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Short-term exposure to air pollution and acute health effects in a low-pollution region, Baden-Wurttemberg, Germany

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Abstract

Background The acute effects of short-term air pollution exposure on human health in regions with low pollution concentrations is not widely explored. This study assesses the risk of mortality and morbidity linked to short-term exposure to NO_2 and $PM_{2.5}$ in Baden-Wurttemberg, Germany, a region that broadly complies with European air quality standards and global guidelines.

Methods We applied a two-stage time-stratified case-crossover design followed by meta-analyses to estimate the relative risks of mortality (all-cause), hospital admission and sick leave (all-cause and cause-specific). Health outcomes between 2013 and 2022 were collected from the regional public insurance records, and exposures were derived from ensemble air quality models. Effect modification by SARS-CoV-2 (COVID-19) years, age, sex and urbanisation were also evaluated.

Results Short-term exposure to $PM_{2.5}$ and NO_2 was associated with increased risks of several acute health outcomes. Associations were observed for all-cause and cardiovascular-related hospital admissions, as well as sick leave, even at concentrations near the current daily limits set by the European Union. Effect estimates were generally more pronounced for NO_2 and concentrated at immediate lag days. Exposure–response relationships were non-linear across health outcomes, and little evidence of effect modification by demographic or urbanisation characteristics was observed.

Conclusion This study provides evidence of acute health risks from short-term exposure to $PM_{2.5}$ and NO_2, even at concentrations below the suggested daily permissible levels, emphasising the need to reassess existing air quality standards.

Keywords Spatiotemporal health risk assessment, Exposure–response functions, PM2.5, NO2, Sick leave, Mortality, Hospital admissions, Cardiovascular

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Introduction

The acute effects of short-term exposure to particulate and gaseous pollutants on all-cause and cause-specific mortality and morbidity are well-established [35, 43, 57]. Currently, exposure to fine particulate matter with a diameter of less than 2.5 μm ($PM_{2.5}$) represents the leading contributor to the global burden of disease and ranks among the top risk factors for mortality globally [24]. Additionally, nitrogen dioxide (NO_2) has been recently identified as a risk factor for chronic respiratory diseases in the Global Disease Burden 2021 report [7], and included in the revised European Union Air Quality Directives (EU AQD) 2024 as a target pollutant, alongside $PM_{2.5}$, for average exposure reduction obligations for member states [16]. Although air pollution levels in the EU have generally declined, only 4% and 28% of monitoring stations, for $PM_{2.5}$ and NO_2 respectively, comply with the more stringent daily recommended values by the World Health Organisation (WHO) [51].

Due to its origin from anthropogenic sources such as traffic and combustion activities, particularly in urban areas, NO_2 tends to have localised effects. In contrast, $PM_{2.5}$ arises from both natural and human sources. It also has a longer atmospheric lifetime, enabling long-range transport that can influence both local and regional air quality, thereby exposing cities with different urban environments as well as surrounding suburban and rural areas [37]. Given this spatial variability in exposure, it is essential to evaluate the distribution of associated health risks and assess whether regions continue to bear a burden of health impacts, despite remaining within the WHO air quality guideline (AQG) levels and EU regulatory limit values.

A large body of research, including the current WHO guidelines [57], suggests a linear association of particulate matter with a monotonic increase of risk, and no apparent safe threshold [44]. Conversely, some studies have reported a nonlinear (supralinear) exposure–response relationship between $PM_{2.5}$ and health outcomes, characterised by a steeper slope at lower concentration (below 20 $\mu g/m^3$) that tends to flatten at higher exposure levels [23, 35, 45, 53]. In contrast, research on exposure–response relationship between NO_2 and health outcomes is comparatively limited. While meta-analyses report linear associations, certain studies have identified non-linear patterns, with an inflection point around the threshold concentration of 38 $\mu g/m^3$ [44, 58].

This study therefore aims to investigate the acute health risk associated with short-term exposure to $PM_{2.5}$ and NO_2 in a low-concentration setting, such as Baden-Wurttemberg, Germany. Leveraging a comprehensive health insurance dataset covering approximately 4.6 million insured individuals, the study examines multiple health endpoints, including all-cause mortality, along with all-cause and cause-specific hospital admissions and sick leave, over the period from 2013 to 2022. Additionally, effect estimates during the coronavirus (COVID-19) pandemic years were compared to those from the pre-COVID-19 and the overall study duration. This study also explores potential effect modification by age and sex subgroups and stratifies findings according to the level of urbanisation of residence. Furthermore, it examines the characteristics of exposure-lag-response relationships of the health outcomes and their variation across subgroups by daily EU AQD limit values and WHO AQG levels.

Methods

Exposure assessment

Near surface concentrations of $PM_{2.5}$ and NO_2 in the Baden-Wurttemberg region from January 2013 to December 2022 were obtained from the Copernicus Atmosphere Monitoring Service (CAMS) reanalysis database produced by the European Centre for Medium-Range Weather Forecasts (ECMWF) [11]. The service provides atmospheric composition from the median ensemble models over Europe that are produced using a long-term assimilation system and validated against consistent observations, thus reducing bias and improved spatiotemporal consistency [32].

Likewise, meteorological variables such as 2 m surface temperature and 2 m dewpoint temperature from the ERA5 reanalysis dataset were sourced from the Copernicus Climate Change Service [12]. The dewpoint temperature was converted to vapour pressure using a method proposed and implemented by [6, 26]. To improve the comparability and reduce confounding driven by differences in the population and urbanisation characteristics, the region was divided into sub-regions (districts) with uniform population. All exposure variables, originally available at an hourly temporal resolution and a spatial resolution of 0.1°×0.1° (approx. 11 km×7.5 km), were therefore aggregated to daily values at the district level using area-weighted spatial means, with bilinear-interpolation oversampling and high-resolution masking to account for partially intersecting raster cells [21].

