Long-term air pollution and road traffic noise exposure and COPD: the Danish Nurse Cohort

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Long-term exposure to air pollution, especially from traffic, and to road traffic noise were associated with increased risk of COPD, independent of each other https://bit.ly/3vaQY6q

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Abstract

Background While air pollution has been linked to the development of chronic obstructive pulmonary disease (COPD), evidence on the role of environmental noise is just emerging. We examined the associations of long-term exposure to air pollution and road traffic noise with COPD incidence.

Methods We defined COPD incidence for 24 538 female nurses from the Danish Nurse Cohort (age >44 years) as the first hospital contact between baseline (1993 or 1999) and 2015. We estimated residential annual mean concentrations of particulate matter with an aerodynamic diameter <2.5 µm ($PM_{2.5}$) since 1990 and nitrogen dioxide (NO_2) since 1970 using the Danish Eulerian Hemispheric Model/Urban Background Model/Air Geographic Information System modelling system, and road traffic noise (L_{den}) since 1970 using the Nord2000 model. Time-varying Cox regression models were applied to assess the associations of air pollution and road traffic noise with COPD incidence.

Results 977 nurses developed COPD during a mean of 18.6 years' follow-up. We observed associations with COPD for all three exposures with HRs and 95% CIs of 1.19 (1.01–1.41) per 6.26 µg·m^{-3} for $PM_{2.5}$, 1.13 (1.05–1.20) per 8.19 µg·m^{-3} for NO_2 and 1.15 (1.06–1.25) per 10 dB for L_{den}. Associations with NO_2 and L_{den} attenuated slightly after mutual adjustment, but were robust to adjustment for $PM_{2.5}$. Associations with $PM_{2.5}$ were attenuated to null after adjustment for either NO_2 or L_{den}. No potential interaction effect was observed between air pollutants and noise.

Conclusion Long-term exposure to air pollution, especially traffic-related NO_2, and to road traffic noise were independently associated with COPD.

Introduction

Chronic obstructive pulmonary disease (COPD) presents a major cause of disability and mortality [1]. Although tobacco smoking remains the main risk factor for COPD, the significant prevalence of COPD in never-smokers stresses other important aetiologies [2].

Ambient air pollution is a major risk factor for mortality and morbidity worldwide, and a trigger of symptoms and exacerbations of COPD [3]. A recent American Thoracic Society report concluded that there is limited and insufficient epidemiological and mechanistic evidence linking long-term air pollution exposure to COPD onset, calling for high-quality research [4]. Epidemiological evidence on long-term exposure to air pollution and COPD incidence [5] is limited to several studies with different types of air pollutants, availability of historical exposures and COPD definitions [6–17].

Environmental noise is an increasingly recognised stressor, ranking as the third most important environmental risk factor in Europe after air pollution and second-hand smoke [18]. Road traffic noise has been linked to cardiovascular disease [19], whereas evidence on respiratory outcomes is just emerging [20]. A single study to date on long-term exposure to road traffic noise and COPD incidence found no association [12], whereas short-term exposure to road traffic noise was found to trigger COPD and respiratory mortality in two studies [21, 22]. A study in children found no association between exposure to noise during different time periods and asthma or wheeze up to adolescence [23]. Nevertheless, a recent review concluded that traffic noise can be a risk factor for respiratory-related morbidity and mortality [24], given that noise, as a psychological stressor, can cause oxidative stress and pulmonary inflammation [25, 26] as well as immune system dysregulation, which increases susceptibility to infection [20]. Other plausible pathways by which noise may increase risk of COPD are *via* sleep disturbance- and stress-related altering of smoking behaviour [27], a reduction in physical activity [28], an increase in obesity [29] and enriched DNA methylation related to C-reactive protein [30]. A study in children found that noise could enhance the association between traffic-related air pollution and lung function [31]. Furthermore, given that road traffic noise and air pollution share a major source, there are increasing concerns about the possible joint and interaction effects of the two exposures [32].

Here, we examined the independent and joint associations of long-term exposure to ambient air pollution and to road traffic noise with COPD incidence.

