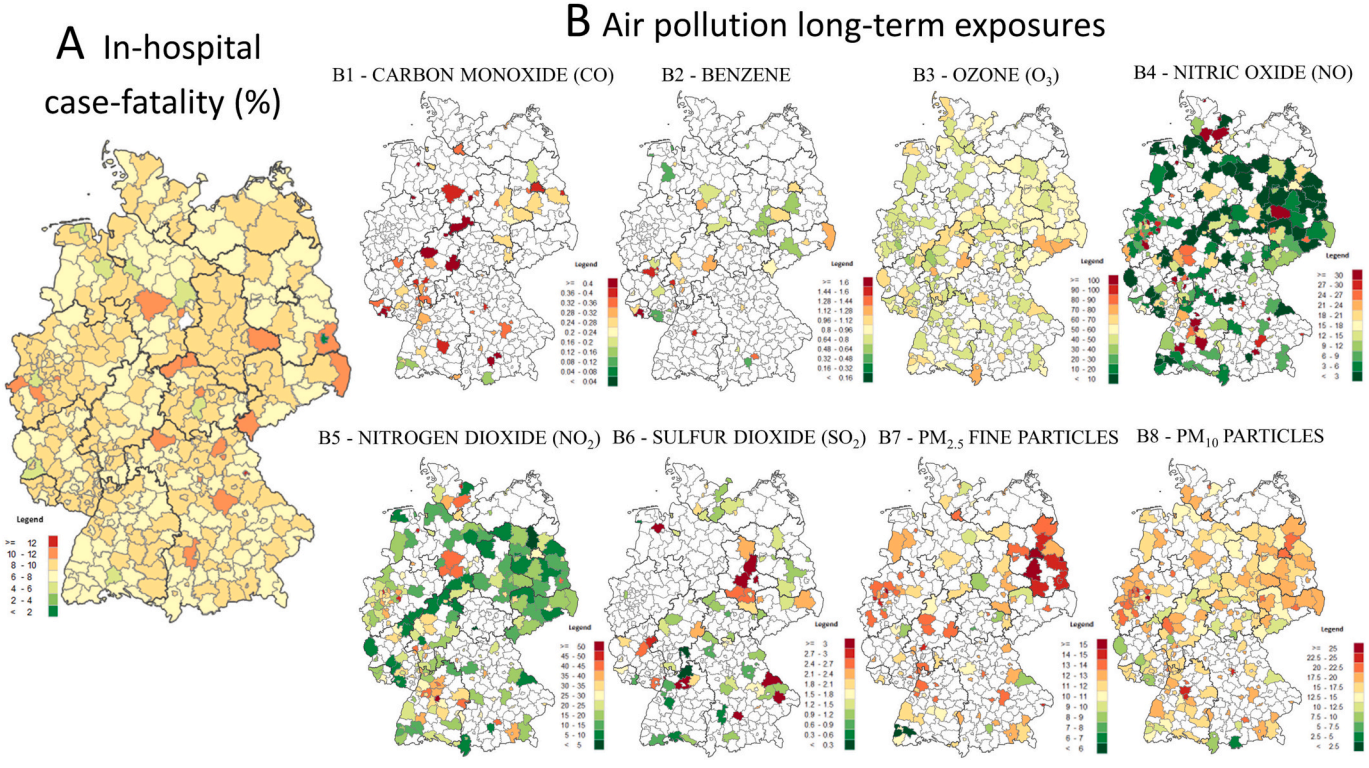

Fig. 2. In-hospital case-fatality rate of ischemic stroke patients residing in the different federal districts of Germany (A) and district-related long-term air pollution exposure (B) 2015–2019. Only air pollution exposure of federal districts with 5-year averages were included.

1227 hospitalizations, ICD-10 code of I63 in any position of the discharge diagnoses identified an ischemic stroke with a positive predictive value and sensitivity of 92.7 % and 99.4 %, respectively [42]. The positive predictive value increased to 99.8 % with a >12 % decrease regarding the sensitivity when the ischemic stroke was restricted to those with I63 as the primary diagnosis only [42]. When ischemic stroke was defined to be I63 as the primary, first secondary, or second secondary diagnosis, both positive predictive value and sensitivity were larger than 97 % [42].

2.3. Study outcome

The primary study outcome was in-hospital case-fatality rates of ischemic stroke patients.

2.4. Study oversight

Since our study did not involve the direct access by our investigators on individual patient-data, as we only had access to summarized results provided by the RDC, being linked to air pollution data of the federal districts, the approval by an ethics committee as well as a patients' informed consent were not required, in accordance with German law [39,40].

2.5. Role of funding source

There was no funding for the present study.

2.6. Statistical analysis

First, we compared the total numbers, patient-characteristics and outcomes of ischemic stroke patients in the ten federal German districts with the lowest long-term 5-year air pollution exposure with those of patients residing in the federal German districts with the highest long-term air pollution concentrations for each of the assessed air pollution parameters. Only federal German districts with air quality measuring stations, which could clearly allocate to one of these two categories, and with measurements for all investigated years were used for this analysis. The districts with lowest and highest levels of the air pollution parameters are marked in Fig. 2. Differences in patient characteristics and outcomes between the groups of hospitalized ischemic stroke patients were calculated with the help of Wilcoxon-Whitney *U* test for continuous variables and Fisher's exact or chi [2] test for categorical variables, as appropriate. Logistic regression models were applied in order to investigate the impact of high air pollution concentrations versus low air pollution concentrations between these two groups on adverse in-hospital events (the group with the ten federal German districts with the lowest air pollution concentration was used as the reference group). The analyses were performed for all ages as well as in patients ≥70 years and patients <70 years of age. The results were presented as Odds Ratios (OR) and 95 % confidence intervals (CI). We used two different adjustments to ensure that the assessed associations between the different air pollution parameters and the in-hospital adverse events were independent of patients' age, sex, established cardiovascular risk factors, important comorbidities as well as revascularization therapies of the brain-supplying arterial vessels:

- Adjustment I: Adjusted for age, sex, cancer, heart failure, obesity, chronic obstructive pulmonary disease, essential arterial hypertension, hyperlipidemia, acute and chronic kidney disease, diabetes mellitus, and atrial fibrillation/flutter.
- Adjustment II: Adjusted for age, sex, cancer, heart failure, obesity, chronic obstructive pulmonary disease, essential arterial hypertension, hyperlipidemia, acute and chronic kidney disease, diabetes mellitus, and atrial fibrillation/flutter, coronary artery disease, systemic thrombolysis, and percutaneous mechanical thrombectomy cerebral artery.
- Adjustment III: Adjusted for age, sex, cancer, heart failure, obesity, chronic obstructive pulmonary disease, essential arterial hypertension, hyperlipidemia, acute and chronic kidney disease, diabetes mellitus, and atrial fibrillation/flutter, coronary artery disease, systemic thrombolysis percutaneous mechanical thrombectomy cerebral artery, and individual parameters with potential health risks due to socioeconomic or psychosocial circumstances (ICD-codes Z55-Z65).

