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Original article

Exposure to air pollution and risk of respiratory tract infections in the adult Danish population—a nationwide study

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ABSTRACT

Objectives: The association between air pollution and risk of respiratory tract infection (RTI) in adults needs to be clarified in settings with low to moderate levels of air pollution. We investigated this in the Danish population between 2004 and 2016.

Methods: We included 3 653 490 persons aged 18–64 years in a nested case-control study. Exposure was defined as the average daily concentration at the individual's residential address of CO, NO_X, NO_2, O_3, SO_2, NH_3, $PPM_{2.5}$, black carbon, organic carbon, mineral dust, sea salt, secondary inorganic aerosols, SO_4^{2-}, NO_3^-, NH_4^+, secondary organic aerosols, $PM_{2.5}$, and PM_{10} during a 3-month exposure window. RTIs were defined by hospitalization for RTIs. Incidence rate ratios (IRRs) and 95% CIs were estimated comparing highest with lowest decile of exposure using conditional logistic regression models.

Results: In total, 188 439 incident cases of RTI were identified. Exposure to most air pollutants was positively associated with risk of RTI. For example, NO_2 showed an IRR of 1.52 (CI: 1.48–1.55), and $PM_{2.5}$ showed an IRR of 1.45 (CI: 1.40–1.50). In contrast, exposure to sea salt, PM_{10}, NH_3, and O_3 was negatively associated with a risk of RTIs.

Discussion: In this nationwide study comprising adults, exposure to air pollution was associated with risk of RTIs and subgroups hereof. Sea salt, PM_{10}, NH_3, and O_3 may be proxies for rural areas, as the levels of these species in Denmark are higher near the western coastlines and/or in rural areas with fewer combustion sources. **Kathrine A. Kaspersen, Clin Microbiol Infect 2024;30:122**

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Introduction

Globally, the WHO estimates that 4.2 million premature deaths are linked to outdoor air pollution annually, and air pollution is responsible for 17% of all deaths and diseases from acute lower respiratory infection [1].

The association between air pollution and health-related outcomes including cardiovascular and respiratory morbidity and

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mortality is well documented [2–4]. Whereas the majority of research on health effects of air pollution has focused on mortality, less attention has been paid to exploring respiratory tract infections (RTIs) [5]. Most of the studies addressing this are conducted in children [6], elderly people [7], in low-income countries, in countries outside Europe [8,9], and generally in settings with higher levels of air pollution [10,11].

In Denmark, air pollution has decreased markedly during the past 10 years, and Denmark is now a country with low to moderate levels of air pollution. Despite that, long-term air pollution exposure is still associated with an increased natural cause mortality in the Danish population [12]. In addition, studies from the multicentre project Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) show that long-term exposure to low levels of air pollution contributes to serious health outcomes such as lung cancer [13], chronic lung diseases [14], chronic obstructive pulmonary disease (COPD) [15], and increased mortality from lower respiratory tractions [3]. More studies exploring susceptibility to RTIs from similar settings are needed, and to our knowledge, no nationwide study exist using an adult population of a high-income European/Western country.

The aim of this study was to provide an overview over associations between each of 18 different air pollutant components and a wide range of RTIs in the adult Danish population. Our hypothesis was that the risk of RTI increases with air pollution exposure.

Material and methods

This study was conducted by combining detailed information of spatio-temporal distribution of air pollution exposure with the Danish population-based health register data using the unique Danish personal identification number as linkage.

Study population and design

Danish-born residents aged 18–64 years were included from 2004 to 2016 in a nested case-control design ($n = 3\,653\,490$). See supplementary material.

Incident cases were defined as people with a first-time RTI diagnosis during follow-up. In each group of RTIs, people with a prior RTI diagnosis within that particular group, as registered in the International Classification of Diseases, Eighth and Tenth Revision (ICD-8/10) before the initiation of follow-up, were excluded from the study to ensure that they did not qualify as either a case or a control. For each incident case, ten controls were selected at random, matched on exact birth date and sex, and required to be alive, residing in Denmark and disease free (no RTI) when the case experienced an event (index date).

Air pollution exposure

The well-known and validated integrated Danish air pollution modelling system (The Danish Eulerian Hemispheric Model and The Urban Background Model) was used to calculate the concentration of air pollution across Denmark down to a spatial resolution of 1 km × 1 km and employing hourly average concentrations; the system has previously been described and evaluated in detail [16–18].

Exposure was defined as the time-weighted average of the daily mean concentration at all residential addresses during the study period accounting for residential changes. The following air pollution components were explored and grouped as gases (CO, NO_x, NO_2, O_3, SO_2, and NH_3), primary particles ($PPM_{2.5}$, comprising black carbon, organic carbon, mineral dust, and sea salt), secondary particles (secondary inorganic aerosols, comprising SO_4^{2}, NO_3^{-}, and NH_4^{+}, and secondary organic aerosols), and total particles ($PM_{2.5}$ and PM_{10}). An *a priori* decision to explore each air pollutant separately was made. See supplementary material.

