Mutual effects of fine particulate matter, nitrogen dioxide, and fireworks on cause-specific acute cardiovascular mortality: A case-crossover study in communities affected by aircraft noise

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ABSTRACT

Ambient air pollution is the leading cause of environmental mortality and morbidity worldwide. However, the individual contributions to acute mortality of traffic-related air pollutants such as nitrogen dioxide (NO2) and fine particulate matter (PM2.5) are still debated. We conducted a time-stratified case-crossover study for a population located around Zurich airport in Switzerland, including 24,886 adult cardiovascular deaths from the Swiss National Cohort. We estimated the risk of cause-specific cardiovascular mortality associated with daily NO2 and PM2.5 concentrations at home using distributed lag models up to 7 days preceding death, adjusted for daily temperature, precipitation, acute night-time aircraft noise, firework celebrations, and holidays. Cardiovascular mortality was associated with NO2, whereas the association with PM2.5 disappeared upon adjustment for NO2. The strongest association was observed between NO2 and ischemic stroke mortality (odds ratio = 1.55 per 10 μg/m³; 95% confidence intervals = 1.20–2.00). Cause-specific mortality analyses showed differences in terms of delayed effect: odds ratios were highest at 1–3 days after exposure for most outcomes but at lags of 3–5 days for heart failure. Individual vulnerabilities to NO2 associated cardiovascular mortality also varied by cause of death, possibly highlighting the role of different behaviours and risk factors in the most susceptible groups. The risk of cardiovascular mortality was also increased on firework days and after public holidays, independent from NO2 and PM2.5 concentrations. This study confirms the association between ambient NO2 as a marker for primary emissions, and acute cardiovascular mortality in a specific setting around a major airport. Future research should clarify the role of additional air pollutants including ultra-fine particles on cardiovascular diseases to inform most efficient control measures.

The authors declare they have no actual or potential competing financial interests.

1. Introduction

Ambient air pollution is one of the leading causes of mortality and morbidity worldwide (World Health Organization, 2018). According to the Global Burden of Disease, approximately 4.5 million deaths were directly attributable to air pollution in 2015 (Cohen et al., 2017). Air pollution is typically assessed based on a range of individual pollutants, including particulate matter of various size fractions (e.g. diameter less than 10 μm [PM10] and less than 2.5 μm [PM2.5]), nitrogen dioxide (NO2), ozone (O3), carbon monoxide (CO) and others. Of these pollutants, the largest part of the estimated excess mortality was attributed to particulate matter and ozone (World Health Organization, 2018; Brook et al., 2010). Chronic exposure to air pollution can affect cardiorespiratory health and cause heart and vascular damage, even at low levels
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Over time, such physiological damage and resulting chronic health conditions can set a susceptible ground for the development of cardiovascular health outcomes, which may be triggered by acute environmental conditions.

Besides chronic health effects, short-term exposure to ambient air pollution is associated with increased cardiovascular and respiratory mortality (Achilleos et al., 2017; Mustafic et al., 2012; Yang et al., 2015) and emergency visits and hospital admissions (Shah et al., 2013; Nawrot et al., 2011). The causal association between particulate matter and acute mortality has been established, even at levels below the regulatory limits (U.S. EPA, 2019; Schwartz et al., 2017). However, establishing causality for specific air pollutants, which are often correlated, is a challenge. So far, the importance of acute PM2.5 exposure has been a set of acute health effects (Sarnat et al., 2001). Finally, epidemiological studies focussing on cause-specific acute cardiovascular mortality could help clarify the role of ambient air pollution on different cardiovascular diseases and their individual biological pathways.

The aim of this paper is to investigate the individual roles of NO2 and PM2.5 on cause-specific acute cardiovascular mortality in a population living in proximity to Zurich airport. We describe the mutual confounding between these two air pollutants, as well as with further environmental triggers of cardiovascular deaths, namely, temperature, precipitation, night-time aircraft noise, and planned fireworks.

2. Methods

2.1. Study population and design

We used data from the Swiss National Cohort (SNC), a longitudinal cohort based on linkage of national census data and complete mortality records for the Swiss population. The cohort contains mortality data (i.e. cause, date and time of death) as well as personal and housing information including age, sex, education, address history, building period and neighbourhood socio-economic position. We selected 24,886 adult cases of cardiovascular death (age >30) occurring between 2000 and 2015 with available address at time of death around Zurich airport, Switzerland. Zurich airport is a medium-sized airport with night curfew (ca. 270,000 flight movements each year between 2010 and 2016 (Zurich Airport, 2020)). The study extent was selected using the envelope of the calculation parameters for the Zurich Aircraft Noise Index of the years 2000–2015 (Saucy et al., 2020a) for the highly annoyed and the highly sleep disturbed persons (Schäffer et al., 2012), which covers an area with distances of up to 50 km around the airport (Supplementary Figure 1). We considered the following primary causes of death: all cardiovascular diseases (CVD) (ICD-10: I00-I99), ischaemic heart diseases (ICD-10: I20-I25), myocardial infarction (ICD-10: I21-I22), stroke (ICD-10: I60-I64), heart failure (ICD-10: I50), hypertensive diseases (ICD-10: I10-I15), and arrhythmias (ICD-10: I44-I49).

