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Short-term exposure to ambient air pollution and severe COVID-19: mortality and hospital admission to COVID-19 in the Netherlands from february to december 2020

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ABSTRACT

This study aimed to examine acute effects of exposure to ambient air pollution on COVID-19 hospital admissions and mortality in the Netherlands. We hypothesized that exposure to increased air pollution in the preceding week might trigger an exacerbation of health of infected individuals.

Associations between daily concentrations of particulate matter with an aerodynamic diameter ≤2.5 μm (PM2.5) and ≤10 μm (PM10), nitrogen dioxide (NO_2), ozone (O_3) and risk of hospital admissions and mortality due to COVID-19 from February to December 2020 was analyzed across all 352 Dutch municipalities grouped into 12 provinces. Time-series models were used to fit province-specific estimates, followed by meta-analyses to produce national estimates. Analyses were based on daily averages of PM2.5, PM10, NO_2, and maximum 8-hour running average of O_3 on a 1×1 km grid and averaged on municipality level by population weight. Models were adjusted for spatiotemporal confounders, including government policies in response to the number of COVID-19 infections. Since there were only few COVID-19 cases during the summertime when O_3 levels were highest, associations between O_3 and COVID-19 health outcomes were not further explored.

We found associations between exposure to air pollution in the preceding week (average of lag 0-7 days) and COVID-19 hospital admissions and mortality. On a national level, an interquartile range increase in PM2.5, PM10 and NO_2 exposure was associated with 11-12% increased mortality risk; the risk for hospital admissions was higher: 19-25%. Observed associations were more robust for PM than NO_2 in two-pollutant models.

Our results suggest that short-term exposure to PM2.5 and PM10 may increase the risk of COVID-19 mortality and hospital admission. This indicates that, consistent with previous studies on air pollution and respiratory infections, the population at risk of being hospitalized or dying of COVID-19 is extra vulnerable to the adverse effects of short-term air pollution exposure.

Introduction

The pandemic of coronavirus disease 2019 (COVID-19) has had huge health impacts: as of March 2023, it resulted in over 760 million confirmed cases and almost 6.9 million deaths worldwide (WHO, 2023).

There is some evidence from studies with individual-level data, that long-term exposure to air pollution increases susceptibility to worse outcomes from COVID-19, such as hospital admission or mortality

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(Walton et al., 2022). However, the link between short-term exposure to air pollution and COVID-19 remains elusive.

Several studies on acute effects of air pollution on COVID-19 found heterogeneous associations, likely because of the differences in study design and setting, and difficulties to control for confounding (Hernandez Carballo et al., 2022). While well-established standard methods exist to study associations between air pollution and chronic non-communicable diseases, studies on air pollution and infectious diseases like COVID-19 are methodologically challenging. This because additional spatiotemporal aspects can affect the occurrence and severity of infection and those aspects are difficult to include correctly. For instance, transmission dynamics, measures taken to prevent the spread of the virus such as lockdowns, or autocorrelation, should be considered.

Yet, the link between short-term elevation in air pollution and COVID-19 occurrence and severity is biologically plausible. Several studies have previously demonstrated an association between short-term exposure to air pollution and all-cause mortality, cardiovascular and respiratory morbidity (EPA, 2019; WHO, 2021), including an increase in respiratory infection-related morbidity and mortality (EPA, 2019; Walton et al., 2022). In addition, air pollution might increase the risk of getting severe COVID-19, through the association with linked comorbidities such as respiratory and cardiovascular diseases which might increase the host susceptibility (Thurston et al., 2017). Also, there is information on the association between air pollution and respiratory infections other than COVID-19, such as pneumonia, bronchiolitis and acute bronchitis in children (Hertz-Picciotto et al., 2007; Hoek et al., 2012; Horne et al., 2018; Karr et al., 2007; Karr et al., 2009; MacIntyre et al., 2014). In adults, air pollution has been associated with hospital admission with pneumonia, and chronic obstructive pulmonary disease (COPD) and influenza (Horne et al., 2018; Li et al., 2016; Neupane et al., 2010). In an overview on studies on air pollution and hospital admission for lower respiratory infections Walton et al.(Walton et al., 2022) concluded that recent literature provides plausibility for an effect of short-term exposure to air pollution on COVID-19.