To evaluate these study results regarding the comparison of ischemic stroke patients in the ten federal German districts with the lowest air pollution concentrations versus those with the highest air pollution concentration for each individual air pollution parameter, we additionally expanded the analysis on all German federal districts with air quality measuring stations (and measurements for all investigated years) and corresponding in-hospital ischemic stroke case-fatality data. We analyzed the impact of the different air pollution parameters measured in all German federal districts on an increased case-fatality rate > 8 % in hospitalized patients with ischemic stroke with the help of bivariate and multivariable logistic regression models. The multivariable regression models were adjusted for the following parameters:

- Adjustment IV: Adjusted for residence area type (urban, suburban and rural areas)
- Adjustment V: Adjusted for type of use regarding the area (industry, traffic, residency)
- Adjustment VI: adjusted for residence area type (urban, suburban and rural areas) as well as for area use (industry, traffic, residency)

All statistical analyses were carried out with the use of SPSS software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Versions 20.0 and 225.0. IBM Corp: Armonk, NY, USA). Only the *P* values <0.05 (two-sided) were considered to be statistically significant. No adjustment for multiple testing was applied in the present analysis.

3. Results

Overall, 1,505,496 hospitalizations of patients with ischemic stroke were counted in Germany during the observational period between 2015 and 2019. Among them, 718,480 (47.7 %) were females and 1,011,944 (67.4 %) aged 70 years and older. Reperfusion treatments were performed in 180,169 patients (12.0 %) with systemic thrombolysis, in 63,354 (4.2 %) with percutaneous mechanical thrombectomy cerebral artery and in 1316 (0.1 %) with surgical carotid embolectomy and thrombectomy. The in-hospital case-fatality rate during the observational period was 8.2 % (123,440 deceased patients) and varied across all federal districts (Fig. 1 and Graphical Abstract).

The results regarding the impacts of the long-term exposure to different air pollutants on the in-hospital case-fatality rate are presented for each parameter in a separate paragraph:

3.1. Carbon monoxide (CO)

When comparing patient characteristics, medical history, presentation, treatment and critical in-hospital events of ischemic stroke patients in ten federal districts with the highest vs. ten federal districts with the lowest CO concentrations, we detected a similar case-fatality rate (8.4 % vs. 8.5 %, $P = 0.750$) between both groups despite an unfavourable cardiovascular risk factors (CVRF) and comorbidity profile in these ischemic stroke patients with lower CO concentrations (Table S1 in the supplementary material). Remarkably, myocardial infarction, VTE events (venous thromboembolism) and intracranial bleedings were more frequent in ischemic stroke patients who live in federal districts with relatively high CO concentrations. High CO concentrations were

not independently associated with an increased case-fatality rate (OR 0.961 [95%CI 0.914–1.009], $P = 0.110$) (Table S2 in the supplementary material, Fig. 3 A, C, D and Graphical Abstract). The multivariable logistic regression analysis investigating the impact of CO concentrations in all federal districts of Germany confirmed that CO concentrations were not independently associated with an increased case-fatality rate > 8 % in hospitalized patients with ischemic stroke (OR 0.933 [95%CI 0.001–1730.971], $P = 0.986$) (Table 1, Fig. 3B).

3.2. Benzene

Patients, who lived in one of the ten federal districts with highest benzene concentrations, revealed higher frequency of the CVRF diabetes mellitus, arterial hypertension and hyperlipidaemia. In addition, the prevalence of heart failure was higher (15.0 % vs. 12.8 %, $P < 0.001$) in federal districts with relatively high compared to lowest benzene concentrations (Table S4 in the supplementary material). The in-hospital case-fatality rate was slightly increased in ischemic stroke patients who live in federal districts with high benzene concentrations (8.6 % vs. 8.2 %, $P = 0.050$). The multivariable regressions showed that residing at a federal district with high benzene concentrations was independently associated with increased in-hospital case-fatality in all patients (OR 1.082 [95%CI 1.034–1.132], $P = 0.001$) and in patients aged 70 years and older (OR 1.060 [95%CI 1.008–1.114], $P = 0.024$), but especially (with strongest association) in the younger patients (<70 years) (OR 1.233 [95%CI 1.109–1.370], $P < 0.001$). This effect was still observed, when additionally adjusted for individual parameters with potential health risks due to socioeconomic or psychosocial circumstances (OR 1.088 [95%CI 1.040–1.139], P < 0.001) (Table S5 in the supplementary material, Fig. 3 A, C, D and Graphical Abstract). The association was also present, if focusing on hospitalized ischemic stroke patients with ischemic stroke coded in main diagnosis only (OR 1.112 [95%CI 1.051–1.175], P < 0.001) (Table S6 in the fementary material). This result was not obtained when taking all federal districts into account and seeking for increased case-fatality rate > 8 % (OR 1.533 [95%CI 0.158–14.831], $P = 0.712$) (Table 1, Fig. 3B).

3.3. Ozone (O_3)

Despite higher prevalence of obesity, diabetes mellitus, heart failure, atrial fibrillation/flutter as well as acute and chronic kidney disease in federal districts with relatively low long-term O_3-exposure, the rate of in-hospital case-fatality was similar between ischemic stroke patients residing in federal districts with lowest O_3 concentrations and those, who live in federal districts with highest O_3 concentrations (8.6 % vs. 8.6 %, $P = 0.658$) (Table S7 in the supplementary material).

After adjustment for age, sex comorbidities and revascularization treatments, the residence in federal districts with high long-term O_3-concentrations was associated with increased in-hospital case fatality rate (OR 1.123 [95%CI 1.070–1.178], $P < 0.001$). The association was stronger in patients <70 years (OR 1.236 [95%CI 1.103–1.386], P < 0.001) than in ischemic stroke patients ≥70 years (OR 1.080 [95%CI 1.024–1.138[, $P = 0.005$) (Table S8 in the supplementary material, Fig. 3 A, C, D and Graphical Abstract). After additional adjustment for individual parameters with potential health risks due to socioeconomic or psychosocial circumstances, the association between O3-concentrations and in-hospital case fatality was still present (OR 1.121 [95%CI 1.069–1.176], P < 0.001) (Table S8 in the supplementary material), but these results were not confirmed in those hospitalized ischemic stroke patients, who were coded in main diagnosis only (Table S9 in the supplementary material).