The average exposure during the 3 months before infection was chosen as the main exposure window. The exposure window for controls was similarly defined as the average daily mean exposure during 3 months before the event date of the individually matched case. The most appropriate length of the window of exposure is unknown. Thus, sensitivity analyses were performed using exposure windows of 3 days, 1 week, and 1, 6, and 12 months.

Delineation of respiratory tract infections

The main outcome (RTIs) was defined by relevant diagnostic codes in the Danish National Patient Register (NPR).

RTIs were sub-classified as upper and lower RTIs (defined as infections in/above trachea and below trachea, respectively). Finally, we explored subgroups: sinusitis, infections of the oral cavity, tonsillitis, influenza, bronchitis, pneumonia, viral and bacterial pneumonia. See supplementary material.

Covariates

The following covariates were considered as potential confounders: sex, age, calendar time, population density at municipality level, socio-economic status, chronic pulmonary disease, COPD, several comorbidities using the Charlson Comorbidity Index, and temperature. See supplementary material.

Statistical analyses

Conditional logistic regression was used to estimate incidence rate ratios (IRRs) and 95% likelihood ratio-based CIs.

Exposure was divided into deciles according to the distribution among controls and modelled as a continuous variable scaled from 0 to 1, estimating the association between air pollution and RTI when comparing the highest decile with the lowest decile (corresponding to a one-unit increase in the exposure variable).

Two confounder models were used: a basic model by design adjusted for age, sex, and calendar time; and a fully adjusted model with further adjustment for population density, socio-economic status, chronic pulmonary disease (including COPD), and Charlson Comorbidity Index (excluding chronic pulmonary disease). To measure the effect of each covariate, the basic model was repeated by alternately including the covariates.

The estimates are presented for all RTIs in the fully adjusted model for the 3-month exposure window unless otherwise specified. See supplementary material for details.

Ethics

This study was approved by the Danish Data Protection Agency, and data access was granted by the Health Data Authority and Statistics Denmark.

The study was based exclusively on register data, and according to Danish legislation informed consent from participants is thus not required.

Results

Cohort characteristics

Tables 1 and 2 show the distribution of characteristics for cases and controls at index date. In total, 188 439 incident cases with RTIs were identified.

Table 1
Descriptive characteristics of the cohort

Characteristics	Cases	Controls
Overall	188 439	1 884 390
Upper respiratory tract infections	113 269 (60.1)	1 132 690 (60.1)
Lower respiratory tract infections	100 766 (53.5)	1 007 660 (53.5)
Sex		
Males	89 398 (47.4)	893 980 (47.4)
Females	99 041 (52.6)	990 410 (52.6)
Index year		
2004–2007	52 217 (27.7)	522 170 (27.7)
2008–2010	38 681 (20.5)	386 810 (20.5)
2011–2013	37 827 (20.1)	378 270 (20.1)
2014–2016	59 714 (31.7)	597 140 (31.7)
Age at index date, y		
18–19	9335 (5.00)	93 350 (5.00)
20–29	30 672 (16.3)	306 720 (16.3)
30–39	31 235 (16.6)	312 350 (16.6)
40–49	34 457 (18.3)	344 570 (18.3)
50–59	49 127 (26.1)	491 270 (26.1)
60–64	33 613 (17.8)	336 130 (17.8)
Chronic pulmonary disease diagnosis before index date	18 353 (9.70)	68 581 (3.60)
COPD diagnosis before index date	7641 (4.10)	14 165 (0.80)
Charlson score at index date		
0	138 293 (73.4)	1 642 390 (87.2)
1	18 365 (9.70)	122 562 (6.50)
≥2	31 781 (16.8)	119 438 (6.30)
Income quartile		
1st (lowest)	54 316 (28.8)	452 058 (24.0)
2nd	46 713 (24.8)	475 756 (25.2)
3rd	43 996 (23.3)	478 529 (25.4)
4th (highest)	43 397 (23.0)	477 887 (25.4)
Missing	17 (0.00)	160 (0.00)
Highest educational attainment		
Primary school	62 623 (33.2)	535 094 (28.4)
High school/vocational training	80 672 (42.8)	837 761 (44.5)
Higher education	43 362 (23.0)	499 780 (26.5)
Missing	1782 (0.90)	11 755 (0.60)
Employment status		
Employed	127 517 (67.7)	1 434 609 (76.1)
Unemployed	5097 (2.70)	48 076 (2.60)
Outside workforce for other reasons	55 817 (29.6)	401 574 (21.3)
Missing	8 (0.00)	131 (0.00)
Population density at municipality l evel, median (IQR)	176 (87–1301)	146 (74–640)
Mean temperature 1 wk before index date, median (IQR)	6.30 (1.60–13.0)	6.20 (1.70–12.8)

The table shows characteristics and distribution of covariates among the 188 439 people with an incident RTI and their 1 884 390 individually matched controls corresponding to a 1:10 case-control sampling rate.
Numbers with percentages or medians with IQR.
COPD, chronic obstructive pulmonary disease; IQR, interquartile ranges; RTI, respiratory tract infection.

