Environmental Research 252 (2024) 118812

Contents lists available at ScienceDirect

Environmental Research

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

Effects of long-term exposure to outdoor air pollution on COVID-19 incidence: A population-based cohort study accounting for SARS-CoV-2 exposure levels in the Netherlands

Jelle Zorn [a], Mariana Simões [b], Guus J.M. Velders [a,e], Miriam Gerlofs-Nijland [a], Maciek Strak [a], José Jacobs [a], Marieke B.A. Dijkema [c], Thomas J. Hagenaars [d], Lidwien A.M. Smit [b], Roel Vermeulen [b], Lapo Mughini-Gras [a,b,*], Lenny Hogerwerf [a,1], Don Klinkenberg [a,1]

[a] National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands
[b] Institute for Risk Assessment Sciences (IRAS), Faculty of Veterinary Medicine, Utrecht University, Utrecht, the Netherlands
[c] Environment and Health in Overijssel and Gelderland, Public Health Services Gelderland-Midden, the Netherlands
[d] Wageningen Bioveterinary Research, Lelystad, the Netherlands
[e] Institute for Marine and Atmospheric Research (IMAU), Utrecht University, Utrecht, the Netherlands

ARTICLE INFO

Keywords:
COVID-19
SARS-CoV-2
PM10
PM2.5
NO2
Force of infection

ABSTRACT

Several studies have linked air pollution to COVID-19 morbidity and severity. However, these studies do not account for exposure levels to SARS-CoV-2, nor for different sources of air pollution. We analyzed individual-level data for 8.3 million adults in the Netherlands to assess associations between long-term exposure to ambient air pollution and SARS-CoV-2 infection (i.e., positive test) and COVID-19 hospitalisation risks, accounting for spatiotemporal variation in SARS-CoV-2 exposure levels during the first two major epidemic waves (February 2020–February 2021). We estimated average annual concentrations of PM_{10}, $PM_{2.5}$ and NO_2 at residential addresses, overall and by PM source (road traffic, industry, livestock, other agricultural sources, foreign sources, other Dutch sources), at 1 × 1 km resolution, and weekly SARS-CoV-2 exposure at municipal level. Using generalized additive models, we performed interval-censored survival analyses to assess associations between individuals' average exposure to PM_{10}, $PM_{2.5}$ and NO_2 in the three years before the pandemic (2017–2019) and COVID-19-outcomes, adjusting for SARS-CoV-2 exposure, individual and area-specific confounders. In single-pollutant models, per interquartile (IQR) increase in exposure, PM_{10} was associated with 7% increased infection risk and 16% increased hospitalisation risk, $PM_{2.5}$ with 8% increased infection risk and 18% increased hospitalisation risk, and NO_2 with 3% increased infection risk and 11% increased hospitalisation risk. Bi-pollutant models suggested that effects were mainly driven by PM. Associations for PM were confirmed when stratifying by urbanization degree, epidemic wave and testing policy. All emission sources of PM, except industry, showed adverse effects on both outcomes. Livestock showed the most detrimental effects per unit exposure, whereas road traffic affected severity (hospitalisation) more than infection risk. This study shows that long-term exposure to air pollution increases both SARS-CoV-2 infection and COVID-19 hospitalisation risks, even after controlling for SARS-CoV-2 exposure levels, and that PM may have differential effects on these COVID-19 outcomes depending on the emission source.

1. Introduction

Outdoor air pollution is a major cause of morbidity and mortality worldwide, accounting for an estimated 4.2 million deaths every year, primarily from cardiovascular and respiratory diseases, including respiratory infections (WHO. WHO Global Air Quality Guidelines, 2021; Sheridan et al., 2022). Since the beginning of the Coronavirus Disease 2019 (COVID-19) pandemic caused by the Severe Acute Respiratory

* Corresponding author. National Institute for Public Health and the Environment (RIVM), Centre for Infectious Disease Control (CIb), Antonie van Leeuwenhoeklaan 9, 3721MA Bilthoven, Utrecht, the Netherlands.
E-mail address: lapo.mughini.gras@rivm.nl (L. Mughini-Gras).
[1] These authors contributed equally to the work.

https://doi.org/10.1016/j.envres.2024.118812
Received 4 February 2024; Received in revised form 25 March 2024; Accepted 26 March 2024
Available online 30 March 2024

Syndrome Coronavirus 2 (SARS-CoV-2), several studies worldwide have linked outdoor air pollution to COVID-19 morbidity and mortality.

The earliest studies were based on ecological study designs that involve aggregate, population-level data, e.g. (Zang et al., 2022; Ali et al., 2021; Marquès and Domingo, 2022), which are notoriously prone to bias (Heederik et al., 2020). More recently, a growing number of studies have examined the association between long-term exposure to air pollution and COVID-19 morbidity and mortality using individual-level data in a cohort design (Bozack et al., 2022; Li et al., 2022; Marquès et al., 2022; Hyman et al., 2023; Bowe et al., 2021; Mendy et al., 2021; Chen et al., 2022a, 2022b; English et al., 2022; Ranzani et al., 2023; Zhang et al., 2023). While these studies are a significant improvement compared to earlier work, they also have their limitations. First, to date, most studies used selected samples instead of country-wide, population-based datasets. Second, and more importantly, risk models have commonly treated air pollution as a main effect without explicitly accounting for dynamics of local virus exposure in the statistical model. If air pollution increases susceptibility, more polluted areas will also see more infections, which themselves cause higher virus exposure, thereby creating a positive feedback loop with disproportionally more cases in those areas. By not accounting explicitly for virus exposure in the statistical model, the effect of virus exposure might be absorbed by the effect of air pollution, thus overestimating the actual effect on individual susceptibility (Heederik et al., 2020). Additionally, taking into account the spatially resolved contributions of different sources of air pollutant emission (e.g., livestock, road traffic, industrial activities, etc.) may help clarify the potential role of those different contributions. This is particularly relevant for particulate matter (PM) with diameter <10 μm (PM_{10}) and <2.5 μm ($PM_{2.5}$), as they may have different compositions depending on their sources.

In the Netherlands, at the beginning of the pandemic, higher COVID-19 morbidity and mortality were observed in areas that also happened to be those with poor air quality largely attributable to emissions from livestock farming. High morbidity and mortality were subsequently observed in other (non-agricultural) areas where air quality was also poor, including in more densely populated parts of the country where higher air pollution from traffic and industry can be found (Hogerwerf et al., 2022).

In this study, we examined associations between long-term exposure to overall ambient air pollution concentrations of PM_{10}, $PM_{2.5}$ and NO_2, at the residential address and both SARS-CoV-2 infection (i.e., positive PCR test) and COVID-19 hospitalisation risks in the Netherlands, using comprehensive nationwide individual-level data and accounting explicitly for spatiotemporal variation in SARS-CoV-2 exposure. We also examined the role of different sources of PM (e.g., livestock, road traffic, industrial activities, etc.) to help clarify the potential role of those different contributions.

2. Methods

2.1. Study population

The study population was selected from the Dutch municipal basis registration of population data. This registration system, known as the Personal Records Database (BRP), is compiled by Statistics Netherlands (CBS) and contains personal demographic records of all residents in the Netherlands (Prins, 2017). From the BRP, we selected all adults (≥18 years of age) on 1 January 2020 who did not change residential address since 1 January 2017, as long-term exposure to air pollution considered here focused on the three years before the start of the COVID-19 pandemic. From this population, we further excluded 1) health workers and people living in institutions (e.g., mental health institutions and nursing homes) due to their different risk of viral exposure and eligibility for testing as compared to the general population, 2) people who lived within 1 km from the borders of the Netherlands with Belgium and Germany (for which air pollution exposure and source attribution could not be accurately estimated), and 3) people with missing information for one or more of the study variables. Further exclusions were specific to the different analyses performed (see Fig. 1).

2.2. Health data

Health data for the period between 1 February 2020 and 31 January 2021, covering the first two major COVID-19 periods in the Netherlands, was included. After this period, vaccination started for the study population and novel SARS-CoV-2 variants became dominant, which complicated estimation of virus exposure (see section 2.6.3) and interpretation of analyses.

2.2.1. Infection data

In June 2020, public testing facilities for SARS-CoV-2 infection were opened in the 25 Public Health Services of the Netherlands. Test-confirmed SARS-CoV-2 infection was mandatorily notifiable in the country, and when such confirmation was made in a public testing facility, it was registered in a centralized database named 'CoronIT'. This database contains individual-level patient information on all test results from all public testing facilities of the country. The policy on which part of the population was eligible to public testing evolved over time. On 1 June 2020, everyone with COVID-19-compatible symptoms (i.e., runny nose, cough, shortness of breath or difficulty breathing, fever, loss of taste or smell) and >12 years of age was eligible for testing. Subsequently, on 1 December 2020, testing was extended to people without symptoms in the context of source and contact tracing, and on 1 January 2021 to children <12 years of age, and by mid-January 2021 to travelers returning from abroad after quarantine. Over the course of the pandemic, part of the testing took place outside the public test facilities. These tests are not included in the CoronIT database. This includes tests from the period before 1 June 2020, when a restricted test policy was in place with testing being limited to severely ill patients and health workers, and tests from later during the epidemic when testing in health care institutions (hospitals, residential care homes, medical practices etc.) was extended to vulnerable people and regular screening practices and commercial test facilities emerged (for testing in the context of work, travelling, access to venues, etc.). Results from these tests are included in another database and were not available in the secure environment (except for the hospitalisation data, see below). For this study, we selected data for all positive SARS-CoV-2 tests from the CoronIT database for the period between 1 June 2020 and 31 January 2021. In case a person had multiple positive tests, only the first one was retained as some people can repeatedly test positive for SARS-CoV-2 months after infection.

2.2.2. Hospital admission data

Data on hospital admission was obtained from the Dutch National Hospital Care Basic Registration. This database is managed by the DHD (Dutch Hospital Data) foundation and contains information on all hospital admissions. At the time of analysis, only data for the year 2020 was available. We selected patients admitted to the hospital with COVID-19 as main diagnosis. For the main analyses, only subjects with confirmed COVID-19 (ICD-10 code U07.1) were included. In sensitivity analyses, subjects with suspected COVID-19 (ICD-10 code U07.2) were also included. In case a patient had multiple admissions, only the first admission was retained. From the beginning of the epidemic onwards, it was common policy to perform SARS-CoV-2 testing on hospitalized cases with suspected COVID-19. However, some patients could still be registered as suspected COVID-19 cases for a variety of reasons, including test refusal, failed test results, or early patient death. Strategies for handling COVID-19 and regulating capacity and patient distribution across all Dutch hospitals were set by a national coordination team. COVID-19 hospital admission was based on the principle of medical benefit, weighted against factors such as the possibility of home treatment and the need to alleviate pressure on hospitals. In practice,

Fig. 1. Flow chart of the criteria applied to select the study populations.
Exclusions applied to obtain the study population for the main analyses on hospitalisation and infection. [1]Only full ISO-weeks were included in the virus exposure modelling, hence these subjects were excluded to match the virus exposure modelling. Not shown in the flowchart are a small number of individuals who were excluded because their infection dates were backsampled to a moment before the infection or hospitalisation study intervals (n = 502 and n = 3, respectively).

this meant that elderly people and mild cases were often treated at home or in residential care institutions.