Nevertheless, higher O_3 concentrations in all federal districts were not independently associated with an increased case-fatality >8 % (OR 1.011 [95%CI 0.970–1.055], $P = 0.593$ (Table 1, Fig. 3B).

3.4. Nitric oxide (NO)

Federal districts with highest NO concentrations more often showed ischemic stroke patients with CVRF and cardiovascular diseases (CVD) accompanied by a slight non-significant increase in the case-fatality rate (8.6 % vs. 8.3 %, $P = 0.075$) (Table S10 in the supplementary material). However, federal districts with highest NO concentrations were significantly and independently associated with increased case-fatality (OR 1.076 [95%CI 1.027–1.127], $P = 0.002$). This association was predominantly seen in patients ≥70 years (OR 1.094 [95%CI 1.039–1.152], $P = 0.001$), but not in younger patients <70 years (OR 1.042 [95%CI 0.935–1.162], $P = 0.457$). This association remained significant after additional adjustment for individual parameters with potential health risks due to socioeconomic or psychosocial circumstances (Table S11 in the supplementary material, Fig. 3 A, C, D and Graphical Abstract) and also in hospitalized ischemic stroke patients, in whom ischemic stroke was coded in main diagnosis position only (Table S12 in the supplementary material). When taking all federal states with air pollution measurements of NO into account, we found no independent association between increase regarding NO concentrations and case-fatality rate > 8 % (OR 1.001 [95%CI 0.986–1.016], $P = 0.906$) (Table 1, Fig. 3B).

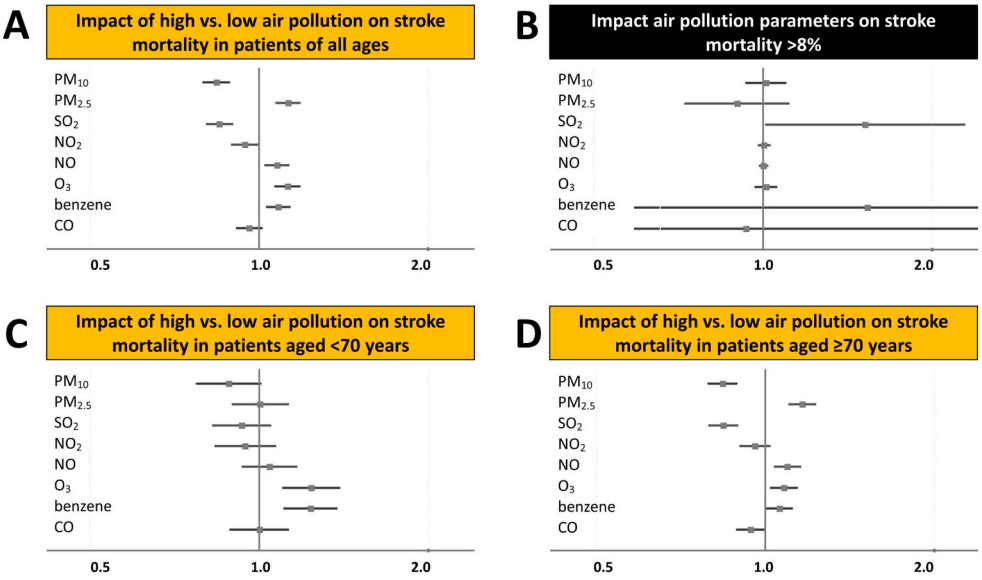

Fig. 3. Impact of air pollution on stroke mortality
Panel A – Impact of high vs. low long-term exposure to air pollution on in-hospital case-fatality of ischemic stroke patients of all ages
Panel B – Impact of long-term exposure to air pollution on in-hospital case-fatality >8 % of ischemic stroke patients of all ages
Panel C – Impact of high vs. low long-term exposure to air pollution on in-hospital case-fatality of ischemic stroke patients aged younger than 70 years
Panel D – Impact of high vs. low long-term exposure to air pollution on in-hospital case-fatality of ischemic stroke patients aged 70 years or older.

Table 1
Association of different air pollution parameters on increased case-fatality rate > 8 % in hospitalized patients with ischemic stroke (bivariate and multivariable logistic regression model).

	Bivariate regression model		Multivariable regression model (adjusted for residence area type [urban, suburban and rural areas])		Multivariable regression model (adjusted for area use [industry, traffic, residency])		Multivariable regression model (adjusted for residence area type (urban, suburban and rural areas) as well as for area use [industry, traffic, residency])	
	OR (95 % CI)	*P*-value	OR (95 % CI)	P-value	OR (95 % CI)	P-value	OR (95 % CI)	P-value
CO concentration	0.272 (0.001–88.991)	0.659	0.242 (0.000–197.492)	0.678	0.846 (0.001–539.210)	0.959	0.933 (0.001–1730.971)	0.986
Benzene	0.785 (0.156–3.946)	0.769	2.425 (0.277–21.225)	0.424	0.514 (0.083–3.172)	0.473	1.533 (0.158–14.831)	0.712
O_3 concentrations	0.988 (0.957–1.019)	0.440	1.006 (0.965–1.048)	0.788	0.991 (0.960–1.023)	0.584	1.011 (0.970–1.055)	0.593
NO concentrations	1.004 (0.992–1.015)	0.540	1.002 (0.988–1.015)	0.814	1.003 (0.989–1.016)	0.697	1.001 (0.986–1.016)	0.906
NO_2 concentrations	1.001 (0.986–1.016)	0.869	0.998 (0.979–1.018)	0.869	1.006 (0.989–1.024)	0.482	1.003 (0.982–1.026)	0.757
SO_2 concentrations	1.450 (1.009–2.084)	**0.045**	1.404 (0.972–2.028)	0.070	1.568 (1.046–2.350)	**0.029**	1.518 (1.012–2.278)	**0.044**
$PM_{2.5}$ fine particle concentrations	0.894 (0.754–1.060)	0.198	0.914 (0.748–1.117)	0.378	0.879 (0.733–1.054)	0.164	0.898 (0.728–1.108)	0.317
PM_{10} coarse particle concentrations	1.022 (0.967–1.081)	0.440	1.016 (0.947–1.091)	0.656	1.018 (0.953–1.088)	0.588	1.011 (0.933–1.096)	0.788

3.5. Nitrogen dioxide (NO_2)

Although ischemic stroke patients who live in federal districts with highest NO_2 concentrations had a higher frequency of diabetes mellitus, coronary artery disease and kidney diseases, the in-hospital adverse events rate of myocardial infarction, ICB and VTE were lower than in patients residing in federal states with lowest NO_2 concentrations. Furthermore, the in-hospital case-fatality was lower in ischemic stroke patients who live in federal districts with highest NO_2 concentrations (7.9 % vs. 8.4 %, $P = 0.006$) (Table S13 in the supplementary material), confirmed by the multivariable regressions (Tables S14 and S15 in the supplementary material, Fig. 3 A, C, D and Graphical Abstract). When expanding the focus to all federal districts with NO_2 measurements, higher NO_2 concentrations were not independently associated with case-fatality rate > 8 % (OR 1.003 [95%CI 0.982–1.026], $P = 0.757$) (Table 1, Fig. 3B).

