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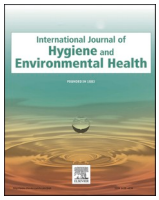

Outdoor air pollution as a risk factor for testing positive for SARS-CoV-2: A nationwide test-negative case-control study in the Netherlands

Mariana Simões [a], Jelle Zorn [b], Lenny Hogerwerf [b], Guus J.M. Velders [c,e], Lützen Portengen [a], Miriam Gerlofs-Nijland [f], Marieke Dijkema [d], Maciek Strak [f], José Jacobs [f], Joost Wesseling [e], Wilco J. de Vries [e], Suzanne Mijnen-Visser [e], Lidwien A.M. Smit [a], Roel Vermeulen [a,1], Lapo Mughini-Gras [a,b,*,1]

[a] Institute for Risk Assessment Sciences (IRAS), Faculty of Veterinary Medicine, Utrecht University, Utrecht, the Netherlands
[b] National Institute for Public Health and the Environment (RIVM), Centre for Infectious Disease Control (CIb), Bilthoven, the Netherlands
[c] Institute for Marine and Atmospheric Research Utrecht, Utrecht University, Utrecht, the Netherlands
[d] Municipal Health Services, Provinces of Overijssel and Gelderland, the Netherlands
[e] National Institute for Public Health and the Environment (RIVM), Center for Environmental Quality (MIL), Bilthoven, the Netherlands
[f] National Institute for Public Health and the Environment (RIVM), Center for Sustainability, Environment and Health (DMG), Bilthoven, the Netherlands

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ABSTRACT

Air pollution is a known risk factor for several diseases, but the extent to which it influences COVID-19 compared to other respiratory diseases remains unclear. We performed a test-negative case-control study among people with COVID-19-compatible symptoms who were tested for SARS-CoV-2 infection, to assess whether their long- and short-term exposure to ambient air pollution (AAP) was associated with testing positive (*vs*. negative) for SARS-CoV-2. We used individual-level data for all adult residents in the Netherlands who were tested for SARS-CoV-2 between June and November 2020, when only symptomatic people were tested, and modeled ambient concentrations of PM10, PM2.5, NO_2 and O_3 at geocoded residential addresses. In long-term exposure analysis, we selected individuals who did not change residential address in 2017–2019 (1.7 million tests) and considered the average concentrations of PM10, PM2.5 and NO_2 in that period, and different sources of PM (industry, livestock, other agricultural activities, road traffic, other Dutch sources, foreign sources). In short-term exposure analysis, individuals not changing residential address in the two weeks before testing day (2.7 million tests) were included in the analyses, thus considering 1- and 2-week average concentrations of PM10, PM2.5, NO_2 and O_3 before testing day as exposure. Mixed-effects logistic regression analysis with adjustment for several confounders, including municipality and testing week to account for spatiotemporal variation in viral circulation, was used. Overall, there was no statistically significant effect of long-term exposure to the studied pollutants on the odds of testing positive *vs*. negative for SARS-CoV-2. However, significant positive associations of long-term exposure to PM10 and PM2.5 from specifically foreign and livestock sources, and to PM10 from other agricultural sources, were observed. Short-term exposure to PM10 (adjusting for NO_2) and PM2.5 were also positively associated with increased odds of testing positive for SARS-CoV-2. While these exposures seemed to increase COVID-19 risk relative to other respiratory diseases, the underlying biological mechanisms remain unclear. This study reinforces the need to continue to strive for better air quality to support public health.

1. Introduction

With the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), the scientific community tried to understand the influence of various environmental factors on virus exposure and infection

* 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 addresses: lapo.mughini.gras@rivm.nl, l.mughinigras@uu.nl (L. Mughini-Gras).
[1] Equal contributors.

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susceptibility and severity. Studies showed that air pollution increased the risk of SARS-CoV-2 infection and COVID-19 severity by increasing host susceptibility to infection and aggravating the course of the disease, also through pre-existing conditions, such as obstructive pulmonary disease (COPD), diabetes and hypertension (Zang et al., 2022). Numerous epidemiological studies have investigated the impact of ambient air pollution (AAP) on different COVID-19 health outcomes using individual-level data, e.g. (Ali et al., 2021; Marquès and Domingo, 2022; Heederik et al., 2020; Vandenbroucke et al., 2022), reporting mainly positive associations. Although these studies are an improvement on earlier ecological studies, reviewed elsewhere (Zang et al., 2022; Ali et al., 2021; Marquès and Domingo, 2022), which are known to be particularly prone to confounding (Heederik et al., 2020), they still suffer from some methodological challenges. A major shortcoming is that the used risk model ignores the main driver of COVID-19, namely exposure to SARS-CoV-2, but models AAP as a main determinant of COVID-19, whereas it is more a moderator of the association with COVID-19. Ignoring this can lead to bias in the obtained risk estimates. To mitigate bias in studies of the drivers of COVID-19, Vandenbroucke et al. proposed the use of a test-negative study design (TND) (Vandenbroucke et al., 2020, 2022).

TNDs compare exposures to risk factors (e.g. AAP) between individuals who tested positive and those who tested negative for the condition of interest (e.g. COVID-19). In this context, testing skews selectively towards individuals seeking medical help and is influenced by factors such as age, gender, socioeconomic status, access to healthcare, proximity to testing facilities, comorbidities, symptom severity, personality traits, etc. However, in a TND, all individuals are tested and the same selective forces can therefore be assumed to operate largely on both the test-positives (i.e., the 'cases') and test-negatives (i.e., the 'controls'), especially when testing is conditional on symptoms. This approach has the potential to yield more robust risk estimates. There is substantial methodological literature on TNDs (Sullivan et al., 2016; Foppa et al., 2016; Vandenbroucke and Pearce, 2019), including specific publications on COVID-19, e.g. (Vandenbroucke et al., 2020, 2022; Eekhout et al., 2023; Cerqueira-Silva et al., 2023). Furthermore, when studying air pollution and COVID-19, it is important to control for variation in viral circulation levels, i.e. the level of exposure to SARS-CoV-2, as person-to-person transmission is the driving force behind the COVID-19 pandemic, and spatiotemporal differences in COVID-19 associated with AAP might be confounded by the degree of concurrent local viral circulation (Heederik et al., 2020). Therefore, by comparing the exposure levels to AAP between test-positives and test-negatives in areas and periods of comparable viral circulation, it is possible to discern the extent to which air pollution has unique or specific effects on COVID-19, as risk factors of equal magnitude for both COVID-19 and other respiratory diseases are filtered out by design (Vandenbroucke et al., 2020, 2022).

A study in the United Kingdom (UK) used a variant of the TND to assess multiple risk factors, including long-term exposure to AAP, for testing positive for SARS-CoV-2 (Chadeau-Hyam et al., 2020), reporting a consistent association with exposure to particulate matter (PM) with an aerodynamic diameter $\leq$2.5 μm (PM2.5). However, spatiotemporal variation in SARS-CoV-2 spread (that is, pattern changes in virus spread related to place and time (i.e., outbreak dynamics) was not explicitly accounted for. In this study, we applied a TND with spatiotemporal matching of test-positives and test-negatives by sampling people with and without a positive SARS-CoV-2 test who lived in the same municipality and were tested on the same week. The aim of this study was to determine whether long- and short-term exposures to ambient concentrations of PM with an aerodynamic diameter $\leq$10 μm (PM10) and $\leq$2.5 μm (PM2.5), nitrogen dioxide (NO_2) and ozone (O_3, only for short-term exposure) were associated with increased risk of testing positive *vs.* negative for SARS-CoV-2. Furthermore, we investigated whether long-term exposure to specific sources of PM in the Netherlands, such as road traffic, agriculture and industry, were associated with increased risk of testing positive.

2. Methods

2.1. Study design, outcomes and populations

We conducted a case-control study based on a TND using individual-level data on symptomatic test-positives and symptomatic test-negatives for SARS-CoV-2 infection in the Netherlands.

In June 2020, public testing facilities for SARS-CoV-2 infection in the Dutch general population were opened in the 25 Public Health Services of the country. Test-confirmed SARS-CoV-2 infection is mandatorily notifiable in the Netherlands, and when such confirmation is made in a public testing facility, it is registered in a centralized database named 'CoronIT'. This database contains individual-level patient information on all test results, both positives and negatives, from all public testing facilities in the country. In this study, we included all test results with a sampling date from June 1st, 2020 to November 30th, 2020 (n $\sim$ 4.4 million tests) because during that period testing was restricted to people aged >12 years who had one or more symptoms compatible with COVID-19 (i.e., runny nose, cough, shortness of breath or difficulty breathing, fever, loss of taste or smell). Since a person could have multiple tests performed over time, we excluded tests from the same person after the first positive test, as some people can repeatedly test positive for SARS-CoV-2 months after infection. Molecular tests (RT-PCR) were the standard until January 2021 in the Netherlands, when rapid antigen tests started being used increasingly. Our study therefore included mainly data from RT-PCR tests. We also excluded tests from people employed in the healthcare sector and from people living in institutions (e.g., mental health institutions and nursing homes) due to their different risk of viral exposure, susceptibility to infection and/or eligibility for testing when compared to the general population. Furthermore, we excluded tests from children (<18 years) and from people who changed addresses (because of relocation, moving abroad, etc.) during the exposure periods considered (see later in section 2.3). Tests from people who lived within 1 km from the borders of the Netherlands with Belgium and Germany (for whom exposure could not be accurately estimated) were also excluded. Finally, we excluded tests with no data available on the urbanization degree of the area where these people lived, their household wealth, household size, neighborhood socioeconomic status, exposure levels to AAP, as well as unmatched tests at municipality of residence and week of testing; see Fig. 1 for detailed exclusion steps.