Methods

Study population and outcome definition

The Danish Nurse Cohort included 28 731 female nurses aged >44 years at baseline (April 1, 1993, or April 1, 1999) who were members of the Danish Nurse Organization (95% of Danish nurses) [33]. Baseline information in 1993 (19 898 nurses) or 1999 (8833 nurses) was collected by self-administered questionnaires, including smoking, dietary habits, education, occupation and other lifestyle factors. The Danish Nurse Cohort was linked to the Danish National Patient Register by the unique personal identification number to identify a first hospital contact for COPD (inpatient, outpatient or emergency room) from baseline until August 10, 2015, using primary discharge diagnoses of International Classification of Diseases (ICD)-8: 490–492 and 10: J40–44. The establishment of the cohort was approved by the Scientific and Ethical Committee of Copenhagen and Frederiksberg Municipalities, and the Danish Data Protection Agency. We excluded participants with COPD hospital contact prior to baseline.

Air pollution and road traffic noise assessment

We linked the cohort to the Danish Civil Registration System to collect information on residential address history from 1970 to December 31, 2014.

Annual mean concentrations of particulate matter with an aerodynamic diameter <2.5 µm ($PM_{2.5}$) and <10 µm (PM_{10}) (since 1990), and nitrogen dioxide (NO_2) and nitrogen oxide (NO_x) (since 1970) until 2014 at residential addresses were estimated by the Danish air pollution modelling system Danish Eulerian Hemispheric Model/Urban Background Model/Air Geographic Information System (DEHM/UBM/AirGIS) [34]. Annual mean road traffic noise levels from 1970 at residential addresses were calculated using the Nord2000 method [35], which included noise contributions from roads within a 3 km radius of participants' residential addresses. Road traffic noise was estimated as the equivalent A-weighted sound pressure level at the most exposed residential facade of all buildings, which was calculated for day (L_d, 07:00–19:00), evening (L_e, 19:00–22:00), night (L_n, 22:00–07:00), unweighted 24-h average (L_{24}) and the overall weighted 24-h noise level adding a penalty of 5 dB to the evening hours and 10 dB to the night hours (L_{den}). We set the noise levels with zero estimates and no road traffic noise contributions to 35 dB

(accounting for <2%), which was considered background noise level. More details about exposure assessment are in the supplementary material.

Statistical analysis

We used time-varying Cox regression models with age as the underlying timescale to examine the associations of air pollution and road traffic noise with COPD incidence, with censoring at the time of death, emigration, COPD hospital contact or the end of follow-up in 2015, whichever came first. The associations were assessed in three steps: Model 1 only adjusted for age (time axis), baseline year (1993/1999) and calendar year (strata); Model 2 was additionally adjusted for smoking status (never/previous/current), duration (years) and intensity ($g \cdot day^{-1}$); and Model 3 (main model, best fit) was further adjusted for the *a priori* defined covariates body mass index (BMI) (<18.5/18.5–24.9/25.0–29.9/$\geqslant$30 $kg \cdot m^{-2}$), marital status (married/separated/divorced/single/widowed), occupational status (working/homeworking/retired/unemployed/other) and physical activity (high/medium/low). We applied 1-, 3-, 10- and 23-year moving averages, with 3-year average (the longest available exposure window for all exposures) considered as the main exposure.

We fitted mutually adjusted models (two- and three-pollutant models) based on Model 3 for pollutant combinations with correlations <0.70. The interaction effect between two exposures was estimated by introducing an interaction term into the model and assessed by the Wald test. We performed a collinearity test for mutually adjusted models, and no multicollinearity was detected (variance inflation factors ranging from 1.0 to 8.8). We calculated the joint effects to examine the cumulative effects of multiple exposures on COPD incidence [36, 37].