3.6. Sulphur dioxide (SO_2)

Ischemic stroke patients residing in federal districts with highest SO_2 concentrations were more often younger than 70 years old, more often male and revealed lower frequency of most CVRF by similar comorbid profile. The in-hospital case-fatality rate was lower in federal districts with highest SO_2 concentrations compared to those with lowest concentrations (7.6 % vs. 8.5 %, $P < 0.001$) (Table S16 in the supplementary material), confirmed by the multivariable regressions for all (OR 0.850 [95%CI 0.807–0.894], $P < 0.001$) and for patients ≥70 years (OR 0.841 [95%CI 0.795–0.891, P < 0.001), but not in patients <70 years (OR 0.930 [95%CI 0.828–1.044], $P = 0.217$) (Table S17 in the supplementary material, Fig. 3 A, C, D and Graphical Abstract). Interestingly, the SO_2 concentration was significantly associated with the case-fatality rate > 8 % in all federal districts of Germany with SO_2 measurements, independent from residence area type (urban, suburban and rural areas) as well as area use (industry, traffic, residency) (OR 1.518 [95%CI 1.012–2.278], $P = 0.044$) (Table 1, Fig. 3B).

3.7. $PM_{2.5}$ fine particles

Besides similar comorbidity profile, ischemic stroke patients who lived in federal districts with the highest long-term $PM_{2.5}$ fine particles concentrations died more often during hospitalization (8.8 % vs. 8.0 %, $P < 0.001$) (Table S19 in the supplementary material). This finding was confirmed in the adjusted logistic regression model for patients of any age (OR 1.126 [95%CI 1.074–1.180], P < 0.001) and in patients ≥70 years (OR 1.163 [95%CI 1.104–1.226], P < 0.001), but not in patients <70 years (OR 1.003 [95%CI 0.896–1.123], $P = 0.960$ (Table S20 in the supplementary material, Fig. 3 A, C, D and Graphical Abstract). This association was still present after additional adjustment for individual parameters with potential health risks due to socioeconomic or psychosocial circumstances (OR 1.127 [95%CI 1.075–1.182], $P < 0.001$) (Table S21 in the supplementary material) and when taken only patients with a main diagnosis of ischemic stroke into account (Table S22 in the supplementary material). In the analysis of all federal districts with fine particle measurements for alle five investigated years, the $PM_{2.5}$ fine particle concentration was not independently associated with case-fatality rate > 8 % (OR 0.898 [95%CI 0.728–1.108], $P = 0.317$) (Table 1, Fig. 3B).

3.8. PM_{10} coarse particles

Although we did not detect large differences between the characteristics of patients who lived in federal districts with relatively high and low PM_{10} concentrations, the in-hospital case-fatality rate was lower in federal districts with high PM_{10} concentrations (7.6 % vs. 8.9 %, P < 0.001) (Table S22 in the supplementary material). The multivariable logistic regressions also showed an independent association of high PM_{10} particle concentrations with lower in-hospital case-fatality rate in ischemic stroke patients (OR 0.839 [95%CI 0.795–0.885], P < 0.001) (Tables S23 and S24 in the supplementary material, Fig. 3 A, C, D and Graphical Abstract). When expanding the analyses over all federal districts with PM_{10} measurements, the analyses did not reveal a significant association between PM_{10} concentrations and case-fatality rate > 8 % (OR 1.011 [95%CI 0.933–1.096], $P = 0.788$) (Table 1, Fig. 3B).

4. Discussion

The global lifetime risk to develop a stroke event from age 25 years onward is approximately 25 % among both sexes [12]. The lifetime risk of stroke shows geographic variations with the highest risks in Asia and Europe [12]. Previous study results suggest that >90 % of the stroke burden can be attributed to modifiable risk factors, which might be reduced by at least 75 % in case of optimal control of behavioral and metabolic risk factors [24]. In recent years, air pollution has been identified as a significant contributor to the global stroke burden [2,3,5,24,34]. Long-term exposure to air pollution can promote atherosclerotic plaque formation and, over time, is associated with the development of various cerebral/cardiovascular diseases, including stroke events [9]. Thus, besides the optimal control of behavioral and metabolic risk factors, reducing air pollution should be a main target to reduce the secondary stroke burden [24]. Studies estimated that the

increased air pollution levels over the past decades were responsible for approximately 14 % of all stroke-associated deaths [2].

Air pollution comprises several hazardous gases as well as aerosol particles (particulate matter; PM), which are subclassified according to size, whereby the relatively coarse particles (PM_{10}) mostly affect the upper airways, while the fine particles ($PM_{2.5}$) can deeply penetrate into the lungs and reach the alveolar region [2,45]. PM_{10} are mostly associated with industrial and natural emissions, notably airborne mineral dust, while $PM_{2.5}$ particles result predominantly from combustion-related emissions [2]. Common pollutants include CO, black and organic carbon, nitrogen oxides (NO_x), sulphate (SO_4^{2-}), and O_3 [2,45]. The regional variation and composition of air pollution depends on the emission sources and the photochemical conversion of gases [2].

By including >1,500,000 hospitalizations of patients with ischemic stroke in Germany between 2015 and 2019, we identified several air pollutants that significantly and independently affect the in-hospital case-fatality of ischemic stroke patients. We demonstrated that long-term enhanced benzene, O_3, NO and $PM_{2.5}$ concentrations were associated with increased in-hospital case-fatality, independent from patient age, sex, CVRF, comorbidities, and revascularization treatments of systemic thrombolysis and percutaneous mechanical thrombectomy cerebral artery as well as individual parameters with potential health risks due to socioeconomic or psychosocial circumstances. In addition, the results of these associations were similar in the analyses of ischemic stroke patients in whom ischemic stroke was coded as main or as secondary diagnosis and in those in whom ischemic stroke was coded as main diagnosis singularly. Due to the data structure and two different, comprehensive data sources with aggregated patient data on the district level, we were not able to provide results of a multi-level modelling for the present analyses, which might be another approach to analyse patient-level data.