We used a case-crossover study design to investigate the individual and combined short-term effects of NO2 and PM2.5 on acute cardiovascular mortality in Switzerland. Each case of death was matched with three to four control days selected on the same day of the week within the same month, following a time-stratified control sampling (Janes et al., 2005). While time-series analyses usually assign exposure data from a central monitoring station, the case-crossover design enables the use of precise individual daily air pollution estimates at the home location, taking advantage of the precise spatiotemporal estimates calculated in this study.

2.2. Exposure data

As ambient air pollution data sources, we used previously modelled daily NO2 and PM2.5 concentrations at 100 m × 100 m resolution for Switzerland, available for the years 2005–2016 and 2003–2013 respectively (de Hoogh et al., 2019; de Hoogh et al., 2017). The exposure estimates are based on a four-stage modelling strategy, combining daily monitored NO2 and PM2.5 data across Switzerland from the regulatory monitoring network NABEL (National Air Pollution Monitoring Network, 2001), satellite-based data from the Ozone Monitoring Instrument (OMI) at 13 km × 24 km resolution for NO2 (OMINOA Team, 2016), Multi-Angle Implementation of Atmospheric Correction (MAIAC) spectral Aerosol Optical Depth (AOD) data derived from MODIS at 1 km × 1 km resolution for PM2.5 (Lyapustin et al., 2011), and further spatial and temporal predictor data including traffic intensity, road density, land use, altitude, Normalized Difference Vegetation Index (NDVI), annual emissions, and daily meteorological data. An adapted modelling strategy was used to extend the exposure model of PM2.5 at 100 m × 100
m resolution to the years 2014–2016 after the original time-series, needed for this study (Supplementary materials).

We used the 2-day average NO$_2$ and PM$_{2.5}$ at home locations for all case and control events. To include individual daily exposure estimates for the earliest years in the time series not covered by the original models (2000–2002 for PM$_{2.5}$ and 2000–2004 for NO$_2$), we applied the following two-stage modelling approach: first, we calibrated the spatial distribution of the annual average concentrations at home location for the first available modelled year with the daily values from routinely collected data at Dübendorf monitoring station (equation (1)). In a second step, the estimates calculated in (1) were refined using a random forest modelling approach calibrated with daily values from Dübendorf monitoring station, Julian day, and x and y coordinates (equation (2)).

\[
P_{ij} = P_{j,\text{mean}} - P_{D,\text{mean}} + P_{D,i}
\]  

(1)

\[
P_{ij} = f(P_{ij}, P_{D,i}, x_i, y_i, \text{jd}_i)
\]  

(2)

- Where $P_{ij}$ is the air pollution estimate calculated on day $i$ and location $j$;
- $P_{j,\text{mean}}$ is the yearly average estimate at location $j$ for the first available year of the 100 m × 100 m resolution model;
- $P_{D,\text{mean}}$ is the yearly average estimate from Dübendorf monitoring station for this same year;
- $P_{D,i}$ is the daily estimate monitored at Dübendorf station on day $i$;
- $x_i$ and $y_i$ are the x and y coordinates from location $j$;
- $\text{jd}_i$ is the Julian day on day $i$.

We used 2 km × 2 km meteorology data from MeteoSwiss (Grid-Data Products) and assigned daily outdoor mean temperature ($T_{\text{mean}}$) and precipitation at home location (MeteoSwiss, 2017; MeteoSwiss, 2016). Night-time aircraft noise exposure was calculated at home locations for the case and control nights by combining a list of all aircraft movements at Zurich airport between 2000 and 2015 with precise outdoor aircraft noise exposure calculations at 250 m × 250 m for specific aircraft types and air routes, as previously described in Saucy et al., 2020a. Building on our previous analysis of the acute noise effects on mortality (Saucy et al., 2020b), we used the average aircraft noise exposure ($L_{\text{Aeq}}$) during the night preceding daytime deaths and the average noise exposure within 2 h preceding night-time deaths. To make these comparable prior to confounding adjustment, we normalized the acute noise exposure values before aggregating the corresponding z-values into a single exposure measure.