Table 2
Distribution of cases in respiratory tract infection subgroups

Characteristics	Cases	Controls
Upper respiratory tract infections		
Ear infections	19 179 (8.07)	191 790 (8.07)
Sinusitis	21 378 (9.00)	213 780 (9.00)
Infections of the oral cavity	13 610 (5.73)	136 100 (5.73)
Tonsillitis	45 927 (19.3)	459 270 (19.3)
Influenza	6663 (2.80)	66 630 (2.80)
Lower respiratory tract infections		
Bronchitis	7399 (3.11)	73 990 (3.11)
Pneumonia	92 275 (38.8)	922 750 (38.8)
Viral pneumonia	1215 (0.51)	12 150 (0.51)
Bacterial pneumonia	29 958 (12.6)	299 580 (12.6)

The table shows the distribution of people with an incident RTI in specific subgroups (cases) and their individually matched controls corresponding to a 1:10 case-control sampling rate.
Numbers with percentages.
RTI, respiratory tract infection.

Characteristics of air pollution

NO_2 and $PM_{2.5}$ are the two air pollutants that are responsible for most negative health outcomes in Denmark, and their concentrations for 2015 in Denmark are illustrated in Fig. 1. Concentrations for PM_{10} are illustrated to improve the understanding of the findings found for PM_{10} and sea salt. Supplementary material holds summer and winter concentrations of NO_2, $PM_{2.5}$, and PM_{10} (Figs. S1–S3), the distribution of each of the air pollutants in the control group (Figs. S4–S21), and Spearman's correlation coefficients between the pollutants (Table S1).

Exposure to air pollution was associated with an increased risk of respiratory infection

Exposure to most air pollutants was associated with risk of RTIs. In example, NO_2 showed an IRR of 1.52, and the IRR for $PM_{2.5}$ was 1.45. Conversely, PM_{10}, NH_3, and O_3 showed inverse associations (Fig. 2, Table 3, and Fig. S22). Effect sizes for associations between air pollution and upper RTIs were higher compared with those for lower RTIs (Figs. S23 and S24).

Estimates were generally similar between subgroups of RTIs with broader CIs (Table 4). Risk of bronchitis, however, was not associated with any air pollutants and even showed an inverse association (secondary inorganic aerosols, NO_3^-, NH_4^+, and $PM_{2.5}$) conversely to our findings for other infections. In addition, O_3 was positively associated with risk of bronchitis. For viral pneumonia, some estimates were non-significant, but the magnitude of the estimates were similar to estimates for all RTIs.

A comparison of the risk of RTIs between individuals according to each decile of air pollution concentration with the lowest decile as reference showed a dose-response relationship for most pollutants (Tables S2–S5).

Exploring confounder models and sensitivity analyses

The estimates for most air pollutants were attenuated in the fully adjusted model when compared with the basic model (Table 3). Adjustments for potential confounders only slightly impacted the estimated effects of the air pollutants except when adding population density to the model. Here estimates decreased (Table 3). Omission of adjustment for population density for subgroups of RTIs did not change conclusions (Table S6).

Findings for all air pollutants were similar according to different exposure windows. However, a slight trend towards attenuated effects for the 12-month exposure window were observed (Table S7).

For participants without chronic pulmonary disease and COPD, the estimates were almost identical to the estimates from the main analyses; similar for participants with a chronic pulmonary disease. For participants with COPD, the association changed markedly, especially for NO_x, NO_2, secondary organic aerosols, and SO_4^{2-}, for which the associations appeared to decrease substantially in magnitude. Conversely, the magnitude of O_3 and PM_{10} showed to increase (Table S8).

Bonferroni corrected CIs for all, upper, and lower RTIs appear in Table S9; the findings were robust.

Discussion

This is the first nationwide study on air pollution and a wide range of RTIs. Most air pollutants exhibited positive associations with RTIs. However, sea salt, PM_{10}, NH_3, and O_3 showed inverse