Much evidence presented in the medical and public health literature is related to the effects of air pollution on the incidence of ischemic stroke, but data on the impact of long-term air pollution exposure on ischemic stroke mortality are still sparse. Recently, Lelieveld et al. estimated that $PM_{2.5}$-induced cerebrovascular events in Europe are responsible for 64,000 (95 % CI 31000–95,000) excess deaths per year. This includes ischemic and hemorrhagic strokes, with annual contributions of about 38,000 and 26,000, respectively [6].

Moreover, studies have shown that the short-term exposure to enhanced $PM_{2.5}$ concentrations contributes to increased numbers of hospital admissions due to cerebrovascular disease, ischemic stroke, and transient ischemic attack, respectively [46]. Other studies confirmed that long-term exposure to ambient $PM_{2.5}$ was also associated with an increased risk of stroke [2,3,5,47,48]. In line with our results, other studies reported that elevated long-term $PM_{2.5}$ exposure is associated with increased stroke mortality especially in high-exposure settings [49,50].

O_3 is a gaseous pollutant with strong oxidizing properties, which is photochemically formed in ambient air, mostly from gaseous precursors emitted by fuel combustion in energy production and traffic [51,52]. Globally, O_3 concentrations were relatively constant in the last two decades [53]. Nevertheless, growing greenhouse gas emissions cause global warming, which may contribute to a further increase of O_3 concentrations in the future [52]. Epidemiological studies provided evidence that short-term O_3 exposure increases the risk of mortality from respiratory and CVD including stroke [52,54,55]. In accordance with our results, other studies but not all revealed that long-term enhanced O_3-concentrations adversely affected stroke mortality [52,56].

Benzene is a ubiquitous, volatile organic air pollutant which is present at high concentrations in tobacco smoke and, like other toxins, known to increase the risk of CVD development [57]. Despite its prevalence, cardiovascular effects triggered or promoted by benzene have rarely been studied [57]. A few studies indicated an effect of enhanced benzene concentrations on the development of CVD [57,58] or a significant impact on cardiovascular mortality [58]. Our study is the first that demonstrates an independent effect of enhanced long-term exposure to benzene concentrations on in-hospital mortality in patients hospitalized with stroke. Apart from the direct health impact of benzene, it is possible that the chemical conversion of this gaseous compound into secondary organic aerosol particles is essential, as this constitutes a significant fraction of $PM_{2.5}$ in urban environments, which is expected to be more toxic than other components of $PM_{2.5}$ [59].

NO, which is a common gas in nature, is often considered to be hazardous since it might instigate pathological processes of many diseases, especially in the regulation of blood flow and cell inflammation [60]. In contrast, studies revealed that inhaled NO, a gas with vasodilating and anti-inflammatory effects, can support treatment strategies to improve penumbral blood flow and neuronal survival in stroke or other ischemic conditions [61,62]. Our study indicates that the long-term exposure to enhanced NO is slightly harmful, affecting in-hospital case fatality.

SO_2 is a gas that is predominantly produced by the burning of fossil fuels, in particular of coal and industrial activities. In accordance with other studies [55,63], our results corroborate that enhanced SO_2 levels affect stroke mortality. SO_2 long-term exposure was significantly associated with the stroke case-fatality rate > 8 %, independent from residence area type (urban, suburban, and rural areas) as well as for area use (industry, traffic, residency). Through its atmospheric oxidation into sulfate, SO_2 is also a main precursor of $PM_{2.5}$.

In contrast to the significant associations between higher benzene, $PM_{2.5}$, O_3, NO, and SO_2 concentrations with increased stroke mortality, air pollutants such as CO, PM_{10}, and NO_2 were not associated with excess mortality in our study. Nevertheless, Liu et at reported in their study that short-term exposure to ambient CO was associated with increased stroke mortality [64]. In addition, Andersen et al. showed an increased age-adjusted risk for fatal stroke by elevated NO_2 concentrations [65]. Our study, however does not confirm any impact of long-term exposure to PM_{10} on ischemic stroke mortality [39,49].

We also differentiated between the age-dependent effects of different air pollution constituents on stroke mortality [2,52]. Remarkably, elevated benzene and O_3 concentrations affected the case-fatality especially of relatively young ischemic stroke patients (<70 years), while long-term enhanced NO and $PM_{2.5}$ concentrations increased the case-fatality predominantly of stroke patients of 70 years and older. In this context, it may be considered that people aged older than 60 years typically spend more time in the indoor environment, which might reduce the health effects of ambient air pollution in this age group, while adults aged younger than 60 years tend to spend more time outside or away from home [2]. An important contributing factor that must be taken into account is that the impact of air pollution regarding ischemic stroke is modulated and increased by a higher incidence of cardiovascular risk factors, especially diabetes mellitus, arterial hypertension, and other comorbidities [2].

Several mechanisms have been proposed by which air pollutants might trigger cardiovascular events [2,45]. The inhaled air pollutants enter the lungs, in which the smaller particles ($PM_{2.5}$ and smaller) as well as the gaseous pollutants penetrate deeply into the respiratory tracts with the potential to translocate through the lung epithelium into the bloodstream [2,45]. On the other hand, relatively larger particles are taken up by macrophages triggering local inflammation [2]. Gaseous pollutants and small particles, which are incorporated into the systemic circulation, can react with NO and result in reactive oxygen species associated with endothelial dysfunction [2,45]. Particularly, $PM_{2.5}$ exposure has been implicated to lead to plaque vulnerability and increased systemic inflammation thus favoring thrombus development [2,45]. Nevertheless, the exact pathogenic mechanisms by which long-term exposure of air pollution increase the risk of CVD still need to be fully elucidated [2,66]. The accelerated inflammation and atherosclerosis development, vulnerability to plaque rupture, and favoring thrombus development are key factors in the air-pollution-triggered occurrence and aggravation of the acute cerebrovascular disease

[2,66]. In addition, an interplay of air pollution with individual modifiable risk factors such as arterial hypertension and obesity seems likely [2,12,67,68].

With the present study we demonstrate that the long-term exposure to the air pollutants benzene, O_3, NO, SO_2 and $PM_{2.5}$ is independently associated with increased in-hospital case-fatality of hospitalized patients with ischemic stroke in Germany. Air pollution has emerged as a substantial contributor to the global stroke burden [2,24,68]. Stroke has an annual global incidence of >15 million patients. It is responsible for >116 million disability-adjusted life years, of which an estimated 16.9 %–29.2 % can be attributed to air pollution [2,24]. The results of our study support the vital and urgent need to reduce the exposure to air pollution through emission controls, and thus reduce the stroke burden and stroke mortality [2,24,69].