2.3. Statistical analyses

We investigated the acute and delayed (up to seven days) effects of daily NO$_2$ and PM$_{2.5}$ concentrations on cardiovascular mortality using a distributed lag modelling approach (DLM). We modelled lag-specific association between acute ambient air pollution and cause-specific cardiovascular mortality using the ‘dlm’ package (Gasparrini, 2011). We specified the lag function as a natural spline with two equally spaced knots on the logarithmic scale. We estimated the lag-specific and cumulative (over 7-days lag) odds of mortality per 10 μg/m$^3$ increase in NO$_2$ and PM$_{2.5}$ separately. Both DLM models were adjusted for the other pollutant, as well as for 3-day average temperature ($T_{\text{mean}} + T_{\text{mean}}^2$), daily precipitation (linear relation), night-time normalized aircraft noise, national holidays (lags 0 and 1) and national firework days (August 1st and December 31st, lags 0 and 1). We investigated mutual confounding of NO$_2$ and PM$_{2.5}$ plus the two other short-term environmental exposures (night-time aircraft noise and temperature) by removing each covariate in turn, thus reporting the cumulative odds ratio (OR) for NO$_2$ and PM$_{2.5}$ with and without adjustment for each covariate. Finally, we evaluated and opted for a simplified model after successfully proving the equivalence of risk estimates. We used the average of lags 0–4 for NO$_2$ and PM$_{2.5}$ identified as meaningful from the DLM and validated using Akaike’s criterion (AIC). This simplified multiple exposures model enabled us to investigate effect modification between air pollution and cardiovascular mortality by individual characteristics (e.g. age, sex, socio-economic position, education, marital status) by introducing, in turn, each individual interaction term (Supplementary Equation S.1). To support the findings from individual interaction analyses, sensitivity analysis was performed by creating additional models combining several interaction terms including age, education, and socio-economic position. All analyses were performed using conditional logistic regression in R version 4.0.2, ‘survival’ package (Therneau, 2021).

3. Results

We identified 24,886 cases of adult (age >30 years) deaths from cardiovascular cause from the SNC between 2000 and 2015. Median NO$_2$ and PM$_{2.5}$ were 23 and 16 μg/m$^3$, respectively. Both NO$_2$ and PM$_{2.5}$ levels were higher in the lower socio-economic groups and in urban and peri-urban settings (Kruskal-Wallis test, p < 0.01). The two pollutants did not differ between the other population subgroups presented in Table 1. Pearson correlation coefficient between daily NO$_2$ and PM$_{2.5}$ levels was 60% (Supplementary Figure 2 shows a detailed correlation matrix for all lags and exposure variables).

The associations between ambient air pollutants and cause-specific cardiovascular mortality from the distributed lag models are presented in Tables 2 and 3. In the mutually adjusted models (main models), only NO$_2$ was significantly associated with an increase in the odds of cardiovascular mortality, showing a 5% increase in the odds of mortality for each increase in 10 μg/m$^3$ (OR NO$_2$ = 1.05 [1.01–1.10]; OR PM$_{2.5}$ = 0.90 [0.95–1.02]). The risk estimates from the NO$_2$ single-pollutant models remained stable with and without adjustment for PM$_{2.5}$ (Main Model vs. Model 2 in Table 2). The strongest association with NO$_2$ was observed for ischaemic stroke (OR NO$_2$ = 1.55 [1.20–2.00]). Suggestive associations were also observed for ischaemic heart diseases, myocardial infarction, heart failure and haemorrhagic stroke in relation to NO$_2$ concentrations; no association for deaths due to hypertensive diseases and arrhythmia were found. For most diagnoses, the strongest association with NO$_2$ was observed for lag days 1–3. The shape of the lag-mortality response was distinct for heart failure, with reduced OR for lag day 1 and increased OR for lag days 3–5 (Fig. 1). In contrast, the effect estimates for PM$_{2.5}$ moved towards OR = 1 when adjusting for NO$_2$, and none of the cause specific associations with PM$_{2.5}$ were significant in the multi-pollutant models (Main Model in Table 3).

The OR coefficients of all exposures included in the multi-pollutant models remained stable through adjustment by the covariates aircraft noise and temperature (Models S2 and S3 in Tables 2 and 3). Similar, the risk estimates remained stable with and without adjustment for precipitation, firework days and national holidays. Overall, except two significant risk estimates for PM$_{2.5}$ disappearing after co-adjustment by NO$_2$ (Model 2 in Table 2), there was only limited mutual confounding between the different short-term exposures (acute night-time aircraft noise, NO$_2$, PM$_{2.5}$, firework days and national holidays) in association with acute cardiovascular mortality (Supplementary Table S1).