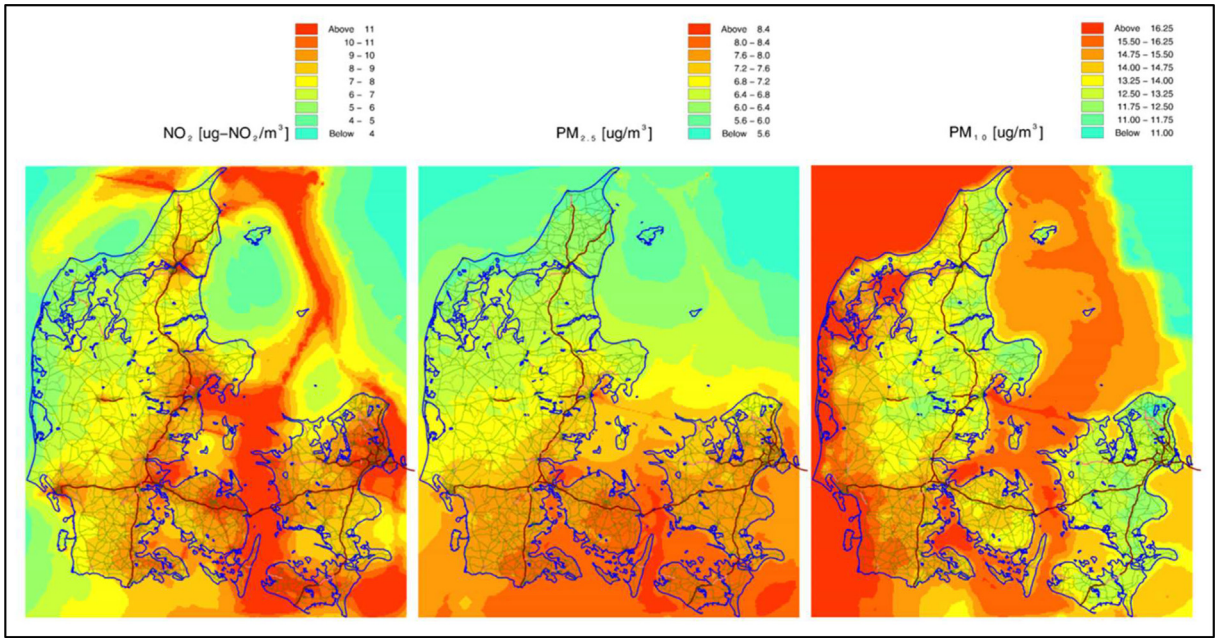

Fig. 1. Annual mean concentrations of NO_2, $PM_{2.5}$, and PM_{10} for 2015 in Denmark. NO_2 and $PM_{2.5}$ are the two air pollutants that are responsible for most negative health outcomes in Denmark. NO_2 is emitted during combustion processes, e.g. related to traffic, industry, and power production, and secondarily formed via a chemical reaction between NO and O_3. The levels of NO_2 are highest in the large cities, on main highways, in south-eastern Denmark, and in Kattegat and the belts where busy ship traffic is observed. Both $PM_{2.5}$ and PM_{10} are the sum of a range of different chemical species; $PM_{2.5}$ includes $PPM_{2.5}$, sea salt, SIA, and SOA; PM_{10} includes $PM_{2.5}$, sea salt (coarse fraction >2.5 μm and <10 μm), NO_3 (coarse fraction), and dust (coarse fraction). $PM_{2.5}$ is most pronounced in south-eastern Denmark, whereas PM_{10} is observed near the western coastal lines partly because of the high fraction of sea salt included in PM_{10} together with the dominant wind direction from west. Please see supplementary material—overview of air pollutants for further description and emission sources in addition to summer and winter gradients (Figs E1–E3). SIA, secondary inorganic aerosols; SOA, secondary organic aerosols.