5. Strengths & limitations

The main strength of the present study is the nationwide analysis of combined, high-quality data of long-term air pollution exposures with stroke events and stroke mortality. Another strength involves the adjustment for patient characteristics regarding cardiovascular risk factors and comorbidities, but also residency specialties such as area type (urban, suburban and rural areas) as well as area use (industry, traffic, residency).

The following limitations are relevant to the present study. Firstly, the present study analysis is based on ICD and OPS discharge codes of hospitalized patients, which might be prone to under-reporting and under-coding; however, due to remuneration, it seems unlikely that acute cardiovascular events are not coded. Secondly, due to the data structure, which includes only the time-frame of the in-hospital stay, follow-up evaluation after discharge is not possible. Thirdly, due to the data structure and two different, comprehensive data sources with aggregated patient data on the district level, we were not able to provide results of a multi-level modelling for the present analyses. Fourthly, the federal districts basic to the analyses regarding the combined data of location of residence of in-hospital treated stroke patients and the investigated air pollution markers might need to be of more resolution to directly link population to chronic exposure. To alleviate this limitation, we included adjustments IV to VI. Fifthly, short-term, highly elevated air pollution during episodic events also impacts public health; therefore, the calculated 5-year averages of the air pollutant concentrations might underestimate or disregard the short-term acute effects of air pollution. Sixthly, since we could not provide socioeconomic status data on patients' neighborhood-level for adjustment, we decided to adjusted the multivariable logistic regressions additionally for individual parameters with potential health risks due to socioeconomic or psychosocial circumstances (adjustment III).

6. Future directions

The results of our study support the urgent need to reduce exposure to air pollution through emission controls to reduce the stroke burden and stroke mortality. Air quality directives should be adjusted accordingly. Additional nationwide studies are needed to analyse the impact of long-term exposure to air pollution on other cardiovascular manifestations. Furthermore, air pollution should be mentioned and discussed in the ESC [70] and AHA/ACC guidelines [71] for the prevention of cardiovascular disease.

7. Conclusions

In our analysis of >1,500,000 hospitalizations of patients with ischemic stroke, the air pollution constituents O3, benzene, NO, SO2, and PM2.5 were associated with increased stroke mortality in Germany between 2015 and 2019.

CRediT authorship contribution statement

KK, SHRH and LH conceptualized the research, combined the data, and were responsible for the data curation and investigation. KK and LH were the main contributors regarding methodology, project administration, resources, and supervision. KK, SHRH, ISc and LH conducted statistical analyses and were involved in software selection and use. KK and LH were responsible for the validation of the results and visualization. KK, SHRH and LH wrote the original draft of the manuscript. All authors provided inputs for the final draft of the manuscript. All authors were involved in drafting the manuscript and approved the final version. All authors had full access to and verified all underlying data in this study.

Funding

None.

Ethical statement

Since our study did not involve the direct access by the investigators to individual patient data but only to summarized results provided by the RDC, approval by an ethics committee as well as the patients' informed consent were not required, in accordance with German law.

Declaration of competing interest

KK, SHRH, OH, ISc, SC and JL report no conflict of interests. TM is PI of the DZHK (German Center for Cardiovascular Research), Partner Site Rhine-Main, Mainz, Germany. LH received lecture/consultant fees from MSD and Actelion, outside the submitted work.

Data availability

The data is available at the Federal Statistical Office of Germany (Statistisches Bundesamt, DEStatis) (source: RDC of the Federal Statistical Office and the Statistical Offices of the federal states, DRG Statistics 2015-2019, and own calculations) and at the Federal Environment Agency of Germany (Umweltbundesamt Deutschland).

Acknowledgements

This work comprises results that are part of the doctoral thesis work of Seyed Hamed Rastguye Haghi.

We thank the Federal Statistical Office of Germany (Statistisches Bundesamt, DEStatis) for providing the data/results and the kind permission to publish these results (source: RDC of the Federal Statistical Office and the Statistical Offices of the federal states, DRG Statistics 2015-2019, own calculations). In addition, we thank the Federal Environment Agency of Germany (Umweltbundesamt Deutschland) for providing the air pollution data and the kind permission to use these data for our study analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2023.03.006.

References

[1] Programme, UNE. Towards a Pollution-free Planet: Background Report, 2017 (accessed 24th July 2022 2022).
[2] J.I. Verhoeven, Y. Allach, I.C.H. Vaartjes, C.J.M. Klijn, F.E. de Leeuw, Ambient air pollution and the risk of ischaemic and haemorrhagic stroke, Lancet Planet Health 5 (8) (2021) e542–e552.