Study context and population

With a population of 11.34 million, the Baden-Wurttemberg region is situated in the southwest of Germany. In addition to the centrally located state capital, Stuttgart, the region has Mannheim, Karlsruhe, and Freiburg as other major cities. The region has a diverse geography with vast rural districts and natural areas, such as the Black Forest, Lake Constance, the Swabian Alps, and the Alpine foothills. Rural areas account for 73.5% of the

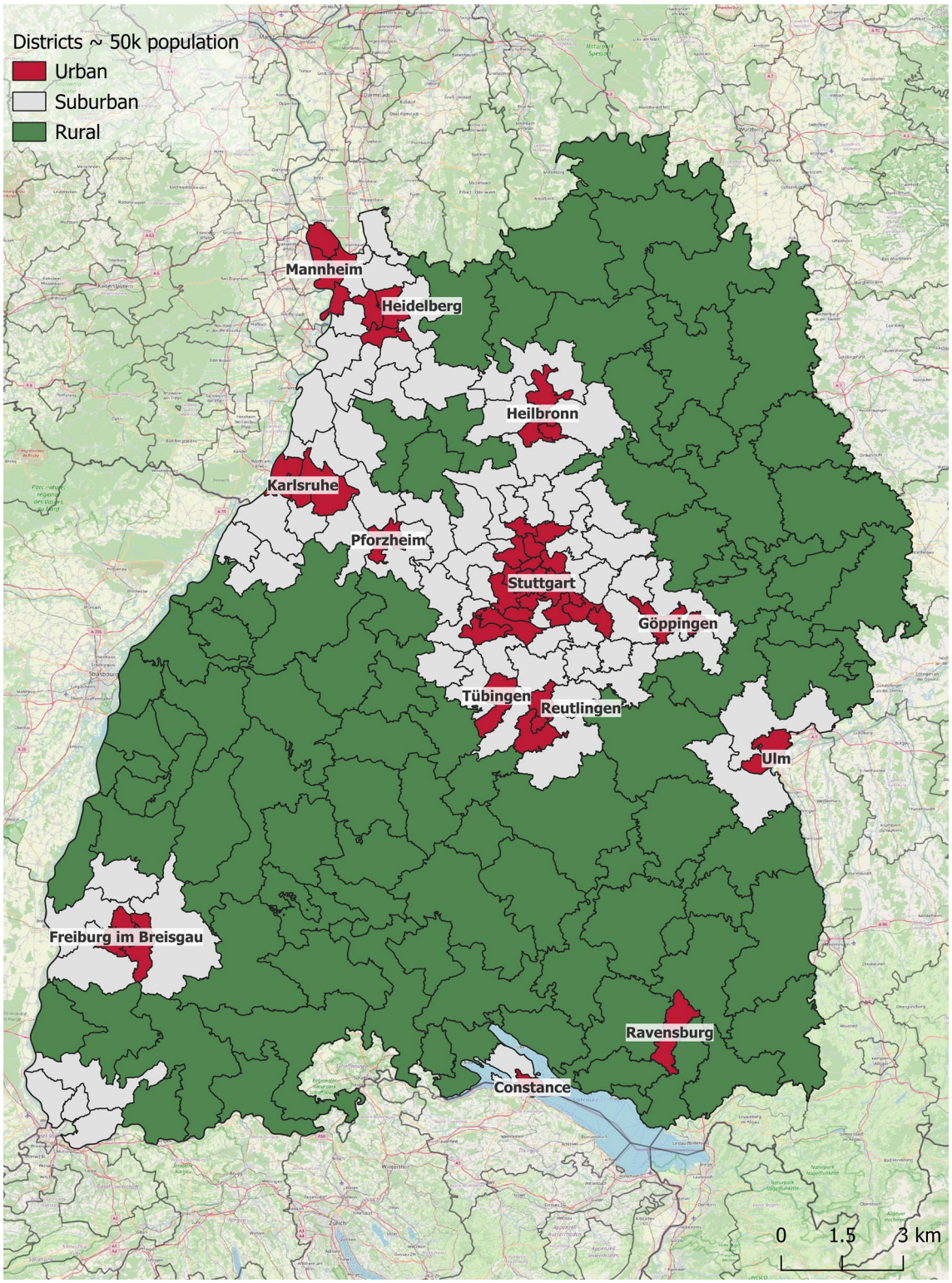

Fig. 1 Baden-Württemberg subdivided into 209 territorial districts of approximately 50,000 residents and uniform urbanisation characteristics, delineated by progressively clustering neighbouring administrative units

region, while urban (5%) and suburban areas cover the rest (Fig. 1).

Health outcomes from January 2013 to December 2022, that included all-cause mortality, all-cause and cardiovascular hospital admission and sick leave, were obtained from health insurance claims submitted to the insurance provider Allgemeine Ortskrankenkasse (AOK). The data covered a population of 4.6 million insured individuals, corresponding 40.56% of the total inhabitants of Baden-Wurttemberg. AOK routinely validates the representativeness of insured population with respect to age, sex and morbidity. However, the effect estimates derived in this study pertain specifically to the clients, and caution is advised when extrapolating the findings to the general population.

To focus on cardiovascular conditions linked to air pollution, hospital admissions and sick leaves were selected using the International Classification of Diseases, 10th Revision (ICD-10) codes for acute ischaemic heart disease (IHD; I20–I24) and heart failure (HF; I50) [59]. The health outcomes were originally aggregated at the postal code level and stratified by sex (male and female) and six age groups: newborn (< 1 year), pre-school (1–5), school (6–20), adult (21–60), senior (61–80) and elderly (over 80 years). However, due to insufficient sample sizes for acute cardiovascular outcomes among children, the following analysis was limited to age groups over 20 years.

Exposure was defined as the daily average concentration of the two selected air pollutants, $PM_{2.5}$ and NO_2, while health outcomes were recorded as the daily total of health events, aggregated across the 209 districts into which the entire study area was subdivided (Fig. 1). These districts were delineated by progressively clustering neighbouring administrative units in the region until each district reached an approximate population of 50,000 residents, while maintaining uniform urbanisation characteristics. The urbanisation criteria were defined by the Global Human Settlement Layer, which classifies spatial areas into urban centres, functional urban areas (suburban) or rural areas [15, 20].

Method

The study applies a two-stage time-stratified case-crossover design using a Distributed Lag Non-linear Model (DLNM) framework [17, 48]. This spatiotemporal approach allows the assessment of short-term effects of air pollution exposure on mortality and acute health endpoints and generates an exposure-lag-response relationship between them, while accounting for spatial heterogeneity within the territory.

The first stage involved application of DLNM framework to individual districts in Baden-Wurttemberg. As the health outcomes were non-negative counts with overdispersion, a quasi-Poisson generalised regression model was fitted as expressed in Eq. (1).

$$\log(\mu_t) = \alpha + cb(A_t) + s(x_t) + s(T) + Holiday_t + \text{offset}(\log(Pop_t)) \quad (1)$$

where μ_t is the expected daily count for the different health outcomes on day t, a is the intercept, $cb(\cdot)$ is the cross-basis function describing the exposure-lag-response relationship of pollutant A, $s(x_t)$ represents the smooth functions for meteorological confounders x (temperature and vapour pressure), while $s(T)$ is the smooth functions to control residual temporal variations. $Holiday_t$ denotes national and local holidays included as binary indicators. To account for changes in the sample population over time, the log of the total insured individuals in each district, Pop_t was included as an offset.