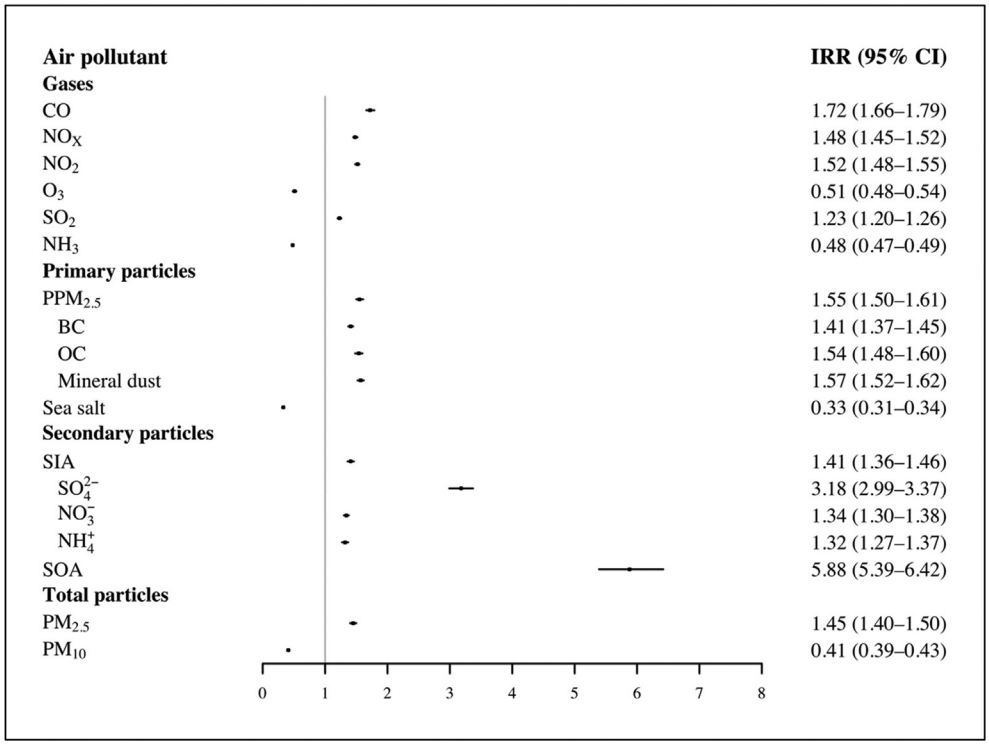

Fig. 2. The association between air pollution and respiratory tract infections. Conditional logistic regression exploring the association between air pollution and all respiratory tract infections comparing the highest decile with the lowest decile of air pollution concentration for the fully adjusted model for the 3-month exposure window. Adjustments include age, sex, calendar time, population density at municipality level, socio-economic status, Charlson Comorbidity Index, chronic pulmonary disease, and temperature. Dot with error bars represents IRRs with 95% CIs. IRR, incidence rate ratio; 95% CI, 95% confidence interval.

Table 3
The association between air pollution and respiratory tract infections by different confounder models

Air pollutant	IRR (95% CI)						
	Basic model[a]	Basic model + POP	Basic model + SES	Basic model + CCI	Basic model + CPD	Basic model + temperature	Fully adjusted model[b]
Gases							
CO	2.65 (2.57–2.73)	1.69 (1.63–1.76)	2.93 (2.84–3.03)	2.61 (2.53–2.69)	2.60 (2.52–2.69)	2.44 (2.37–2.52)	1.72 (1.66–1.79)
NO_X	1.83 (1.80–1.86)	1.48 (1.45–1.51)	1.93 (1.90–1.97)	1.81 (1.78–1.85)	1.81 (1.78–1.84)	1.74 (1.71–1.78)	1.48 (1.45–1.52)
NO_2	1.87 (1.84–1.91)	1.51 (1.48–1.54)	1.98 (1.94–2.02)	1.85 (1.82–1.89)	1.85 (1.82–1.89)	1.79 (1.75–1.82)	1.52 (1.48–1.55)
O_3	0.31 (0.30–0.33)	0.55 (0.52–0.58)	0.28 (0.27–0.29)	0.32 (0.30–0.34)	0.32 (0.31–0.34)	0.33 (0.31–0.34)	0.51 (0.48–0.54)
SO_2	1.61 (1.57–1.66)	1.31 (1.27–1.34)	1.63 (1.59–1.67)	1.57 (1.53–1.61)	1.59 (1.55–1.63)	1.49 (1.45–1.53)	1.23 (1.20–1.26)
NH_3	0.42 (0.41–0.43)	0.50 (0.49–0.51)	0.39 (0.38–0.40)	0.42 (0.41–0.43)	0.42 (0.41–0.43)	0.42 (0.42–0.43)	0.48 (0.47–0.49)
Primary particles							
$PPM_{2.5}$	2.08 (2.02–2.16)	1.48 (1.43–1.53)	2.29 (2.21–2.36)	2.06 (1.99–2.13)	2.06 (1.99–2.13)	2.00 (1.93–2.06)	1.55 (1.50–1.61)
BC	1.91 (1.86–1.96)	1.38 (1.34–1.42)	2.05 (2.00–2.11)	1.89 (1.84–1.94)	1.89 (1.84–1.94)	1.80 (1.75–1.85)	1.41 (1.37–1.45)
OC	1.92 (1.85–1.99)	1.44 (1.38–1.50)	2.11 (2.03–2.19)	1.90 (1.83–1.97)	1.90 (1.83–1.97)	1.90 (1.83–1.97)	1.54 (1.48–1.60)
Mineral dust	2.13 (2.06–2.19)	1.50 (1.46–1.55)	2.33 (2.26–2.40)	2.11 (2.04–2.17)	2.10 (2.03–2.16)	2.03 (1.97–2.09)	1.57 (1.52–1.62)
Sea salt	0.23 (0.22–0.24)	0.33 (0.32–0.35)	0.21 (0.20–0.22)	0.24 (0.23–0.24)	0.23 (0.23–0.24)	0.25 (0.24–0.26)	0.33 (0.31–0.34)
Secondary particles							
SIA	1.58 (1.53–1.63)	1.45 (1.40–1.50)	1.56 (1.51–1.61)	1.56 (1.51–1.61)	1.60 (1.55–1.65)	1.54 (1.49–1.59)	1.41 (1.36–1.46)
SO_4^{2-}	5.37 (5.08–5.68)	3.31 (3.12–3.51)	5.57 (5.26–5.89)	5.19 (4.91–5.50)	5.38 (5.08–5.69)	4.81 (4.55–5.09)	3.18 (2.99–3.37)
NO_3^-	1.45 (1.41–1.49)	1.38 (1.34–1.42)	1.43 (1.39–1.47)	1.43 (1.39–1.47)	1.47 (1.43–1.51)	1.39 (1.35–1.43)	1.34 (1.30–1.38)
NH_4^+	1.22 (1.18–1.26)	1.29 (1.24–1.33)	1.19 (1.15–1.24)	1.21 (1.17–1.25)	1.24 (1.19–1.28)	1.33 (1.28–1.38)	1.32 (1.27–1.37)
SOA	12.6 (11.7–13.7)	5.44 (4.99–5.92)	15.2 (14.0–16.4)	12.5 (11.5–13.5)	12.3 (11.4–13.3)	11.2 (10.3–12.1)	5.88 (5.39–6.42)
Total particles							
$PM_{2.5}$	1.83 (1.77–1.89)	1.42 (1.38–1.47)	1.91 (1.84–1.97)	1.80 (1.74–1.86)	1.82 (1.77–1.88)	1.77 (1.72–1.83)	1.45 (1.40–1.50)
PM_{10}	0.37 (0.35–0.38)	0.42 (0.40–0.44)	0.36 (0.35–0.38)	0.36 (0.35–0.38)	0.36 (0.35–0.38)	0.36 (0.35–0.38)	0.41 (0.39–0.43)