Within the Netherlands, a densely populated country with 17.5 million inhabitants, daily concentrations of air pollutants are highly correlated. This is a result of the small size of the country, the lack of small size geographical and meteorological differences, such as mountains, that can affect local climate, and the importance of long-range transport of air pollution. Due to the presence of source areas (*e.g.*, intensive farming) and the proximity to source areas abroad (*e.g.*, industrial sources from Germany and Belgium), particulate matter (PM) concentrations are generally higher in the southern and eastern part of the Netherlands. NO_2 concentrations are highest in the country's more densely populated western part, with the highest traffic intensity and increased levels of air pollution from local industry

The present study aimed to examine the effects of short-term exposure to particulate matter (PM) with an aerodynamic diameter ≤ 2.5 μm (PM2.5) and ≤ 10 μm (PM10), nitrogen dioxide (NO_2), and ozone (O_3) on COVID-19 hospital admissions and mortality among subjects infected with SARS-CoV-2. We hypothesized that exposure to increased air pollution levels in the preceding week might trigger an exacerbation of the health status of infected individuals, by: (1) requiring hospital admission, or (2) causing premature mortality. Analyses were stratified by degree of urbanization and province as population characteristics and sources of major air pollutants differ across the country and may lead to different associations in different regions.

Methods

Study design

We conducted a time series analysis across all 352 Dutch municipalities of the Netherlands to assess the associations between daily ambient air pollution levels (PM2.5, PM10, NO_2, O_3) and risk of hospital admissions and mortality due to COVID-19 for the whole Dutch population. We used data from existing health registries and surveys, available at the Central Bureau of Statistics (CBS).

Consistent with previous air pollution studies, that observed acute health effects of air pollution within a few hours to one week, we used a cumulative lag time of exposure to air pollution of one week (lag 0 to 7) to investigate the hypothesis that air pollution aggravated already existing symptoms of COVID-19 diseased individuals.

Data sources

We focused on the period from 1 February, when the first COVID-19 cases were confirmed in the Netherlands, to 31 December 2020. After this period, the vaccination campaign against SARS-CoV-2 started and novel virus variants start to emerge, which complicates the interpretation of analyses.

Daily COVID-19 mortality data per municipality were obtained from the Municipal Population Registers (Dutch: *Gemeentelijke Basisadministratie persoonsgegevens*) via Statistics Netherlands (CBS). Mortality was defined based on the underlying cause of death recorded on death certificates as ICD-10 (International Classification of Diseases, 10th revision) codes. We selected mortality due to COVID-19 (ICD-10: U07.1, U07.2).

Daily data on hospital admissions for COVID-19 was provided by the Dutch Hospital Data (DHD) repository and accessed through Statistics Netherlands. We aggregated this data on municipal level. The DHD database includes information from all hospitals in the Netherlands. We selected patients admitted to hospitals for the first time with COVID-19 (ICD-10: U07.1, U07.2) as the primary diagnosis.

Daily average meteorological variables (derived from hourly data on mean temperature (°C) and relative humidity (%)) for each municipality was available from the nearest monitoring station of the Royal Netherlands Meteorological Institute (www.KNMI.nl) and aggregated on municipal level.

Information on weekly changes in governmental public health measures in response to COVID-19 pandemic was obtained from the Oxford COVID-19 Government Response Tracker. We used their COVID-19 Containment and Health Index (CHI), which is a national-level composite measure, ranging from 0 to 100, based on thirteen policy response indicators, *e.g.*, school and workplace closures, travel bans, testing policy, contact tracing, face coverings, and vaccination policy (Hale et al., 2021).

We derived daily maps of the concentrations of PM2.5, PM10, NO_2, and O_3 for the year 2020 by spatial interpolation of measurements from the air quality monitoring networks in the Netherlands. The hourly observations at 35 rural and 45 urban background measurement locations were spatially interpolated using an extension of the Residual Interpolation Optimized for Ozone (RIO) model of VITO (Janssen et al., 2008). The RIO model was introduced and tested in the Netherlands for use in hourly air quality maps (Hoogerbrugge, 2015; Mooibroek, 2014). In a later update, more measurement locations were used in the hourly RIO runs and hourly modeling of PM2.5 was started. The model removes local site-dependent increases or decreases in concentrations, then performs a spatial interpolation using Ordinary Kriging, after which the local effects are added to the maps. The RIO maps are on a 4×4 km spatial resolution and for the present analysis they were downscaled to 1×1 km^2 by spatial interpolation. The availability of sufficient hours with valid data was checked. We calculated daily averages of PM2.5, PM10, NO_2, and maximum 8-hour running average of O_3 on a 1×1 km grid from the hourly maps. We then calculated population-weighted averages for each Dutch municipality using 1×1 km estimated population (year 2021) as weights.

Statistical analyses

We employed a two-stage analytical strategy, first analyzing province-specific data (n = 12 provinces in the Netherlands; Fig. 1)

Fig. 1. Map of the provinces of the Netherlands.

using a time-series approach, followed by a meta-analysis of the obtained provincial estimates to produce a national estimate. Detailed information on the statistical model can be found in the appendix. The rationale for using province data was twofold: first, the alternative of analyzing the time series of the 352 municipalities individually was unfeasible as most of them had very few cases, producing highly unstable effect estimates; second, the provinces were small enough to guarantee adequate control for confounding factors, and had large enough numbers of cases to ensure robustness of the effect estimates.