In a preliminary analysis, exposure variables exhibited distinct seasonal patterns and long-term trends, whereas health events followed a seasonal and intra-week variations (Figs. S.1–S.4). A time-stratified case-crossover design accounts for such temporal structures by using time *strata* which allow each event day to serve as its own control by retrospectively matching exposures on the same day of the week, month and year as controls for exposure on the event day [34]. Through sensitivity analysis, adjustment for residual long-term and seasonal variations, not fully captured by the time-stratified design, were incorporated using a natural cubic spline with up to six degrees of freedom per year [18].

Daily average concentrations of each air pollutant were transformed into a cross-basis function, a bi-dimensional matrix structure in which one dimension represents the exposure–response relationship and the other represents their lag-response relationship across delayed effects up to seven days (lag 0–7). Guided by sensitivity analyses and literature [35, 40, 41, 56], alternative lag specifications, assuming a linear exposure–response relationship, were first evaluated to identify temporal pattern of acute effects and to derive relative risks at 10 $\mu g/m^3$ in exposure. Based on the observed lag-response structure, cumulative exposures were then defined using a moving average from lag day 0 to the last day with a positive relative risk. In the final models, exposure–response associations were modelled using natural cubic splines to allow for potential non-linear effects.

Likewise for time-varying confounders, temperature was modelled using a natural cubic spline, with delayed effects incorporated through lag terms of up to 14 days. Knot placement, particularly at the tails of the temperature distribution, was evaluated to capture potential effects at extreme temperatures. Vapour pressure was

included as a one-dimensional basis function to reduce model complexity. Nonetheless, a sensitivity analysis was performed to compare same-day values of vapour pressure with a 3-day moving average to assess potential short-term cumulative effects [27].

Model performances in sensitivity analyses were compared using the quasi-Akaike Information Criterion (QAIC) which is a statistical measure that estimates the trade-offs between the goodness of fit of the model and its simplicity [19]. As determined by these analyses for each set of air pollutant and health outcome, uniform model specifications were applied across all districts to ensure comparability and consistency in the estimation of district-specific effects.

In the second stage, the district-wise variance–covariance matrices of the lag-response function, evaluated at a reference concentration of 10 μg/m^3 in the first stage, were pooled using a random-effect meta-analysis. Based on the results from lag-response relationship, regional exposure–response models were developed using the most consistent and pronounced lag structures. Exposure–response curves for each pollutant were expressed as relative risks (RR) values across the full range of pollutant levels, from zero to the maximum recorded value with RR referenced at zero pollution level. Additionally, RR associated to each pollutant at its daily WHO AQG levels and EU AQD permissible limits were predicted. Results were considered statistically significant at $\rho < 0.05$ with confidence intervals (CI) of 95% not including the null value of 1.

Given the observations from the trend analyses of health outcomes being different during the COVID-19 years (2020–2022) (Figs. S.2 and S.3), three separate 2-stage models were carried out for the overall study period (2013–2022), the pre-COVID (2013–2019), and the COVID (2020–2022) periods, and the statistical difference between their effect estimates were compared using the 2-sample test [2]. As the preliminary results from the main model demonstrated that effect sizes during the COVID-19 period were significantly different than those of the overall and pre-COVID years, further subgroup analyses were undertaken only on the pre-COVID data. The main model, based on pre-COVID years, was stratified by age groups (adults [21–60], seniors [61–80] and elderly persons [>80]), sex (male and female) and urbanisation characteristic (urban, suburban and rural). Each group was compared to a reference group—adults (age), males (sex), and urban (urbanisation characteristic), to assess their statistical difference in effect modification using the 2-sample test.

The data were pre-processed using Python 3.11; the models were developed, and results were visualised in R (version 4.3.0, primarily using the *dlnm, spline, gnm* and *mixmeta* libraries).

Results

Site context

The daily median pollution concentration of $PM_{2.5}$ and NO_2 for the period from 2013 to 2022 are 8.67 μg/m^3 and 10.93 μg/m^3, respectively, with high concentration hotspots in the north-west (Karlsruhe) and central (Stuttgart) part of Baden-Wurttemberg [26, 47]. Over the study period from 2013 to 2022, the median concentrations of $PM_{2.5}$ and NO_2 declined by 2.0 μg/m^3 and 3.5 μg/m^3, respectively. NO_2 followed a seasonal pattern, with higher levels during colder months (October to March) whereas the monthly variation of $PM_{2.5}$ was not remarkable (Fig. S.1).

Non-parametric Kruskal–Wallis test, followed by the Dunn's post-hoc test with the Bonferroni correction, was used to assess differences in median pollution levels across regional and territorial areas (urban, suburban and rural). Table 1 shows that urban districts exhibited higher pollution levels than suburban or rural districts. These differences were significant across all comparisons, except for $PM_{2.5}$ concentrations between urban and suburban districts. Nevertheless, ambient concentrations across all district types generally remained within the limit values set by the EU AQD, although they exceed the stricter WHO AQG levels.

Data description

Between 2013 to 2022, the number of AOK-insured individuals in the region increased by approximately 70,000. During this period, the incidence rate of health outcomes per 100,000 population showed varying trends. All-cause mortality declined up to 2019, after which it began to gradually increase (Fig. S.2). Contrarily, the incidence of total and cardiovascular-specific hospital admissions declined, starting in 2017–2018 and continued to decrease through the COVID-19 years, 2020 through 2022. In terms of sick leave, cases related to acute heart failure (HF) and ischemic heart diseases (IHD) remained relatively stable throughout the study period, including the COVID-19 years, whereas total sick leave started to increase from the mid-2020 onwards (Fig. S.3).