Based on the results from the distributed lag models (Tables 2 and 3), we created a multi-pollutant model using air pollution levels (NO$_2$ and PM$_{2.5}$) averaged over lags 0 to 4 for all cardiovascular deaths (Table 4, Overall Model). Correlation between daily NO$_2$ and PM$_{2.5}$ was 60%, but the variation inflation factor (VIF) remained below 3 for all variables. From this model, the OR for cardiovascular mortality was 1.04 (95% CI = 1.00–1.08) for NO$_2$ and 0.98 (95% CI = 0.95–1.02) for PM$_{2.5}$, which closely corresponds to the values of the Main Models in Tables 2 and 3.
## Table 1
Summary statistics of the characteristics of all deaths included in the study with respect to the NO₂ and PM₀.₅₂₅ distribution on the day of death and control days.

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>N (%)</th>
<th>25th</th>
<th>50th</th>
<th>75th</th>
<th>25th</th>
<th>50th</th>
<th>75th</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cardiovascular deaths</td>
<td>24,886 (100)</td>
<td>14.1</td>
<td>22.6</td>
<td>33.0</td>
<td>11.1</td>
<td>16.2</td>
<td>23.6</td>
</tr>
<tr>
<td>Ischaemic heart diseases</td>
<td>10,521 (41)</td>
<td>14.3</td>
<td>22.6</td>
<td>33.0</td>
<td>11.4</td>
<td>16.5</td>
<td>24.0</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>3248 (13)</td>
<td>13.7</td>
<td>22.3</td>
<td>33.1</td>
<td>11.2</td>
<td>16.3</td>
<td>24.2</td>
</tr>
<tr>
<td>Stroke</td>
<td>3750 (15)</td>
<td>14.3</td>
<td>23.2</td>
<td>34.1</td>
<td>11.3</td>
<td>16.6</td>
<td>24.1</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1753 (7)</td>
<td>13.7</td>
<td>22.0</td>
<td>32.7</td>
<td>11.0</td>
<td>15.9</td>
<td>24.0</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>1392 (6)</td>
<td>13.4</td>
<td>22.0</td>
<td>32.9</td>
<td>11.1</td>
<td>16.0</td>
<td>22.7</td>
</tr>
</tbody>
</table>

### Sex
- Female: 13,269 (53)
- Male: 11,617 (47)

### Age groups
- <75: 5632 (23)
- 75-85: 8324 (33)
- >85: 10,930 (44)

### Neighbourhood SEP
- Q1: 2512 (10)
- Q2: 3685 (15)
- Q3: 4470 (18)
- Q4: 6263 (25)
- Q5: 6572 (26)
- Unknown: 1384 (6)

### Education (lowest to highest)
- Compulsory or less: 8830 (35)
- Upper secondary level: 12,353 (50)
- Tertiary level: 3150 (13)
- Unknown: 553 (2)

### Civil status
- Married: 9286 (37)
- Non married: 15,600 (60)

### Urbanisation
- Urban: 9108 (36)
- Peri-urban: 14,347 (58)
- Rural: 1431 (6)

### Building period
- Before 1970: 14,957 (60)
- 1970-1990: 17,982 (70)
- After 1990: 2372 (10)
- Unknown: 475 (2)

### Summary statistics of the characteristics of all deaths included in the study with respect to the NO₂ and PM₀.₅₂₅ distribution on the day of death and control days.

<table>
<thead>
<tr>
<th>Percentiles</th>
<th>NO₂</th>
<th>PM₀.₅₂₅</th>
</tr>
</thead>
<tbody>
<tr>
<td>25th</td>
<td>14.1</td>
<td>22.6</td>
</tr>
<tr>
<td>50th</td>
<td>33.0</td>
<td>11.1</td>
</tr>
<tr>
<td>75th</td>
<td>16.2</td>
<td>23.6</td>
</tr>
</tbody>
</table>

## Table 2
OR of cardiovascular mortality for all and cause-specific cardiovascular deaths per 10 µg/m³ increase in PM₀.₅₂₅, cumulative over 0-7 lag days. Statistically significant results (α = 5%) are marked in bold.