2.2. Air pollution data

2.2.1. Long-term exposure

For estimating long-term exposure to PM10, PM2.5 and NO_2, a comprehensive methodology was employed (Velders et al., 2020; Velders and Diederen, 2009; Hoogerbrugge et al., 2021; Velders et al., 2017). These methods are also used by the Dutch government to monitor compliance with the European Union (EU) air quality limit values (Directive, 2008/50/EC) within the Dutch National Air Quality Cooperation Program. These are annual averages of background concentrations of these pollutant at a spatial resolution of 1 × 1 km (Velders et al., 2020). To determine the spatial distribution maps, the Operational Priority Substances (OPS) dispersion model (van Jaarsveld and de Leeuw, 1993; van Pul et al., 2011; Sauter et al.) was used. This model estimates the yearly average PM concentrations by considering emissions, dispersion, transport, chemical conversion, deposition, and meteorological conditions specific to each year. The OPS model relies on input data from official emissions reported to the Netherlands Pollutant Release and Transfer Register (Wever et al., 2020) and emissions from neighboring countries (EMEP Centre on Emission Inventories and Projections) (Hoogerbrugge et al., 2021; Projections ECoEIa, 2023). Data on type, strength and discharge height of emissions, as well as temporal and

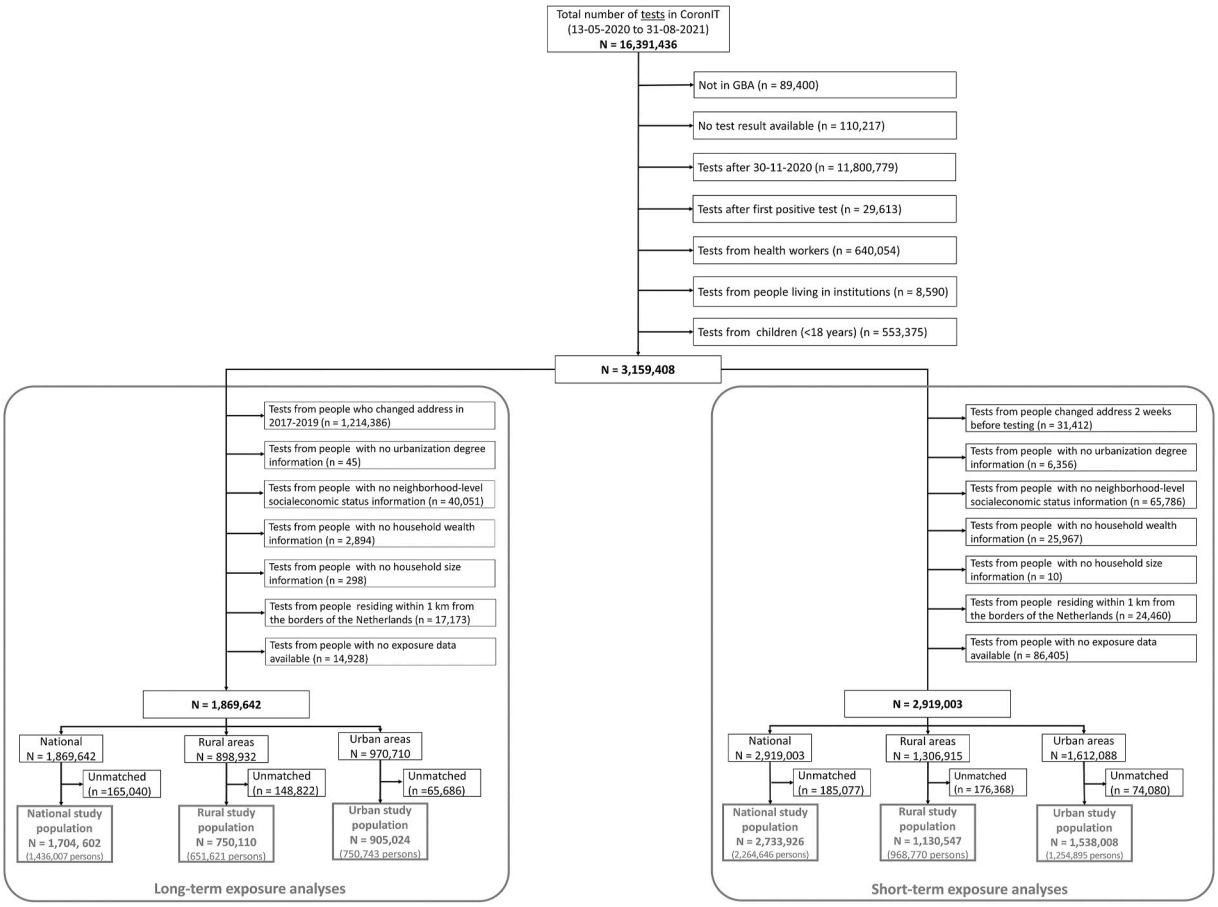

Fig. 1. Flow chart of selection criteria applied to the SARS-CoV-2 tests included in the analysis.
GBA = Municipal population census register ("*Gemeentelijke Basisadministratie*" in Dutch).

spatial distribution of the collectively registered emissions, is therefore obtained per source from the register itself. Emission data is spatially distributed based on where emissions are released; data from companies subject to emission reporting, storage and transshipment, ports, sewage treatment plants and aviation, are known on location. Due to chemical reactivity of NO_2 in the atmosphere, direct modeling of NO_2 in the OPS model is not feasible. Instead, NO_2 concentrations are calculated from the modeled 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). Total PM10 and PM2.5 concentrations represent the sum of the contributions from primary PM emissions, secondary aerosols, and sea salt. These concentrations are estimated on an annual basis and calibrated against the results from Air Quality Monitoring Networks at background locations in the Netherlands (www.luchtmeetnet.nl). The model is therefore calibrated using measurements from 35 to 45 stations distributed across the whole country that are part of this network. Each emission source contribution to the overall concentrations is estimated separately by the OPS model. Five main categories were considered here: industry, livestock farming, other agricultural activities, road traffic, foreign sources (i.e., outside the Netherlands), and other Dutch sources (miscellaneous) (Velders et al., 2017). Detailed methodologies for the calculation of emissions from these sources are available elsewhere: industry (Honig et al., 2023), agriculture (van der Zee et al., 2023), traffic (Gerben Geilenkirchen et al., 2023), and other sources (Honig et al., 2023; Visschedijk et al., 2023). In this study, we focused on emission sources of PM10 and PM2.5, as they can have varying mixtures of components depending on their origin, whereas NO_2 is the same molecule. To assess exposure, we extracted the annual average ambient concentrations of PM10, PM2.5 and NO_2 for each address in the study population for the years 2017, 2018 and 2019: the average concentrations over this three-year period served as the long-term exposure variable in our analyses.

2.2.2. *Short-term exposure*

Air pollution data for the short-term exposure were obtained using the Residual Interpolation Optimized for Ozone (RIO) method, an interpolation method that produces hourly air pollution maps based on the spatial interpolation of AAP measurements (Mooibroek, 2014). This model first removes local site-dependent increases or decreases in concentrations, then performs a spatial interpolation using Ordinary Kriging, after which the local effects are added again to the maps. Similarly to the OPS model used to estimate annual averages, the RIO model is also calibrated using measured data from the Dutch air quality monitoring network. Hourly data coverage for each station in the network is >90% (often larger >95%). From the hourly maps, daily averages of PM10, PM2.5, and NO_2 and the maximum 8-h running average of O_3 are calculated on a 4 × 4 km grid. This coarser resolution, compared to the annual (long-term exposure) maps, is due to lack of information on emissions and of measurement data on a finer scale. For this reason, obtaining emission source contributions for short-term exposure is not feasible, so an analysis by emission source was not performed for the short-term exposure. For our analysis, we estimated the average air pollution concentration for both one week and two weeks preceding the testing day. Average incubation period for SARS-CoV-2 infection is about 5 days (Galmiche et al., 2023), hence the average AAP concentrations 1 week before testing would capture the exposure around the time of infection, assuming that this could influence the risk of acquiring

the infection and allowing the infection to establish itself upon exposure. Moreover, assuming that air pollution also plays a role in infection severity, this period also entails the possibility that air pollution might have influenced the need for testing after infection because of, e.g., aggravation of symptoms. On the other hand, some people develop symptoms later than 5 days, hence the 2-week period as well.