For both outcomes, analyses were first performed on all health data (1 June 2020–31 January 2021 for infection and 1 February 2020–31 December 2020 for hospitalisation). To check for consistency of effects, analyses were then performed on subsets of the data. For infection, analyses were restricted to the period in which only symptomatic people were allowed to test (1 June 2020–30 November 2020). For hospitalisation, analyses were performed separately for the 1st (1 February 2020–31 May 2020) and 2nd COVID-19 period (1 June 2020–31

December 2020), or "wave".

2.3. Air pollution data

The methods used to estimate long-term exposure to PM_{10}, $PM_{2.5}$ and NO_2 concentrations are described in detail elsewhere (Velders et al., 2017, 2020; Velders and Diederen, 2009; Hoogerbrugge et al., 2021). In brief, 1 × 1 km maps representing the annual average background concentrations were generated from emissions (as reported to the Netherlands Pollutant Release and Transfer Register (Wever et al., 2020) and the EMEP-database (Hoogerbrugge et al., 2021; Projections ECoEIa, 2023)) and their dispersion, transport, chemical conversion and deposition were modelled using the Operational Priority Substances (OPS) dispersion model, taking into account meteorological conditions (van Jaarsveld and de Leeuw, 1993; Sauter et al.). Total PM_{10} and $PM_{2.5}$ concentrations represent the sum of the contributions from primary PM emissions, secondary aerosols, and sea salt, calibrated against measurements from 35 to 45 background locations in the Netherlands. The spatially resolved contribution of several emission source-categories to the total concentrations was calculated separately as different compositions of particulate matter due to its origin may pose a different health impact. Here, we broke down the emission sources into 6 main categories: industry, livestock farming, other agricultural activities, road traffic, foreign sources (i.e., outside the Netherlands), and other Dutch sources (miscellaneous) (Velders et al., 2017). NO_2 concentrations were calculated from the OPS-modelled NO_x concentration and an empirical relationship between annual average measured NO_x and NO_2 concentrations (Velders et al., 2014; van de Kassteele and Velders, 2006). As NO_2 is the same molecule regardless of the source, source contributions were not calculated. For each home address in the study population, we derived the estimated annual averages for the years 2017–2019 for the total and source-specific concentrations of PM_{10}, $PM_{2.5}$ and NO_2 from the maps; average concentrations over the three years were used as the exposure variables in our analyses.

2.4. Confounders

2.4.1. Individual variables

We adjusted for the following variables at the individual level: sex, age, migration background, household size, and socio-economic status. Information on sex (male/female), age (years on 1st of January 2020), migration background (as defined by CBS: autochthonous Dutch, Moroccan, Turkish, Surinamese, Former Dutch Antilles and Aruba, other non-Western countries, and other Western countries) and household size (number of people in household in 2020) was extracted from the BRP. Information on highest attained educational level (primary and lower secondary education, higher and senior secondary education and pre-university education, higher professional and university education, and unknown educational level) and household wealth (operationalized as the difference between a household's assets and liabilities based on tax registration data and categorized into percentiles ranging from 1 [1% households with lowest wealth] to 100 [1% households with highest wealth]), was available from CBS and used as a proxy for socio-economic status.

2.4.2. Spatial variables

This study included variables at the municipal, district and neighbourhood level (see this section and section 2.6.1 and 2.6.5). At the end of 2020, the Netherlands counted 352 municipalities (median population: 31,376 (interquartile range (IQR): 21,907–49,962); median land area: 798 km^2 (IQR: 365-1382 km^2)), 3248 districts (median population: 3125 (IQR: 975-7229); median land area: 62 km^2 (IQR: 18–145 km^2)) and 14,080 neighbourhoods (median population: 690 (IQR: 175-1695), median land area: 5.7 km^2 (IQR: 2.6–20.2 km^2)). Information on socioeconomic status (SES) of the neighbourhood was used as overall proxy for local conditions that may influence behaviour (e.g., compliance with COVID-19 measures, test propensity). Socioeconomic scores for private households (SES-WOA) were used to describe the SES of neighbourhoods. The SES-WOA (Arts et al., 2021), was developed by CBS and is a composite measure based on financial welfare, level of education and recent employment status of households. The most recent scores for the year 2019 were used. Data on urbanisation degree of the residence location for the year 2020 was obtained from CBS and based on 500 × 500 m grid. Urbanisation degree was categorized as: extremely urbanised (≥2500 addresses/km^2), strongly urbanised (1500–2499 addresses/km^2), moderately urbanised (1000–1499 addresses/km^2), hardly urbanised (500-999 addresses/km^2) to not urbanised (<500 addresses/km^2). For this study, rural regions and urban regions were classified as addresses with an urbanisation degree of <1500 addresses/km^2 and≥1500 addresses/km^2), respectively. Urbanisation degree was used to stratify the study population into rural and urban populations in the analyses.

2.5. Data privacy regime

Data was analyzed in a secure computational environment provided by CBS where researchers had access to pseudo-anonymized datasets at the individual level. Each individual was given a personal Record Identification Number (RIN) used to link the different datasets with one another. Air pollution and virus exposure variables (see below) were calculated outside of the secure environment and linked to a general address code (BAG), which was then pseudo-anonymized by CBS and linked to the study subjects.

2.6. Statistical analyses

2.6.1. The infection model

We modelled the time to infection (or in case of hospitalisation, time to infection followed by hospitalisation) with an interval-censored survival model with time intervals of one week (Hosmer and Lemeshow, 1999; Suresh et al., 2022). The weekly hazard is equal to the force of infection, as known in infectious disease models, defined as the probability (per week) by which a susceptible person is infected, which can itself be defined as the product of the contact rate (how many contacts do people make per week), the prevalence of infectious people among those contacts (what proportion of contacts is made with infectious persons), and the infection probability per contact (see Fig. 2). As a proxy for the risk of being exposed to infectious people, we chose to estimate and utilize the prevalence of infectious people at the municipal level, as this was assumed to be the level where individuals had most of their contacts during the study phase of the pandemic.

For an individual with covariates $\mathbf{X}$ (air pollution levels, confounders and spatial random effects) in municipality L, the force of infection in week T is

$$\lambda(T,\mathbf{X},L) = c(T)I_L(T)p(\mathbf{X}) = v_L(T)p(\mathbf{X})$$

In $\lambda(T,\mathbf{X},L)$, the covariates $\mathbf{X}$ are fixed in time and associated (proportional hazards) with the infection probability per contact $p(\mathbf{X})$, whereas the contact rate $c(T)$ and prevalence $I_L(T)$ in municipality L are different in each week T. The product of contact rate and prevalence will be referred to as the virus exposure $V_L(T)$, which was estimated from incidence data (see Fig. 2 and below).

2.6.2. The regression model

In the survival model, all individuals i in the dataset start as susceptible, which means that they are at risk of infection each week until they become infected or are right-censored (in case of death or when reaching the end of the study period) in week T_i ($T_i = \infty$ for those that did not get infected during the observation period). These observations were turned into records for a regression analysis, with a binomial response Y denoting escape or infection, virus exposure V, and

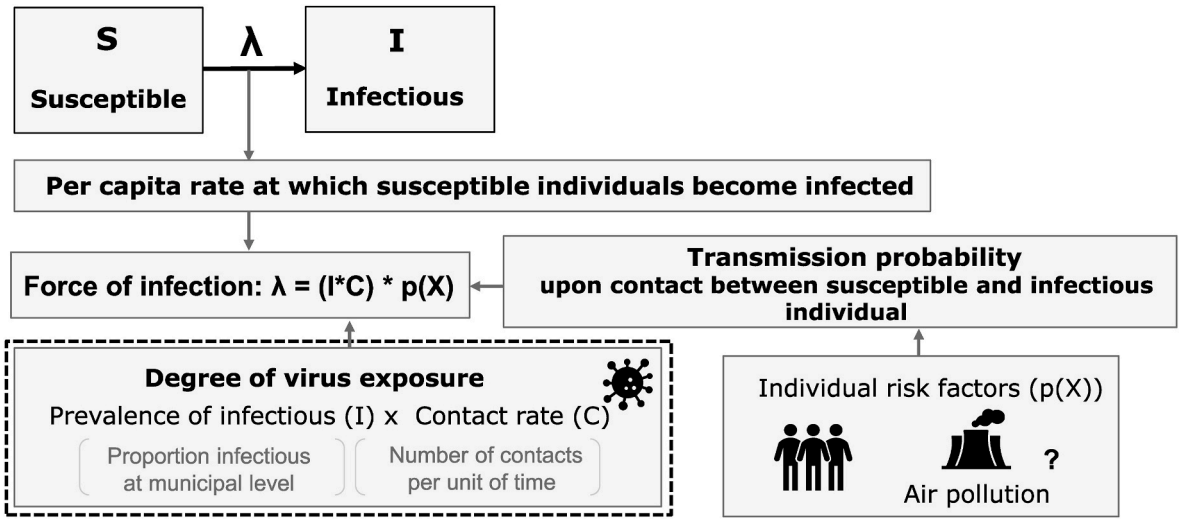

Fig. 2. Conceptual analysis framework of individual virus exposure modelling.
Overview of the conceptual analysis framework underlying the virus exposure modelling. The framework used is based on the so-called SIR infectious disease model, in which individuals in the population are divided into compartments based on their infection status (Susceptible, Infectious, Removed). In the stochastic SIR model the movement of individuals between compartments is described by rates. The (per capita) rate (probability per unit of time, or hazard) at which Susceptible (S) individuals become infected (I), is known as the (per-capita) force of infection (λ) and can be expressed as λ = (I*C) *p(X). Here, (I*C) represents the degree of virus exposure, which is determined by two factors: the contact rate (C) (the number of contacts that individuals make, per unit of time) and the prevalence of infectious (I) (the proportion of contacts with infectious people, per unit of time), whereas p(X), represents the transmission probability (chance of infection given contact between a susceptible and infectious individual). The force of infection is thus determined by two factors, the degree of virus exposure (number of infectious contacts) and the transmission probability (probability of infection per infectious contact). The latter is dependent on individual risk factors (X) determining an individual's susceptibility. The analysis can thus be interpreted as a survival model where the force of infection acts as the hazard rate and infection or hospitalisation is the response. It follows that if the degree of virus exposure is known, it becomes possible to estimate hazard ratios for potential individual risk factors including air pollution. Accordingly, for this work, the degree of virus exposure was reconstructed in space (per municipality) and time (per week) based on hospitalisation incidence data, using the reproduction number (Rt) as proxy for the contact rate. From this, individual virus exposure was then estimated and included as offset variable in generalized additive regression models allowing estimation of the unknown hazard ratios for the individual risk factors (see methods).

explanatory variables **X** (as described in (Hosmer and Lemeshow, 1999; Suresh et al., 2022)). Two records were made for individuals who became infected, one record for individuals who escaped infection or were right-censored:

- For all individuals, with V equal to the cumulative virus exposure until infection or censoring, a record with: $Y = 0$, $\mathbf{X} = \mathbf{X}_i$, $V = \sum_{T<T_i} \nu_{L_i}(T)$.
- For individuals who became infected, with V equal to the virus exposure in the week of infection, a record with: $Y = 1$, $\mathbf{X} = \mathbf{X}_i$, $V = \nu_{L_i}(T_i)$.