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>NO₂ Model 1</th>
<th>NO₂ Model 2</th>
<th>NO₂ Model 3</th>
<th>NO₂ Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cardiovascular diseases</td>
<td>1.05 (1.01-1.10)</td>
<td>1.03 (1.00-1.07)</td>
<td>1.05 (1.01-1.10)</td>
<td>1.04 (1.00-1.09)</td>
</tr>
<tr>
<td>Ischaemic heart diseases</td>
<td>1.05 (0.99-1.13)</td>
<td>1.03 (0.98-1.08)</td>
<td>1.05 (0.99-1.13)</td>
<td>1.04 (0.97-1.11)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.08 (0.95-1.12)</td>
<td>1.02 (0.93-1.12)</td>
<td>1.06 (0.95-1.22)</td>
<td>1.01 (0.94-1.20)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.13 (1.01-1.26)</td>
<td>1.14 (1.01-1.26)</td>
<td>1.13 (1.01-1.26)</td>
<td>1.02 (1.00-1.26)</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>1.03 (0.81-1.31)</td>
<td>1.11 (0.93-1.32)</td>
<td>1.03 (0.81-1.31)</td>
<td>1.06 (0.84-1.34)</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>1.55 (1.26-2.00)</td>
<td>1.41 (1.17-1.71)</td>
<td>1.55 (1.20-2.00)</td>
<td>1.46 (1.14-1.87)</td>
</tr>
</tbody>
</table>

### Model 1
- Model 1 (Main Model) is adjusted for PM₀.₅₂₅, temperature, precipitation, night-time aircraft noise, holidays and firework days.

### Model 2
- Model 2: Main Model without adjustment for PM₀.₅₂₅.

### Model 3
- Model 3: Main Model without adjustment for aircraft noise.

### Model 4
- Model 4: Main Model without adjustment for temperature.

## Table 3
OR of cardiovascular mortality for all and cause-specific cardiovascular deaths per 10 µg/m³ increase in PM₀.₅₂₅, cumulative over 0-7 lag days. Statistically significant results (α = 5%) are marked in bold.

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>PM₀.₅₂₅ Model 1</th>
<th>PM₀.₅₂₅ Model 2</th>
<th>PM₀.₅₂₅ Model 3</th>
<th>PM₀.₅₂₅ Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cardiovascular diseases</td>
<td>0.99 (0.95-1.02)</td>
<td>1.01 (0.99-1.04)</td>
<td>0.99 (0.95-1.02)</td>
<td>1.00 (0.97-1.03)</td>
</tr>
<tr>
<td>Ischaemic heart diseases</td>
<td>0.98 (0.92-1.03)</td>
<td>1.01 (0.97-1.06)</td>
<td>0.98 (0.92-1.03)</td>
<td>1.00 (0.95-1.05)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.96 (0.87-1.07)</td>
<td>1.01 (0.93-1.09)</td>
<td>0.98 (0.87-1.07)</td>
<td>0.98 (0.89-1.06)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.01 (0.92-1.11)</td>
<td>1.08 (1.01-1.15)</td>
<td>1.00 (0.92-1.11)</td>
<td>1.00 (0.93-1.09)</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>0.94 (0.78-1.14)</td>
<td>1.21 (0.88-1.67)</td>
<td>0.94 (0.78-1.14)</td>
<td>0.89 (0.75-1.07)</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>1.02 (0.81-1.27)</td>
<td>1.24 (1.03-1.43)</td>
<td>1.22 (1.03-1.43)</td>
<td>1.12 (0.91-1.37)</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>1.02 (0.89-1.16)</td>
<td>1.02 (0.89-1.16)</td>
<td>1.02 (0.89-1.16)</td>
<td>1.02 (0.89-1.16)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.94 (0.84-1.05)</td>
<td>0.97 (0.85-1.06)</td>
<td>0.97 (0.85-1.06)</td>
<td>0.97 (0.88-1.08)</td>
</tr>
<tr>
<td>Arteriosclerosis</td>
<td>1.02 (0.87-1.20)</td>
<td>1.05 (0.84-1.17)</td>
<td>1.02 (0.87-1.20)</td>
<td>1.03 (0.89-1.19)</td>
</tr>
</tbody>
</table>

### Model 1
- Model 1 (Main Model) is adjusted for NO₂, temperature, precipitation, night-time aircraft noise, holidays and firework days.

### Model 2
- Model 2: Main Model without adjustment for NO₂.

### Model 3
- Model 3: Main Model without adjustment for aircraft noise.

### Model 4
- Model 4: Main Model without adjustment for temperature.

Since only NO₂ was associated with an increased risk of mortality in the fully adjusted model, interaction analysis was performed for this pollutant only. An increased OR was also observed for all cardiovascular deaths in relation to national firework days (August 1st and December 31st) (OR = 1.29 [1.08–1.54]) and national public holidays with lagged effect for the day after (ORlag1 = 0.98 [0.89–1.08]; ORlag2 = 1.08 [0.99–1.18]).