2.3. Data anonymization and linkage

Statistics Netherlands (CBS) acted as a trusted third party for data anonymization and linkage by coupling a Record Identification Number (RIN) as a unique identifier to each individual in the CoronIT database. To this end, CBS uses a census reference register containing all mutations due to death or relocation in the Dutch general population, including a complete housing history of all residents in the Netherlands. Through the residential addresses, the air pollution data were linked to the CoronIT data. The RIN numbers also allowed coupling to other information at CBS to define the study population and adjust for potential contextual confounding in the analyses (see section 2.3): household wealth (continuous variable, expressed in Euro, including income plus assets), household size (ordinal variable: 1, 2, 3, 4, ≥5 people), highest educational attainment (categorical variable, as defined by CBS: primary and lower secondary education, higher and senior secondary education and pre-university education, and higher professional and university education), migration background (categorical variable, as defined by CBS: autochthonous Dutch, Moroccan, Turkish, Surinamese, Former Dutch Antilles and Aruba, other non-Western countries, and other Western countries), occupation and nursing home attendance (categorical variable, both used to identify and exclude healthcare workers, Fig. 1), urbanicity of residence location (categorical variable, based on 500 m^2 spatial resolution: extremely urbanised [≥2500 addresses/km^2], strongly urbanised [1500–2500 addresses/km^2], moderately urbanised [1000–1500 addresses/km^2], hardly urbanised [500-1000 addresses/km^2] not urbanised [<500 addresses/km^2], and neighborhood-level socio-economic status (SES, continuous variable, based on residential four-digit postal code [on average, circa 2000 residential addresses] as function of income level, unemployment rate, and education level).

2.4. Statistical analysis

Mixed-effects logistic regression was used to assess the association between exposure to AAP and the odds of testing positive for SARS-CoV-2 among symptomatic people, controlling for the matching variables 'municipality of residence location' and 'week of testing', as recommended (Pearce, 2016). For long-term exposure analysis, PM10, PM2.5 and NO_2 over three years preceding the pandemic (2017–2019) were considered, whereas for short-term exposure analysis, 1- and 2-week average concentrations before testing day were considered. Effects of long- and short-term exposure were studied in separate analyses. Primary analyses consisted of single-pollutant models, followed by multi-pollutant models including either PM10 or PM2.5 plus NO_2 (long-term exposure), or either PM10 or PM2.5 plus NO_2 and O_3 (short-term exposure). Emission source contributions for long-term exposure included all sources of PM10 or PM2.5. All models were adjusted for several covariates obtained from CBS: age (natural spline with five degrees of freedom), sex (binary, male or female), household wealth (natural spline with 15 degrees of freedom), household size, migration background, highest attained educational level (categorical) and neighborhood-level socioeconomic status (SES, a standardized score based on wealth, education and employment history of households in the neighborhood). A random intercept at district level was included in all models to account for spatial correlation of tests. Analyses were first performed at national level and then stratified by urban (1500 or more addresses/km^2) and rural (1499 or less addresses/km^2) areas. The reason for this stratification was two-fold: 1) the populations in these areas can differ in lifestyle factors and other exposures for which full control is difficult using demographic variables, and 2) the degree of urbanization can influence the composition and therefore the toxicity of the different PM fractions, although this is less relevant when individual emission sources are considered in the analyses. Generalized variance inflation factor (GVIF) was used to assess multicollinearity. Risk estimates were expressed as odds ratios (OR) with corresponding 95% confidence intervals (CIs) per 1 μg/m^3 increase in exposure. Risk estimates at national level were also expressed per interquartile range (IQR) increase, as the IQR incorporates a measure of magnitude of exposure in the population. Statistical significance was set at p value < 0.05. All analyses were performed in R version 4.1.3 (2022-03-10) with packages "lme4" and "MatchIt", within the remote secure environment of CBS.

2.5. Sensitivity analyses

To assess the robustness of results, several sensitivity analyses were performed in both long- and short-term analyses, as follows.

- Restricting analyses in rural areas to the least urbanised areas with <1000 addresses/km^2, in order to assess potential bias from including semi-urban environments in the analyses for rural areas.
- Restricting analyses in urban areas to the most urbanised ones (≥2500 addresses/km^2) where the highest air pollution concentrations are usually found.
- Using a longer period for the long-term exposure, 2015–2019 (instead of 2017–2019), thereby also restricting the analysis to tests from people who did not change address in that period.
- Including either 'livestock' or 'other agricultural sources' in the model for the long-term exposure to sources of PM, due to the observed correlations (Pearson $r = 0.62–0.78$, Fig. S2) and indications of potential collinearity issues (GVIF >3) between these two sources.

3. Results

3.1. Descriptive statistics

After applying the exclusion criteria for the long-term exposure analysis (Fig. 1), a total of 1,704,602 tests (of which 196,025 [11.5%] were positive) remained at national level, 750,110 tests (of which 87,093 [11.6%] were positive) in rural areas, and 905,024 tests (of which 108,928 [12.0%] were positive) in urban areas. The distribution of positive and negative tests over age groups, gender, household wealth, household size, highest educational attainment, SES, migration background, urbanization and province are reported in Table 1; the spatial distribution of the cumulative proportion of positive tests is depicted in Fig. S1 (Appendix). Overall, the proportion of cases was higher among men, older individuals, larger households, and non-autochthonous people, particularly people of non-Western migration background, all variables controlled for in the models. This was observed in both rural and urban areas. Household wealth was slightly larger among cases from rural areas and lower among cases from urban areas. In general, similar to slightly higher AAP concentrations were observed among cases. Median air pollution concentrations (average for the period 2017–2019) were 18.63 μg/m^3 [Interquartile range (IQR) 17.63–19.26] for PM10, 11.20 μg/m^3 [10.51–11.69] PM2.5 and 18.69 μg/m^3 [16.13–22.20] for NO_2, at national level (concentrations for cases and controls are presented in Table 1). Concentrations from specific sources ranged from 0.13 μg/m^3 from other agricultural sources and 6.53 μg/m^3 [5.96–7.56] from foreign sources. In general, national median air pollution concentrations were similar or slightly higher for cases, with exception of PM from livestock sources, which concentrations were slightly higher for cases only in rural areas.

For the short-term exposure analysis, 2,733,926 tests (of which 280,398 [10.3%] were positive) were included at national level,

Table 1
Characteristics of test-positives (cases) and test-negatives (controls) in the long-term exposure analyses.