Conditional logistic regression exploring the association between air pollution and all respiratory tract infections comparing the highest decile with the lowest decile of air pollution concentration for the 3-month exposure window. To measure the effect of each covariate, the basic model was repeated by alternately including covariates of interest.

BC, black carbon; CCI, Charlson Comorbidity Index; CPD, chronic pulmonary disease; IRR, incidence rate ratio; OC, organic carbon; POP, population density at municipality level; SES, socio-economic status; SIA, secondary inorganic aerosols; SOA, secondary organic aerosols.

[a] Basic model: by design adjusted for age, sex, and calendar time.

[b] Fully adjusted model: basic model with further adjustment for population density at municipality level, socio-economic status, Charlson Comorbidity Index, chronic pulmonary disease, and temperature.

associations with infection risk, presumably because these air pollutants act as proxies for areas of low levels of exposure to other air pollutants, e.g. from combustion. Hence, higher levels are observed along the North Sea coastline (sea salt, PM_{10}, and O_3) and the large rural areas of the peninsula of Jutland (NH_3)—areas with lower combustion-related air pollutant exposure levels giving higher O_3 levels, areas with higher sea salt at the western coastal areas of Denmark, as well as areas with large-scale animal production in the rural areas. Ozone is scavenged by other air pollutants and therefore inversely correlated with NO_x (Table S1). In itself, O_3 exposure is associated with deleterious effects such as diffuse inflammation in the entire respiratory tract, and O_3 affects the pulmonary defence [19]. Our finding for PM_{10} may be explained by the fact that the coarse fraction of sea salt is a strong contributor to PM_{10} in a Danish context, and sea salt also appeared to be negatively associated with RTIs (Fig. 1).

Regarding specific subgroups of RTIs, findings were similar except for bronchitis. The reason for this discrepancy is unknown, but may be an incidental finding.

Population density attenuated the estimates for most air pollutants. Cases in our study were over-represented in areas with higher population density than controls. Population density facilitates transmission of communicable diseases, and it is a limitation that modelling of pathogen exposure could not be included in this study. Increasing population density is also associated with higher air pollution emissions. It is reassuring that the associations persisted after adjustment for population density although an over-adjustment may occur.

Regarding generalizability, the findings seemed robust to variation in exposure window. Only for the 12-month exposure window, the estimates appeared attenuated.

Possible mechanisms of pathogenesis give no certain clues about the optimal exposure window to observe. It is suggested that air pollutants stimulate a pro-inflammatory immune response across multiple immune cell classes. Air pollution may enhance T helper lymphocyte type 2 and T helper lymphocyte type 17 adaptive immune responses and dysregulate anti-viral immune responses like the mechanism seen for allergy and asthma [20]. Locally, air pollutants also act as airway irritants and render the epithelial barrier ineffective thereby increasing infection susceptibility [19]. Lasting exposure may compromise the immune surveillance of the lung and affects the immune function and lymphoid architecture [21]. We speculate that activation of immune cell subsets and the dysregulation may lead to increased susceptibility to infection.

For participants with (or without) chronic pulmonary disease or without a COPD diagnosis, the findings did not change markedly, indicating that they are not driven by infections among individuals with pre-existing pulmonary disease. However, for participants with COPD, the effects of several air pollutants changed. Smoking, the primary cause of COPD in Denmark, may introduce analysis variability in this group.

Other studies support our findings: one study found that ambient NO_2 and $PM_{2.5}$ exposure was associated with hospitalization for community-acquired pneumonia in elderly adults [7]. Similarly, a meta-analysis found a strong association between NO_2, NO_X, and PM_{10} and pneumonia in early childhood [6]. Correspondingly, a large study confirmed that O_3 and PM_{10} exposure was associated with respiratory hospital admissions [22]. However, for the latter two studies, the direction of the associations for PM_{10} and O_3 was inverted when compared with our study. In addition, exposure to $PM_{2.5}$ has been shown to increase risk of both influenza and pneumonia, whereas increased sea salt was associated with decreased risk of influenza [9]. As in our study, earlier studies have shown an increased risk of both viral and bacterial RTIs [23,24].