We did not observe any effect modification for the association between 4-day average NO₂ and all cardiovascular deaths by sex,
4. Discussion

4.1. Summary and main findings

The aim of this study was to assess the mutual independent associations of short-term NO$_2$ and PM$_{2.5}$ with cause-specific cardiovascular mortality in Switzerland while adjusting for the acute effect of other environmental exposures with adverse cardiovascular health effects. In single pollutant models NO$_2$, and to a lesser extent PM$_{2.5}$, was associated with all cardiovascular deaths or specific causes of death for a cumulative exposure lag-period of 7 days preceding death. However, two-pollutant models point to an association with NO$_2$ and ischaemic stroke mortality. The largest point estimate was observed between NO$_2$ and ischemic stroke death (Table 2).

4.2. Confounding in the multiple exposures models

The distributed lag model was useful to identify the most relevant exposure period for each health outcome and inform the multi-pollutant models adjusted for PM$_{2.5}$, temperature, precipitation, night-time aircraft noise, holidays and firework days. Statistically significant results ($p=0.05$) are marked in bold. Interaction terms for continuous variables (e.g. age, socio-economic position) were introduced as linear interaction variables, and ORs are reported for different levels within the range of the interaction variable.

Table 4

<table>
<thead>
<tr>
<th>Groups</th>
<th>All CVD (N = 24,886)</th>
<th>p-int*</th>
<th>Myocardial infarction (N = 3,248)</th>
<th>p-int*</th>
<th>Heart failure (N = 2,728)</th>
<th>p-int*</th>
<th>Ischaemic stroke (N = 627)</th>
<th>p-int*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Model</td>
<td>1.04 (1.00–1.08)</td>
<td>0.64</td>
<td>1.08 (0.97-1.20)</td>
<td>0.95</td>
<td>1.05 (0.94-1.19)</td>
<td>0.33</td>
<td>1.35 (1.07-1.69)</td>
<td>0.33</td>
</tr>
<tr>
<td>Sex</td>
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<tr>
<td>Males</td>
<td>1.05 (1.00–1.10)</td>
<td></td>
<td>1.08 (0.95-1.22)</td>
<td></td>
<td>1.00 (0.85-1.17)</td>
<td></td>
<td>1.48 (1.10–1.99)</td>
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<tr>
<td>Females</td>
<td>1.04 (0.99–1.09)</td>
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<td>1.09 (0.94-1.25)</td>
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<td>1.09 (0.95-1.24)</td>
<td></td>
<td>1.28 (0.99–1.64)</td>
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<tr>
<td>Age</td>
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<td>0.93</td>
<td>1.06 (0.92-1.21)</td>
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<td>after 1990</td>
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<td>1.09 (0.76–1.32)</td>
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<td>1.11 (0.85–1.48)</td>
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<td>1.16 (0.62–2.17)</td>
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<td>1.11 (0.97-1.27)</td>
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other hand, the association between PM\textsubscript{2.5} and cardiovascular mortality was strongly reduced when adjusting for NO\textsubscript{2}, leaving only individual effect of PM\textsubscript{2.5} in this study. The models did not show much autocorrelation (VIF) between these two variables, supporting the relevance of NO\textsubscript{2} for acute cardiovascular mortality.

Air pollution mixtures and the composition of fine particulate matter are subject to large variations across regions and may depend on major types of pollution sources. Few studies have systematically assessed the mutual confounding between NO\textsubscript{2} and PM\textsubscript{2.5} in Europe or in regions exposed to air traffic related pollution. Our study thus contributes to a better understanding of the short-term effects of combined particulate matter and NO\textsubscript{2} on cardiovascular mortality in populations living near a major airport, where an increased contribution of UFP can be expected (Rivas et al., 2020). In this context, NO\textsubscript{2} may thus be a proxy measure of other, unmeasured vehicle emissions such as air-traffic related UFP or volatile organic compounds (Brook et al., 2007). This may explain our somewhat different results with previous studies, mostly observing associations of PM\textsubscript{2.5} with acute cardiovascular mortality (Schwartz et al., 2015; Orellano et al., 2020; Liu et al., 2019; Lee et al., 2014). Nevertheless, the causal role of NO\textsubscript{2} for acute cardiovascular mortality may be supported by its gaseous nature and quick passage into the bloodstream (U.S. EPA, 2016). Generally, increased knowledge on the physiological action of NO\textsubscript{2}, UFP, and particulate composition on the cardiovascular system is needed to interpret and disentangle the underlying origins of cause-specific cardiovascular mortality.