Characteristic	National		Rural areas		Urban areas	
	Controls	Cases	Controls	Cases	Controls	Cases
N	1,508,577	196,025	663,017	87,093	796,096	108,928
Women [n (%)]	783,148 (51.9)	92,100 (47.0)	337,950 (51.0)	39,280 (45.1)	419,619 (52.7)	52,818 (48.5)
Age [median (IQR)]	46 (24.0)	49 (24.0)	47 (25.0)	50 (24.0)	45.00 (24.0)	48.00 (24.0)
Household wealth (centile) [median (IQR)]	64 (42.0)	61 (45.0)	68 (38.0)	69 (38.0)	60.00 (45.0)	54.00 (48.0)
Neighborhood socioeconomic status [mean (SD)]	0.05 (0.29)	0.01 (0.31)	0.15 (0.22)	0.15 (0.21)	−0.04 (0.31)	−0.11 (0.33)
Household size [n (%)]						
1 person	229,251 (15.2)	22,825 (11.6)	65,526 (9.9)	7188 (8.3)	156,999 (19.7)	15,637 (14.4)
2 people	439,239 (29.1)	55,089 (28.1)	194,638 (29.4)	25,711 (29.5)	228,868 (28.7)	29,374 (27.0)
3 people	286,720 (19.0)	36,990 (18.9)	129,256 (19.5)	16,647 (19.1)	148,126 (18.6)	20,343 (18.7)
4 people	393,426 (26.1)	50,809 (25.9)	193,986 (29.3)	24,795 (28.5)	186,454 (23.4)	26,014 (23.9)
≥5 people	159,941 (10.6)	30,312 (15.5)	79,611 (12.0)	12,752 (14.6)	75,649 (9.5)	17,560 (16.1)
Migration background [n (%)]						
Autochthonous	1,196,039 (79.3)	131,885 (67.3)	582,979 (87.9)	73,610 (84.5)	571,796 (71.8)	58,271 (53.5)
Moroccan	32,154 (2.1)	13,600 (6.9)	4929 (0.7)	1727 (2.0)	26,608 (3.3)	11,873 (10.9)
Turkish	40,406 (2.7)	14,992 (7.6)	7000 (1.1)	2285 (2.6)	32,589 (4.1)	12,707 (11.7)
Surinamese	35,520 (2.4)	7299 (3.7)	6251 (0.9)	1102 (1.3)	28,602 (3.6)	6197 (5.7)
Former Dutch Antilles and Aruba	11,218 (0.7)	1971 (1.0)	2413 (0.4)	339 (0.4)	8539 (1.1)	1632 (1.5)
Other non-Western countries	52,745 (3.5)	11,378 (5.8)	12,767 (1.9)	2503 (2.9)	38,695 (4.9)	8875 (8.1)
Western countries	140,495 (9.3)	14,900 (7.6)	46,678 (7.0)	5527 (6.3)	89,267 (11.2)	9373 (8.6)
Highest educational attainment [n (%)]						
Primary and lower secondary education	186,976 (12.4)	32,422 (16.5)	77,798 (11.7)	11,100 (12.7)	103,815 (13.0)	21,322 (19.6)
Higher secondary education	311,827 (20.7)	41,801 (21.3)	150,331 (22.7)	19,392 (22.3)	151,516 (19.0)	22,409 (20.6)
Senior general secondary education and pre-university education	124,842 (8.3)	16,448 (8.4)	52703 (7.9)	7231 (8.3)	68068 (8.6)	9217 (8.5)
Higher professional and university education	478,799 (31.7)	42,721 (21.8)	188,643 (28.5)	18,232 (20.9)	27,4871 (34.5)	24,488 (22.5)
Unknown	406,133 (26.9)	62,633 (32.0)	193,542 (29.2)	31,138 (35.8)	197,826 (24.8)	31,492 (28.9)
Urbanization degree [n (%)]						
Very highly urbanised (≥2500 addresses/km^2)	403,743 (26.8)	56,771 (29.0)	n/a	n/a	400,663 (50.3)	56,771 (52.1)
Highly urbanised (1500–2499 addresses/km^2)	413,118 (27.4)	52,161 (26.6)	n/a	n/a	395,433 (49.7)	52,157 (47.9)
Moderately urbanised (1000–1499 addresses/km^2)	266,875 (17.7)	33,201 (16.9)	25,0656 (37.8)	33,201 (38.1)	n/a	n/a
Lowly urbanised (500-999 addresses/km^2)	242,697 (16.1)	30,093 (15.4)	23,4237 (35.3)	30,093 (34.6)	n/a	n/a
Not urbanised (<500 addresses/km^2)	182,144 (12.1)	23,799 (12.1)	17,8124 (26.9)	23,799 (27.3)	n/a	n/a
PM10 overall [median (IQR)] (μg/m^3)	18.61 (1.63)	18.72 (1.53)	17.99 (1.83)	18.08 (1.63)	19.09 (1.19)	19.14 (1.09)
PM2.5 overall [median (IQR)] (μg/m^3)	11.19 (1.19)	11.26 (1.08)	10.79 (1.55)	10.86 (1.28)	11.47 (1.02)	11.52 (0.96)
NO_2 overall [median (IQR)] (μg/m^3)	18.64 (6.05)	19.13 (6.25)	16.68 (4.48)	16.85 (4.2)	21.24 (5.58)	21.80 (5.76)
PM10 foreign [median (IQR)] (μg/m^3)	6.52 (1.59)	6.61 (1.51)	6.87 (1.72)	7.01 (1.69)	6.43 (1.00)	6.47 (0.91)
PM10 industry [median (IQR)] (μg/m^3)	0.78 (0.23)	0.79 (0.24)	0.71 (0.21)	0.72 (0.2)	0.84 (0.25)	0.87 (0.27)
PM10 agriculture, livestock [median (IQR)] ((μg/m^3)	0.65 (0.42)	0.64 (0.41)	0.77 (0.53)	0.79 (0.53)	0.62 (0.36)	0.60 (0.29)
PM10 agriculture, other [median (IQR)] (μg/m^3)	0.13 (0.02)	0.13 (0.02)	0.13 (0.04)	0.13 (0.03)	0.13 (0.02)	0.13 (0.01)
PM10 traffic [median (IQR)] (μg/m^3)	1.22 (0.54)	1.24 (0.52)	1.01 (0.55)	1.02 (0.52)	1.34 (0.42)	1.36 (0.38)
PM10 other sources [median (IQR)] (μg/m^3)	2.45 (1.19)	2.54 (1.22)	1.92 (0.92)	1.96 (0.89)	2.97 (0.95)	3.04 (0.95)
PM2.5 foreign [median (IQR)] (μg/m^3)	5.48 (1.31)	5.55 (1.21)	5.73 (1.41)	5.83 (1.37)	5.39 (0.81)	5.44 (0.75)
PM2.5 industry [median (IQR)] (μg/m^3)	0.55 (0.14)	0.56 (0.15)	0.51 (0.14)	0.52 (0.14)	0.59 (0.15)	0.60 (0.16)
PM2.5 agriculture, livestock [median (IQR)] (μg/m^3)	0.56 (0.27)	0.55 (0.25)	0.59 (0.33)	0.60 (0.32)	0.55 (0.23)	0.53 (0.18)
PM2.5 agriculture, other [median (IQR)] (μg/m^3)	0.1 (0.01)	0.1 (0.01)	0.09 (0.02)	0.09 (0.03)	0.10 (0.01)	0.10 (0.01)
PM2.5 traffic [median (IQR)] (μg/m^3)	0.88 (0.37)	0.89 (0.35)	0.73 (0.41)	0.74 (0.38)	0.96 (0.28)	0.97 (0.26)
PM2.5 other sources [median (IQR)] (μg/m^3)	2.05 (0.97)	2.12 (0.98)	1.62 (0.77)	1.64 (0.74)	2.46 (0.74)	2.52 (0.74)

n/a = not applicable.

1,130,547 tests (of which 116,088 [10.3%] were positive) in rural areas, and 1,538,008 tests (of which 164,309 [10.7%] were positive) in urban areas. The distribution of positive and negative tests included in the short-term exposure analysis, over age groups, gender, household wealth, household size, highest educational attainment, SES, migration background, urbanization and province are reported in Table 2. Also here, higher proportions of cases were found among men, older individuals, larger households, and people with a non-Dutch background (i.e., people not born in the Netherlands or with their parents not born in the Netherlands, according to CBS definitions), both in rural and urban areas. Across the 12 Dutch provinces, the proportion of positive tests over time showed a peak in October, especially around the week of 19–25 October, with no visual indication of coincidental peaks in exposure (Fig. S2, Appendix). Nationally, median 2-week average concentrations were slightly higher than 1-week average concentrations for all pollutants: 12.07 μg/m^3 [10.30–15.31] and 12.43 μg/m3 [10.53–15.83] for PM10, 6.37 μg/m^3 [4.71–9.28] and 6.80 μg/m^3 [5.20–9.27] for PM2.5, 16.88 μg/m^3 [13.20–20.76] and 16.94 μg/m^3 [13.45–20.45] for NO_2, and 52.1^3 μg/m3 [45.56–65.18] and 51.78 μg/m^3 [45.37–67.82] for O_3 (1-week and 2-week medians, respectively). Cases had somewhat lower PM10 and O_3 median 1-week and 2-week average concentrations, while the opposite was observed for NO_2 (Table 2). For PM2.5, median 1-week concentration was lower for cases while median 2-week concentration was higher.

In the long-term analyses, both total PM10 and PM2.5 correlated with total NO_2, both nationally and in rural and urban areas (Pearson r = 0.75–0.82) (Fig. S3, Appendix). PM10 and PM2.5 from other agricultural sources than livestock were moderately to highly correlated with livestock sources (Fig. S4, Appendix). Moderate to high correlations between road traffic and other Dutch sources of PM10 and PM2.5 were also observed. Spatial distribution of the three-year (2017–2019) average concentrations of PM10, PM2.5 and NO_2, overall and by emission source, are reported in Figs. S5 and S6. For both overall PM10 and PM2.5, concentrations were lowest in the northern and highest at the central and southern parts of the country. Certain sources of PM were region-specific, with foreign concentrations being highest near the borders with Germany and Belgium, agricultural sources in the central and eastern parts, road traffic near the largest cities, and industry and other Dutch sources in the western part. Concentrations for NO_2 were lowest in the northern and highest in the western parts of the country.

Table 2
Characteristics of test-positives (cases) and test-negatives (controls) in the short-term exposure analyses.