In the first stage, we performed a pooled analysis on the time series of municipalities in their respective provinces (Gariazzo et al., 2023; Stafoggia et al., 2022). In each of the 12 Dutch provinces, we fitted conditional over-dispersed Poisson generalized nonlinear models with municipality-specific daily mortality / hospital admissions and air pollution as outcome and exposure variables, respectively. We adjusted for municipality-specific time trends, temperature, relative humidity, and CHI. We also included an autocorrelation term to account for the strong serial correlation between COVID-19 patterns that might not be entirely captured by our trend adjustment (Imai et al., 2015; Nottmeyer et al., 2023).

Following the case-crossover approach, we defined a three-way interaction term between municipality, month, and day of week to adjust for municipality-specific time trends (Lu & Zeger, 2007). This means that differential time trends across municipalities of the same province are adjusted by design. We modelled temperature, relative humidity and CHI using distributed lag non-linear models (DLNMs) (Gasparrini, 2014). The basis function for the exposure and lag dimensions were modelled with natural cubic splines, with knots placed at 1 and 7 days. We defined two alternative lags for air pollution: the average of days 0–7 (used as main exposure window), and the average of days 0–14 (used in sensitivity analysis). We entered either in the models as linear term. We explored two different averaging periods as one could expect longer delay for mortality and shorter for hospital admissions.

In the second analysis stage, we performed a random-effects meta-analysis using the restricted maximum-likelihood estimator of the between-province variance to pool the province-specific estimates to obtain a national estimate. A random-effects model was used to account for potential difference in estimates between locations (Hardy & Thompson, 1996).

As sensitivity analysis, we repeated the first stage analyses, but instead of pooling the time-series of municipalities belonging to the same province, we pooled these per five different categories of urbanization: extremely urbanized (> 2,500 addresses per km^2), strongly urbanized (1,500-2,500 per km^2), moderately urbanized (1,000-1,500 per km^2), hardly urbanized (500-1,000 per km^2), and not urbanized (< 500 per km^2). This analysis allowed investigating whether associations differed in higher (*e.g.*, major cities) versus lower (*e.g.*, countryside) populated areas. This was done because source-specific contributions to PM can differ across areas with different urbanization degree, but also because residual confounding from omitted covariates related to population mobility and lifestyle might play a different role based on the underlying population density and behavior.

We also explored independent effects of each pollutant by applying two-pollutant models.

We report the results as relative risk of outcome (mortality or hospital admission), with corresponding 95% confidence intervals (95% CI), per interquartile range (IQR) increases in the exposure. We conducted the analyses in the secure remote access environment of Statistics Netherlands using R statistical software, version 4.1.3 using the dlnm, gnm and metafor packages.

Results

Descriptives

In Fig. 2 we show the distribution of the daily environmental data during the 11 months study period across the Dutch provinces. There is a small spatial gradient in the median particulate matter concentrations, with concentrations generally increasing from north to south. For NO_2 the pattern is slightly different; the highest median concentrations are