The health outcomes exhibited notable intraweek variations. As expected, sick leave occurrences were much lower on weekends, with hospital admissions also at their lowest during weekends and slightly above average on Mondays. Additionally, sick leave rates were much higher on Mondays compared to other four weekdays (Fig. S.4). These health outcomes did not show any consistent seasonal or monthly patterns, except for all-cause sick leave, which tended to be higher during the colder months

Table 1 Descriptive statistics of the daily pollution concentration of $PM_{2.5}$ (μg/m^3) and NO_2 (μg/m^3) across spatial typologies of Baden-Wurttemberg from 2013 to 2022

Pollutant	Mean	Range (Min–Max)	Median (IQR)	Days over WHO[a] (%)	Days over EU AQD[a] (%)
$PM_{2.5}$					
Overall	10.01	0.81–70.30	8.67 (5.72–12.78)	16.61	2.65
Urban	10.52	1.10–70.30	9.07 (6.00–13.40)	18.96	3.31
Suburban	10.23	1.04–68.17	8.86 (5.87–13.02)	17.5	2.81
Rural	9.53	0.81–60.45	8.28 (5.45–12.19)	14.43	2.12
NO_2					
Overall	12.78	1.21–66.05	10.93 (7.17–16.57)	7.70	0.04
Urban	15.84	1.73–65.78	14.00 (9.55–20.37)	14.43	0.10
Suburban	13.91	1.53–66.05	12.08 (8.40–17.80)	9.20	0.03
Rural	9.98	1.21–48.50	8.34 (5.67–12.90)	2.28	0

IQR interquartile range

[a] Reference levels: WHO AQG ($PM_{2.5}$: 15 μg/m^3, NO_2: 25 μg/m^3), EU AQD ($PM_{2.5}$: 25 μg/m^3, NO_2: 50 g/m^3)

(excluding December), and lowest in August, coinciding with the major vacation periods.

All-cause mortality was highest among the elderly (> 80 years) and among females (Table 2). All-cause hospital admissions were most frequent in the adult (21–60) and senior (61–80) age groups, whereas HF-related hospital admissions were more numerous among the senior (61–80) and the elderly (> 80) age groups. In the case of sick leave, individuals over the age of 80 (typically retired) were excluded from the analysis. Sick leave was primarily concentrated in the adults (21–60), with disproportionally higher levels of HF related sick leave observed in the senior (61–80) age group. However, due to the small number of such cases

Table 2 Descriptive statistics (total count and percentage) of daily all-cause and cause-specific health outcomes during different time durations, and across demographic and territorial subgroups in Baden-Wurttemberg from 2013 to 2022

Group	All-cause mortality	Hospital admissions			Sick leave		
		Total	IHD	HF	Total	IHD	HF
Pre-COVID (2013–2020)	338,094 (67.86%)	7,121,934 (72.37%)	183,212 (73.87%)	183,486 (71.28%)	21,208,141 (65.86%)	71,458 (69.94%)	40,347 (64.88%)
COVID (2020–2022)	160,123 (32.14%)	2,718,434 (27.62%)	64,782 (26.12%)	73,907 (28.71%)	10,992,640 (34.13%)	30,701 (30.05%)	21,835 (35.11%)
Overall (2013–2022)	**498,217**	**9,840,368**	**247,994**	**257,393**	**32,200,781**	**102,159**	**62,182**
Adult (21—60)	46,761 (9.4%)	4,608,267 (46.8%)	71,967 (29.0%)	17,609 (6.8%)	30,451,496 (94.6%)	85,517 (83.7%)	48,511 (78.0%)
Senior (61—80)	173,126 (34.7%)	3,491,831 (35.5%)	127,128 (51.3%)	104,460 (40.6%)	1,748,370 (5.4%)	16,633 (16.3%)	13,613 (21.9%)
Elderly (> 80 years)	278,330 (55.9%)	1,740,270 (17.7%)	48,899 (19.7%)	135,324 (52.6%)	915 (0.0%)	9 (0.0%)	58 (0.1%)
Male	235,106 (47.2%)	4,497,526 (45.7%)	159,408 (64.3%)	121,098 (47.0%)	17,541,752 (54.5%)	78,315 (76.7%)	47,702 (76.7%)
Female	263,111 (52.8%)	5,342,842 (54.3%)	88,586 (35.7%)	136,295 (53.0%)	14,659,029 (45.5%)	23,844 (23.3%)	14,480 (23.3%)
Urban	130,393 (26.2%)	2,587,247 (26.3%)	65,429 (26.4%)	67,408 (26.2%)	8,468,642 (26.3%)	26,875 (26.3%)	16,263 (26.2%)
Suburban	160,352 (32.2%)	3,154,294 (32.1%)	79,020 (31.9%)	82,608 (32.1%)	10,320,996 (32.1%)	32,679 (32.0%)	20,100 (32.3%)
Rural	207,472 (41.6%)	4,098,827 (41.7%)	103,545 (41.8%)	107,377 (41.7%)	13,411,143 (41.6%)	42,605 (41.7%)	25,819 (41.5%)

Values in bold represent total sum across the study period

IHD acute ischemic heart disease, *HF* heart failure

across multiple districts, the sick leave data for HF were excluded from further analysis.

Males consistently represented a higher proportion of sick leaves, whereas hospital admissions were more evenly distributed between the sexes. Across all health outcomes, the highest proportions were observed in rural areas (≈42%), followed by suburban (≈32%), and urban areas (≈26%), which contrasts with their respective spatial coverage where only 5% is classified as urban, 21.5% as suburban and the rest 73.5% as rural (Fig. 1).

COVID-stratified associations

The results of the main model were stratified into three periods: the overall study duration, the COVID years, and the pre-COVID years. The effect estimates from the COVID period model were significantly different from those of the overall model (Figs. S.5 and S.6). These differences were particularly notable for all-cause sick leaves, and all-cause and cause-specific hospital admissions for both the pollutants, likely reflecting the surge in sick leave and the considerable decline in cardiovascular-related hospital admissions following the onset of COVID-19 (Figs. S.2 and S.3).

In contrast, the RR estimates from the overall period (2013–2022) did not differ significantly from the pre-COVID estimates. Nonetheless, in certain cases, particularly in the lag-response relationship between sick leaves and both the pollutants, notable differences in RR were observed. Therefore, subsequent analyses were focused only on the pre-COVID period.

Lag-response relationship

The pre-COVID lag-response effect estimates revealed diverse lag patterns across the health outcomes for both pollutants (Figs. S.5 and S.6). For $PM_{2.5}$, significant associations were observed only for all-cause mortality, hospital admissions and sick leaves. The strongest effect was found for all-cause sick leaves at lag 7 (RR: 1.011; 95% CI: 1.009–1.012) per 10 μg/m^3 increase in $PM_{2.5}$, with a positive effect persistent across the entire lag period. For all-cause hospital admission, effects emerged from lag 5 onwards, while for all-cause mortality, the strongest effect was observed only at lag 7 (RR: 1.008; 95% CI: 1.002–1.013). Cause-specific health outcomes displayed no significant association at any lag.

Short-term exposure to NO_2 exhibited a distinct lag-response pattern of diminishing effect sizes with increasing lag. Significant associations were observed for all-cause hospital admissions and sick leaves, with highest effect for sick leaves at lag 0 (RR: 1.035; 95% CI: 1.033–1.037) per 10 μg/m^3 increase in NO_2. Furthermore, a temporary reduction in relative risk at lag 2, followed by a subsequent increase in the later lag was observed. Cardiovascular-related hospital admissions also showed significant associations, with highest effect at lag 0, which weakened and lost significance beyond lag 2. Association to all-cause mortality was positive but not significant.