Characteristic	National		Rural areas		Urban areas	
	Controls	Cases	Controls	Cases	Controls	Cases
N	2,453,528	280,398	101,4459	116,088	137,3699	164,309
Women [n (%)]	1,273,230 (51.9)	131,346 (46.8)	518,141 (51.1)	52,514 (45.2)	721,272 (52.5)	78,831 (48.0)
Age [median (IQR)]	39 (24.0)	43 (28.0)	41 (25.0)	47 (27.0)	37 (24.0)	40 (27.0)
Household wealth (centile) [median (IQR)]	61 (44.0)	59 (47.0)	65 (39.0)	67 (39.0)	56 (48.0)	51 (50.0)
Neighborhood socioeconomic status [mean (SD)]	0.03 (0.29)	−0.01 (0.31)	0.15 (0.22)	0.15 (0.22)	−0.06 (0.31)	−0.12 (0.32)
Household size [n (%)]						
1 person	473,148 (19.3)	45,322 (16.2)	117,815 (11.6)	11,593 (10.0)	345,165 (25.1)	33,729 (20.5)
2 people	746,896 (30.4)	83,043 (29.6)	299,672 (29.5)	35,074 (30.2)	426,424 (31.0)	47,968 (29.2)
3 people	462,813 (18.9)	50,972 (18.2)	207,312 (20.4)	22,300 (19.2)	242,895 (17.7)	28,672 (17.5)
4 people	550,404 (22.4)	63,553 (22.7)	277,194 (27.3)	31,177 (26.9)	257,210 (18.7)	32,376 (19.7)
≥5 people	220,267 (9.0)	37,508 (13.4)	112,466 (11.1)	15,944 (13.7)	102,005 (7.4)	21,564 (13.1)
Migration background [n (%)]						
Autochthonous	1,900,907 (77.5)	185,101 (66.0)	879,087 (86.7)	96,040 (82.7)	968,114 (70.5)	89,060 (54.2)
Moroccan	49,742 (2.0)	18,597 (6.6)	8213 (0.8)	2535 (2.2)	40,663 (3.0)	16,062 (9.8)
Turkish	61,718 (2.5)	19,936 (7.1)	11,645 (1.1)	3251 (2.8)	49,031 (3.6)	16,685 (10.2)
Surinamese	54,801 (2.2)	10,136 (3.6)	10,039 (1.0)	1586 (1.4)	43,842 (3.2)	8550 (5.2)
Former Dutch Antilles and Aruba	21,471 (0.9)	3308 (1.2)	4530 (0.4)	590 (0.5)	16,549 (1.2)	2718 (1.7)
Other non-Western countries	107,976 (4.4)	19,132 (6.8)	24,638 (2.4)	4115 (3.5)	81,156 (5.9)	15,017 (9.1)
Western countries	256,913 (10.5)	24,188 (8.6)	76,307 (7.5)	7971 (6.9)	174,344 (12.7)	16,217 (9.9)
Highest educational attainment [n (%)]						
Primary and lower secondary education	274,759 (11.2)	41,497 (14.8)	113,544 (11.2)	14,030 (12.1)	154,418 (11.2)	27,467 (16.7)
Higher secondary education	521,870 (21.3)	62,508 (22.3)	246,995 (24.3)	27,828 (24.0)	260,858 (19.0)	34,680 (21.1)
Senior general secondary education and pre-university education	239,090 (9.7)	28,507 (10.2)	81,548 (8.0)	9880 (8.5)	151,872 (11.1)	18,627 (11.3)
Higher professional and university education	884,198 (36.0)	71,580 (25.5)	325,249 (32.1)	27,662 (23.8)	536,205 (39.0)	43,918 (26.7)
Unknown	533,611 (21.7)	76,306 (27.2)	247,123 (24.4)	36,688 (31.6)	270,346 (19.7)	39,617 (24.1)
Urbanization degree [n (%)]						
Extremely urbanised (≥2500 addresses/km^2)	768,818 (31.3)	92,945 (33.1)	n/a	n/a	609,307 (55.6)	71,364 (56.6)
Strongly urbanised (1500–2499 addresses/km^2)	633,023 (25.8)	71,365 (25.5)	n/a	n/a	609,307 (44.4)	71,364 (43.4)
Moderately urbanised (1000–1499 addresses/km^2)	400,657 (16.3)	44,289 (15.8)	380,628 (37.5)	44,289 (38.2)	n/a	n/a
Hardly urbanised (500-999 addresses/km^2)	368,776 (15.0)	40,124 (14.3)	357,716 (35.3)	40,124 (34.6)	n/a	n/a
Not urbanised (<500 addresses/km^2)	282,254 (11.5)	31,675 (11.3)	276,115 (27.2)	31,675 (27.3)	n/a	n/a
PM10 overall [median (IQR)] (μg/m^3)						
1 week average	12.10 (5.03)	11.93 (4.62)	11.69 (5.21)	11.45 (4.59)	12.37 (4.93)	12.19 (4.59)
2 weeks average	12.50 (5.34)	12.04 (4.94)	12.17 (5.29)	11.63 (4.86)	12.72 (5.46)	12.27 (5.09)
PM2.5 overall [median (IQR)] (μg/m^3)						
1 week average	6.37 (4.55)	6.51 (4.47)	6.25 (4.73)	6.33 (4.69)	6.48 (4.52)	6.62 (4.34)
2 weeks average	6.79 (4.10)	6.73 (3.79)	6.80 (4.06)	6.65 (3.75)	6.85 (4.20)	6.77 (3.85)
NO_2 overall [median (IQR)] (μg/m^3)						
1 week average	17.00 (7.53)	18.04 (7.96)	13.92 (6.87)	14.34 (7.10)	19.03 (6.51)	20.10 (6.73)
2 weeks average	17.06 (7.04)	18.09 (7.17)	14.00 (6.20)	14.46 (6.14)	19.18 (5.94)	20.23 (5.75)
O_3 overall [median (IQR)] (μg/m^3)						
1 week average	53.26 (21.63)	48.89 (10.41)	52.34 (19.50)	49.18 (9.57)	53.46 (22.33)	48.66 (11.00)
2 weeks average	53.41 (24.53)	48.63 (9.67)	51.93 (22.35)	48.94 (8.78)	54.43 (25.08)	48.39 (10.87)

n/a = not applicable.

Also in the short-term analyses, both total PM10 and PM2.5 correlated with total NO_2, both nationally and in rural and urban areas (Pearson r = 0.49–0.72), and far less with O_3 (Pearson r = 0.25–0.41) (Fig. S7, Appendix).

In both single- and multi-pollutant models, all confounders were significantly associated with testing positive for SARS-CoV-2 (Tables S1–S3, Appendix). In the multi-pollutant models for the overall analysis, there was no indication of strong collinearity ($(GVIF^{(1/(2*df))})^2 < 2$). However, the models for the source contribution analyses of PM10 and of PM2.5 showed potential for collinearity between livestock and other agricultural sources ($(GVIF^{(1/(2*df))})^2 > 3$); no other indications of potential collinearity were found (all other $(GVIF^{(1/(2*df))})^2 < 3$).

Table 3
Overall effects (adjusted Odds Ratios) of the long-term exposure to air pollution (total PM10 and PM2.5 and NO_2 concentrations) on testing positive for SARS-CoV-2.

Pollutant	Analysis	Odds Ratio (95% Confidence Interval)[a]			
		per IQR μg/m^3 increase[b]	per 1 μg/m^3 increase		
		National	National	Rural areas	Urban areas
PM10	1 pollutant	1.005 (0.985–1.025)	1.003 (0.990–1.015)	1.017 (0.997–1.037)	0.992 (0.976–1.008)
	2 pollutants (+NO_2)	1.010 (0.987–1.034)	1.006 (0.992–1.021)	1.020 (0.998–1.043)	0.991 (0.972–1.010)
PM2.5	1 pollutant	0.994 (0.972–1.017)	0.995 (0.976–1.014)	1.013 (0.976–1.052)	0.988 (0.966–1.011)
	2 pollutants (+NO_2)	0.996 (0.971–1.023)	0.997 (0.975–1.019)	0.998 (0.993–1.003)	0.987 (0.961–1.013)
NO_2	1 pollutant	0.994 (0.975–1.014)	0.999 (0.996–1.002)	1.000 (0.995–1.005)	0.999 (0.995–1.003)
	2 pollutants (+PM10)	0.990 (0.968–1.012)	0.998 (0.995–1.002)	1.018 (0.975–1.064)	1.001 (0.996–1.006)
	2 pollutants (+PM2.5)	0.996 (0.974–1.018)	0.999 (0.996–1.003)	0.999 (0.993–1.004)	1.001 (0.996–1.005)

[a] Adjusted for sex, age, household wealth, household size, migration background, highest attained education level, neighborhood SES score, municipality and test week.

[b] Interquartile range (IQR) for PM10 = 1.63 μg/m^3, for PM2.5 = 1.18 μg/m^3 and NO_2 = 6.07 μg/m^3.

3.2. Effects of long-term exposure

3.2.1. Overall effects

Single-pollutant models showed no statistically significant associations between exposure to PM10, PM2.5 and NO_2 concentrations in the three years before the COVID-19 pandemic and the odds of testing positive for SARS-CoV-2 (*vs.* other respiratory diseases) among symptomatic people, at national level, and in urban and rural areas. The same was also observed in multi-pollutant models (Table 3).

3.2.2. Emission source contributions

Of the total PM10 to which the study population was exposed, 35.1% was accounted for by foreign sources, followed by other Dutch sources (13.2%), road traffic (6.5%), industry (4.2%), livestock (3.5%), and other agricultural sources (0.7%). For total PM2.5, 48.9% of exposure in the study population was accounted for by foreign sources, followed by other Dutch sources (18.4%), road traffic (7.9%), livestock (5.0%), industry (4.9%), and other agricultural sources (0.9%).

When looking at the effects of long-term exposure to different sources of air pollution (Table 4), significantly positive associations were found for PM10 from foreign sources (both at national level and in rural areas), livestock (nationally and in both rural and urban areas) and other agricultural sources (nationally). Other Dutch sources showed a significantly negative association. For PM2.5, a significantly positive association was observed for foreign sources at all levels and for livestock sources nationally, whereas a negative association was observed for industry nationally.

Heterogeneity of the effect sizes of the source contributions was high (I^2 >70%) in the national and rural strata, but low (I^2 <25%) in the urban stratum.

3.3. Effects of short-term exposure

In single-pollutant models, average concentrations of PM10 1- or 2-weeks before the testing day were negatively associated with the odds of testing positive for SARS-CoV-2, whereas for PM2.5 the associations were positive. When adjusting for NO_2 and O_3, the associations with PM10 became positive, while those with PM2.5 remained positive. For NO_2 and O_3, all models showed negative associations with the odds of testing positive for SARS-CoV-2 (Table 5).

3.4. Sensitivity analyses

In general, results were robust to sensitivity analyses for both long- and short-term exposures (Figs. S8–S10, Appendix). Statistically significant changes in direction of the association were observed in the long-term exposure analysis, where positive associations with foreign sources of PM10 and PM2.5 appeared when the analysis was restricted to areas with the highest degrees of urbanization. No other changes were observed in the sensitivity analyses.