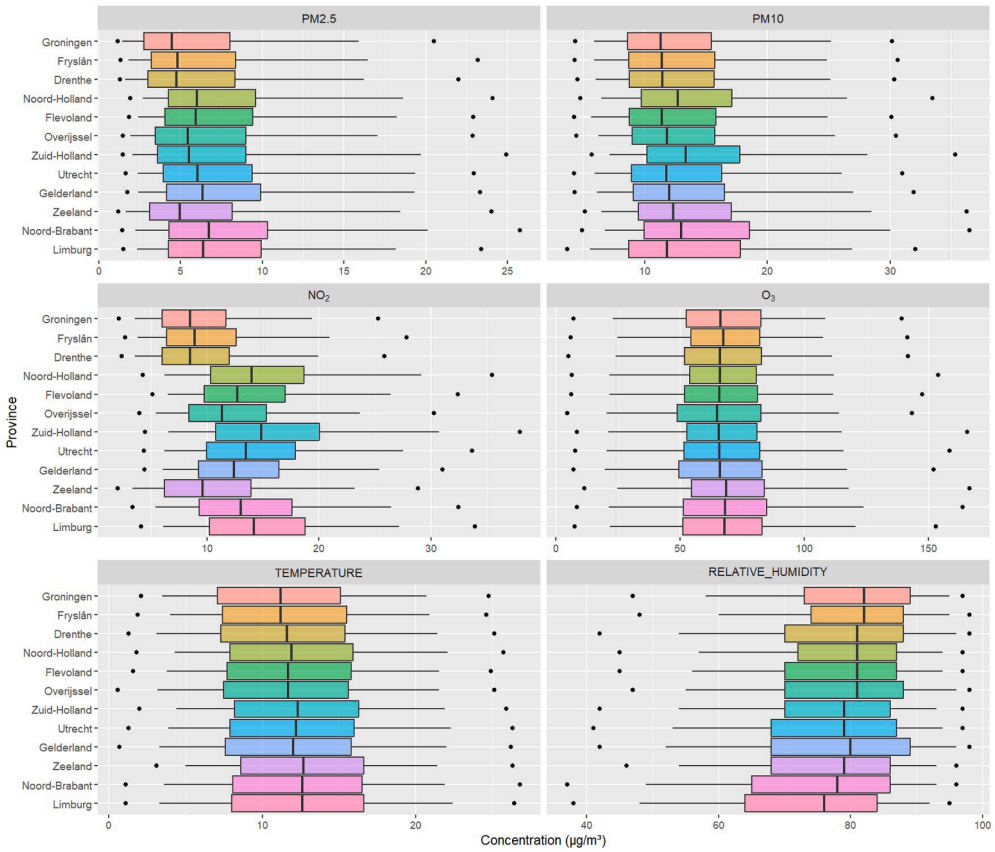

Fig. 2. Distribution of daily average air pollution concentrations and meteorological variables across Dutch provinces.
The boundaries of the box indicate 25th and 75th percentile, the bold line in the middle of the box indicates median; and the whiskers indicate 5th and 95th percentile; dots are 1st and 99th percentile. Provinces are ordered from north (top) to south (bottom) and colors correspond to the colors used for the map of provinces of the Netherlands (Fig. 1).

found in the country's most densely populated western part. The same patterns are found for the range in daily average concentrations (defined here as difference between the 99th and the 1st percentile; Figs. S1–S8 in the Appendix). Average daily air pollution concentrations calculated for the Netherlands were 7.5 (SD: 5.2) µg/m^3 for PM2.5, 14.0 (6.5) µg/m^3 for PM10 and 13.9 (6.6) µg/m^3 for NO_2. Average of maximum 8-hour running averages for O_3 was 68.0 (27.9) µg/m^3. IQRs were 5.6 µg/m^3 for PM2.5, 7.7 µg/m^3 for PM10, 8.3 µg/m^3 for NO_2, and 30.7 µg/m^3 for O_3. Correlations between daily average PM2.5 and NO_2 concentration ranged from 0.57 to 0.74 across provinces, whereas correlation between PM10 and NO_2 was lower, ranging 0.33–0.50 (Table S1). Levels of PM2.5 and PM10 were highly correlated, ranging 0.73–0.82. Ozone had a low-to-moderate negative correlation with NO_2 (-0.37–-0.11). Mean CHI was 50 (SD 17), ranging from 2 (1st percentile) to 67 (99th percentile).

During the study period, 18,277 deaths and 32,848 hospital admissions due to COVID-19 were recorded. We present spatio-temporal distribution of COVID-19 mortality and hospital admissions in Figures S9-S10. The two severity indicators differed substantially regarding age at which the event occurred: the average age at death was 82.5 (SD: 9.8) years, whereas the average age at hospital admission was 67.3 (15.1) years.

Since there were only few COVID-19 cases during the summer when the O_3 levels were the highest (and vice versa; Figs. S11, S12), we decided not to investigate further the associations between O_3 and COVID-19 mortality and hospital admission.

Mortality

We present the associations between short-term exposure to air pollution and COVID-19 mortality in Fig. 3 and Table S2. Overall, we found an increased risk of COVID-19 mortality after exposure to PM2.5 in the preceding week (lag 0-7), RR: 1.12 (95% CI = 1.08, 1.17) per IQR (5.6 µg/m^3). Exposure to PM10 was associated with a RR of 1.11 (CI = 1.03, 1.20) per IQR (7.7 µg/m^3), and exposure to NO_2 with a RR of 1.12 (CI = 1.06, 1.18) increased mortality risk (IQR=8.3 µg/m^3).

Comparing the estimates of the single and two-pollutant model indicate that the associations with PM2.5 and PM10 were more robust than those with NO_2. After adjustment for NO_2, estimates became 1.17 (CI = 1.04, 1.32) for PM2.5 and 1.16 (CI = 0.95, 1.42) for PM10. In contrast, the associations with NO2 became negative after adjustment for PM (Table S3). We did not investigate two-pollutant models including both PM2.5 and PM10, since the two were highly correlated (Table S1).

We observed the strongest associations between all the pollutants and mortality for the provinces "Gelderland", "Noord-Brabant", "Noord-Holland" and "Zuid-Holland" (Fig. 3 and Table S2). We did not observe any (statistically significant) associations in other provinces.

The observed associations with exposure to PM2.5, PM10 and NO_2 were most robust in urbanized areas ("moderately" to "extremely urbanized"), essentially disappearing in "hardly urbanized" and "not urbanized areas" (Table S4).