Compared to previous studies, air pollution concentrations in our study population were rather low, and exposure was specifically modelled for the place of residence using spatiotemporal models, yielding more precise individual estimates as opposed to the more simple approach to use central monitors (Chiusolo et al., 2011; Samoli et al., 2006). With this spatial resolution, NO\textsubscript{2} may be an important primary air pollution indicator for traffic including UFP from the airport or for secondary pollutants like O\textsubscript{3}, not included in this study. For instance, Luo and colleagues reported greater health effects in association with NO\textsubscript{2} in highly populated areas and increased civil air traffic than in rural areas (Luo et al., 2016). Peters and colleagues observed an association between time spent in traffic and acute myocardial infarction (Peters et al., 2004). UFP, a pollutant easily crossing the alveoli-capillary barrier, may therefore be more relevant than PM\textsubscript{2.5} with regards to acute cardiovascular mortality. In Switzerland, PM\textsubscript{2.5} is predominantly an indicator of background air pollution resulting to a large extent from long range air transport (FOEN, 2013). With urban population and air traffic density expected to increase (Güneralp et al., 2017), it is especially important to further disentangle the individual contributions of NO\textsubscript{2}, PM\textsubscript{2.5}, and UFP as well as particle composition on cardiovascular health to inform future health policies.

To the best of our knowledge, this is the first study to adjust for acute aircraft noise in air pollution studies. For long-term exposure, Héritier et al. provided evidence that the association between NO\textsubscript{2} and particulate matter in Switzerland was confounded by transportation noise (Héritier et al., 2018). In this study, we did not find an indication of confounding of the association between short-term air pollution and cardiovascular mortality by short-term night-time aircraft noise. Further, no confounding is to be expected from long-term environmental exposures due to the individual matching in this case-crossover study. We found that for acute cardiovascular mortality, the different environmental exposures investigated here were rather stable, showing no sign of mutual confounding. This confirms that at least on the short term, the cardiovascular effects of NO\textsubscript{2}, night-time aircraft noise, temperature and precipitation are independent from each other.

The risk of cardiovascular mortality was increased by 29% on ‘firework’ days (August 1st and December 31st), independent from NO\textsubscript{2} and PM\textsubscript{2.5} concentrations, which is in line with Greven and colleagues (Greven et al., 2019). Fireworks on national day and New Year’s eve are known to affect ambient air quality (Godri et al., 2010; Seidel and Birnbaum, 2015), but this observed excess mortality may also be the consequence of specific behaviours (e.g. excess consumption of food and alcohol, lack of sleep) or firework associated noise exposure, which may be the reason for the different lag structure compared to air pollution.

4.3. Cause-specific cardiovascular mortality in relation to ambient air pollution

While ischaemic and haemorrhagic strokes are often considered as a single group of diseases in epidemiological studies, they may be caused by different underlying physiological mechanisms, resulting in differential association with air pollution (Bourdrel et al., 2017; Wichmann and Voyi, 2012). In this study, we observed a strong risk increase for ischaemic but not haemorrhagic stroke in association with ambient NO\textsubscript{2}, supporting the differential action of environmental exposures on these two disease groups. Despite a relatively small sample size, the association between NO\textsubscript{2} and ischaemic stroke was strongly significant due to a large effect size, but reduced power may explain the inconclusive results observed for arrhythmias. More generally, the risk of mortality was increased for all disease groups involving some type of ischaemia (i.e. ischaemic heart diseases, myocardial infarctions and ischaemic strokes), coherent with the suspected physiological response described for NO\textsubscript{2}, including acute inflammation, and increased coagulation. However, the cardiorespiratory physiological changes in response to NO\textsubscript{2} exposure need to be further studied and described, as specific knowledge is currently limited (U.S. EPA, 2016).

Unlike a previous study, which reported an increased risk of heart failure associated with same-day NO\textsubscript{2} and PM\textsubscript{2.5} levels (Shah et al., 2013), we found that the risk of heart failure in association with NO\textsubscript{2} was highest 3–5 days after exposure, following an initial risk reduction. The physiology of heart failure is different from the ischaemic events. Patients with heart failure have already been described to be at higher risk of cardiovascular mortality in association with air pollution, mainly due to subsequent increased heart rate and diastolic blood pressure (Buteau et al., 2018; Goldberg et al., 2015; Goldberg et al., 2011). In a previous study, we demonstrated that the association between heat and mortality from heart failure was modified by the presence of ambient air pollution (Saucy et al., 2021). A generalized vasodilatation and volume depletion as a response to a heat event may explain the initial risk decrease in our study population, followed by increased mortality in relation to the combined stress event.