4. Discussion

This study assessed whether long- and short-term exposure to ambient concentrations of AAP increases the risk of acquiring SARS-CoV-2 infection as compared to other diseases showing symptoms compatible with COVID-19. We found that, overall, long-term exposure to PM10, PM2.5 or NO_2 concentrations did not pose significant increased risks of testing positive for SARS-CoV-2, whereas significant risks from short-term exposure, particularly to PM2.5, were observed. However, when looking at specific sources of PM, we found that long-term exposure to PM10 and PM2.5 from foreign and livestock sources, and to PM10 from other agricultural sources, were associated with increased odds of SARS-CoV-2 positivity. It is worth stressing that the adopted study design can only detect effects of AAP on COVID-19 that are significantly different than the ones for other respiratory diseases composing our control group. In other words, the setting of the study filters out any effect of AAP that is common to all respiratory diseases, including COVID-19, thereby detecting only those effects that are specific or unique for COVID-19.

Decades before the COVID-19 pandemic, it was recognized that exposure to AAP increases morbidity and mortality of several diseases, notably cardiovascular and respiratory diseases (Burnett et al., 2018), but also viral infections of the upper (Jaakkola et al., 1991; Fusco et al., 2001) and lower (GBD 2016 Lower Respiratory Infections Collaborators, 2018; Wong et al., 1999; Horne et al., 2018; Carugno et al., 2018) respiratory tract, including pneumonia (Nhung et al., 2017; Croft et al., 2019; Neupane et al., 2010). Both short-term (Hirota et al., 2015; Ciencewicki et al., 2007; Li et al., 2010) and long-term exposure (Neupane et al., 2010) to air pollution have been shown to weaken the immune system and increase systemic inflammation, rendering individuals more susceptible to being infected with SARS-CoV-2. Experimental evidence has shown that both PM and NO_2 impact susceptibility and

Table 4
Emission source-specific effects (adjusted Odds Ratios) of the long-term exposure to air pollution from specific sources on testing positive for SARS-CoV-2.

Pollutant	Source	Odds Ratio (95% Confidence Interval)[a]			
		per IQR μg/m^3 increase[b]	per 1 μg/m^3 increase		
		National	National	Rural areas	Urban areas
PM10	Foreign sources	1.152 (1.043–1.274)	1.093 (1.027–1.163)	1.116 (1.038–1.201)	0.950 (0.828–1.091)
	Industry	0.994 (0.987–1.001)	0.974 (0.946–1.003)	0.972 (0.929–1.017)	0.970 (0.934–1.008)
	Livestock	1.022 (1.008–1.036)	1.053 (1.020–1.088)	1.044 (1.009–1.080)	1.221 (1.024–1.456)
	Other agricultural sources	1.016 (1.005–1.027)	2.195 (1.271–3.791)	1.829 (0.955–3.502)	0.826 (0.221–3.088)
	Road traffic	1.006 (0.986–1.026)	1.011 (0.975–1.048)	1.024 (0.969–1.081)	0.996 (0.949–1.045)
	Other Dutch sources	0.971 (0.947–0.996)	0.976 (0.956–0.996)	0.960 (0.919–1.004)	1.005 (0.976–1.034)
	Heterogeneity test (I^2)	*85.9%*		*78.2%*	*8.9%*
PM2.5	Foreign sources	1.180 (1.063–1.311)	1.136 (1.048–1.231)	1.162 (1.057–1.277)	0.948 (0.793–1.134)
	Industry	0.991 (0.984–0.999)	0.938 (0.888–0.991)	0.956 (0.879–1.040)	0.927 (0.864–0.995)
	Livestock	1.073 (1.024–1.124)	1.310 (1.095–1.568)	1.211 (0.989–1.482)	2.662 (1.367–5.183)
	Other agricultural sources	1.006 (0.991–1.023)	1.909 (0.393–9.274)	1.880 (0.275–12.842)	0.095 (0.004–2.422)
	Road traffic	1.005 (0.982–1.028)	1.013 (0.952–1.078)	1.031 (0.940–1.131)	0.978 (0.898–1.065)
	Other Dutch sources	0.972 (0.946–1.000)	0.971 (0.943–1.000)	0.953 (0.899–1.010)	1.018 (0.976–1.061)
	Heterogeneity test (I^2)	*90.9%*		*74.4%*	*36.4%*

[a] Adjusted for sex, age, household wealth, household size, migration background, highest attained education level, neighborhood SES score, municipality and test week.

[b] Interquartile range (IQR) for PM10 'foreign sources' = 1.60 μg/m^3, 'industry' = 0.23 μg/m^3, 'livestock' = 0.42 μg/m^3, 'other agricultural sources' = 0.02 μg/m^3, 'road traffic' = 0.54 μg/m^3 and 'other Dutch sources' = 1.2 μg/m^3. IQR for PM2.5 'foreign sources' = 1.30 μg/m^3, 'industry' = 0.14 μg/m^3, 'livestock' = 0.26 μg/m^3, 'other agricultural sources' = 0.01 μg/m^3, 'road traffic' = 0.37 μg/m^3 and 'other Dutch sources' = 0.96 μg/m^3.

Table 5
Effects (adjusted Odds Ratios)of short-term exposure (average air pollution concentrations one and two weeks before testing day) at national level (whole country of the Netherlands) and stratified by rural and urban areas.

Pollutant	Analysis	Odds Ratio (95% Confidence Interval)[a]							
		One week before				Two weeks before			
		per IQR μg/m^3 increase[b]	per 1 μg/m^3 increase			per IQR μg/m^3 increase[a]	per 1 μg/m^3 increase		
		National	National	Rural areas	Urban areas	National	National	Rural areas	Urban areas
PM10	1 pollutant	**0.961 (0.949–0.973)**	**0.992 (0.990–0.994)**	0.997 (0.994–1.001)	**0.991 (0.987–0.994)**	**0.887 (0.869–0.906)**	**0.978 (0.974–0.982)**	**0.986 (0.980–0.993)**	**0.977 (0.972–0.982)**
	2 pollutants (+NO_2)	**1.024 (1.007–1.040)**	**1.005 (1.001–1.008)**	**1.007 (1.002–1.012)**	1.000 (0.995–1.004)	**0.956 (0.932–0.980)**	**0.991 (0.987–0.996)**	0.994 (0.987–1.001)	**0.986 (0.980–0.992)**
	2 pollutants (+O_3)	**0.955 (0.944–0.967)**	**0.991 (0.989–0.993)**	**0.994 (0.991–0.998)**	**0.991 (0.988–0.994)**	**0.973 (0.951–0.996)**	**0.995 (0.991–0.999)**	0.999 (0.993–1.006)	**0.994 (0.988–1.000)**
	3 pollutants (+NO_2+O_3)	**1.073 (1.056–1.091)**	**1.014 (1.011–1.018)**	**1.011 (1.006–1.016)**	**1.011 (1.007–1.016)**	**1.132 (1.101–1.164)**	**1.024 (1.018–1.029)**	**1.018 (1.010–1.026)**	**1.016 (1.009–1.024)**
PM2.5	1 pollutant	**1.024 (1.012–1.036)**	**1.005 (1.003–1.008)**	**1.006 (1.002–1.010)**	1.003 (0.999–1.006)	**1.055 (1.035–1.075)**	**1.013 (1.009–1.018)**	**1.014 (1.007–1.021)**	**1.009 (1.003–1.016)**
	2 pollutants (+NO_2)	**1.151 (1.133–1.169)**	**1.031 (1.028–1.035)**	**1.025 (1.020–1.031)**	**1.025 (1.020–1.030)**	**1.169 (1.145–1.194)**	**1.039 (1.034–1.045)**	**1.031 (1.022–1.039)**	**1.031 (1.023–1.038)**
	2 pollutants (+O_3)	0.997 (0.985–1.009)	0.999 (0.997–1.002)	0.999 (0.995–1.003)	1.000 (0.996–1.003)	**1.079 (1.059–1.100)**	**1.019 (1.014–1.024)**	**1.015 (1.008–1.022)**	**1.019 (1.013–1.025)**
	3 pollutants (+NO_2+O_3)	**1.140 (1.122–1.158)**	**1.029 (1.025–1.033)**	**1.020 (1.015–1.025)**	**1.027 (1.022–1.032)**	**1.222 (1.196–1.249)**	**1.051 (1.045–1.056)**	**1.036 (1.028–1.044)**	**1.046 (1.039–1.054)**
NO_2	1 pollutant	**0.919 (0.907–0.931)**	**0.989 (0.987–0.991)**	**0.993 (0.990–0.996)**	**0.990 (0.988–0.992)**	**0.880 (0.866–0.895)**	**0.982 (0.980–0.984)**	**0.990 (0.986–0.993)**	**0.984 (0.981–0.988)**
	2 pollutants (+PM_{10})	**0.903 (0.888–0.919)**	**0.987 (0.984–0.989)**	**0.990 (0.987–0.993)**	**0.991 (0.988–0.994)**	**0.895 (0.878–0.912)**	**0.984 (0.982–0.987)**	**0.991 (0.987–0.995)**	**0.990 (0.986–0.994)**
	2 pollutants (+$PM_{2.5}$)	**0.825 (0.811–0.840)**	**0.975 (0.973–0.977)**	**0.981 (0.978–0.985)**	**0.979 (0.976–0.982)**	**0.824 (0.809–0.839)**	**0.973 (0.970–0.975)**	**0.983 (0.979–0.987)**	**0.977 (0.973–0.981)**
	2 pollutants (+O_3)	**0.868 (0.856–0.880)**	**0.981 (0.980–0.983)**	**0.986 (0.983–0.989)**	**0.985 (0.982–0.987)**	**0.867 (0.853–0.881)**	**0.980 (0.978–0.982)**	**0.987 (0.984–0.991)**	**0.984 (0.981–0.987)**
	3 pollutants (+PM10+O_3)	**0.823 (0.807–0.838)**	**0.975 (0.972–0.977)**	**0.981 (0.977–0.984)**	**0.979 (0.975–0.982)**	**0.824 (0.808–0.841)**	**0.973 (0.970–0.976)**	**0.982 (0.978–0.986)**	**0.978 (0.974–0.983)**
	3 pollutants (+PM2.5+O_3)	**0.788 (0.774–0.802)**	**0.969 (0.967–0.971)**	**0.977 (0.974–0.981)**	**0.972 (0.969–0.975)**	**0.797 (0.782–0.812)**	**0.968 (0.965–0.971)**	**0.979 (0.975–0.983)**	**0.972 (0.968–0.975)**
O_3	1 pollutant	**0.891 (0.878–0.904)**	**0.994 (0.993–0.995)**	**0.995 (0.993–0.996)**	**0.995 (0.994–0.996)**	**0.711 (0.692–0.730)**	**0.985 (0.984–0.986)**	**0.987 (0.985–0.989)**	**0.987 (0.985–0.988)**
	2 pollutants (+NO_2)	**0.841 (0.828–0.854)**	**0.991 (0.990–0.992)**	**0.992 (0.991–0.993)**	**0.993 (0.992–0.994)**	**0.702 (0.684–0.721)**	**0.984 (0.983–0.986)**	**0.986 (0.984–0.988)**	**0.987 (0.985–0.988)**
	2 pollutants (+PM10)	**0.889 (0.876–0.902)**	**0.994 (0.993–0.995)**	**0.994 (0.993–0.995)**	**0.995 (0.994–0.996)**	**0.722 (0.701–0.743)**	**0.986 (0.984–0.987)**	**0.987 (0.985–0.989)**	**0.988 (0.986–0.989)**
	2 pollutants (+PM2.5)	**0.891 (0.878–0.905)**	**0.994 (0.993–0.995)**	**0.994 (0.993–0.996)**	**0.995 (0.994–0.996)**	**0.706 (0.687–0.725)**	**0.985 (0.983–0.986)**	**0.987 (0.985–0.989)**	**0.986 (0.985–0.988)**
	3 pollutants (+PM10+NO_2)	**0.827 (0.814–0.841)**	**0.990 (0.990–0.991)**	**0.992 (0.990–0.993)**	**0.992 (0.991–0.993)**	**0.662 (0.643–0.682)**	**0.982 (0.981–0.983)**	**0.984 (0.982–0.986)**	**0.985 (0.983–0.986)**
	3 pollutants (+PM2.5+NO_2)	**0.848 (0.834–0.861)**	**0.992 (0.991–0.992)**	**0.993 (0.992–0.994)**	**0.993 (0.992–0.994)**	**0.677 (0.659–0.696)**	**0.983 (0.982–0.984)**	**0.986 (0.984–0.988)**	**0.984 (0.983–0.986)**