In subset analyses, we repeated the single and mutually adjusted models by applying pre-defined cut-off values: 25, 20, 15 $\mu g \cdot m^{-3}$ for $PM_{2.5}$; 40, 30, 20, 15, 10 $\mu g \cdot m^{-3}$ for NO_2; and 48, 53 dB for L_{den}. We also applied natural cubic splines with three degrees of freedom for exposures to evaluate the shape of the concentration–response functions. We assessed potential effect modification of the associations for $PM_{2.5}$, NO_2 and L_{den} exposures by baseline year, age, obesity, smoking status and physical activity by introducing an interaction term in Model 3.

We conducted several sensitivity analyses. First, we evaluated the associations for the year before baseline and baseline year exposures by fixed Cox regression model. Second, we evaluated different approaches for adjustment for calendar year as linear term, nonlinear (spline) and strata for 1 and 5 years. Finally, we estimated the effects by adjusting for different groups of covariates, excluding observations with imputed exposure values (~4.2%), with additional adjustment for municipality-level income, and limiting to participants who did not relocate during follow-up or participants without any comorbidities at baseline. We also identified the minimum set of variables for confounder adjustment using a directed acyclic graph (DAG) and estimated the associations using these variables.

All statistical analyses were performed using R (version 3.6.1; The R Project, www.r–project.org). Results are presented as HR (95% CI) per interquartile range (IQR) for air pollutants and 10 dB increase (close to IQR=9.4) for L_{den}.

Results

Of the 28 731 participants, we excluded four with inactive status before baseline, 108 with COPD diagnosis before baseline, 859 with missing exposure information and 3222 with missing information on one or more covariates, leaving 24 538 participants for the main analyses, of whom 977 developed COPD during a mean follow-up of 18.6 years (the crude incidence rate was 214.4 cases per 100 000 person-years in this cohort) (table 1). Participants who developed COPD were more likely to be underweight, retired, current smokers, less physically active and have co-morbidity with asthma, hypertension or myocardial infarction compared to those who did not develop COPD (table 1).

Air pollution and noise levels were significantly higher in participants with COPD (table 2). The mean $PM_{2.5}$ and NO_2 levels were well below the current European Union (EU) limit values of 25 and 40 $\mu g \cdot m^{-3}$, while the average level for road traffic noise was equal to the current World Health Organization environmental noise guideline limit value for the European region of 53 dB for L_{den} [38]. Air pollution levels in Denmark were steadily decreasing while levels of road traffic noise remained stable during the study period (1993–2015) (supplementary figure S1). The highest concentrations were observed in south-eastern Denmark for $PM_{2.5}$ and along the west coastlines for PM_{10} (figure 1 and supplementary figure S2), while the levels of NO_2, NO_x and L_{den} were highest in urban areas. We observed low

TABLE 1 Descriptive characteristics of covariates at the baseline year (1993 and 1999) in the Danish Nurse Cohort