Air pollution levels were associated with the same acute cardiovascular diagnoses as previously observed for short-term night-time aircraft noise (Saucy et al., 2020b), highlighting some common pathophysiological mechanisms as a response to short-term air pollution and aircraft noise, both suspected to be involved in vascular oxidative stress reactions (Bourdrel et al., 2017; Münzel et al., 2020). However, aircraft noise exposure in the night preceding death events did not affect the risk of NO\textsubscript{2} associated cardiovascular mortality.

4.4. Effect modification and vulnerability groups

The distribution of PM\textsubscript{2.5} and NO\textsubscript{2} was uneven with respect to socio-economic position, with higher pollution levels in locations with lower socio-economic position, showing that social inequity related to air quality reported in previous studies (Fairburn et al., 2019) was also present in our study population. Individual vulnerabilities to NO\textsubscript{2} related mortality varied across the specific causes of death, highlighting potential variations of risk factors in relation to these different pathologies. For example, social determinants of health such as sex, education and socio-economic position did not modify the short-term association between NO\textsubscript{2} and all cardiovascular deaths. Despite a higher susceptibility to cardiovascular mortality with older age (mean age was 80 years old in our study population), the relative acute risks were lower in the oldest age groups. This observation was consistent for heart failure and ischaemic stroke, but not for myocardial infarction, where the OR
(non-significantly) increased with older age. In these three groups of diseases, increased susceptibility was observed for people with lower socio-economic position, who were also exposed to increased levels air pollution and were therefore more vulnerable to air pollution overall. In contrast, increased OR was only observed with increasing education for ischaemic stroke, possibly in relation with specific behaviours and risk factors in this group of the population. Sensitivity analysis including multiple interactions suggest that the described effect modification by education and socio-economic status is not influenced by differential age and sex in these groups.

4.5. Strengths and limitations

While time-series analyses rely on centralized data from monitoring stations, the case-crossover design enables the use of individual exposure data, considering spatial fluctuations at different locations on a daily basis, which is an asset of this study. The NO\textsubscript{2} and PM\textsubscript{2.5} exposure data used in this study were extracted at home location from longitudinal nationwide air pollution models with high spatial and temporal resolution, thus minimizing potential exposure misclassification. Due to the individual matching between case and control events within a short period of one month, all analyses were adjusted by design for individual characteristics such as age, sex, and socio-economic position. Combined with distributed lag models, this approach enabled us to investigate the delayed cause-specific exposure-response between ambient air pollution and cardiovascular mortality with minimum bias. Potential confounders that also vary over a short time, such as meteorological conditions, were similarly included from high resolution models designed for Switzerland. This study additionally adjusts for acute environmental (specifically aircraft) noise, which is rarely considered in air pollution studies, but has been described as a potential confounder on the association between long-term air pollution exposure and cardiovascular mortality.

A limitation of this study is that we did not include ozone, ultra-fine particles and relative humidity, as they were not available in our study area at a similar spatial resolution. Our study population was selected around Zurich airport (up to 50 km distance), which is an interesting setting from an air pollution emission perspective with possible specific air pollution mixtures in relation to air traffic. While this choice may limit the generalization of our results to other neighbourhoods, not exposed to air traffic, it offers unique information for future discussion of health outcomes in various exposure settings. Finally, a larger range around Zurich airport (up to 50 km distance), which is an interesting area at a similar spatial resolution. Our study population was selected from high resolution models designed for Switzerland. This study additionally adjusts for acute environmental (specifically aircraft) noise, which is rarely considered in air pollution studies, but has been described as a potential confounder on the association between long-term air pollution exposure and cardiovascular mortality.

5. Conclusion

Based on precise individual exposure estimates and a robust study design, this study confirms the association between short-term ambient NO\textsubscript{2} and acute cardiovascular mortality in a specific setting around a major airport. The association between PM\textsubscript{2.5} and cardiovascular mortality was strongly reduced when adjusting for NO\textsubscript{2}, leaving only little individual effect of PM\textsubscript{2.5}. Future research should further investigate the role of different air pollutants such as UFP emitted by the air traffic as well as particles composition in relation to acute cardiovascular diseases to inform most efficient control measures.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2021.118066.

Credit author statement

Conceptualization; M.Rö. and A.S.; Formal analysis: A.S.; Funding acquisition: M.Rö.; Methodology: A.S., M.Rö.; Resources: K.dH., B.S., J-M.W., D.V.; Supervision: M.Rö. and N.P.-H.; Writing – original draft: A.S.; Review & editing: M.Rö., N.P.-H., J-M.W., B.S., D.V., L.T, K.dH. All authors have read and approved the current version of this manuscript.

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