The risk of death after (averaged) exposure over the last two weeks (lag 0-14; Table S2) was higher for PM2.5 and PM10 (1.10 (CI = 1.02, 1.18) and 1.10 (CI = 0.99, 1.22) per IQR), respectively. We did not observe an association with NO_2 (0.96 (CI = 0.86, 1.06)).

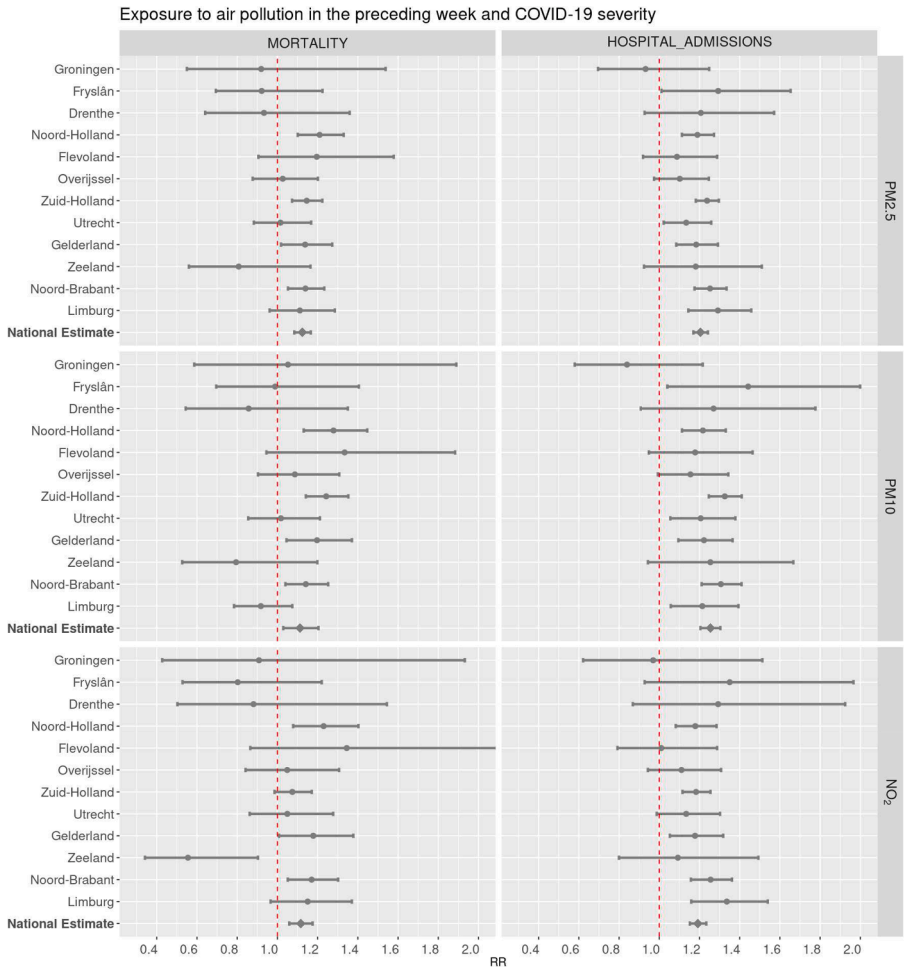

Fig. 3. Associations between exposure to air pollution in the preceding week and COVID-19 mortality and hospital admissions.
Associations per province and national meta-analysis estimates (META). RR is relative risk. Error bars denote 95% confidence intervals. IQRs were 5.6 μg/m^3 for PM2.5, 7.7 μg/m^3 for PM10, 8.3 μg/m^3 for NO_2. I^2 for mortality were 0 for PM2.5, 55.8 for PM10, 4.7 for NO_2; I^2 for hospital admissions were 9.3 for PM2.5, 13.1 for PM10, 0 for NO_2. Provinces are ordered from north (top) to south (bottom).

Hospital admissions

Fig. 3 and Table S5 show the associations between short-term air pollution exposure and COVID-19 hospital admissions. We found a 21% increased risk of hospital admission on national level due to COVID-19 after exposure to PM2.5 (1.21 (CI = 1.17, 1.24)), 25% increased risk after exposure to PM10 (1.25 (CI = 1.21, 1.30)), and 19% increased risk after exposure to NO_2 (1.19 (CI = 1.15, 1.23)) in the week before admission (lag 0-7; all expressed per IQR).

In two-pollutant models, the associations with exposure to PM2.5 and PM10 were more robust than those with NO_2. The association with PM10 and PM2.5 increased to 1.28 (CI = 1.14, 1.44) and 1.32 (CI = 1.21, 1.43), respectively, while those with NO_2 attenuated to unity (Table S6).

The strongest associations with all investigated pollutants were for the provinces "Gelderland", "Limburg", "Noord-Brabant", "Noord-Holland" and "Zuid-Holland" (Table S5). The associations in other provinces were also positive (except "Groningen"), but not statistically significant.