Exposure–response relationship

The exposure–response curves were modelled up to concentrations of 70 μg/m^3, as certain urban and suburban districts occasionally reached such elevated levels of ambient air pollution, although very rarely.

For $PM_{2.5}$, the exposure–response relationships (Fig. 2) show that all-cause sick leaves exhibited significant relative risk even below the WHO AQG level (15 μg/m^3) with a sublinear (convex) curve. All-cause hospital admissions, on the other hand, show a near-linear relationship, with significant effect emerging only beyond 40 μg/m^3. Likewise, IHD-related hospital admissions and sick leaves did not show elevated RR values at lower concentrations, with increased effect only at levels above 50 μg/m^3. All-cause mortality was positively associated but non-significant with $PM_{2.5}$, whereas no association was observed for HF-related hospital admissions across the exposure range.

For NO_2, the exposure–response relationships (Fig. 2) were either near-linear or supralinear (concave), with risk increasing steadily at lower concentrations before flattening off at higher levels, and showing significant effects for all health outcomes, except for all-cause mortality, at EU AQD daily limit value (50 μg/m^3). However, at WHO AQG level (25 μg/m^3), cardiovascular-related sick leaves and hospital admissions were less predictable and remained non-significant. Given that the median daily NO_2 levels in the region were lower than the WHO daily level, the average RR would not be significant except for all-cause hospital admissions and all-cause sick leaves.

Subgroup analysis

The effect estimates at the EU AQD daily limit values for $PM_{2.5}$ and NO_2, stratified by demographic subgroups and spatial typologies, based on models fitted to the pre-COVID study period, are presented in Fig. 3.

Stratification by age

For $PM_{2.5}$, none of the stratified estimates was statistically significant or differed significantly from the estimates of the reference group, adults (21–60), except for all-cause sick leaves, where adults exhibited significantly higher relative risk (RR: 1.024; 95% CI: 1.018–1.029) compared to senior (61–80 years) age group. In terms of age-specific exposure–response curves (Fig. S.7), the non-linear relationship, as observed for overall population, persisted across age strata. However, differences in the steepness of curves were evident with seniors (61–80 years)

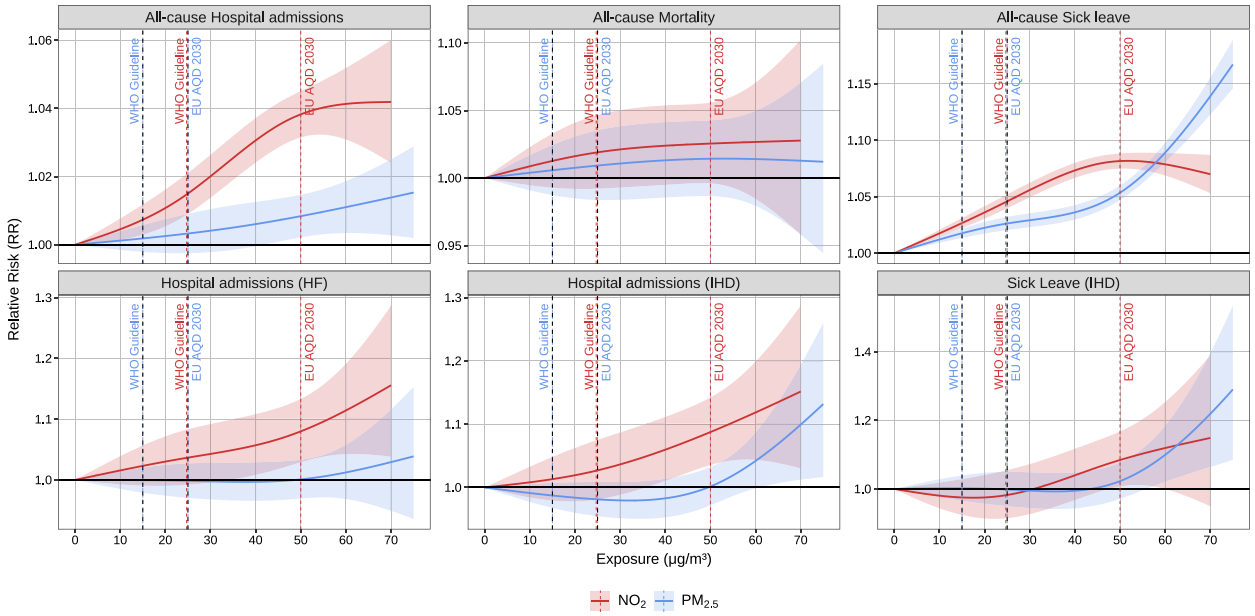

Fig. 2 Exposure–response associations between $PM_{2.5}$ and NO_2 concentrations and relative risk (95%CI) of health outcomes in the region of Baden-Wurttemberg (2013–2020), estimated using a two-stage DLNM framework with non-linear exposure functions based on selected lag structures

and elderly (> 80 years) exhibiting higher RR values for all-cause mortality and HF-related hospital admissions at lower $PM_{2.5}$ concentrations, whereas adult subgroup showed elevated risks at higher concentration levels, particularly beyond 50 µg/m^3.

In contrast, NO_2 showed more pronounced age-specific risk patterns with the strongest effect observed among the elderly (> 80 years) for IHD-related hospital admissions at RR: 1.165 (95% CI: 1.040–1.305) (Fig. 3). This group, together with seniors (61–80 years) consistently showed higher RR across health outcomes compared with adults, although they were not significantly different. Their exposure–response curves, consistently above that to the adults, indicated higher susceptibility across the concentration range (Fig. S.8).

Stratification by sex

Sex-stratified exposure–response relationships revealed a heterogeneous risk pattern for both pollutants. At EU AQD daily limits (Fig. 3), positive associations were observed primarily for NO_2. The strongest effect was identified for heart failure related hospital admission with NO_2 among male (RR: 1.183; 95% CI: 1.102–1.271), which was significantly higher than the corresponding estimate among females, a pattern that was also reflected in their exposure–response curves (Fig. S.10).

The exposure–response curves further illustrate that NO_2 related IHD-specific sick leaves and hospital admissions were higher among females across the exposure range. In contrast, NO_2 related all-cause hospital admissions showed higher relative risks among males. Lastly, all-cause sick leaves were significantly associated with both the pollutants across the entire exposure range with no evident effect modification by sex.