The expected response for each record is equal to the probability of infection (1 minus the probability of escaping infection from the cumulative force of infection)

$$E(Y) = 1 - \exp(-V \cdot p(\mathbf{X})),$$

which can be fitted with a generalized additive model (GAM), with binomially distributed response Y, a complementary log-log link function, and log(V) as offset (Hosmer and Lemeshow, 1999; Suresh et al., 2022). Essentially, this is equivalent to a Cox model for time-to-event data on a weekly resolution, with all confounders and locations (for the random spatial intercepts) in **X**, and virus exposure in V.

2.6.3. Virus exposure modelling

In the regression model, we used log(V) as offset, where V denotes the cumulative virus exposure in the time interval and location of the corresponding record as explained in the section above. Virus exposure $\nu_L(T)$ in week T and location L was modelled as the product of the contact rate $c(T)$ and the prevalence of infectious people $I_L(T)$. The contact rate $c(T)$ was assumed to be proportional to the mean reproduction number $R(T)$ in week T, divided by the proportion of the population still susceptible $s(T)$. We assumed $R(T)$ to be spatially uniform across the Netherlands. Calculation of $R(T)$, $s(T)$, and $I_L(T)$ was done with daily hospitalisations registered by NICE (National Intensive Care Evaluation), as during the COVID-19 epidemic in the Netherlands. Briefly, age-stratified daily hospitalisations were inflated to an underlying incidence of infections by an age-dependent infection-hospitalisation ratio (estimated from seroprevalence data), then distributed across municipalities weighed by local incidence and population size, and sampled back in time to the day of symptom onset. The resulting daily incidence was used to estimate weekly reproduction number $R(T)$ (Wallinga and Teunis, 2004), to calculate cumulative incidence and thus the proportion of the population still susceptible $s(T)$, and prevalence by municipality $I_L(T)$ by assuming an infectious period from two days before until five days after symptom onset (see Supplementary Material for detail).

2.6.4. Generalized additive models (GAM)

GAMs were run to assess the association between exposure to air pollution and risk of SARS-CoV-2 infection (i.e. positive SARS-CoV-2 test at a community test centre) and COVID-19 hospitalisation. The GAM is an expansion of the traditional general linear model that allows the relationship between the explanatory and response variables to be described by smooth functions. We employed penalized cubic splines, a smoothing method requiring a relatively large number of knots, which causes the model to be relatively insensitive to the choice of the knot locations. Overfitting by the number of knots is prevented through the implementation of a roughness penalty, which controls the 'wiggliness' of the smooth through an automatic smoothing parameter selection procedure (Wood, 2002). We included air pollution with linear terms in the regression equation, while other predictors were included with linear or non-linear terms (see section 2.6.5).

2.6.5. Main analyses

To examine overall effects, all analyses were first performed at the national level. Since the degree of urbanisation can influence air pollution concentrations and composition of the different PM fractions, and there are important differences in lifestyle factors and other exposures between rural and urban populations for which full control is difficult using demographic variables alone, analyses were also stratified by rural and urban areas. For analyses on total exposure, both single-pollutant and multi-pollutant models (including either PM_{10} or $PM_{2.5}$ plus NO_2) were built. For emission source analyses, all sources of PM_{10} or all sources of $PM_{2.5}$, except other agricultural sources, were included in the same models. The contribution from other agricultural sources was excluded from the source models due to high collinearity with livestock sources and low absolute concentrations with low variation. The following variables were always included for adjustment: age (penalized spline with 20 degrees of freedom), sex (categorical, male/female), household wealth (penalized spline with 20 degrees of freedom), household size (categorical, 1, 2, 3, 4 $\geq$ 5), migration background (categorical, see 2.4.1). All models also included a random intercept at district-level to correct for area-specific confounders. The latter was done to account for small-scale unobserved heterogeneity (e.g., local differences in test propensity, SES, frailty etc.). Generalized variance inflation factor (GVIF >3) was used to assess multicollinearity. All risk estimates were expressed as hazard ratios (HR) and 95% confidence intervals (95% CI) per 1 $\mu g/m^3$ increase in exposure. Risk estimates at national level were also expressed per interquartile range (IQR), as this measure also incorporates the range of each exposure magnitude in the country. Statistical significance was set at p-value <0.05, but given the relatively high number of tests, the Benjamini-Hochberg method was applied to identify significant associations accounting for false discovery rate.

2.6.6. Sensitivity analyses

Sensitivity analyses were performed for the single-pollutant models and analyses on emission source contributions. The following general sensitivity analyses were performed for all models: 1) inclusion of highest educational attainment as a covariate as an important indicator of socio-economic status. Educational attainment was missing for about 45% of the study population, mainly for older people, hence it was not included in the main analyses, 2) inclusion of neighbourhood-level SES as covariate, which was missing for about 2% of the population, 3) assessment of the effects at the extremes of the urbanisation gradient by restricting the analyses to the most rural areas (0-999 addresses/km^2) and to the most urbanised areas ($\geq$2500 addresses/km^2). This was done to examine the robustness of the urbanisation stratification used in the main analyses and to further assess potential effects of different PM compositions linked to different urbanisation levels, 4) analyses of the effect of five-year long-term exposure (2015–2019), to examine the robustness of the exposure period used in the main analyses. In addition, some specific sensitivity analyses were done for part of the models: a) for the source contribution analyses, an additional sensitivity analysis involved including other agricultural sources instead of livestock sources in the models, b) for the hospitalisation outcome, analyses were performed in which cases with suspected COVID-19 were also included, c) for the hospitalisation outcome, analyses were performed separately for the 1st and 2nd COVID-19 period, d) for the infection outcome, analyses were restricted to the period in which only symptomatic people were allowed to test, e) to aid interpretation of results (to rule out possible residual seeding effects), a post-hoc analysis was performed on hospitalisation data, restricting analyses to the first COVID-19 period and stratifying analyses by two high density livestock provinces in the Southeast of the Netherlands (Brabant and Limburg) vs. the rest of the Netherlands.

2.6.7. Software

Data management and analysis was carried out in R version 4.1.3 within the remote environment of CBS. Estimation of parameters was performed via restricted maximum likelihood (REML) with the R package mgcv (Wood, 2017).

3. Results

3.1. Descriptive statistics

The study populations for the main analyses on infections (June 2020–January 2021) and hospitalisations (February 2020–December 2020) consisted of 8,299,321 and 8,357,159 persons, respectively (Fig. 1, full descriptives in Tables 1A and 1B). There were 367,250 infections (4.3%) and 22,919 hospitalized cases (0.3%) in total. Study population characteristics are provided in Table 1. Overall, the proportion of infections was higher among men, younger individuals, larger households, household with higher wealth and people with a non-Western migration background. The proportion of hospitalisations was higher among men, older individuals, smaller households, households with lower wealth and people with a non-Western migration background. These patterns were observed in both rural and urban areas.

Fig. S1 shows how incident cases of SARS-CoV-2 infection and COVID-19 hospitalisation were spatially distributed across the Netherlands for the different study periods. Figs. S2–4 show the spatial distribution of PM_{10}, $PM_{2.5}$ and NO_2 air pollution exposures in the three years before the COVID-19 pandemic, overall and by emission source. Note that the Netherlands has no major geographical features causing large meteorological differences. The Netherlands is a densely populated country, and also has the largest livestock density in Europe (Freidl et al., 2017), due to widespread intensive farming, which is mainly situated in the Southeastern parts of the country. Moreover, because of its relatively small territorial extension and immediacy with Germany and Belgium, air pollution concentrations from foreign sources also tend to be high, especially in the most south east parts of the country. NO_2 concentrations are highest in the more densely populated western parts of the country where higher pollution from traffic and industry can also be found. Table S1 shows the correlations between total individual PM_{10}, $PM_{2.5}$ and NO_2 exposure concentrations at the residential address. Correlations between PM_{10}, $PM_{2.5}$ and NO_2 were relatively high: above 0.9 between PM_{10}, $PM_{2.5}$ and about 0.8 between the different PM fractions and NO_2. Table S2 shows the correlations between source-specific exposure concentrations for PM_{10} and $PM_{2.5}$ at the residential address. Correlations between different source exposures were generally lower (>0.7), with the exception of road traffic and other Dutch sources. Exposure to road traffic and other Dutch sources were also highly correlated with total NO_2 exposure (>0.7).

In both single- and multi-pollutant models, all confounders (including sex, age, household size, household wealth, migration background) were significantly associated with COVID-19 outcomes (see Table S3).

3.2. Effects of exposure to total concentrations of PM_{10}, $PM_{2.5}$ and NO_2

3.2.1. Infection risk

As shown in Table 2A, in single-pollutant models, there were significant positive associations between an individual's average residential exposure to PM_{10}, $PM_{2.5}$ and NO_2 in the three years before the pandemic and risk of SARS-CoV-2 infection. At national level, per IQR increase in exposure, PM_{10} was associated with 7% increased infection risk (HR: 1.072, 95% CI: 1.061, 1.083), $PM_{2.5}$ with 8% increased risk (HR: 1.081, 95% CI: 1.070, 1.091), and NO_2 with 3 % increased risk (HR: 1.027, 95% CI: 1.016, 1.039). Effects for PM_{10} and $PM_{2.5}$ were confirmed at both rural and urban levels. Effects for NO_2 were confirmed at the rural but not urban level, which showed an inverse effect. In bi-pollutant models, positive associations for PM_{10} and $PM_{2.5}$ persisted when adjusting for NO_2 (HR: 1.100, 95% CI: 1.086, 1.116 and HR: 1.117, 95%CI: 1.103, 1.132 at national level, respectively). Conversely,

Table 1 A
Descriptive statistics of the study population for the analyses on SARS-CoV-2 infection, at national level and stratified by rural and urban areas.