The degree of urbanization did not seem to play a major role in the observed associations with PM2.5, PM10, and NO_2, except for "not urbanized areas", where the associations attenuated and were not statistically significant (Table S7).

At lags 0-14 (Table S5), the risks associated with PM2.5 and PM10 were 1.31 (CI = 1.20, 1.43) and 1.38 (CI = 1.31, 1.45), respectively. The association with NO_2 was 1.14 (CI = 1.04, 1.25).

Discussion

We found statistically significant associations between exposure to air pollution in the preceding week (lag 0–7) and the risk of COVID-19 hospital admissions and mortality. Exposure to an IQR increase in PM2.5, PM10 and NO_2 concentration (5.6 μg/m^3, 7.7 μg/m^3 and 8.3 μg/m^3 respectively) in the preceding week was associated with an 11–12% increased mortality risk. The risk for hospital admissions was higher: 19–25%. Expressed per 10 μg/m^3 exposure increase this is an elevation of 22% (PM2.5) and 15% (PM10 and NO_2) for mortality and 41% (PM2.5), 34% (PM10) and 22% (NO_2) for hospital admission. The associations were more robust for exposure to PM in two-pollutant models. The associations were strongest in southern provinces of the Netherlands and the provinces with major urban agglomerations (Amsterdam in "Noord-Holland", Rotterdam and The Hague in "Zuid-Holland").

We used a time series design to study the effects of the temporal variation in air pollution on COVID-19 outcomes. Most of the published time series studies on the acute effects of air pollution used confirmed COVID-19 cases, followed by the number of COVID-19 deaths as health outcome. A time series study conducted in 63 Chinese cities showed that a short-term increase (with a cumulative lag 0 to 14 days) of 10 μg/m^3 PM10 or PM2.5 was associated with an increase of 18% (PM10) and 23% (PM2.5) confirmed daily COVID-19 cases, respectively (Wang et al.,

2020). Another study in 120 cities in China found associations with PM2.5, PM10, NO_2 and O_3 in the last two weeks, with an increase up to 7% newly confirmed COVID-19 cases per 10 μg/m^3 increase (Zhu et al., 2020). A study conducted in the New York area found no associations between short-term exposure to PM2.5 and COVID-19 infections, but some effects with maximum 8-hour average O_3 concentrations. No effects were found between PM2.5, O_3 and COVID-19 mortality (Adhikari & Yin, 2020). A case-crossover study among Swedish young adults has suggested that short-term exposure to PM is associated with an increased risk of testing positive for SARS-CoV-2 of 18% (PM2.5) and 10% (PM10) per 10 μg/m3 (Yu et al., 2022). In Canada, associations have been found between COVID-19 Emergency Department (ED) visits and short-term cumulative exposure over 0-3 days to PM2.5 (+1.6%) and NO2 (+2.7%) per 10 μg/m3 increase (Lavigne et al., 2022). Associations between increased air pollution levels and increased risk of COVID-19 mortality (+277% per 10 μg/m3 PM2.5 and +36% per 10 μg/m3 O3) have been reported in a case-control study in the US (Kim et al., 2022) and in Italy (Ye et al., 2021), where each 10 μg/m3 increase in PM was associated with much higher increase in daily all-cause mortality during the pandemic period compared to the same months during 2015-2019 (7.2% versus 1.7% for PM2.5; 3.5% vs 1.1% for PM10).

Overall, the relationship between short-term air pollution exposure and COVID-19 in existing literature remains elusive (Brunekreef et al., 2021; Hernandez Carballo et al., 2022; Katoto et al., 2021; Walton et al., 2022), probably because most time-series studies published so far on air pollution and COVID-19 suffer from a very short time-period, *i.e.*, one or two months, which makes it challenging to include sufficient exposure contrast (Walton et al., 2022). Also, because of the dynamics of infectious diseases in general and COVID-19 specifically, it is challenging to control for important confounders, such as population density, mobility, spatial autocorrelation and interventions that are taken to prevent virus transmission, but also affect air pollution levels. Also, a link between weather conditions and COVID-19 is likely, as many viruses show strong seasonal patterns that affect people's behavior (e.g. time spend indoors, ventilation), the human immune system response (in winter generally more susceptible) and virus viability and transmissibility. There is a tendency that low temperature and humidity levels were associated with increased risks of COVID-19 incidence (Linares et al., 2021; Nottmeyer et al., 2023), although the role of air pollution on COVID-19 was considered dominant compared to temperature and absolute humidity (Culqui et al., 2022; Linares et al., 2021). This results in a high risk of bias and may lead to spurious associations.