[3] L. Stockfelt, E.M. Andersson, P. Molnar, Long-term effects of total and source-specific particulate air pollution on incident cardiovascular disease in Gothenburg, Sweden, Environ. Res. 158 (2017) 61–71.
[4] A.S. Shah, K.K. Lee, D.A. McAllister, et al., Short term exposure to air pollution and stroke: systematic review and meta-analysis, BMJ 350 (2015), h1295.
[5] H. Amini, C. Dehlendorff, Y.H. Lim, et al., Long-term exposure to air pollution and stroke incidence: a danish nurse cohort study, Environ. Int. 142 (2020), 105891.
[6] J. Lelieveld, K. Klingmuller, A. Pozzer, et al., Cardiovascular disease burden from ambient air pollution in Europe reassessed using novel hazard ratio functions, Eur. Heart J. 40 (20) (2019) 1590–1596.
[7] T. Munzel, M. Sorensen, T. Gori, et al., Environmental stressors and cardio-metabolic disease: part I-epidemiologic evidence supporting a role for noise and air pollution and effects of mitigation strategies, Eur. Heart J. 38 (8) (2017) 550–556.
[8] T. Munzel, J. Herzog, F.P. Schmidt, M. Sorensen, Environmental stressors and cardiovascular disease: the evidence is growing, Eur. Heart J. 38 (29) (2017) 2297–2299.
[9] O. Hahad, J. Lelieveld, F. Birklein, K. Lieb, A. Daiber, T. Munzel, Ambient air pollution increases the risk of cerebrovascular and neuropsychiatric disorders through induction of inflammation and oxidative stress, Int. J. Mol. Sci. 21 (12) (2020).
[10] Y. Xian, J.J. Federspiel, M. Grau-Sepulveda, et al., Risks and benefits associated with prestroke antiplatelet therapy among patients with acute ischemic stroke treated with intravenous tissue plasminogen activator, JAMA Neurol. 73 (1) (2016) 50–59.
[11] K. Keller, L. Hobohm, P. Wenzel, T. Munzel, C. Espinola-Klein, M.A. Ostad, Impact of atrial fibrillation/flutter on the in-hospital mortality of ischemic stroke patients, Heart Rhythm. 17 (3) (2020) 383–390.
[12] Collaborators GBDLRoS, V.L. Feigin, G. Nguyen, Global, regional, and country-specific lifetime risks of stroke, 1990 and 2016, N. Engl. J. Med. 379 (25) (2018) 2429–2437.
[13] Collaborators GBDS, Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019, Lancet Neurol. 20 (10) (2021) 795–820.
[14] M. Goyal, A.M. Demchuk, B.K. Menon, et al., Randomized assessment of rapid endovascular treatment of ischemic stroke, N. Engl. J. Med. 372 (11) (2015) 1019–1030.
[15] E. Bandera, M. Botteri, C. Minelli, A. Sutton, K.R. Abrams, N. Latronico, Cerebral blood flow threshold of ischemic penumbra and infarct core in acute ischemic stroke: a systematic review, Stroke 37 (5) (2006) 1334–1339.
[16] R.L. Sacco, S.E. Kasner, J.P. Broderick, et al., An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association, Stroke 44 (7) (2013) 2064–2089.
[17] S. Prabhakaran, I. Ruff, R.A. Bernstein, Acute stroke intervention: a systematic review, JAMA 313 (14) (2015) 1451–1462.
[18] D.J. Gladstone, M. Spring, P. Dorian, et al., Atrial fibrillation in patients with cryptogenic stroke, N. Engl. J. Med. 370 (26) (2014) 2467–2477.
[19] T. Sanna, H.C. Diener, R.S. Passman, et al., Cryptogenic stroke and underlying atrial fibrillation, N. Engl. J. Med. 370 (26) (2014) 2478–2486.
[20] W.N. Kernan, B. Ovbiagele, H.R. Black, et al., Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association, Stroke 45 (7) (2014) 2160–2236.
[21] K. Keller, L. Hobohm, T. Munzel, M. Lankeit, M.A. Ostad, Impact of pulmonary embolism on in-hospital mortality of patients with ischemic stroke, J. Neurol. Sci. 419 (2020), 117174.
[22] A.K. Boehme, C. Esenwa, M.S. Elkind, Stroke risk factors, genetics, and prevention, Circ. Res. 120 (3) (2017) 472–495.
[23] G.J. Hankey, Potential new risk factors for ischemic stroke: what is their potential? Stroke 37 (8) (2006) 2181–2188.
[24] V.L. Feigin, G.A. Roth, M. Naghavi, et al., Global burden of stroke and risk factors in 188 countries, during 1990–2013: a systematic analysis for the global burden of disease study 2013, Lancet Neurol. 15 (9) (2016) 913–924.
[25] L.A. Simons, J. McCallum, Y. Friedlander, J. Simons, Risk factors for ischemic stroke: Dubbo study of the elderly, Stroke 29 (7) (1998) 1341–1346.
[26] A.J. Camm, P. Kirchhof, G.Y. Lip, et al., Guidelines for the management of atrial fibrillation: the task force for the management of atrial fibrillation of the european Society of Cardiology (ESC), Eur. Heart J. 31 (19) (2010) 2369–2429.
[27] P.A. Wolf, R.D. Abbott, W.B. Kannel, Atrial fibrillation as an independent risk factor for stroke: the Framingham study, Stroke 22 (8) (1991) 983–988.
[28] J.B. Olesen, G.Y. Lip, M.L. Hansen, et al., Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study, BMJ 342 (2011), d124.
[29] C.B. Granger, J.H. Alexander, J.J. McMurray, et al., Apixaban versus warfarin in patients with atrial fibrillation, N. Engl. J. Med. 365 (11) (2011) 981–992.
[30] S.J. Connolly, M.D. Ezekowitz, S. Yusuf, et al., Dabigatran versus warfarin in patients with atrial fibrillation, N. Engl. J. Med. 361 (12) (2009) 1139–1151.
[31] S.M. Lockwood, J.F. Alison, M.N. Obeyesekere, P.M. Mottram, Imaging the left atrial appendage prior to, during, and after occlusion, J. Am. Coll. Cardiol. Img. 4 (3) (2011) 303–306.
[32] K. Keller, M. Geyer, T. Munzel, M.A. Ostad, T. Gori, Impact of atrial fibrillation on in-hospital mortality of ischemic stroke patients and identification of promoting factors of atrial thrombi - results from the german nationwide inpatient sample and a single-center retrospective cohort, Medicine (Baltimore) 98 (4) (2019), e14086.
[33] R.G. Hart, S.J. Connolly, H. Mundl, Rivaroxaban for stroke prevention after embolic stroke of undetermined source, N. Engl. J. Med. 379 (10) (2018) 987.
[34] G.A. Wellenius, M.R. Burger, B.A. Coull, et al., Ambient air pollution and the risk of acute ischemic stroke, Arch. Intern. Med. 172 (3) (2012) 229–234.
[35] P. Giani, S. Castruccio, A. Anav, D. Howard, W. Hu, P. Crippa, Short-term and long-term health impacts of air pollution reductions from COVID-19 lockdowns in China and Europe: a modelling study, Lancet Planet Health 4 (10) (2020) e474–e482.
[36] S. Hameed, M. Khan, Z. Fatmi, M. Wasay, Exploring the relationship between air quality and ischemic stroke admissions during the COVID-19 pandemic, J. Stroke Cerebrovasc. Dis. 30 (8) (2021), 105860.
[37] H. Diegoli, P.S.C. Magalhaes, S.C.O. Martins, et al., Decrease in hospital admissions for transient ischemic attack, mild, and moderate stroke during the COVID-19 era, Stroke 51 (8) (2020) 2315–2321.
[38] Z.S. Venter, K. Aunan, S. Chowdhury, J. Lelieveld, Air pollution declines during COVID-19 lockdowns mitigate the global health burden, Environ. Res. 192 (2021), 110403.
[39] J. Reinohl, K. Kaier, H. Reinecke, et al., Effect of availability of transcatheter aortic-valve replacement on clinical practice, N. Engl. J. Med. 373 (25) (2015) 2438–2447.
[40] K. Keller, L. Hobohm, M. Ebner, et al., Trends in thrombolytic treatment and outcomes of acute pulmonary embolism in Germany, Eur. Heart J. 41 (4) (2020) 522–529.
[41] J.L. Thigpen, C. Dillon, K.B. Forster, et al., Validity of international classification of disease codes to identify ischemic stroke and intracranial hemorrhage among individuals with associated diagnosis of atrial fibrillation, Circ. Cardiovasc. Qual. Outcomes 8 (1) (2015) 8–14.
[42] M.T. Hsieh, C.Y. Hsieh, T.T. Tsai, Y.C. Wang, S.F. Sung, Performance of ICD-10-CM diagnosis codes for identifying acute ischemic stroke in a National Health Insurance Claims Database, Clin. Epidemiol. 12 (2020) 1007–1013.
[43] K.S. Zachrison, S. Li, M.J. Reeves, et al., Strategy for reliable identification of ischaemic stroke, thrombolytics and thrombectomy in large administrative databases, Stroke Vasc. Neurol. 6 (2) (2021) 194–200.
[44] N. McCormick, V. Bhole, D. Lacaille, J.A. Avina-Zubieta, Validity of diagnostic codes for acute stroke in administrative databases: a systematic review, PLoS One 10 (8) (2015), e0135834.
[45] T. Munzel, T. Gori, S. Al-Kindi, et al., Effects of gaseous and solid constituents of air pollution on endothelial function, Eur. Heart J. 39 (38) (2018) 3543–3550.
[46] J. Gu, Y. Shi, N. Chen, H. Wang, T. Chen, Ambient fine particulate matter and hospital admissions for ischemic and hemorrhagic strokes and transient ischemic attack in 248 chinese cities, Sci. Total Environ. 715 (2020), 136896.
[47] K. Huang, F. Liang, X. Yang, et al., Long term exposure to ambient fine particulate matter and incidence of stroke: prospective cohort study from the China-PAR project, BMJ 367 (2019), l6720.
[48] S. Yuan, J. Wang, Q. Jiang, et al., Long-term exposure to PM2.5 and stroke: a systematic review and meta-analysis of cohort studies, Environ. Res. 177 (2019), 108587.
[49] X. Yang, L. Zhang, X. Chen, et al., Long-term exposure to ambient PM2.5 and stroke mortality among urban residents in northern China, Ecotoxicol. Environ. Saf. 213 (2021), 112063.
[50] I. Gutierrez-Avila, L. Rojas-Bracho, H. Riojas-Rodriguez, I. Kloog, A.C. Just, S. J. Rothenberg, Cardiovascular and cerebrovascular mortality associated with acute exposure to PM2.5 in Mexico City, Stroke 49 (7) (2018) 1734–1736.
[51] X. Liu, Z. Li, J. Zhang, The association between ozone and ischemic stroke morbidity among patients with type 2 diabetes in Beijing, China, Sci. Total Environ. 818 (2022), 151733.
[52] S. Liu, Y. Zhang, R. Ma, et al., Long-term exposure to ozone and cardiovascular mortality in a large chinese cohort, Environ. Int. 165 (2022), 107280.
[53] Collaborators GBDRF, Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019, Lancet 396 (10258) (2020) 1223–1249.
[54] J.D. Berman, N. Fann, J.W. Hollingsworth, et al., Health benefits from large-scale ozone reduction in the United States, Environ. Health Perspect. 120 (10) (2012) 1404–1410.
[55] Y.C. Hong, J.T. Lee, H. Kim, E.H. Ha, J. Schwartz, D.C. Christiani, Effects of air pollutants on acute stroke mortality, Environ. Health Perspect. 110 (2) (2002) 187–191.
[56] M. Mazidi, J.R. Speakman, Impact of obesity and ozone on the association between particulate air pollution and cardiovascular disease and stroke mortality among US adults, J. Am. Heart Assoc. 7 (11) (2018).
[57] W. Abplanalp, N. DeJarnett, D.W. Riggs, et al., Benzene exposure is associated with cardiovascular disease risk, PLoS One 12 (9) (2017), e0183602.
[58] D.H. Tsai, J.L. Wang, K.J. Chuang, C.C. Chan, Traffic-related air pollution and cardiovascular mortality in Central Taiwan, Sci. Total Environ. 408 (8) (2010) 1818–1823.
[59] S. Chowdhury, A. Pozzer, A. Haines, et al., Global health burden of ambient PM2.5 and the contribution of anthropogenic black carbon and organic aerosols, Environ. Int. 159 (2022), 107020.
[60] Z.Q. Chen, R.T. Mou, D.X. Feng, Z. Wang, G. Chen, The role of nitric oxide in stroke, Med. Gas Res. 7 (3) (2017) 194–203.
[61] N.A. Terpolilli, S.W. Kim, S.C. Thal, et al., Inhalation of nitric oxide prevents ischemic brain damage in experimental stroke by selective dilatation of collateral arterioles, Circ. Res. 110 (5) (2012) 727–738.
[62] P.S. Garry, M. Ezra, M.J. Rowland, J. Westbrook, K.T. Pattinson, The role of the nitric oxide pathway in brain injury and its treatment–from bench to bedside, Exp. Neurol. 263 (2015) 235–243.
[63] P. Orellano, J. Reynoso, N. Quaranta, Short-term exposure to Sulphur dioxide (SO2) and all-cause and respiratory mortality: a systematic review and meta-analysis, Environ. Int. 150 (2021), 106434.