[a] Adjusted for sex, age, housolhd wealth, household size, migration background, highest attained education level, neighborhood SES score, municipality and test week.
[b] Interquartile range (IQR) for 1-week PM10 = 5.01 μg/m^3, PM2.5 = 4.57 μg/m^3, NO_2 = 7.56 μg/m^3, O_3 = 19.62 μg/m^3. IQR for 2-week PM10 = 5.30 μg/m^3, PM2.5 = 4.07 μg/m^3, NO_2 = 7.00 μg/m^3, O_3 = 22.45 μg/m^3.

immune response to viral infections through various mechanisms, such as augmented or impaired innate and adaptive immunity (Hirota et al., 2015; Ciencewicki et al., 2007), including skewed immune responses from predominantly antiviral to allergic Th2-predominant responses (Li et al., 2010), disrupted airway epithelial barrier function (Woodby et al., 2021; Liu et al., 2019a), impaired cytotoxicity (Becker and Soukup, 1999), and altered cell surface receptor expression (Lin et al., 2018; Spannhake et al., 2002). This latter is of particular interest for explaining how air pollution might affect COVID-19 differently. Indeed, air pollution can alter host cell surface receptor expression in a way that would favor coronavirus, including SARS-CoV-2, infection. This is because coronaviruses target the angiotensin converting enzyme 2 (ACE-2) receptor for entry into the cells (Lin et al., 2018; Frontera et al., 2020; Paital and Agrawal, 2021). The ACE-2 acts as the sole receptor for SARS-CoV-2 via its spike protein, and ACE-2 has been found to be overexpressed on airway epithelial cells under chronic exposure to PM (Lin et al., 2018; Frontera et al., 2020). A 'double hit' hypothesis has also been proposed (Frontera et al., 2020) in which chronic exposure to PM inducing alveolar ACE-2 receptor overexpression would increase viral load, depleting ACE-2 receptors and impairing host defenses (i.e., the 'first hit'). Concurrently, exposure to NO_2 would provide a 'second hit' that would cause a more severe SARS-CoV-2 infection in ACE-2 depleted lungs, resulting in worse health outcomes (Frontera et al., 2020; Paital and Agrawal, 2021). Moreover, pre-existing health conditions, such as cardiovascular disease and lung cancer, for which long-term air pollution exposure is a risk factor, are, in turn, risk factors for COVID-19 by compromising overall health status and weakening immune responses over time (Singh et al., 2021). Although our study did not focus on severity of COVID-19 given infection (e.g. hospitalization, ICU admission or mortality), it is conceivable that worsening of health outcomes might increase the urgency of testing. Interestingly, we observed that in the short-term exposure analysis, adding NO_2 led PM10 to become a risk factor, and increased the effect size of the already positive association of PM2.5.

While long-term exposure to PM10 and PM2.5 from foreign and livestock sources, and to PM2.5 from other agricultural sources, showed significant positive (i.e., adverse for COVID-19) effects, other Dutch sources of PM10 and industrial sources of PM2.5 showed significant negative effects for COVID-19 risk. Given the study design, this does not mean that these two latter exposures are beneficial for COVID-19, but rather that they have significantly stronger detrimental effects for the different respiratory conditions other than COVID-19 present among the test-negatives. Without further information on these etiologies, it is not possible to provide a biological interpretation of the underlying mechanisms. Moreover, the effects observed for foreign sources and other Dutch sources (i.e., other than agriculture, industry and road traffic) cannot be interpreted in the same manner as the other sources. Indeed, while different sources emit different PM compositions with potentially different toxicities, hence potentially different effects on health, this cannot be disentangled when the sources are so broadly defined, as they are in turn composed of emissions from mixed sources as well. Moreover, their composition can differ per area (e.g., close to industries or not). Therefore, we included these sources to account for their background concentrations in the analysis, but the interpretation of these estimates remains limited. Similarly, source contribution of PM2.5, as compared to PM10, is more limited, as PM2.5 concentrations per source are more complicated to interpret due to co-dependence between sources for formation of secondary aerosols.

In general, the effects observed nationally were also observed in either urban or rural areas, but relatively more consistently for PM from livestock. The Netherlands is a densely populated country with no major topographical features causing large climatological differences. Moreover, due to widespread intensive farming, the country also happens to have the largest livestock density in Europe (https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Agri-environmental_indicator_-_livestock_patterns). Furthermore, because of its relatively small territorial extension and immediacy with Germany and Belgium, contributions to PM concentrations from sources from abroad are generally high, especially in the most southern and eastern parts of the country, which also happen to be more devoted to agricultural activities (especially poultry and pig farms). Conversely, NO_2 concentrations are highest in the more densely populated western parts where higher pollution from traffic and industrial activities can be found. The magnitude of the contribution of the different sources of air pollution varies between urban and rural areas (and so does the corresponding mixture of PM components and distribution of primary and secondary pollutants, as mentioned before), but this is also true for the exposed population in terms of density, susceptibility, lifestyle, mobility, behaviours, etc., including virus transmission patterns (Matz et al., 2015). Indeed, risk factors other than AAP also have a spatial distribution, and studies on these factors may also be confounded by patterns of virus spread. Jointly all factors shape virus spread. This might explain, at least in part, why the effects of PM observed here varied across sources and urbanization degrees. Our results add further evidence to the several studies that have shown that proximity to farms is associated with increased risk of various health outcomes, including respiratory conditions (Freidl et al., 2017; Kalkowska et al., 2018; Klous et al., 2018; Post et al., 2021; Simões et al., 2022; Smit et al., 2012) and SARS-CoV-2 infection as well (Hogerwerf et al., 2022). The proposed hypotheses about the underlying biological mechanisms include hypersensitization towards livestock-borne PM, including PM contaminated with microbes and endotoxins, also called bioPM, which would trigger innate immune responses contributing to respiratory disease, including COVID-19 (Liu et al., 2019b; Poole and Romberger, 2012; Sahlander et al., 2012; Diamond and Kanneganti, 2022). However, the effects found here are, once again, signaling at best and more research is needed to corroborate whether and how these hypotheses would apply to COVID-19 as well.