Stratification by urbanisation characteristics

No significant effect modifications by urbanisation level were observed for both pollutants, although distinct spatial patterns were noticeable (Fig. 3). At EU AQD limit value, relative risk associated with NO_2 remained positive across all health outcomes, whereas $PM_{2.5}$ exhibited no urbanisation-specific effect modification with the exception for all-cause hospital admission. Exposure–response curves for $PM_{2.5}$ indicated that overall estimates across spatial typologies remained largely within non-significant values ranges across exposure levels (Fig. S.11).

In the case of NO_2, no single spatial typology consistently dominated the risk estimates. The highest relative risks were observed in urban category for IHD-related hospital admissions, in suburban category for IHD-related sick leaves and in rural areas for HF-related hospital admissions. All-cause hospital admission and sick leave were significantly associated to NO_2 exposure across all urbanisation categories.

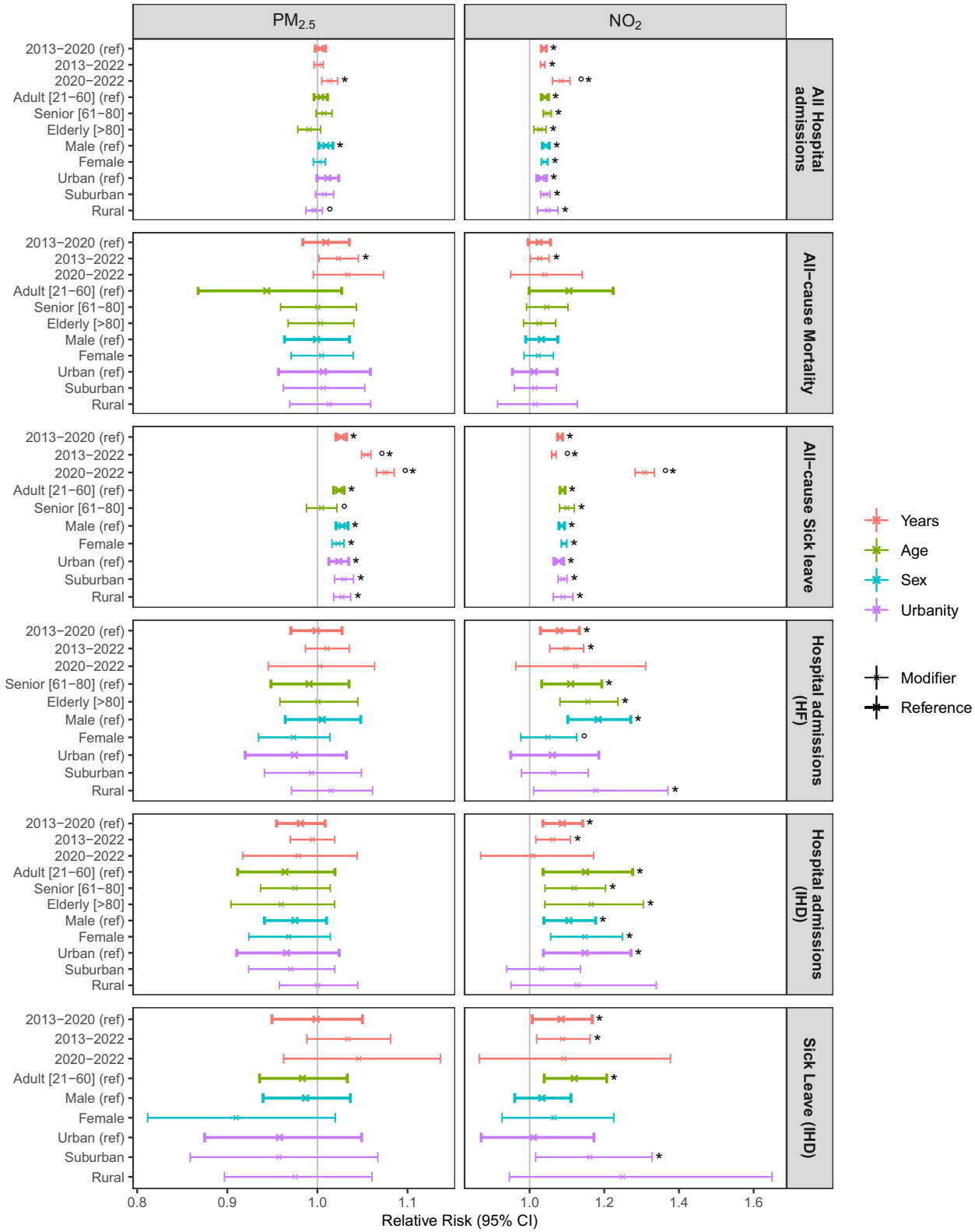

Fig. 3 Relative risks (95%CI) at EU AQD daily limit values for $PM_{2.5}$ (25 µg/m^3) and NO_2 (50 µg/m^3) for different time periods, and across demographic subgroups and spatial typologies fitted on the pre-COVID (2013–2020) duration estimated from exposure–response associations using a two-stage DLNM framework. * Model with ρ-value < 0.05. ° Significant difference between the reference and the comparison group ($\rho_{interaction} < 0.05$)

Discussion

This study applied a spatiotemporal approach with a time-stratified case-crossover design to examine the association between short-term exposure to ambient air pollution and a range of health outcomes, including all-cause mortality, and both all-cause and cause-specific morbidity.

This study provides evidence of acute health effects associated with short-term exposure to $PM_{2.5}$ and NO_2 in a region that is characterised by low pollution concentrations, largely compliant with current EU AQD limit values and WHO AQG levels. Nonetheless, significant associations were found primarily for NO_2 across all health outcomes, with the exception of all-cause mortality. In contrast, for $PM_{2.5}$, elevated risks were observed for fewer health outcomes and emerged only at higher concentrations at the upper end of the exposure range. Notably, sick leave, an underexplored health outcome in environmental epidemiology, also showed significant associations.

The study, which leveraged insurance data from 2013 to 2022, also stratified the model results based on the pre-COVID and COVID periods. Due to the absence of significant RR values for cardiovascular-related hospital admissions during the COVID period, all subsequent analyses included only the pre-COVID years. This effect outcome during the COVID period may represent a reduction in discretionary (avoidable or planned) hospital admissions, including those for acute cardiovascular diseases, during the early months of the pandemic in Germany, a factor not explicitly accounted for in our models but explained in other COVID-specific studies [29, 50].