[64] C. Liu, P. Yin, R. Chen, et al., Ambient carbon monoxide and cardiovascular mortality: a nationwide time-series analysis in 272 cities in China, Lancet Planet Health 2 (1) (2018) e12–e18.
[65] Z.J. Andersen, L.C. Kristiansen, K.K. Andersen, et al., Stroke and long-term exposure to outdoor air pollution from nitrogen dioxide: a cohort study, Stroke 43 (2) (2012) 320–325.
[66] K.A. Miller, D.S. Siscovick, L. Sheppard, et al., Long-term exposure to air pollution and incidence of cardiovascular events in women, N. Engl. J. Med. 356 (5) (2007) 447–458.
[67] Collaborators GBDRF, Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016, Lancet 390 (10100) (2017) 1345–1422.
[68] C.R. Bartoli, G.A. Wellenius, E.A. Diaz, et al., Mechanisms of inhaled fine particulate air pollution-induced arterial blood pressure changes, Environ. Health Perspect. 117 (3) (2009) 361–366.
[69] S. Jalali, M. Karbakhsh, M. Momeni, et al., Long-term exposure to PM2.5 and cardiovascular disease incidence and mortality in an eastern Mediterranean country: findings based on a 15-year cohort study, Environ. Health 20 (1) (2021) 112.
[70] F.L.J. Visseren, F. Mach, Y.M. Smulders, et al., 2021 ESC guidelines on cardiovascular disease prevention in clinical practice, Eur. Heart J. 42 (34) (2021) 3227–3337.
[71] D.K. Arnett, R.S. Blumenthal, M.A. Albert, et al., 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the american College of Cardiology/American Heart Association task force on clinical practice guidelines, Circulation 140 (11) (2019) e596–e646.