We observed negative associations for NO_2 and O_3 in the short-term exposure analyses. Again, this does not mean that they are beneficial for COVID-19, but rather that they pose a more pronounced risk for respiratory conditions other than COVID-19, although the underlying reasons remain unclear. What we know is that increases in O_3 are associated with decreased NO_2 levels (Quan et al., 2014; Hashim et al., 2021), as also observed in our study (Fig. S7, Appendix). Measures implemented to contain the spread of COVID-19, such as lockdowns, are known to have impacted air quality due to reduction of certain economic activities and particularly less road traffic in general (and therefore reduced NO_2 concentrations as a consequence) due to fewer commuting and widely implemented 'stay at home' recommendations (Velders et al., 2021; Zheng et al., 2020; Bashir et al., 2020). Yet, staying at (and working from) home remained common even after the most stringent measures were lifted, as it was generally encouraged when/where possible to limit SARS-CoV-2 transmission; thus, it cannot be excluded that this might have also influenced the negative association observed here, as people might have increasingly refrained from moving during periods of increasing SARS-CoV-2 circulation. However, staying more at home also means increased exposure to indoor NO_2 from, e.g., cooking on gas, whose possible compensatory effect cannot be studied here. While other studies on the short-term effects of air pollution on COVID-19 have also reported negative associations with NO_2 (Bashir et al., 2020; Sangkham et al., 2021; Akan, 2022), it seems that in general NO_2 has stronger effects on disease severity (Zang et al., 2022; Ali et al., 2021; Marquès and Domingo, 2022), supporting the aforementioned double hit hypothesis (Frontera et al., 2020). In general, however, the association with short-term exposure remains difficult to study (Katoto et al., 2021; Brunekreef et al., 2021; Walton et al., 2022; Carballo et al., 2022) because most analyses are based on very short periods with limited exposure contrast (Walton et al., 2022) against a background of complex SARS-CoV-2 infection dynamics, including different measures implemented, vaccination campaigns, emergence of variants, altered mobility patterns, etc.

This study has several limitations, some of which are intrinsic to the

outcome definition. For example, both sensitivity and specificity of SARS-CoV-2 tests may vary, and even when PCR is performed, it can vary in relation to the timing of symptom onset (Zou et al., 2020; Wölfel et al., 2020) and type of samples tested (Teo et al., 2021). Therefore, it is inevitable that there would be some misclassification of the outcome, and in the test-negative design, all false-negatives would fall in the control group and all false-positives in the case group. The resulting misclassification would then have most consequences in situations wherein the proportion of COVID-19 relative to other diseases is either very high or very low. However, in the relatively limited study period (i.e., 6 months, from June to November 2020), such situation did not really occur. Linked to this point, we could only analyze data of the so-called 'second wave'. The study period chosen was the best compromise possible between data availability/quality and study characteristics, as before June 2020 no suited data was available and after November 2020 testing was extended to people without symptoms, and later on at the beginning of 2021 vaccination started and virus variants began to emerge, which complicates the interpretation of analyses due to potential effects of immunity. In this regard, though, focusing on the second wave also implies inclusion of potential effects of immunity. Indeed, it is known that as the epidemic progressed, some risk factors for SARS-CoV-2 infection at the beginning of the pandemic (e.g., having a job entailing contact with other people), paradoxically, became protective against new infections later. This is because people who acquired the infection first also built immunity against new infection earlier than others (Vandenbroucke et al., 2020). Regarding air pollution, therefore, it is possible that people at highest risk of COVID-19 because of exposure to air pollution acquired the infection earlier during the first wave, thereby turning up later in the study period mainly as seemingly test-negatives when having symptoms (from another cause). Although we excluded healthcare workers and people living in nursing homes in an effort to address this issue, the fact that other persons with acquired immunity that we could not account for were still included in our analyses might have muddled our risk estimates. Moreover, looking at later phases of the pandemic when the virus had spread everywhere in the country might have helped compensating for potential seeding effects and data reporting issues present at the beginning of the pandemic.

One of the biggest sources of exposure misclassification in epidemiological studies on health effects of exposure to air pollution is not taking time activity-patterns into account. Since this study was based on administrative data, it was impossible to obtain mobility information for the study population. As discussed above, the study period coincided with lockdown periods, when mobility of individuals outside their homes was greatly reduced, thereby decreasing the potential for exposure misclassification. However, potential indoor sources might concomitantly have had a greater weight to the overall exposure to air pollutants, namely NO_2 and it is difficult to ascertain how these two aspects might influence results.

The spatial resolution of the exposure maps may also have contributed, to some extent, to exposure misclassification, especially for NO_2, as this pollutant is known to have significant spatial variability close to busy roads. However, building higher resolutions maps of annual averages becomes problematic because of loss of granularity in the emission data, that is, errors are introduced when building maps with resolution higher than 1×1 km. For example, while it is always known where roads are located, the respective volume of traffic and type of cars driven is not. This is less of an issue for PM10 and PM2.5, which can be transported over longer distances and are therefore more homogenously distributed over large areas. Exposure misclassification, which would be non-differential, and coarser resolution maps in the short-term exposure analysis, which would result in lower exposure contrast, might have both introduced bias towards the null.

While test-negatives would have another reason than COVID-19 for their symptoms, most likely another respiratory infection, it cannot be excluded that some symptoms were also due to non-infectious conditions (e.g., allergies, asthma, etc.) or even faked symptoms to access testing. Yet, our study period (June–November 2020) excludes the main allergy season (spring), so common conditions like hay fever can be expected to have played a relatively minor role. A first hypothesis was that AAP increases the baseline risk of the population exposed, resulting in higher prevalence of comorbidities associated with increased COVID-19 risk. However, mediation effects of comorbidities might be expected to be similar both for test-negatives and test-positives, and any difference would be likely to depend on the nature of the test-negatives and comorbidities in question, and whether these vary over space and time. Although we lacked specific data on comorbidities, other individual-level studies that included adjustment for comorbidities found minimal changes in the estimates (English et al., 2022; Nobile et al., 2022; Ranzani et al., 2023). Moreover, adjustment for several other factors known to be associated with poor health outcomes, lifestyles and behaviors, as well as viral transmission (e.g., age, SES, income, country of origin, occupation, etc.) were accounted for in our analysis. While the effects are suggestive of certain mechanisms being at play, further studies are needed to understand the specific biological pathways involved. On the other hand, major strengths of the study include full nationwide coverage of the Netherlands' population spanning both urban and rural areas in a period of varying viral circulation, with high-quality individual-level data on (both long- and short-term) exposure and several potential confounders to include in the analyses. Moreover, the analyses addressed explicitly also potentially differential effects of various sources of air pollution emission. Although COVID-19 diagnoses for cases that were not confirmed in public testing facilities could not be included in this study, altogether this study yielded high statistical power, robust analyses (as also confirmed by the sensitivity analyses), and quality of estimates due to availability of high-resolution data as well as limited residual confounding expected.

In conclusion, there was no evidence that, overall, the AAP concentrations in the years before the COVID-19 pandemic had significantly different effects on the incidence of COVID-19 as compared to other respiratory diseases. Therefore, general recommendations about improving air quality to mitigate COVID-19 risk would be the same as for other respiratory diseases. However, there were signals that increased long-term exposure to PM emissions from agricultural sources, namely from livestock, was associated with higher odds of testing positive *vs*. negative for SARS-CoV-2 among people with COVID-19-compatible symptoms. This deserves more attention for full appraisal of the underlying biological mechanisms. The same can be said for the observed higher odds of testing positive for SARS-CoV-2 infection when exposed to higher concentrations of PM in in the prior 1–2 weeks. Overall, this study reinforces the need to continue current efforts for better air quality to support public health.

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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.

CRediT authorship contribution statement

Mariana Simões: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Jelle Zorn:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Lenny Hogerwerf:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Guus J.M. Velders:** Writing – review & editing, Data curation. **Lützen Portengen:** Writing – review & editing, Methodology. **Miriam Gerlofs-Nijland:** Writing – review & editing, Project administration, Investigation, Funding acquisition, Conceptualization. **Marieke Dijkema:** Writing – review & editing, Investigation. **Maciek Strak:** Writing – review & editing, Investigation, Formal analysis, Data curation. **José Jacobs:** Writing – review & editing, Investigation, Data curation. **Joost Wesseling:** Data curation, Methodology, Writing – review & editing. **Wilco J. de Vries:** Data curation, Methodology, Writing – review & editing. **Suzanne Mijnen-Visser:** Data curation, Methodology, Writing – review & editing. **Lidwien A.M. Smit:** Writing – review & editing, Investigation, Conceptualization. **Roel Vermeulen:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Lapo Mughini-Gras:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2024.114382.

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