	Total	No COPD	COPD	p-values[#]
Subjects, n	24 538	23 561	977	
Year of enrolment, n (%)				
1993	16 196 (66)	15 344 (65)	852 (87)	<0.001
1999	8342 (34)	8217 (35)	125 (13)	
Follow-up, person-years (mean±SD)	18.6±4.7	18.8±4.4	12.1±6.0	<0.001
Age, years (mean±SD)	53.0±7.9	52.8±7.9	57.4±7.7	<0.001
Age <65 years old, n (%)	22 212 (91)	21 412 (91)	800 (82)	<0.001
BMI, kg·m^{-2} (mean±SD)	23.7±3.5	23.7±3.5	23.3±3.8	<0.001
BMI categories, n (%)				
Underweight (<18.5 kg·m^{-2})	601 (2)	546 (2)	55 (6)	<0.001
Normal weight (18.5–24.9 kg·m^{-2})	16 920 (69)	16 260 (69)	660 (68)	
Overweight (25.0–29.9 kg·m^{-2})	5628 (23)	5421 (23)	207 (21)	
Obese (⩾30 kg·m^{-2})	1389 (6)	1334 (6)	55 (6)	
Smoking status, n (%)				
Never	8777 (36)	8690 (37)	87 (9)	<0.001
Previous	7343 (30)	7136 (30)	207 (21)	
Current	8418 (34)	7735 (33)	683 (70)	
Smoking duration, years (mean±SD)	10.3±15.2	9.7±14.8	24.4±17.6	<0.001
Smoking intensity, g·day^{-1} (mean±SD)	4.7±8.0	4.4±7.8	11.7±10.0	<0.001
Marital status, n (%)				
Married	17 365 (71)	16 802 (71)	563 (58)	<0.001
Separated	415 (2)	398 (2)	17 (2)	
Divorced	2751 (11)	2607 (11)	144 (15)	
Single	2410 (10)	2283 (10)	127 (13)	
Widowed	1597 (7)	1471 (6)	126 (13)	
Occupational status, n (%)				
Working	19 416 (79)	18 829 (80)	587 (60)	<0.001
Homeworking	439 (2)	418 (2)	21 (2)	
Retired	4295 (18)	3937 (17)	358 (37)	
Unemployed	164 (1)	155 (1)	9 (1)	
Other	224 (1)	222 (1)	2 (0.2)	
Leisure time physical activity, n (%)				
High	6579 (27)	6344 (27)	235 (24)	<0.001
Medium	16 331 (67)	15 691 (67)	640 (66)	
Low	1628 (7)	1526 (6)	102 (10)	
Comorbidities, n (%)[¶]				
Asthma	169 (0.7)	139 (0.6)	30 (3.1)	<0.001
Hypertension	3199 (13.1)	2946 (12.5)	173 (17.7)	<0.001
Myocardial infarction	173 (0.7)	158 (0.7)	15 (1.5)	0.003
Diabetes	283 (1.2)	269 (1.2)	14 (1.4)	0.50

COPD: chronic obstructive pulmonary disease; BMI: body mass index. [#]: p-values for difference of no COPD and COPD groups were obtained from one-way ANOVA and Pearson's Chi-squared test; [¶]: there were 29, 118 and 179 participants with missing disease information for hypertension, myocardial infarction and diabetes, respectively.

correlation between $PM_{2.5}$ and L_{den} (0.29), and moderate correlation between $PM_{2.5}$ and NO_2 (0.48) as well as L_{den} and NO_2 (0.60) (supplementary table S1).

In the crude models 1-, 3-, 10- and 23-year moving average exposures to all air pollutants and L_{den} were positively and significantly associated with the incidence of COPD, which attenuated in the adjusted models, mainly due to adjustment for smoking (Model 2) (table 3 and supplementary table S2). The associations for 3-year moving average exposures remained significant except for PM_{10} in Model 3, with a HR (95% CI) of 1.19 (1.01–1.41) per 6.26 μg·m^{-3} for $PM_{2.5}$, 1.13 (1.05–1.20) per 8.19 μg·m^{-3} for NO_2, 1.05 (1.01–1.08) per 12.17 μg·m^{-3} for NO_2 and 1.15 (1.06–1.25) per 10 dB for L_{den} (table 3). HRs for $PM_{2.5}$ and NO_2 were enhanced at the levels below the current EU limit values (table 3). The concentration–response curves showed steeper upward-sloping curves at lower range of exposures, with no evidence of a threshold, which levelled off at higher levels of $PM_{2.5}$ and NO_2, but became steeper for L_{den} at high-range levels (figure 2).

TABLE 2 Distributions of residential air pollutants and road traffic noise at the year before baseline (1992 and 1998) for participants from the Danish Nurse Cohort