	National level		Rural level		Urban level	
Characteristic	*Baseline cohort*	*Cases*	*Baseline cohort*	*Cases*	*Baseline cohort*	*Cases*
N	8299321	367250	4343239	186695	3956082	180555
Women **[n (%)]**	3894130 (46.9)	169525 (46.2)	1983253 (45.7)	82774 (44.3)	1910877 (48.3)	86751 (48.0)
Age **[median (IQR)]**	55.11 (17.62)	49.36 (16.66)	55.65 (17.44)	50.02 (16.72)	54.52 (17.80)	48.67 (16.56)
Household wealth **[median (IQR)]**	56.90 (27.96)	59.53 (26.92)	61.74 (26.36)	65.45 (24.59)	51.59 (28.70)	53.40 (27.83)
Household size [n (%)]						
1 person	1725447 (20.8)	41770 (11.4)	692966 (16.0)	15463 (8.3)	1032481 (26.1)	26307 (14.6)
2 persons	3246853 (39.1)	112197 (30.6)	1794416 (41.3)	58850 (31.5)	1452437 (36.7)	53347 (29.5)
3 persons	1254071 (15.1)	68082 (18.5)	674918 (15.5)	34688 (18.6)	579153 (14.6)	33394 (18.5)
4 persons	1412531 (17.0)	92443 (25.2)	808715 (18.6)	50711 (27.2)	603816 (15.3)	41732 (23.1)
≥5 persons	660419 (8.0)	52758 (14.4)	372224 (8.6)	26983 (14.5)	288195 (7.3)	25775 (14.3)
Migration background [n (%)]						
Autochtonous	6562514 (79.1)	270180 (73.6)	3813279 (87.8)	162583 (87.1)	2749235 (69.5)	107597 (59.6)
Moroccan	171579 (2.1)	17057 (4.6)	27209 (0.6)	2373 (1.3)	144370 (3.6)	14684 (8.1)
Turkish	200759 (2.4)	20838 (5.7)	37076 (0.9)	3575 (1.9)	163683 (4.1)	17263 (9.6)
Surinamese	172584 (2.1)	10824 (2.9)	32171 (0.7)	1841 (1.0)	140413 (3.5)	8983 (5.0)
Former Dutch Antilles and Aruba	57997 (0.7)	2993 (0.8)	12849 (0.3)	601 (0.3)	45148 (1.1)	2392 (1.3)
Other non-Western countries	338361 (4.1)	17816 (4.9)	92198 (2.1)	4390 (2.4)	246163 (6.2)	13426 (7.4)
Western countries	795527 (9.6)	27542 (7.5)	328457 (7.6)	11332 (6.1)	467070 (11.8)	16210 (9.0)
Urbanisation degree **[n (%)]**						
Extremely urbanised	1824341 (22.0)	85763 (23.4)	na	na	1824341 (46.1)	85763 (47.5)
Strongly urbanised	2131741 (25.7)	94792 (25.8)	na	na	2131741 (53.9)	94792 (52.5)
Moderately urbanised	1463675 (17.6)	64448 (17.5)	1463675 (33.7)	64448 (34.5)	na	na
Hardly urbanised	1443758 (17.4)	62980 (17.1)	1443758 (33.2)	62980 (33.7)	na	na
Not urbanised	1435806 (17.3)	59267 (16.1)	1435806 (33.1)	59267 (31.7)	na	na
Average air pollution concentration 2017–2019 (μg/m^3) **[median (IQR)]**						
PM_{10}						
Total	18.40 [1.87]	18.57 [1.67]	17.75 [2.03]	17.99 [1.81]	19.03 [1.28]	19.08 [1.12]
Foreign	6.61 [1.66]	6.67 [1.58]	6.88 [1.84]	7.02 [1.78]	6.46 [1.16]	6.48 [1.05]
Industry	0.76 [0.26]	0.77 [0.25]	0.69 [0.24]	0.70 [0.22]	0.83 [0.26]	0.85 [0.27]
Agriculture, livestock	0.65 [0.44]	0.66 [0.45]	0.75 [0.52]	0.81 [0.56]	0.61 [0.37]	0.61 [0.35]
Agriculture, other	0.13 [0.03]	0.13 [0.02]	0.13 [0.04]	0.13 [0.104]	0.13 [0.01]	0.13 [0.01]
Road traffic	1.15 [0.59]	1.19 [0.57	0.93 [0.57]	0.98 [0.53]	1.30 [0.43]	1.33 [0.4]
Other Dutch sources	2.27 [1.26]	2.36 [1.25]	1.79 [0.91]	1.86 [0.89]	2.86 [0.98]	2.94 [0.94]
$PM_{2.5}$						
Total	11.07 [1.35]	11.18 [1.16]	10.65 [1.82]	10.82 [1.47]	11.41 [1.03]	11.46 [0.97]
Foreign	5.54 [1.37]	5.59 [1.28]	5.74 [1.5]	5.84 [1.45]	5.43 [0.95]	5.45 [0.88]
Industry	0.54 [0.16]	0.55 [0.15]	0.49 [0.17]	0.50 [0.14]	0.58 [0.14]	0.59 [0.15]
Agriculture, livestock	0.55 [0.28]	0.56 [0.27]	0.58 [0.33]	0.60 [0.33]	0.53 [0.22]	0.54 [0.2]
Agriculture, other	0.10 [0.02]	0.10 [0.01]	0.09 [0.02]	0.09 [0.03]	0.10 [0.01]	0.10 [0.01]
Road traffic	0.83 [0.42]	0.86 [0.39]	0.68 [0.42]	0.71 [0.39]	0.93 [0.29]	0.95 [0.26]
Other Dutch sources	1.90 [1.02]	1.97 [1.01]	1.51 [0.77]	1.56 [0.74]	2.37 [0.77]	2.44 [0.73]
NO_2						
Total	17.87 [6.07]	18.27 [6]	16.18 [4.81]	16.51 [4.32]	20.66 [5.73]	21.21 [5.76]

n/a = not applicable.
Extremely urbanised: ≥2500 addresses/km^2; Strongly urbanised: 1500–2499 addresses/km^2; Moderately urbanised: 1000–1499 addresses/km^2; Hardly urbanised: 500-999 addresses/km^2, Not urbanised: <500 addresses/km.^{2}.

after adjusting for either PM_{10} or $PM_{2.5}$, associations between NO_2 and infection reversed or remained negative (HR: 0.960, 95% CI: 0.947,0.974 and HR: 0.948, 95% CI: 0.934, 0.962, at national level, respectively).

3.2.2. Hospitalisation risk

As shown in Table 2B, in single-pollutant models, there were significant positive associations between long-term exposure to PM_{10}, $PM_{2.5}$ and NO_2 and COVID-19 hospitalisation risk. At national level, per IQR increase in exposure, PM_{10} was associated with 16% increased hospitalisation risk (HR: 1.162, 95% CI: 1.135, 1.190), $PM_{2.5}$ with 18% increased risk (HR: 1.175, 95% CI: 1.149, 1.202), and NO_2 with 11% increased risk (HR: 1.112, 95% CI: 1.084, 1.140). Effects were confirmed at both rural and urban levels. In bi-pollutant models, positive associations for PM_{10}, $PM_{2.5}$ persisted when adjusting for NO_2 (HR: 1.202, 95% CI: 1.59, 1.247 and HR: 1.234, 95% CI: 1.94, 1.275 at national level, respectively). Conversely, after adjusting for either PM_{10} and $PM_{2.5}$, the association between NO_2 and hospitalisation disappeared/faded or reversed (HR: 0.954, 95% CI: 0.917, 0.992 and HR: 0.928, 95% CI: 0.894, 0.964, at national level, respectively).

3.3. Effects of PM_{10} and $PM_{2.5}$ exposure by emission source

Analyses on source contributions showed significant positive effects of PM_{10} and $PM_{2.5}$ on both SARS-CoV-2 infection and COVID-19 hospitalisation, in line with the results of the main analyses. At national level, exposures from all sources, except industry, were positively associated with SARS-CoV-2 infection and COVID-19 hospitalisation risks (Table 3).

3.3.1. Infection risk per source

Results on infection risk are presented in Table 3A. At national level, per IQR increase in exposure, PM_{10} from foreign sources was associated with 11% increased infection risk (HR: 1.105, 95% CI: 1.089, 1.121, IQR: 1.66 μg/m^3), from other Dutch sources with 5% increased risk (HR: 1.050, 95% CI: 1.034, 1.066, IQR: 1.26 μg/m^3) and from livestock and road traffic with 2% increased risk (HR: 1.022, 95% CI: 1.015, 1.029, IQR: 0.44 μg/m^3 and HR: 1.017, 95% CI: 1.004, 1.031, IQR: 0.59 μg/m^3, respectively). For $PM_{2.5}$, exposure to emissions from foreign sources was associated with 10% increased risk (HR: 1.104, 95% CI: 1.088, 1.120, IQR: 1.36 μg/m^3), and from livestock and other Dutch sources with 5% increased risk (HR: 1.052, 95% CI: 1.037, 1.066, IQR: 0.28 μg/m^3 and

Table 1 B
Descriptive statistics of the study population for the analyses on COVID-19 hospitalisation, at national level and stratified by rural and urban areas.