Table 4
The association between air pollution and subgroups of respiratory tract infections

	IRR (95% CI)								
	Upper respiratory tract infections					Lower respiratory tract infections			
Air pollutant	Ear infections	Sinusitis	Infections of the oral cavity	Tonsillitis	Influenza	Bronchitis	Pneumonia	Viral pneumonia	Bacterial pneumonia
Gases									
CO	2.26 (2.00–2.56)	2.48 (2.21–2.78)	1.29 (1.11–1.50)	1.91 (1.77–2.07)	2.41 (2.03–2.85)	0.98 (0.80–1.19)	1.66 (1.57–1.75)	1.69 (1.06–2.72)	1.96 (1.77–2.17)
NO_X	1.75 (1.64–1.87)	1.90 (1.78–2.02)	1.27 (1.17–1.37)	1.67 (1.60–1.74)	2.32 (2.07–2.61)	1.03 (0.93–1.15)	1.39 (1.35–1.43)	1.44 (1.09–1.88)	1.45 (1.37–1.54)
NO_2	1.82 (1.70–1.95)	1.97 (1.85–2.10)	1.28 (1.18–1.38)	1.71 (1.63–1.78)	2.42 (2.15–2.72)	1.05 (0.93–1.17)	1.42 (1.38–1.47)	1.44 (1.09–1.89)	1.48 (1.40–1.57)
O_3	0.45 (0.38–0.53)	0.38 (0.32–0.44)	0.74 (0.61–0.90)	0.40 (0.36–0.44)	0.26 (0.21–0.32)	1.06 (0.82–1.39)	0.54 (0.50–0.58)	0.59 (0.31–1.12)	0.48 (0.42–0.56)
SO_2	1.39 (1.28–1.52)	1.24 (1.14–1.35)	1.10 (0.99–1.22)	1.27 (1.20–1.34)	1.54 (1.34–1.76)	0.88 (0.76–1.02)	1.21 (1.16–1.26)	1.27 (0.90–1.80)	1.20 (1.12–1.29)
NH_3	0.35 (0.33–0.38)	0.27 (0.25–0.29)	0.82 (0.75–0.90)	0.31 (0.29–0.33)	0.29 (0.26–0.33)	0.47 (0.41–0.53)	0.57 (0.55–0.59)	0.46 (0.34–0.63)	0.60 (0.56–0.63)
Primary particles									
$PPM_{2.5}$	1.90 (1.69–2.14)	2.07 (1.86–2.31)	1.26 (1.09–1.46)	1.80 (1.67–1.94)	1.91 (1.64–2.23)	0.89 (0.74–1.06)	1.43 (1.36–1.51)	1.60 (1.04–2.47)	1.76 (1.60–1.93)
BC	1.67 (1.52–1.83)	1.71 (1.56–1.86)	1.30 (1.16–1.45)	1.52 (1.44–1.62)	1.71 (1.49–1.96)	0.87 (0.75–1.01)	1.32 (1.27–1.38)	1.28 (0.89–1.84)	1.51 (1.40–1.64)
OC	1.89 (1.66–2.16)	2.07 (1.84–2.33)	1.26 (1.07–1.47)	1.81 (1.67–1.97)	1.97 (1.68–2.30)	0.83 (0.69–1.01)	1.41 (1.33–1.49)	1.74 (1.10–2.76)	1.87 (1.69–2.08)
Mineral dust	1.91 (1.71–2.13)	2.04 (1.84–2.25)	1.17 (1.03–1.34)	1.91 (1.78–2.05)	1.92 (1.66–2.23)	1.03 (0.87–1.22)	1.41 (1.34–1.48)	1.56 (1.03–2.34)	1.59 (1.45–1.74)
Sea salt	0.19 (0.17–0.22)	0.10 (0.08–0.11)	0.58 (0.50–0.67)	0.21 (0.19–0.23)	0.07 (0.05–0.08)	0.46 (0.37–0.57)	0.41 (0.38–0.43)	0.24 (0.14–0.43)	0.46 (0.41–0.51)
Secondary particles									
SIA	1.81 (1.62–2.01)	2.02 (1.84–2.23)	2.03 (1.79–2.29)	1.27 (1.19–1.36)	1.82 (1.54–2.15)	0.53 (0.45–0.62)	1.43 (1.36–1.50)	1.62 (1.07–2.45)	1.88 (1.73–2.05)
SO_4^{2-}	6.79 (5.57–8.29)	9.62 (8.01–11.5)	2.97 (2.38–3.70)	4.99 (4.40–5.67)	5.42 (4.11–7.14)	0.75 (0.56–1.01)	2.89 (2.65–3.15)	3.10 (1.49–6.45)	4.12 (3.54–4.80)
NO_3^-	1.58 (1.45–1.74)	1.93 (1.77–2.10)	1.83 (1.64–2.04)	1.17 (1.10–1.24)	1.91 (1.62–2.25)	0.58 (0.50–0.67)	1.35 (1.30–1.41)	1.58 (1.07–2.33)	1.74 (1.61–1.89)
NH_4^+	1.55 (1.37–1.74)	1.67 (1.50–1.86)	1.97 (1.72–2.26)	1.26 (1.17–1.36)	1.45 (1.22–1.71)	0.53 (0.44–0.63)	1.30 (1.24–1.37)	1.14 (0.74–1.77)	1.73 (1.57–1.90)
SOA	15.1 (11.4–20.1)	30.5 (23.5–39.7)	2.93 (2.09–4.10)	10.5 (8.76–12.7)	7.12 (5.38–9.43)	2.60 (1.69–4.01)	4.53 (3.99–5.13)	4.91 (1.84–13.1)	5.95 (4.76–7.43)
Total particles									
$PM_{2.5}$	1.93 (1.72–2.16)	2.01 (1.82–2.23)	1.79 (1.57–2.04)	1.46 (1.36–1.57)	1.76 (1.51–2.05)	0.55 (0.46–0.64)	1.41 (1.34–1.48)	1.50 (1.00–2.25)	1.96 (1.79–2.14)
PM_{10}	0.28 (0.24–0.33)	0.18 (0.15–0.20)	0.84 (0.70–1.00)	0.21 (0.19–0.23)	0.23 (0.19–0.28)	0.22 (0.17–0.27)	0.51 (0.47–0.54)	0.69 (0.40–1.18)	0.80 (0.71–0.90)