Exposure levels	Total (n=24 538)			No COPD (n=23 561)			COPD (n=977)			p-values[#]
	Mean±SD	IQR	Range	Mean±SD	IQR	Range	Mean±SD	IQR	Range	
Air pollution, μg·m^{-3}										
$PM_{2.5}$	19.00±4.11	6.26	5.73–46.39	18.95±4.10	6.30	5.73–46.39	20.17±4.24	5.68	7.78–41.48	<0.001
PM_{10}	22.70±4.55	7.01	9.13–56.29	22.65±4.54	7.01	9.13–56.29	23.93±4.53	4.45	10.26–49.57	<0.001
NO_2	12.77±7.89	8.19	2.55–78.76	12.73±7.84	8.13	2.55–78.76	13.86±8.95	8.69	2.94–70.94	<0.001
NO_x	19.97±23.54	12.17	2.70–434.98	19.84±23.35	12.10	2.70–434.98	23.20±27.49	13.19	3.20–337.97	<0.001
Road traffic noise[¶]										
L_{den}, dB	52.65±8.11	9.40	5.30–79.50	52.61±8.13	9.30	5.30–79.50	53.75±7.54	9.60	18.30–73.70	<0.001
L_{den}, n (%)										
Low (<48 dB)	5455 (22)	–	–	5291 (22)	–	–	164 (17)	–	–	<0.001
Medium (48–53 dB)	6819 (28)	–	–	6527 (28)	–	–	292 (30)	–	–	
High (>53 dB)	12 264 (50)	–	–	11 743 (50)	–	–	521 (53)	–	–	
L_{24}, dB	48.57±8.08	9.30	5.10–75.20	48.52±8.09	9.30	5.10–75.20	49.66±7.64	9.50	13.90–69.90	<0.001
L_d, dB	50.40±8.14	9.30	5.80–77.10	50.36±8.16	9.30	5.80–77.10	51.53±7.69	9.50	15.70–72.00	<0.001
L_e, dB	48.04±8.05	9.30	5.20–74.60	48.00±8.07	9.30	5.20–74.60	49.13±7.60	9.50	13.10–69.10	<0.001
L_n, dB	44.52±7.87	9.30	5.40–71.50	44.48±7.89	9.30	5.40–71.50	45.50±7.42	9.50	10.30–65.40	<0.001

COPD: chronic obstructive pulmonary disease; IQR: interquartile range; $PM_{2.5}$: particulate matter with an aerodynamic diameter <2.5 μm; PM_{10}: particulate matter with an aerodynamic diameter <10 μm; NO_2: nitrogen dioxide; NO_x: nitrogen oxide; L: road traffic noise estimated as the equivalent A-weighted sound pressure level at the most exposed residential facade of all buildings; L_{den}: overall weighted 24-h noise level; L_{24}: unweighted 24-h noise level; L_d: daytime noise level; L_e: evening noise level; L_n: night-time noise level. [#]: p-values for difference of no asthma and asthma groups were obtained from one-way ANOVA and Pearson's Chi-squared test; [¶]: the current World Health Organization environmental noise guideline limit value for the European region for exposure to outdoor road traffic noise is 53 dB.

In the two-pollutant models, the HRs for NO_2 and L_{den} remained unchanged after adjustment for $PM_{2.5}$, whereas the HR for $PM_{2.5}$ attenuated to unity after adjustment for either NO_2 or L_{den} (table 4). The HRs for NO_2 and L_{den} were attenuated slightly after adjustment for each other, maintaining positive associations (table 4 and supplementary figure S3). Similar trends were observed for 1-, 10- and 23-year moving average exposures (supplementary tables S3 and S4). We did not detect clear interaction effects between these three exposures (supplementary tables S5 and S8).

Similar to two-pollutant models, the mutually adjusted associations for NO_2 and L_{den} were more robust in three-pollutant models (figure 3), where the HRs of 1.08 and 1.09 for NO_2 and L_{den} in three-pollutant models were equivalent to the HRs (1.08 and 1.08) in two-pollutant models adjusting for each other,