Characteristic	National level		Rural level		Urban level	
	Baseline cohort	*Cases*	*Baseline cohort*	*Cases*	*Baseline cohort*	*Cases*
N	8357159	22919	4370445	10178	3986714	12741
Women [n (%)]	3918562 (46.9)	8478 (37.0)	1994364 (45.6)	3523 (34.6)	1924198 (48.3)	4955 (38.9)
Age [median (IQR)]	55.22 (17.67)	68.32 (13.19)	55.76 (17.48)	69.12 (12.52)	54.63 (17.85)	67.69 (13.67)
Household wealth [median (IQR)]	56.76 (28.02)	45.75 (28.70)	61.62 (26.42)	53.35 (27.82)	51.44 (28.75)	39.67 (27.93)
Household size [n (%)]						
1 person	1734373 (20.8)	5675 (24.8)	695332 (15.9)	2179 (21.4)	1039041 (26.1)	3496 (27.4)
2 persons	3267773 (39.1)	11477 (50.1)	1803078 (41.3)	5691 (55.9)	1464695 (36.7)	5786 (45.4)
3 persons	1259948 (15.1)	2450 (10.7)	678164 (15.5)	1028 (10.1)	581784 (14.6)	1422 (11.2)
4 persons	1426615 (17.1)	1920 (8.4)	817108 (18.7)	788 (7.7)	609507 (15.3)	1132 (8.9)
> = 5 persons	668450 (8.0)	1397 (6.1)	376763 (8.6)	492 (4.8)	291687 (7.3)	905 (7.1)
Migration background [n (%)]						
Autochtonous	6606143 (79.0)	15644 (68.3)	3836590 (87.8)	8641 (84.9)	2769553 (69.5)	7003 (55.0)
Moroccan	173166 (2.1)	1548 (6.8)	27416 (0.6)	156 (1.5)	145750 (3.7)	1392 (10.9)
Turkish	202171 (2.4)	1384 (6.0)	37286 (0.9)	180 (1.8)	164885 (4.1)	1204 (9.4)
Surinamese	173791 (2.1)	1044 (4.6)	32318 (0.7)	136 (1.3)	141473 (3.5)	908 (7.1)
Former Dutch Antilles and Aruba	58344 (0.7)	193 (0.8)	12922 (0.3)	33 (0.3)	45422 (1.1)	160 (1.3)
Other non-Western countries	340251 (4.1)	989 (4.3)	92582 (2.1)	190 (1.9)	247669 (6.2)	799 (6.3)
Western countries	803293 (9.6)	2117 (9.2)	331331 (7.6)	842 (8.3)	471962 (11.8)	1275 (10.0)
Urbanisation degree [n (%)]						
Extremely urbanised	1839496 (22.0)	6432 (28.1)	na	na	1839496 (46.1)	6432 (51.5)
Strongly urbanised	2147218 (25.7)	6309 (27.5)	na	na	2147218 (53.9)	6309 (49.5)
Moderately urbanised	1473327 (17.6)	3829 (16.7)	1473327 (33.7)	3829 (37.6)	na	na
Hardly urbanised	1452721 (17.4)	3420 (14.9)	1452721 (33.2)	3420 (33.6)	na	na
Not urbanised	1444397 (17.3)	2929 (12.8)	1444397 (33.0)	2929 (28.8)	na	na
Average air pollution concentration 2017–2019 ($\mu g/m^3$) [median (IQR)]						
PM_{10}						
Total	18.40 [1.87]	18.71 [1.57	17.75 [2.03]	18.09 [1.66]	19.03 [1.29]	19.14 [1.13]
Foreign	6.61 [1.66]	6.73 [1.59]	6.88 [1.84]	7.26 [1.82]	6.46 [1.16]	6.54 [1.33]
Industry	0.76 [0.26]	0.78 [0.24]	0.69 [0.24]	0.71 [0.2]	0.83 [0.26]	0.86 [0.27]
Agriculture, livestock	0.65 [0.44]	0.66 [0.45]	0.75 [0.52]	0.85 [0.58]	0.61 [0.37]	0.61 [0.36]
Agriculture, other	0.13 [0.02]	0.13 [0.02]	0.13 [0.04]	0.13 [0.03]	0.13 [0.01]	0.13 [0.01]
Road traffic	1.15 [0.59]	1.22 [0.52]	0.93 [0.57]	1.01 [0.51]	1.30 [0.43]	1.35 [0.38]
Other Dutch sources	2.27 [1.26]	2.42 [1.52]	1.79 [0.91]	1.87 [0.82]	2.86 [0.98]	2.98 [1.06]
$PM_{2.5}$						
Total	11.07 [1.35]	11.30 [1.08]	10.65 [1.82]	10.97 [1.3]	11.41 [1.03]	11.55 [0.95]
Foreign	5.54 [1.36]	5.65 [1.29]	5.74 [1.5]	6.06 [1.46]	5.43 [0.95]	5.50 [1.08]
Industry	0.54 [0.17]	0.55 [0.14]	0.49 [0.17]	0.51 [0.13]	0.58 [0.14]	0.59 [0.15]
Agriculture, livestock	0.55 [0.28]	0.56 [0.28]	0.58 [0.33]	0.62 [0.34]	0.53 [0.22]	0.54 [0.19]
Agriculture, other	0.10 [0.02]	0.10 [0.01]	0.09 [0.02]	0.10 [0.03]	0.10 [0.01]	0.10 [0.01]
Road traffic	0.83 [0.42]	0.88 [0.35]	0.68 [0.42]	0.74 [0.37]	0.93 [0.29]	0.96 [0.25]
Other Dutch sources	1.90 [1.02]	2.03 [1.01]	1.51 [0.77]	1.58 [0.68]	2.37 [0.77]	2.47 [0.8]
NO_2						
Total	17.88 [6.07]	18.90 [16.14]	16.18 [4.80]	16.82 [3.84]	20.67 [5.74]	21.63 [5.91]

n/a = not applicable.
Extremely urbanised: ≥2500 addresses/km^2; Strongly urbanised: 1500–2499 addresses/km^2; Moderately urbanised: 1000–1499 addresses/km^2; Hardly urbanised: 500-999 addresses/km^2, Not urbanised: <500 addresses/km.^{2}.

HR: 1.050, 95% CI: 1.034, 1.066, IQR: 1.02 μg/m^3, respectively). No significant effect was observed for the $PM_{2.5}$-concentration contribution of road traffic. Note that source estimates are not directly comparable to the estimates for total exposure as exposure ranges and compositions may differ (e.g., a source with a relatively small exposure range but large effect may contribute little to the overall estimate when the exposure range of the latter is much larger). When considered on a 1 μg/m3 comparable basis, at national level, the largest significant effect was observed for exposure to livestock $PM_{2.5}$ (HR: 1.197, 95% CI: 1.139, 1.258). At rural level, significant effects of exposure to PM_{10} and $PM_{2.5}$ were only observed for foreign, livestock and other Dutch sources. At urban level, significant effects were only observed for foreign and livestock sources. No significant effects were observed for road traffic, neither at the rural nor urban level.

3.3.2. Hospitalisation risk per source

Results on hospitalisation are presented in Table 3B. At national level, per IQR increase, PM_{10} from foreign sources was associated with 15% increased hospitalisation risk (HR: 1.150, 95% CI: 1.117, 1.184, IQR: 1.66 μg/m^3), from road traffic and other Dutch sources with 8–9% increased risk (HR: 1.076, 95% CI: 1.033, 1.122, 2.26 μg/m^3 and HR: 1.092, 95% CI: 1.050, 1.135, IQR: 0.59 μg/m^3, respectively), and from livestock with 5% increased risk (HR: 1.054, 95% CI: 1.034, 1.074, IQR: 0.44 μg/m^3). For $PM_{2.5}$, exposure to emissions from foreign sources was associated with 16% increased hospitalisation risk (HR: 1.159, 95% CI: 1.127, 1.193, IQR: 1.36 μg/m^3), from livestock with 10% increased risk (HR: 1.095, 95% CI: 1.060, 1.132, IQR: 0.28 μg/m^3), and from road traffic and other Dutch sources with 7–8% increased risk (HR: 1.070, 95% CI: 1.019, 1.124, IQR: 0.42 μg/m^3 and HR: 1.079, 95% CI: 1.033, 1.128, IQR: 1.02 μg/m^3, respectively). When considered on a 1 μg/m^3 comparable basis, at national level, the highest significant HR was again observed for livestock $PM_{2.5}$ (HR: 1.385, CI: 1.233, 1.555), while HRs for road traffic and livestock PM_{10} and road traffic $PM_{2.5}$ were also relatively high. At rural level, significant effects of PM_{10} and $PM_{2.5}$ were again only observed for foreign, livestock and other Dutch sources. At urban level, significant effects of PM_{10} and $PM_{2.5}$ were only observed for foreign and road traffic sources.

3.4. Sensitivity analyses

3.4.1. General sensitivity analyses

Results were generally robust to sensitivity analyses. Sensitivity

Table 2
Hazard ratios (95% confidence intervals) for effects of individual exposure to PM_{10}, $PM_{2.5}$ and NO_2 in the three years before the COVID-19 pandemic, by outcome measure, A) SARS-CoV-2 infection (June 2020–January 2021), B) COVID-19 hospitalisation (February 2020–December 2020).

Air pollutant		HR (95% CI) per IQR increase	HR (95% CI) per 1 μg/m^3 increase		
		National	National	Rural areas	Urban areas
PM_{10}		1.072 [1.061, 1.083] ***	1.038 [1.032, 1.044] ***	1.056 [1.049, 1.064] ***	1.012 [1.003, 1.021] *
PM_{10} adj. NO_2		1.100 [1.086, 1.116] ***	1.053 [1.045, 1.060] ***	1.065 [1.055, 1.075] ***	1.033 [1.021, 1.046] ***
$PM_{2.5}$		1.081 [1.070, 1.091] ***	1.059 [1.052, 1.067] ***	1.086 [1.076, 1.096] ***	1.019 [1.007, 1.031] **
$PM_{2.5}$ adj. NO_2		1.117 [1.103, 1.132] ***	1.086 [1.075, 1.096] ***	1.111 [1.097, 1.125] ***	1.045 [1.029, 1.060] ***
NO_2		1.027 [1.016, 1.039] ***	1.004 [1.003, 1.006] ***	1.010 [1.007, 1.012] ***	0.997 [0.995, 1.000] *
NO_2	adj. PM_{10}	0.960 [0.947, 0.974] ***	0.993 [0.991, 0.996] ***	0.996 [0.992, 0.999] **	0.991 [0.988, 0.994] ***
	adj. $PM_{2.5}$	0.948 [0.934, 0.962] ***	0.991 [0.989, 0.994] ***	0.991 [0.988, 0.994] ***	0.991 [0.988, 0.995] ***
PM_{10}		1.162 [1.135,1.190] ***	1.084 [1.070, 1.098] ***	1.128 [1.109, 1.148] ***	1.045 [1.024, 1.067] ***
PM_{10} adj. NO_2		1.202 [1.159, 1.247] ***	1.104 [1.082, 1.126] ***	1.138 [1.110, 1.167] ***	1.045 [1.014, 1.077] **
$PM_{2.5}$		1.175 [1.149, 1.202] ***	1.127 [1.109, 1.146] ***	1.178 [1.152, 1.204] ***	1.076 [1.047, 1.105] ***
$PM_{2.5}$ adj. NO_2		1.234 [1.194, 1.275] ***	1.169 [1.140, 1.198] ***	1.212 [1.174, 1.251] ***	1.089 [1.049, 1.131] ***
NO_2		1.112 [1.084, 1.140] ***	1.018 [1.013, 1.022] ***	1.031 [1.024, 1.037] ***	1.009 [1.003, 1.016] **
NO_2	adj. PM_{10}	0.954 [0.917, 0.992] *	0.992 [0.986, 0.999] *	0.996 [0.986, 1.005]	1.000 [0.991, 1.009]
	adj. $PM_{2.5}$	0.928 [0.894, 0.964] ***	0.988 [0.982, 0.994] ***	0.988 [0.979, 0.988] *	0.996 [0.988, 1.004]

adj. = Adjusted for. HR = Hazard Ratio. 95% CI = 95% Confidence Interval. Significance levels: * <0.036; ** <0.01; *** <0.001. The value of 0.036 for the first significance level was determined from the applied Benjamini-Hochberg procedure for multiple-hypothesis testing correction.

analyses did not change the results of the analyses on total exposure to PM_{10}, $PM_{2.5}$ and NO_2, except when restricting urban level analyses to the urbanisation extremes (loss of significance, Figs. S5–6). The same was true for results by source of air pollution (Figs. S7–8). Furthermore, like most other sources, other agricultural sources showed significant positive associations with the infection and hospitalisation outcomes (Table S4).

3.4.2. Other sensitivity analyses

For exposure to total concentrations of PM_{10}, $PM_{2.5}$ and NO_2, no major differences compared to the main results were observed when including only symptomatic people for infection as outcome. The same was true when analyses on hospitalisation were performed separately for the 1st and 2nd COVID-19 period (see Table S5 for descriptives and Table S6 for results). For analyses by emission source (Table S7), some differences compared to the main results were observed. When analyses

Table 3
Hazard ratios (and 95% confidence interval) for effects of individual exposure to emission source contributions of PM_{10} and $PM_{2.5}$ in the three years before the pandemic, by outcome measure. A) SARS-CoV-2 infection (June 2020–January 2021), B) COVID-19 hospitalisation (February 2020–December 2020).