In the lag-response relationships with NO_2, the observed relative risks were most pronounced in the immediate lag days following exposure, consistent with findings from large-scale studies and meta-analyses [10, 44, 55, 60], whereas risk of hospital admission at longer lags of up to six days was also observed in certain cases [10, 52]. With regards to $PM_{2.5}$, the lag structure was uncertain and inconsistent with the literature [4, 38, 45]. Systematic reviews and meta-analyses specifically focusing on adverse health effects in low pollution settings remain limited. [45] examined regions in North America with daily $PM_{2.5}$ concentration at or below 12 $\mu g/m^3$ and reported predominantly positive associations between short-term $PM_{2.5}$ exposure and mortality, identifying a supralinear exposure–response relationship. Although such supralinearity is commonly observed in long-term exposure studies [46], our analysis observed supralinear (concave) as well as sublinear (convex) and near-linear exposure–response relationships across different health outcomes. Supralinear curves may suggest heightened biological sensitivity at lower pollution levels, possibly due to the saturation of detoxification or inflammatory pathways at higher concentrations. Conversely, a sublinear curve may reflect a more gradual increase in risk at lower ambient air pollution concentrations, with sharper escalation beyond certain thresholds [22, 42].

To explore whether decline in air pollution levels in the region was reflected in changes in health risks, we estimated the RR from exposure–response curves at median concentration levels observed in 2013 and 2022. Over this period, $PM_{2.5}$ decreased from 9 to 7 $\mu g/m^3$ NO_2 decreased from 11 to 7.5 $\mu g/m^3$. Meaningful risk reductions were observed only for NO_2-related all-cause sick leave, while changes for other outcomes were not statistically significant (Table S.2).

For both pollutants, this study observed modest effect sizes for all-cause mortality, a widely studied health endpoint. Previous meta-analyses, assuming linear exposure–response relationships, have similarly reported modest but significant short-term effects of $PM_{2.5}$ exposure from day 0 up to lag day 14, even in European settings with relatively lower pollution concentrations [4, 44]. For NO_2, [44] reported a global pooled all-cause mortality effect of RR: 1.007 (95% CI: 1.006–1.009) per 10 $\mu g/m^3$ increase, which is comparable to our estimate (RR: 1.008; 95% CI: 0.995–1.023). However, regionally stratified meta-analyses by [43, 55] demonstrated that total mortality risks in Europe tend to be lower than in other regions, further contextualising the modest effect sizes observed in our study.

In terms of hospital admissions, [4] found a significant increase in admissions for HF with $PM_{2.5}$ exposure but observed no association with IHD-related admissions. Similarly, in a large meta-analysis focused on NO_2 exposure, [43] reported significant associations with both all-cause hospital admission 1.010 (95% CI: 1.003–1.017), and IHD-related admissions, while links with HF-related admissions were non-significant in Europe. In contrast, this study found significant associations between NO_2 exposure and all-cause as well as cardiovascular-related admission. Overall, observations from both this study and existing literature highlight the ongoing uncertainty related to acute health risks at low ambient pollution levels.

Evidence on the acute effects of air pollution on sick leave remains particularly sparse with no comprehensive systematic reviews or meta-analyses existing as per our knowledge. A study conducted in Sweden reported a significant and non-linear association between low daily concentrations of $PM_{2.5}$ and sick leaves at lag days 2–4, whereas a study conducted in Oslo found an ambiguous effect of NO_2 on sick leaves [1, 31]. In contrast, this study demonstrates a strong association of both $PM_{2.5}$ and NO_2

with all-cause sick leaves and, notably, between NO_2 and IHD-related sick leaves.

For both the pollutants, exposure–response associations with all-cause sick leave were estimated with greater precision, likely due to higher information content of this outcome, which improved the statistical stability of the first-stage models. While some degree of spatial autocorrelation was observed in the effect estimates across districts, any residual spatial dependence is expected to primarily affect variance estimates rather than the magnitude of the associations.

In terms of effect modification, the study did not record remarkable risk difference by age. While previous studies report elevated risk among older population [5, 43], our findings observed only marginally higher risks for older age groups for cardiovascular-related hospital admission associated with NO_2 exposure. In contrast, literature on effect modification by sex remains inconclusive [25, 30], while our results suggest outcome-specific differences between males and females for NO_2-related health effects.

The observation of higher cardiovascular risk linked to NO_2 in suburban and rural areas diverges from the conventional evidence base, which often shows stronger air pollution-related health risks in densely populated urban areas where pollutant concentrations are typically higher. In Baden-Wurttemberg, however, both pollutants were only marginally higher in urban districts, implying that the elevated adverse effects in suburban and rural areas may be linked to other underlying vulnerabilities stemming from physical and social infrastructural limitations in suburban environments, where reduced access to healthcare services, essential amenities, longer commutes and limited walkability could contribute to poorer health outcomes [14, 39]. Nevertheless, this interpretation remains speculative and warrants further investigation.

In terms of policy relevance, the EU AQD has proposed information and alert thresholds of 50 $\mu g/m^3$ (daily) for $PM_{2.5}$ and 150 $\mu g/m^3$ and 200 $\mu g/m^3$ (hourly) for NO_2, respectively. Our findings indicate that cardiovascular risk associated with $PM_{2.5}$ becomes statistically significant at concentrations that are comparable to these thresholds. Nonetheless, achieving lower pollution levels recommended by the WHO AQG should remain an urgent public health priority, given the well-established long-term morbidity and mortality risks associated with air pollution. At a minimum, regions should aim to consistently meet daily EU limits while pursuing further reductions wherever feasible. In contrast, the results indicated that NO_2 related health risks occur at daily concentrations well below the current permissible limit of at 50 $\mu g/m^3$, a target set for achievement by 2030. This emphasises the need to also include daily NO_2 concentrations into the existing alert and information frameworks. This evidence also warrants closer attention from the governmental agencies and healthcare stakeholders, including medical insurance services, particularly in the development of protective strategies for individuals with cardiovascular vulnerability.

From a clinical perspective, extensive evidence exists on the pathophysiologic mechanisms related to $PM_{2.5}$ and NO_2, with particularly robust findings for $PM_{2.5}$. In vivo and in vitro studies on animals and humans have demonstrated how ultrafine particles could accumulate in the lung parenchyma, causing severe acute respiratory conditions [36]. Both $PM_{2.5}$ and NO_2 have been shown to disrupt cellular functions through mechanisms involving oxidative stress and systemic inflammation. These processes could contribute to arterial stiffness, increased plaque vulnerability, and, particularly after short-term exposure, could lead to thrombosis, thereby triggering acute cardiovascular events such as myocardial infraction, stroke, and heart failure [9, 13].