Because of the start of the COVID-19 vaccination program in early January 2021, we included time-series data up until December 2020, covering 11 months. This is longer than most other time series studies on air pollution and COVID-19, but is still rather short. By adding an interaction term (month, day of week and municipality), we adjusted for short-term temporal variation caused by, e.g., seasonal effects and measures to prevent the virus spread, which is an improvement compared to many other time series studies on the acute effects of air pollution on COVID-19. In addition, we could adjust for governmental public health measures and took into account autocorrelation. With this we addressed for at least some part the complex temporal (inverse) relationship between a high number of COVID-19 cases followed by government restrictions that could affect air pollution levels.

As urban and rural environments may have different sources of air pollution, and differ in population density, mobility patterns, socio-economic status, lifestyle and diet, and as there may also be other virus transmission patterns playing a role (Matz et al., 2015), we stratified our analyses per province and degree of urbanization. Our findings were in general consistent across regions, but associations were strongest in the western provinces, "Noord- and Zuid-Holland" as well as in the regions situated in the south-eastern part of the Netherlands ("Noord-Brabant, Gelderland and Limburg"). However, also in other regions air pollution might affect COVID-19-related outcomes. In general, peaks in exposure and the number of severe COVID-19-cases were lower in some regions, which makes it more difficult to detect a significant association in areas with lower air pollution and number of cases. Overall, across most provinces in the Netherlands, associations were positive (RR > 1), indicating that air pollution may affect COVID-19 related hospitalization and mortality across the country.

Associations between air pollution exposure and increased mortality and morbidity risk had been shown in regions with generally higher air pollution concentrations, but in recent years these associations were also reported in areas with low air pollution concentrations (Brauer, 2019; Brunekreef, 2021; Dominici, 2022). A systematic review that was conducted to revise the WHO air quality guidelines, found an increase in all-cause mortality of 0.65% per 10 μg/m^3 PM2.5, 0.41% per 10 μg/m^3 PM10 and 0.72% per 10 μg/m^3 NO_2 (Orellano, 2020). These effects on all-cause mortality are much smaller than the effects we found of air pollution on COVID-19 mortality, *i.e.*, 22% per 10 μg/m^3 PM2.5 and 15% per 10 μg/m^3 PM10 and NO_2, and other studies that investigate short-term exposure effects of air pollution on COVID-19-related mortality. This suggests that the population at risk of being hospitalized or dying of COVID-19 (people infected with COVID-19 with e.g. respiratory or cardiovascular illness or dysregulated immune system) is extra vulnerable to the adverse effects of short-term air pollution exposure.

Several mechanisms are proposed to explain the associations between air pollution and COVID-19–related outcomes. Air pollution may increase COVID-19 morbidity and mortality, through the association with linked comorbidities such as respiratory and cardiovascular diseases (Thurston, et al., 2017). In addition, air pollution might lead to a more severe course of COVID-19, by affecting the immune system and airway inflammation by modifying host susceptibility to infection and/or disease severity through overexpression of the receptor for SARS-CoV-2, the angiotensin converting enzyme 2 (ACE2), damaged airway epithelium, reduced ability of macrophages to phagocytize or inactivate viruses, and oxidative stress (Woodby et al., 2021). In some early studies performed during the beginning of the pandemic, it was suggested that the SARS-CoV-2 infection could be spread by air pollution through transportation of the virus by the attachment to PM. This is however not confirmed by later studies and reviews (Hernandez Carballo et al., 2022).

Also increased associations were found for subjects living close to livestock farms and several health effects, such as increased pneumonia (Lotterman et al., 2023; Post et al., 2019), lower lung function (Smit & Heederik, 2017), increased COPD exacerbation (Borlée et al., 2015), Q fever (Smit et al., 2012) and respiratory mortality (Simões et al., 2022). An ecological study by Cole and colleagues (Cole et al., 2020) found associations between ambient air pollution levels in the Netherlands and SARS-CoV-2 incidence, hospital admissions and deaths and suggested that intensive livestock farming might at least partly explain the positive relationships due to increased PM levels as a result of the emission of ammonia (NH_3), that contributes to increased PM levels by formation of secondary inorganic aerosols. A study by Hogerwerf and colleagues suggests that living near livestock farms (< 1000 m) increase SARS-CoV-2 infections in individuals in the period 2020-2021, also after analyses were stratified by age group, geographical area and time period (Hogerwerf et al., 2022). However, we did not have information on source-specific contribution to daily PM, so this should be explored further. Our sensitivity analyses demonstrated that although the associations between short-term exposure to particulate matter and the risk of COVID-19 mortality were, together with the associations in the western part of the Netherlands, the strongest in the regions situated in the south-eastern part of the Netherlands, with a high density of intensive livestock farming, the most robust associations were found in urban areas and not in rural areas. For hospital admissions, the degree of urbanization did not play a major role except for rural areas, where the association disappeared. Altogether, the results of our study do not support our initial hypothesis that inhabitants of rural areas are at greater risk. Other characteristics, such as differences in socio-economic status, population age, population density or mobility patterns might be

interesting effect modifiers to be investigated in future studies.