Conditional logistic regression exploring the association between air pollution and subgroups of respiratory tract infections comparing the highest decile to the lowest decile of air pollution concentration for the fully adjusted model for the 3-month exposure window. Adjustments include age, sex, calendar time, population density at municipality level, socio-economic status, Charlson Comorbidity Index, chronic pulmonary disease, and temperature. BC, black carbon; IRR, incidence rate ratio; OC, organic carbon; SIA, secondary inorganic aerosols; SOA, secondary organic aerosols.

Strengths and limitations

A major strength in this study is its use of the well-established national registers and the large cohort, assuring well-powered analyses coupled to results from a high-resolution state-of-the-art air pollution modelling system. Missing data on specific socio-economic variables were observed for less than 1% of the study population with a subsequent low risk of bias.

The findings remained consistent after adjustments. However, other relevant exposures, e.g. related to socio-economic positions, were unknown, which could result in residual confounding. Thus, in an earlier study, we found a positive association between obesity and RTIs among women [25]. In addition, RTIs have been associated with household air pollution exposure [26], and both passive and active tobacco smoking are a well-known risk factors for developing community-acquired pneumonia [27]. We recently confirmed that smoking was associated with a wide range of infections including RTIs in healthy blood donors [28].

Uniquely, our study examined 18 different air pollutants; however, air pollution comprises a complex mixture of correlated pollutants. It is important to acknowledge the possibility that the observed association between an individual pollutant and RTI may be influenced by confounding from a correlated pollutant or the overall mixture in which the pollutant is present. Currently, unravelling the effects of highly correlated pollutants poses a challenge. A promising method, exemplified by Mostofsky et al. [29], employs a two-step approach. However, the complexity of our study, involving numerous pollutants without a nested structure, precludes us from adopting this method. Typically, studies attempting to incorporate highly correlated pollutants simultaneously have yielded conflicting results.

In this context, the possibility of false positive findings because of multiple comparisons may be present. Yet, Bonferroni corrected CIs showed almost identical estimates as the main findings.

One limitation is using diagnostic codes in the NPR as proxies for RTIs without the ability to accurately distinguishing between bacterial and viral causes. Although the NPR has shown validity, with a reported positive predictive value of 92.5% for pneumonia [30], another limitation is the data availability, which extends only until the end of 2016.

Although focusing on severe RTIs, this study stands out because of its unique approach of modelling air pollution exposure at the individual level, resulting in a more precise association between actual exposure and the risk of RTIs. We find these associations despite the moderate air pollution exposure present in Denmark thus highlighting public health and clinical impact.

Conclusion

In a context of low to moderate levels of air pollution, this study showed that exposure to air pollution was associated with risk of RTIs among adults. Conversely, sea salt, PM_{10}, NH_3, and O_3 showed inverse associations. However, these species may be proxies for rural areas. Our findings highlight the importance of reassessing political strategies to optimally reduce the negative impact of air pollution.

Author contributions

KAK and CE drafted the manuscript. KAK, SA, HTH, BK, CS, KMD, OH, TS, CBP, and CE designed the study. SA performed the statistical analyses. KAK, SA, HTH, BK, CS, OH, TS, CBP, and CE interpreted the data. JB, CG, JHC, and LMF provided, analysed, and interpreted the air quality data. All authors were involved in critically revising the manuscript and have approved the final version before submission.

Transparency declaration

The authors declare that they have no conflicts of interest.

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Data availability

Access to individual-level data is governed by the Danish Authorities. Each scientific project must be approved before initiation, and approval is granted to a specific Danish research institution. Researchers at Danish research institutions may obtain the relevant approval and data. International researchers may gain data access if governed by a Danish research institution as approval and data access are required.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2023.10.013.

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