Air pollutant	Source	HR (95% CI) per IQR increase	HR (95% CI) per 1 μg/m^3 increase		
		National	National	Rural areas	Urban areas
PM_{10}	*Foreign sources*	1.105 [1.089, 1.121] ***	1.062 [1.052, 1.071] ***	1.076 [1.065, 1.087] ***	1.011 [0.997, 1.025]
	Industry	1.000 [0.995, 1.006]	1.001 [0.982, 1.021]	0.989 [0.961, 1.018]	0.987 [0.960, 1.015]
	Livestock	1.022 [1.015, 1.029] ***	1.050 [1.035, 1.066] ***	1.038 [1.021, 1.055] ***	1.138 [1.087, 1.191] ***
	Road traffic	1.017 [1.004, 1.031] **	1.029 [1.007, 1.052] **	1.011 [0.980, 1.043]	0.998 [0.966, 1.031]
	Other Dutch sources	1.050 [1.034, 1.066] ***	1.040 [1.027, 1.052] ***	1.111 [1.087, 1.135] ***	1.009 [0.993, 1.025]
$PM_{2.5}$	*Foreign sources*	1.104 [1.088, 1.120] ***	1.075 [1.064, 1.087] ***	1.092 [1.079, 1.106] ***	1.021 [1.005, 1.038] **
	Industry	0.999 [0.993, 1.005]	0.992 [0.957, 1.029]	0.981 [0.930, 1.035]	0.955 [0.908, 1.004]
	Livestock	1.052 [1.037, 1.066] ***	1.197 [1.139, 1.258] ***	1.155 [1.089, 1.225] ***	1.234 [1.128, 1.351] ***
	Road traffic	1.007 [0.991, 1.023]	1.017 [0.980, 1.056]	0.974 [0.923, 1.028]	1.003 [0.949, 1.061]
	Other Dutch sources	1.050 [1.034, 1.066] ***	1.049 [1.034, 1.065] ***	1.142 [1.111, 1.174] ***	1.006 [0.985, 1.027]
PM_{10}	*Foreign sources*	1.150 [1.117, 1.184] ***	1.087 [1.068, 1.107] ***	1.117 [1.092, 1.142] ***	1.047 [1.019, 1.077] **
	Industry	1.008 [0.992, 1.024]	1.030 [0.970, 1.095]	0.988 [0.894, 1.091]	1.015 [0.941, 1.095]
	Livestock	1.054 [1.034, 1.074] ***	1.126 [1.079, 1.175] ***	1.122 [1.068, 1.179] ***	1.097 [0.998, 1.206]
	Road traffic	1.092 [1.050, 1.135] ***	1.160 [1.086, 1.239] ***	1.100 [0.996, 1.214]	1.161 [1.058, 1.275] **
	Other Dutch sources	1.076 [1.033, 1.122] ***	1.060 [1.026, 1.096] ***	1.211 [1.130, 1.299] ***	1.014 [0.972, 1.058]
$PM_{2.5}$	*Foreign sources*	1.159 [1.127, 1.193] ***	1.114 [1.091, 1.138] ***	1.148 [1.118, 1.179] ***	1.065 [1.031, 1.100] ***
	Industry	1.004 [0.986, 1.022]	1.026 [0.917, 1.148]	0.954 [0.790, 1.151]	0.997 [0.866, 1.148]
	Livestock	1.095 [1.060, 1.132] ***	1.385 [1.233, 1.555] ***	1.462 [1.260, 1.696] ***	1.194 [0.992, 1.437]
	Road traffic	1.070 [1.019, 1.124] **	1.176 [1.046, 1.321] **	0.998 [0.836, 1.190]	1.287 [1.096, 1.511] **
	Other Dutch sources	1.079 [1.033, 1.128] ***	1.078 [1.033, 1.126] ***	1.290 [1.177, 1.415] ***	1.003 [0.949, 1.061]

HR = Hazard Ratio. 95% CI = 95% Confidence Interval. adj. = Adjusted for. HR = Hazard Ratio. 95% CI = 95% Confidence Interval. Significance levels: * <0.036; ** <0.01; *** <0.001. The value of 0.036 for the first significance level was determined from the applied Benjamini-Hochberg procedure for multiple-hypothesis testing correction.

of infections by emission source were restricted to the period in which only symptomatic people were allowed to test, exposures to road traffic PM_{10} and $PM_{2.5}$ became positively associated with infection at both national and urban levels. Furthermore, associations for $PM_{2.5}$ exposure from foreign sources at urban level and livestock sources at rural level were no longer significant. For analyses on hospitalisation by emission source, significant effects of PM_{10} and $PM_{2.5}$ exposure from livestock farming were only observed for the 1st but not 2nd COVID-19 period and for other Dutch sources only the 2nd but not the 1st.

To rule out that the effects of livestock emissions on hospitalisation observed for the 1st but not 2nd wave were merely driven by seeding events taking place coincidentally in the most livestock-rich parts of the country, further analyses were restricted to the provinces of Brabant and Limburg in the Southeastern parts of the Netherlands that formed the initial hotspots of COVID-19 spread in the country (see Fig. S1 (Hogerwerf et al., 2022),). Results were then compared to those for the rest of the Netherlands. For the 1st wave, effects of livestock PM_{10} and $PM_{2.5}$ were observed throughout the country, both in the provinces of Brabant and Limburg and the rest of the country, with effects being similar in size (Table S8).

4. Discussion

This study assessed whether long-term exposure to ambient air pollution concentrations of PM_{10}, $PM_{2.5}$ and NO_2 in the years before the pandemic was associated with increased risk of SARS-CoV-2 infection and COVID-19 hospitalisation in the Netherlands, before vaccination campaigns started, and while explicitly accounting for SARS-CoV-2 exposure levels to control for varying magnitudes of viral circulation in space and time. This was done to minimize bias in the estimates of air pollution. Overall, we found significant positive associations for all pollutants with both infection and hospitalisation outcomes, which were stronger and more robust for PM than for NO_2, of which the effects reversed in bi-pollutant models. Due to the high correlation between pollutants, these models need to be interpreted with caution, although they do support a more important role of PM than NO_2 in the investigated risks. Analyses by emission source revealed that all sources of PM but industry contributed significantly to increased risks at population level, with livestock and road traffic showing the strongest effects per unit increase in exposure.

Our results for the effect of long-term air pollution exposure on infection are generally consistent with the previous literature. A Danish nation-wide population-based cohort study (n = 3,721,810) by Zhang et al. (2023), observed strong effects for the associations between long-term exposure to PM_{10}, $PM_{2.5}$ and NO_2 and infections with HRs of 1.09 (95% CI, 1.06, 1.12) per IQR 1.14 $\mu g/m^3$ increase, 1.10 (95% CI, 1.05, 1.14) per IQR 0.54 $\mu g/m^3$ increase, and 1.18 (95% CI, 1.14, 1.23) per IQR 3.6 $\mu g/m^3$ increase, respectively. In contrast, a population-based cohort study with a selected sample from the UK Biobank (n = 424,721) by Sheridan et al. (2022), reported smaller estimates for $PM_{2.5}$ and NO_2 with odds ratios of 1.05 (95% CI, 1.02, 1.08) per IQR 1.27 $\mu g/m^3$ increase, and 1.05 (95% CI, 1.01, 1.08) per IQR 9.93 $\mu g/m^3$ increase, respectively, but did not find evidence for an association with PM_{10}. Although direct comparison with other studies is not straightforward due to differences in exposure, confounder adjustment, modelling framework and outcome definition, estimates for $PM_{2.5}$ and NO_2 of the latter study are more similar to estimates in this study ($PM_{2.5}$, HR: 1.06, 95% CI 1.05, 1.07; NO_2, HR: 1.004, 95% CI 1.003, 1.006, per 1 $\mu g/m^3$ increase), and ecological studies on COVID-19 incidence (English et al., 2022; Veronesi et al., 2022).

Estimates for the effect of long-term air pollution exposure on hospitalisation are less consistent across previous studies. In Denmark, Zhang et al. (2023), observed strong effects for the effect of PM_{10}, $PM_{2.5}$ and NO_2 on hospitalisations, with HRs of 1.14 (95% CI, 1.07, 1.20) per IQR 1.14 $\mu g/m^3$ increase, 1.10 (95% CI, 1.05, 1.14) per IQR 0.54 $\mu g/m^3$ increase, and 1.18 (95% CI, 1.01, 1.08) per IQR 3.6 $\mu g/m^3$ increase, respectively. With UK biobank data, Sheridan et al. (2022), did not find evidence for associations of PM_{10}, $PM_{2.5}$ and NO_2 with hospitalisations, possibly because of a lack of power due to small sample size. A third population-based cohort-study (n = 4,660,502) from Catalonia, Spain, by Ranzani et al. (2023), reported associations between $PM_{2.5}$ and NO_2 and hospitalisations with HRs of 1.19 (95% CI, 1.16,1.21), per IQR 3.2 $\mu g/m^3$ increase, and 1.25 (95% CI, 1.16, 1.21), per IQR 16.1 $\mu g/m^3$ increase, respectively. Our estimates were smaller in magnitude than reported by Zhang et al. (2023), but larger than reported by Ranzani et al. (2023) ($PM_{2.5}$, 1.13, 95% CI, 1.12, 1.15; NO_2, 1.018, 1.013, 1.022, per 1 $\mu g/m^3$ increase). It is further worth mentioning that our study corroborates the results of the only other Dutch study that investigated the effect of long-term air pollution on COVID-19. This ecological study (Cole et al., 2020), reported risks estimates for $PM_{2.5}$, the equivalent of a 7–11% increase in infections and a 9–13% increase in hospitalisations per 1 $\mu g/m^3$ increase (compared to 6 and 13% in this study, respectively).

Regarding NO_2, we observed negative associations when stratifying by urban and rural regions, or when adjusting for PM in bi-pollutant models. This is in contrast to other comparable studies, which observed positive associations for NO_2 which persisted in bi-pollutant models. Compared to PM, NO_2 exhibits higher spatial contrast within small areas, with sharp gradients around roads and other pollution sources (Velders and Diederen, 2009). This small-scale variation, in combination with the 1 × 1 km resolution air quality data used in this study, may have produced exposure misclassification which could explain part of the unexpected results. Alternatively, the reversal of effects in bi-pollutant models may also be due to the high correlation between PM and NO_2 observed in this study (>0.8).

In addition to the analyses on overall exposure, we examined whether exposures from different emission sources of PM, because of different PM compositions, have potentially different health effects. Of 6 pre-defined source categories (road traffic, industry, agriculture livestock, agriculture other, foreign and other Dutch sources), we found exposures from all sources but industry to be positively associated with both infection and hospitalisation outcomes. Associations at national level were largely confirmed at either the urban or rural level. Overall, associations showed a largely similar pattern across infection and hospitalisation outcomes, with some notable exceptions. Specifically, for infection, road traffic was only associated with PM_{10} at national level, and not with $PM_{2.5}$ or with PM_{10} at urban or rural level, although associations became stronger and significant in sensitivity analyses when restricting to the period in which only symptomatic people were allowed to test. The effects for the other two source categories with highest contribution, foreign and other Dutch sources, are not easily interpretable, as these source categories encompass a mix of sources (all sources other than agriculture, industry and road traffic for other Dutch sources and all sources for foreign sources). Therefore, they merely act as background concentrations against which the effects of the more specific sources should be interpreted.