Our study has several strengths and limitations. A strength of our study was that air pollution and health outcome information was available at a fine scale, a municipality, reducing potential measurement error. Also, this made it possible to account for health effects in areas with relatively low exposure, and to differentiate health effects by different degrees of urbanization. Another major strength of this study is that information was available on government policies that were taken to limit the spread of COVID-19, and that we could adjust for these measures by using the CHI in our models. Third, using the three-way interaction method (month, day of week, municipality) allows us to adjust for all spatiotemporal confounders, known or not, available or not, which vary differently over time among municipalities. Finally, as an additional step, to be on the conservative side, we included an autocorrelation term to take into account the infectious disease dynamics as the number of cases is directly dependent on the number of cases in the recent past.

A limitation of our study is that we could not explore the potential role of individual-level information on lifestyle factors, such as smoking, and co-morbidities as effect modifiers in the relationship between short-term variation in air pollution and COVID-19 mortality or hospital admissions. Our hypothesis was that increased air pollution levels might trigger an exacerbation of the health status of already infected individuals, and therefore we focus on an one-week moving average exposure window. Also an exposure lag of 0-14 days was tested. In addition an exposure lag of 0-21 days was considered, which allow us to take into account the effect of air pollution on the SARS-CoV-2 infection incidence, but we decided that the interpretation of these models would be too complex and did not include this. Especially in the first months of the pandemic, testing policy and testing capacity for new COVID-19 cases was not standardized and inconsistent. Because of that, we decided not to investigate SARS-CoV-2 infection incidence as an additional outcome variable. Furthermore, although we consider government policy to prevent the spread of COVID-19 by using the CHI, this indicator records only number and degree of government policies, and no information was available on the level of compliance and how well the policies are implemented or enforced (Hale et al., 2021). Finally, time series should preferably include daily data from multiple years to account for long-term trends, while we could only include daily data over 11 months.

Conclusion

Our results suggest that short-term exposure to PM2.5 and PM10 may increase the risk of COVID-19 mortality and hospital admission. This indicates that, consistent with previous studies on air pollution and respiratory infections, the population at risk of being hospitalized or dying of COVID-19 is extra vulnerable to the adverse effects of short-term air pollution exposure.

Recommendations

The results of our study provides additional support for the need to reduce air pollution emissions in order to enhance air quality levels. This results not only in an improvement of the long-term health of populations but also to reduce the immediate impacts on respiratory health and vulnerability to respiratory infections like COVID-19.

Ethics and data statement

Statistics Netherlands (CBS) is mandated to collect administrative data on Dutch residents and enterprises for the production of official statistics by law. Under the Statistics Netherlands Act, CBS can grant access to data for research purposes, with the aim of optimizing the value of collected data. Only authorized researchers can access data within CBS' secured online environment, using a remote-access facility, so that maximum control over intended uses, privacy and information security is guaranteed. Within this framework, the linked and anonymized data sets were made available to the researchers of this study for analysis. Dutch Civil Code allows the use of health records for statistics or research in the field of public health. No informed consent from patients nor approval by a medical ethics committee is required for registry-based health studies of this type in the Netherlands: the Medical Ethical Review Committee of Utrecht University Medical Centre (NedMec) confirmed that the Dutch Scientific Research Involving Human Subjects Act (WMO) does not apply to this study (nr. 22/059). The present study fully complied with EU General Data Protection Regulation (2016/679) and all methods were carried out in accordance with the Declaration of Helsinki. Results of this study are based on calculations by the authors using non-public microdata from CBS. Under certain conditions, these microdata are accessible for statistical and scientific research. For further information: microdata@cbs.nl.

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CRediT authorship contribution statement

José H. Jacobs: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Maciej Strak:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Guus J.M. Velders:** Writing – review & editing, Data curation. **Jelle Zorn:** Writing – review & editing, Investigation, Data curation. **Lenny Hogerwerf:** Writing – review & editing, Investigation, Conceptualization. **Mariana Simões:** Writing – review & editing, Investigation. **Suzanne Mijnen-Visser:** Writing – review & editing, Data curation. **Joost Wesseling:** Writing – review & editing, Data curation. **Miriam E. Gerlofs-Nijland:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization. **Lidwien A.M. Smit:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization. **Roel Vermeulen:** Writing – review & editing, Project administration, Investigation, Conceptualization. **Saskia van der Zee:** Writing – review & editing. **Lapo Mughini-Gras:** Writing – review & editing, Supervision, Project administration, Investigation, Funding acquisition, Conceptualization. **Massimo Stafoggia:** Writing – review & editing, Supervision, Methodology.

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.

Data availability

The data that has been used is confidential.

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Supplementary materials

Supplementary material associated with this article can be found, in

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