Such clinical and toxicological findings shaped the development of the current WHO AQG levels, which in turn guided the EQ AQD that has laid down a staged approach to align with WHO guidelines by 2050, and has prompted calls for a revision of pollution standards, such as the European Union's Zero Pollution Action Plan that aims to reduce air pollution to the levels that is no longer considered harmful to human health by 2050 [16]. However, growing epidemiological evidence from Europe demonstrates that the adverse health effects persist even when pollution levels are below the existing EU regulatory limit values. Given the accelerating rate of climate change across Europe and slower than expected decline in pollution concentrations, the goal of achieving near-zero pollution must be treated with greater urgency.

Strengths and limitations

One of the key strengths of this study lies in its scale, analysing over 4.6 million individual health records spanning a ten-year period, and encompassing age and sex groups across varying spatial areas. By clustering the region into districts of uniform population of 50,000 residents with similar urbanisation characteristics, we reduced the potential confounding effects related to differences in population and urbanisation, thereby enhancing the internal validity of our findings. Furthermore, the two-stage statistical approach applied through an extensive sensitivity analysis (Tables S.3–S.6) strengthened the robustness of the results by testing alternative model specifications across pollutants and health outcomes.

In contrast to many previous epidemiological studies that relied solely on ground-based monitoring, we employed ensemble reanalysis data modelled by

assimilating in situ measurements and earth observation records that are geographically and temporally continuous, thus offering a consistent spatial resolution [11].

Another important contribution of this study is the assessment of all-cause and cause specific sick leave. Existing limited research in this domain mostly relies on self-reported cases and is primarily focused on $PM_{2.5}$ exposure. Our study is the first to document significant associations between short-term exposure to both $PM_{2.5}$ and NO_2 and sick leave, including for IHD. While certain cases of overlap between sick leaves and hospital admissions related to IHD may exist, they both represent different dimensions of disease burden. Findings on hospital admissions are informative for assessing burdens on healthcare system and infrastructure, whereas insights from analysing sick leaves highlight the need for further research into the implications of air pollution on workforce productivity and associated economic burdens. Such evidence can strengthen the case for lower air quality limit values by linking environmental exposures not only to health outcomes but also economic impacts. Therefore, the risk estimates based on the two types of health outcomes provide complementary insights rather than redundant information.

Our study has several limitations, primarily stemming from data constraints, exposure assessment and methodological assumptions as followed:

Health outcomes: The health outcome data, although derived from a large statutory health insurance source, are not completely representative of the general population, as the insured population is not a random sample. However, their representativeness has been examined in previous studies and found to be generally suitable for epidemiological investigations [8, 28]. Furthermore, as these data are primarily collected for insurance and reimbursement purpose rather than research, they may not fully capture disease severity, clinical details or have potential misclassification of diagnoses.

Moreover, in terms of data processing, the data were aggregated at the source, wherein the German working-age population (18–65 years) partially overlaps with the broader age group categories of children (6–20) and seniors (61–80). This introduces potential misclassification in age-specific analysis and obscure the true differences in risk across age strata to some extent. Therefore, observed effects may reflect a mixture of age-related vulnerabilities rather than age-specific responses. Lastly, the health event profiles were limited to age, sex, and location. The inclusion of individual-level variables such as ethnicity, education, income, or comorbidities would have further refined effect modification assessments.

Exposure assessment: CAMS air quality models represent state-of-the-art exposure estimates but have relatively coarse spatial resolution (11 km×7.5 km). As modelled data, CAMS estimates inherently carry biases and errors, and low-resolution modelling or reliance on background station data may lead to underestimation of pollutant levels [32]. Future work could benefit from air pollution data with higher spatial and temporal resolution, to better capture local exposure variability.

More broadly, the use of ambient pollution concentration as a proxy for individual exposure has inherent limitations, including exposure misclassification and the ecological fallacy arising from extrapolating population-level risks to individuals [54]. Although this study partially addresses these issues by subgroup analysis to better identify more vulnerable populations, such approach cannot truly account for individual level variability in exposure. New methods such as high-resolution exposure modelling, personal monitoring combined with biomarker measurement can vastly improve exposure precision and strengthen causal inference [3, 33].

Methodological considerations: The two-stage analytical framework has some inherent methodological limitations, specifically related to the dimensionality reduction required between the stages. The complex two-dimension exposure-lag-response surfaces must be reduced into one-dimensional summary matrices for the second meta-analysis stage. This transformation may cause partial loss of information about the temporal and non-linear structure of the exposure–response relationship [49].

Moreover, parameters identified through the sensitivity analyses could not be uniformly applied to all subgroups, particularly when event counts for specific health outcomes were very low in certain districts. In such cases, model complexity was reduced by lowering the degree of freedom for temporal and exposure spline functions, potentially affecting model fit and precision of effect estimates. Lastly, although this analysis focused on single pollutant estimates of $PM_{2.5}$ and NO_2, future research should explore their joint effects of multiple pollutants to better explore potential confounding, collinearity, and interaction between pollutants.

Conclusion

This study provides evidence of acute health effects associated with short-term exposure to $PM_{2.5}$ and NO_2 in a region characterised by low pollution concentrations that largely comply with the current EU limit values and WHO AQG levels. Nonetheless, significant associations were observed, particularly for NO_2 with all-cause and cardiovascular hospital admissions, and notably sick leave, an underexplored health outcome in environmental epidemiology. The analyses also identified non-linear exposure–response relationships across several health outcomes, while little evidence of effect

modification by demographic or urbanisation characteristics was detected.

Overall, these findings highlight the gaps in current ambient air quality policy and expand the epidemiological evidence base by including productivity-related outcomes such as sick leave. To address the limitations of this study, future research should aim to incorporate higher temporal and spatial resolution exposure data, individual level information on comorbidities and socio-economic status, and explore multi-pollutant modelling approaches to better quantify vulnerability and inform targeted public health interventions.

Abbreviations

AOK	Allgemeine Ortskrankenkasse
AQG	Air quality guideline
CI	Confidence interval
DLNM	Distributed lag non-linear model
EU AQD	European Union air quality directive
HF	Heart failure
IHD	Acute ischemic heart disease
IQR	Interquartile range
NO_2	Nitrogen dioxide
$PM_{2.5}$	Particulate matter with aerodynamic diameter ≤ 2.5 µm
QAIC	Quasi-Akaike information criterion
RR	Relative risk
COVID-19	Coronavirus disease 2019
WHO	World Health Organization

Supplementary Information

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Additional file 1.

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Data availability
The exposure datasets used and analysed during the current study are publicly available from the Copernicus Atmosphere Monitoring Service and the Copernicus Climate Change Service. The health outcome data contain were accessed under a contractual agreement with the insurance provider Allgemeine Ortskrankenkasse (AOK). Due to legal restrictions, these data cannot be shared.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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