While the contribution of livestock and road traffic per IQR is not particularly large, their health effect per unit exposure is much larger. We found particularly potent effects of livestock $PM_{2.5}$ on both infection risk (HR: 1.197, 95% CI: 1.139, 1.258) and hospitalisation risk (HR: 1.385, 95% CI: 1.233, 1.555), while HRs for hospitalisation risk were also relatively high for road traffic and livestock PM_{10} and road traffic $PM_{2.5}$. The effects for livestock are in line with several other studies that showed that living near livestock farms influences human respiratory health and immunological responses (Hogerwerf et al., 2022; Freidl et al., 2017; Smit et al., 2012; Simoes et al., 2022; Post et al., 2021; Klous et al., 2018; Kalkowska et al., 2018). The proposed hypotheses about the underlying biological mechanisms include hypersensitization towards livestock-borne PM, including PM contaminated with microbes and endotoxins, or bioPM, which would trigger innate immune responses contributing to respiratory disease (Diamond and Kanneganti, 2022; Sahlander et al., 2012; Poole and Romberger, 2012; Liu et al., 2019).

However, more research is needed to corroborate whether and how these hypotheses would also apply to COVID-19. The large effect of road traffic on hospitalisation and not infection suggests a role in severity of disease rather than susceptibility to infection. This is further suggested by the fact that, for infection, significant effects for road traffic (at national and urban but not rural level) were only observed when analyses were restricted to the period in which only symptomatic people were allowed to test. This effect should be interpreted with caution, however, as other aspects may have differed between periods and asymptomatic people may still have tested against directions (e.g., after an infectious contact). Therefore, this effect should be confirmed by directly comparing symptomatic and non-symptomatic cases or with a test-negative design, which was beyond the scope of this study.

In the Netherlands, the initial hotspots of COVID-19 appeared in the Southeastern provinces of the country, which overlapped with the country's main livestock-rich areas, which we recognised as a risk for finding incorrect associations between infection or hospitalisation and exposure to livestock-associated pollutants. We addressed this risk by correcting for virus exposure in our regression model, but still, in sensitivity analyses, we observed a distinct pattern for hospitalizations in which associations for livestock where only observed for the first but not second COVID-19 period. Therefore, we carried out additional sensitivity analyses with only cases during the first epidemic period in provinces outside the original hotspot, which showed that the effect of livestock sources on hospitalisations remained the same. The observed differences in emission source contributions between the first and second wave confirms an earlier study on proximity of livestock farms and COVID-19 risk in the Netherlands (Hogerwerf et al., 2022). The difference might be due to seasonal effects, e.g., by ammonia emissions from manure spread on fields, which mainly took place in the first epidemic period), but this is still unclear. This also illustrates the difficulty in discriminating between long- and short-term effects. Although we studied associations with a long-term air pollution exposure index, it cannot be ruled out that some of the associations we found were driven by short-term effects, particularly when analyses were performed by subperiod.

Our study results corroborate a larger literature, showing that air pollution impacts COVID-19 outcomes. Notwithstanding these findings, it should be emphasized that person-to-person transmission remains the driving force behind the COVID-19 pandemic. This is also evidenced by the fact that hazard ratios for other risk factors included in the analyses, including migration background and household size, were an order of magnitude larger than those for air pollution (with HRs up to 2–3). In addition to affecting COVID-19 spread, these risk factors, may have also directly affected COVID-19 outcomes.

This study had some limitations, which depended on the data and analyses in question. For instance, infection data suffered from potential testing bias due to varying testing policy and propensity. Public testing was performed on a voluntary basis, and test propensity was likely influenced by individual factors such as age and SES among others. We therefore performed analyses controlling for these and other factors to the extend allowed by our data availability. In addition to controlling for individual characteristics, we included local random intercepts, as a way of accounting for small-scale unobserved heterogeneities. This should be able to control for local differences in test propensity related to factors that were not explicitly controlled for in the models, such as an individual's distance to the nearest test facility. Related to this issue, we observed clear demographic differences between infection and hospitalisation outcomes and rural and urban populations. This indicates the presence of health-seeking and testing bias, which we attempted to control for by correcting for individual characteristics. Nevertheless, it cannot be ruled out that this explains some of the differences in the observed effects, for example between rural and urban populations. Furthermore, due to restrictive test policies during the first phase of the epidemic, many infections went unnoticed in that period. This may be problematic if these cases were mostly those at higher risk from air pollution exposure, as these cases may have incorrectly ended up as controls in subsequent analyses, because of conferred immunity. However, serological data, suggest that about 4.5% of the Dutch population got infected during the first wave (Vos et al., 2021), which should limit this bias. Another limitation is that people with a positive SARS-CoV-2 test acquired outside community test centres were excluded from the infection analyses for the reason that, during the study period, those people were mostly tested in the context of severe disease. As we were able to observe all hospitalizations but only part of all SARS-CoV-2 infections (due to asymptomatic infections and not all people testing), including those people, would have resulted in an overestimation of the effect of infection in case of an additional effect on severity. Conversely, not including those people, might have resulted in a small underestimation of infection effects, but allowed us to look with specificity at the effect of infection. A further limitation is that we lacked symptom data. For the largest part of our study period, symptomatic infection was required for testing. Hence, our infection estimates mainly apply to symptomatic disease as opposed to asymptomatic infections. However, given the lack of symptom data, we could not specifically estimate associations for symptomatic or asymptomatic SARS-CoV-2 infections. We also lacked specific data on comorbidities. However, other individual-level studies that included adjustment for comorbidities found only small changes in effect estimates (English et al., 2022; Ranzani et al., 2023; Nobile et al., 2022). Moreover, our study included adjustment for several other factors known to be associated with poor health outcomes, lifestyles and behaviors (e.g., age, SES, income, migration background, occupation, etc.), as well as viral transmission. Finally, we focused here on linear effects, but exploring potential non-effects would add another layer of complexity and represents a natural step forward in this research.

A strength of this study is that it is the first of its kind to incorporate infectious disease models to reconstruct the spatiotemporal dynamics of SARS-CoV-2 spread, so that analyses could account explicitly for varying infection pressure during the study period. This allowed us to discern whether air pollution had significant effects on COVID-19 susceptibility and severity without the risk of overestimating those effects resulting from a positive feedback caused by increased virus circulation in more polluted areas. Since person-to-person transmission of SARS-CoV-2 is the driving force behind the COVID-19 pandemic, this could shed new lights on observed associations (Heederik et al., 2020). Other population-based cohort studies that did not explicitly model virus exposure, but instead controlled for spatiotemporal components by other means (e.g., use of daily timescales in Cox models, area-wise adjustment or stratification, control for test positive proportion or control measures) (Ranzani et al., 2023; Zhang et al., 2023), reached largely similar conclusions. Nevertheless, our estimates tend to fall on the lower end of the spectrum, especially for the infection outcome measure, which could be due to the virus exposure term. The virus exposure modelling required us to make several basic assumptions that were partially constrained by limited data availability. Our main consideration was to have the best possible spatiotemporal resolution that was still supported by sufficient underlying data. The choice to model virus exposure by week and municipality was the best possible compromise in this matter. Moreover, hospitalisation data was considered the most suitable for the virus exposure modelling, since this data source was not prone to test bias and the chance of COVID-19 hospitalisation was assumed to be relatively constant for the duration of the study period.

5. Conclusions

In conclusion, this study confirmed previous observations that there are significant adverse effects of long-term exposure to outdoor air pollution on both SARS-CoV-2 infection and COVID-19 hospitalisation risks. All emission sources of PM, except industry, showed adverse effects on both outcomes, with significance varying mainly according to urbanicity. Livestock showed the most detrimental health effects per

unit exposure, whereas road traffic seemed to affect severity (hospitalisation) more than infection. The outcomes of this study stress the importance of improving air quality in Europe. Moving toward the WHO air quality guidelines would improve health generally and reduce the impact of severe acute respiratory infections.

Funding

This study was supported by the Dutch Ministry of Public Health, Welfare and Sport (VWS), Dutch Ministry of Agriculture, Nature and Food Quality (LNV), and Dutch Ministry of Infrastructure and Water Management (IenW).

Ethics and data statement

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.

CRediT authorship contribution statement

Jelle Zorn: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Mariana Simões:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Guus J.M. Velders:** Writing – review & editing, Data curation. **Miriam Gerlofs-Nijland:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization. **Maciek Strak:** Writing – review & editing, Investigation, Data curation. **José Jacobs:** Writing – review & editing, Investigation, Data curation. **Marieke B.A. Dijkema:** Writing – review & editing, Investigation. **Thomas J. Hagenaars:** Writing – review & editing, Methodology, Conceptualization. **Lidwien A.M. Smit:** Writing – review & editing, Investigation, Conceptualization. **Roel Vermeulen:** Writing – review & editing, Project administration, Investigation, Conceptualization. **Lapo Mughini-Gras:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Investigation, Funding acquisition, Conceptualization. **Lenny Hogerwerf:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Don Klinkenberg:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis.

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.

Acknowledgements

The authors would like to thank Erik Lebret, Francesco Forastiere, Neil Pearce, and Samuel Alizon for advice and critical review of this study and Jan van de Kassteele and Maarten Schipper for their statistical help. We also acknowledge the use of the Dutch National supercomputer Snellius in running the analyses.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2024.118812.

References

Ali, N., Fariha, K.A., Islam, F., Mishu, M.A., Mohanto, N.C., Hosen, M.J., Hossain, K., 2021. Exposure to air pollution and COVID-19 severity: a review of current insights, management and challenges. Integrated Environ. Assess. Manag. 17 (6), 1114–1122.
Arts, K., van Gaalen, R., van der Laan, J., et al., 2021. Berekenwijze Sociaal Economische Status Scores.
Bowe, B., Xie, Y., Gibson, A.K., Cai, M., van Donkelaar, A., Martin, R.V., et al., 2021. Ambient fine particulate matter air pollution and the risk of hospitalization among COVID-19 positive individuals: cohort study. Environ. Int. 154, 106564.
Bozack, A., Pierre, S., DeFelice, N., Colicino, E., Jack, D., Chillrud, S.N., et al., 2022. Long-term air pollution exposure and COVID-19 mortality: a patient-level analysis from New York city. Am. J. Respir. Crit. Care Med. 205 (6), 651–662.
Chen, C., Wang, J., Kwong, J., Kim, J., van Donkelaar, A., Martin, R.V., et al., 2022a. Association between long-term exposure to ambient air pollution and COVID-19 severity: a prospective cohort study. CMAJ (Can. Med. Assoc. J.) 194 (20), E693–e700.
Chen, Z., Sidell, M.A., Huang, B.Z., Chow, T., Eckel, S.P., Martinez, M.P., et al., 2022b. Ambient air pollutant exposures and COVID-19 severity and mortality in a cohort of patients with COVID-19 in southern California. Am. J. Respir. Crit. Care Med. 206 (4), 440–448.
Cole, M.A., Ozgen, C., Strobl, E., 2020. Air pollution exposure and Covid-19 in Dutch municipalities. Environ. Resour. Econ. 76 (4), 581–610.
Diamond, M.S., Kanneganti, T.D., 2022. Innate immunity: the first line of defense against SARS-CoV-2. Nat. Immunol. 23 (2), 165–176.
English, P.B., Von Behren, J., Balmes, J.R., Boscardin, J., Carpenter, C., Goldberg, D.E., et al., 2022. Association between long-term exposure to particulate air pollution with SARS-CoV-2 infections and COVID-19 deaths in California, U.S.A. Environ Adv 9, 100270.
Freidl, G.S., Spruijt, I.T., Borlee, F., Smit, L.A., van Gageldonk-Lafeber, A.B., Heederik, D. J., et al., 2017. Livestock-associated risk factors for pneumonia in an area of intensive animal farming in the Netherlands. PLoS One 12 (3), e0174796.
Heederik, D.J.J., Smit, L.A.M., Vermeulen, R.C.H., 2020. Go slow to go fast: a plea for sustained scientific rigour in air pollution research during the COVID-19 pandemic. Eur. Respir. J. 56 (1).
Hogerwerf, L., Post, P.M., Bom, B., van der Hoek, W., van de Kassteele, J., Stemerding, A. M., et al., 2022. Proximity to livestock farms and COVID-19 in the Netherlands, 2020-2021. Int. J. Hyg Environ. Health 245, 114022.
Hoogerbrugge, R., Geilenkirchen, G., den Hollander, H., Siteur, K., Smeets, W., van der Swaluw, E., et al., 2021. Grootschalige concentratie- en depositiekaarten Nederland. Rapportage 2021. Large-scale concentration and deposition maps of the Netherlands 2021 report: Rijksinstituut voor Volksgezondheid en Milieu. RIVM.
Hosmer, Jr DW., Lemeshow, S., 1999. Extensions of the Proportional Hazards Model. Regression Modeling of Time to Event Data. John Wiley and Sons, New York (Chapter 7) in Applied Survival Analysis.
Hyman, S., Zhang, J., Andersen, Z.J., Cruickshank, S., Møller, P., Daras, K., et al., 2023. Long-term exposure to air pollution and COVID-19 severity: A cohort study in Greater Manchester, United Kingdom. Environ. Pollut., 121594
Kalkowska, D.A., Boender, G.J., Smit, L.A.M., Baliatsas, C., Yzermans, J., Heederik, D.J. J., Hagenaars, T.J., 2018. Associations between pneumonia and residential distance to livestock farms over a five-year period in a large population-based study. PLoS One 13 (7), e0200813.
Klous, G., Smit, L.A.M., Freidl, G.S., Borlee, F., van der Hoek, W., Cj, I.J., et al., 2018. Pneumonia risk of people living close to goat and poultry farms - Taking GPS derived mobility patterns into account. Environ. Int. 115, 150–160.
Li, Z., Tao, B., Hu, Z., Yi, Y., Wang, J., 2022. Effects of short-term ambient particulate matter exposure on the risk of severe COVID-19. J. Infect. 84 (5), 684–691.
Liu, D., Mariman, R., Gerlofs-Nijland, M.E., Boere, J.F., Folkerts, G., Cassee, F.R., Pinelli, E., 2019. Microbiome composition of airborne particulate matter from livestock farms and their effect on innate immune receptors and cells. Sci. Total Environ. 688, 1298–1307.

Marquès, M., Domingo, J.L., 2022. Positive association between outdoor air pollution and the incidence and severity of COVID-19. A review of the recent scientific evidences. Environ. Res. 203.
Marquès, M., Correig, E., Ibarretxe, D., Anoro, E., Antonio Arroyo, J., Jericó, C., et al., 2022. Long-term exposure to PM10 above WHO guidelines exacerbates COVID-19 severity and mortality. Environ. Int. 158.
Mendy, A., Wu, X., Keller, J.L., Fassler, C.S., Apewokin, S., Mersha, T.B., et al., 2021. Air pollution and the pandemic: Long-term PM(2.5) exposure and disease severity in COVID-19 patients. Respirology 26 (12), 1181–1187.
Nobile, F., Michelozzi, P., Ancona, C., Cappai, G., Cesaroni, G., Davoli, M., et al., 2022. Air pollution, SARS-CoV-2 incidence and COVID-19 mortality in Rome - a longitudinal study. Eur. Respir. J. 60 (3).
Poole, J.A., Romberger, D.J., 2012. Immunological and inflammatory responses to organic dust in agriculture. Curr. Opin. Allergy Clin. Immunol. 12 (2), 126–132.
Post, P.M., Houthuijs, D., Sterk, H.A.M., Marra, M., van de Kassteele, J., van Pul, A., et al., 2021. Proximity to livestock farms and exposure to livestock-related particulate matter are associated with lower probability of medication dispensing for obstructive airway diseases. Int. J. Hyg Environ. Health 231, 113651.
Prins, K., 2017. Population register data, basis for the Netherlands Population Statistics. Bevolkingstrends 9, 1–32.
Projections ECoEIa, 2023. Officially Reported Emission Data [Available from: https://www.ceip.at/webdab-emission-database/reported-emissiondata.
Ranzani, O., Alari, A., Olmos, S., Mila, C., Rico, A., Ballester, J., et al., 2023. Long-term exposure to air pollution and severe COVID-19 in Catalonia: a population-based cohort study. Nat. Commun. 14 (1), 2916.
Sahlander, K., Larsson, K., Palmberg, L., 2012. Daily exposure to dust alters innate immunity. PLoS One 7 (2), e31646.
Sauter F, Van Zanten, M., Van der Swaluw, E., Aben, J.M.M., De Leeuw, F., Van Jaarsveld, H. The OPS-Model, Description of OPS 4.5.2. Bilthoven, the Netherlands: National Institute for Public Health and the Environment (RIVM)..
Sheridan, C., Klompmaker, J., Cummins, S., James, P., Fecht, D., Roscoe, C., 2022. Associations of air pollution with COVID-19 positivity, hospitalisations, and mortality: Observational evidence from UK Biobank. Environ. Pollut. 308, 119686.
Simoes, M., Janssen, N., Heederik, D.J.J., Smit, L.A.M., Vermeulen, R., Huss, A., 2022. Residential proximity to livestock animals and mortality from respiratory diseases in The Netherlands: A prospective census-based cohort study. Environ. Int. 161, 107140.
Smit, L.A., van der Sman-de Beer, F., Opstal-van Winden, A.W., Hooiveld, M., Beekhuizen, J., Wouters, I.M., et al., 2012. Q fever and pneumonia in an area with a high livestock density: a large population-based study. PLoS One 7 (6), e38843.
Suresh, K., Severn, C., Ghosh, D., 2022. Survival prediction models: an introduction to discrete-time modeling. BMC Med. Res. Methodol. 22 (1), 207.
van de Kassteele, J., Velders, G.J.M., 2006. Uncertainty assessment of local NO2 concentrations derived from error-in-variable external drift kriging and its relationship to the 2010 air quality standard. Atmos. Environ. 40 (14), 2583–2595.
van Jaarsveld, J.A., de Leeuw, F.A.A.M., 1993. OPS: An operational atmospheric transport model for priority substances. Environ. Software 8 (2), 91–100.
Velders, G.J.M., Diederen, H.S.M.A., 2009. Likelihood of meeting the EU limit values for NO2 and PM10 concentrations in the Netherlands. Atmos. Environ. 43 (19), 3060–3069.
Velders, G.J.M., Aben, J.M.M., Geilenkirchen, G.P., den Hollander, H.A., Noordijk, H., van der Swaluw, E., et al., 2014. Grootschalige concentratie- en depositiekaarten Nederland : Rapportage 2014. Rijksinstituut voor Volksgezondheid en Milieu RIVM.
Velders, G.J.M., Aben, J.M.M., Geilenkirchen, G.P., den Hollander, H.A., Nguyen, L., van den Broek, I., et al., 2017. Grootschalige concentratie- en depositiekaarten Nederland : Rapportage 2017. New Maps of Concentrations and Depositions for NSL and PAS: : 2016. Rijksinstituut voor Volksgezondheid en Milieu RIVM.
Velders, G.J.M., Maas, R.J.M., Geilenkirchen, G.P., de Leeuw, F.A.A.M., Ligterink, N.E., Ruyssenaars, P., et al., 2020. Effects of European emission reductions on air quality in the Netherlands and the associated health effects. Atmos. Environ. 221, 117109.
Veronesi, G., De Matteis, S., Calori, G., Pepe, N., Ferrario, M.M., 2022. Long-term exposure to air pollution and COVID-19 incidence: a prospective study of residents in the city of Varese, Northern Italy. Occup. Environ. Med. 79 (3), 192–199.
Vos, E.R.A., van Boven, M., den Hartog, G., Backer, J.A., Klinkenberg, D., van Hagen, C. C.E., Boshuizen, H., van Binnendijk, R.S., Mollema, L., van der Klis, F.R.M., de Melker, H.E., 2021. Associations Between Measures of Social Distancing and Severe Acute Respiratory Syndrome Coronavirus 2 Seropositivity: A Nationwide Population-based Study in the Netherlands. Clin. Infect. Dis. 73 (12), 2318–2321.
Wallinga, J., Teunis, P., 2004. Different epidemic curves for severe acute respiratory syndrome reveal similar impacts of control measures. Am. J. Epidemiol. 160 (6), 509–516.
Wever, D., Coenen, P., Dröge, R., Geilenkirchen, G., t Hoen, M., Honig, E., et al., 2020. Informative Inventory Report 2020 : Emissions of transboundary air pollutants in the Netherlands 1990-2018. Informative Inventory Report 2020: Rijksinstituut voor Volksgezondheid en Milieu. RIVM.
WHO. WHO Global Air Quality Guidelines, 2021. Particulate Matter (PM2.5 and PM10), Ozone, Nitrogen Dioxide, Sulphur Dioxide and Carbon Monoxide.
Wood, S., 2002. GAMs with integrated model selection using penalized regression splines and applications to environmental modelling. Ecol. Model. 157.
Wood, S., 2017. Generalized Additive Models: an Introduction with R, 2 edition. Chapman and Hall/CRC.
Zang, S.T., Luan, J., Li, L., Yu, H.X., Wu, Q.J., Chang, Q., Zhao, Y.H., 2022. Ambient air pollution and COVID-19 risk: Evidence from 35 observational studies. Environ. Res. 204.
Zhang, J., Lim, Y.H., So, R., Jorgensen, J.T., Mortensen, L.H., Napolitano, G.M., et al., 2023. Long-term exposure to air pollution and risk of SARS-CoV-2 infection and COVID-19 hospitalisation or death: Danish nationwide cohort study. Eur. Respir. J. 62 (1).