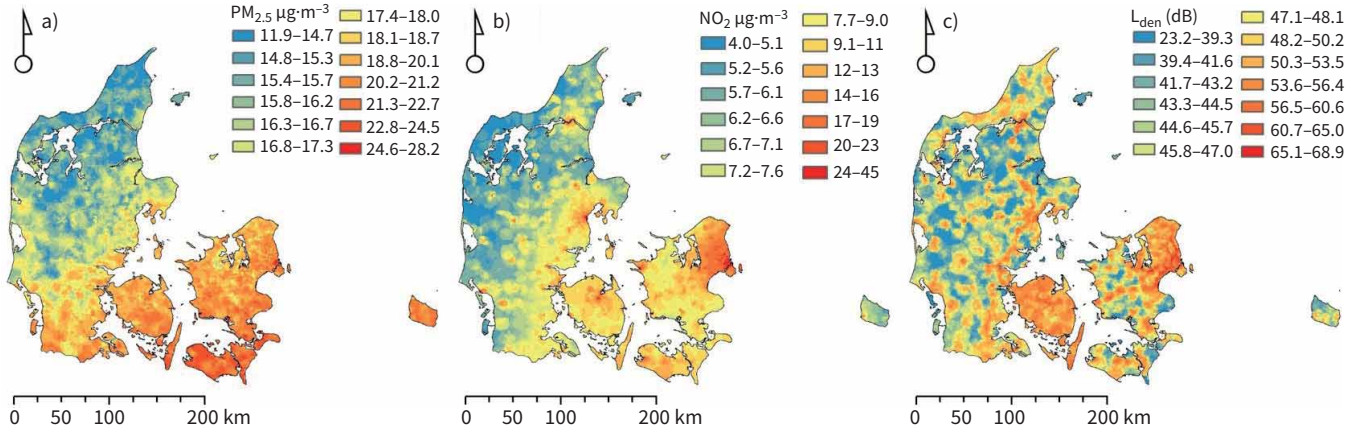

FIGURE 1 Smoothed maps of annual residential exposure levels at the year before baseline (1992 or 1998) for a) particulate matter with an aerodynamic diameter <2.5 μm ($PM_{2.5}$), b) nitrogen oxide (NO_2) and c) overall weighted 24-h traffic noise (L_{den}) in the Danish Nurse Cohort. Smoothed pollution maps at 1×1 km spatial resolution were based on 24 538 participants' residential exposure estimates at the year before baseline. We applied an ordinary kriging method using a spherical semivariogram model based on a variable search radius with data from the 12 nearest participants.

TABLE 3 Associations between 3-year moving average air pollution and road traffic noise exposures and COPD incidence in main and subset analyses in the Danish Nurse Cohort

Exposures[#]	Subjects n	Model 1[¶] HR (95% CI)	Model 2[+] HR (95% CI)	Model 3[§] HR (95% CI)
$PM_{2.5}$	977	1.36 (1.16–1.60)	1.24 (1.05–1.46)	1.19 (1.01–1.41)
PM_{10}	977	1.28 (1.09–1.51)	1.19 (1.01–1.41)	1.15 (0.98–1.37)
NO_2	977	1.18 (1.11–1.26)	1.15 (1.08–1.22)	1.13 (1.05–1.20)
NO_x	977	1.07 (1.03–1.10)	1.06 (1.02–1.09)	1.05 (1.01–1.08)
$PM_{2.5}$				
<25 μg·m^{-3}	971	1.47 (1.23–1.76)	1.32 (1.11–1.58)	1.28 (1.07–1.53)
<20 μg·m^{-3}	873	1.66 (1.33–2.08)	1.46 (1.17–1.82)	1.41 (1.13–1.77)
<15 μg·m^{-3}	460	1.25 (0.81–1.91)	1.03 (0.67–1.58)	1.04 (0.68–1.60)
NO_2				
<40 μg·m^{-3}	963	1.26 (1.13–1.40)	1.24 (1.11–1.38)	1.26 (1.10–1.45)
<30 μg·m^{-3}	932	1.33 (1.17–1.52)	1.32 (1.15–1.51)	1.36 (1.15–1.62)
<20 μg·m^{-3}	856	1.37 (1.14–1.65)	1.35 (1.12–1.63)	1.45 (1.15–1.83)
<15 μg·m^{-3}	714	1.35 (1.11–1.65)	1.27 (1.04–1.56)	1.26 (1.03–1.55)
<10 μg·m^{-3}	451	1.30 (0.80–2.10)	1.08 (0.66–1.75)	1.09 (0.66–1.78)
L_{den} (continuous)				
All levels	977	1.21 (1.11–1.32)	1.17 (1.08–1.27)	1.15 (1.06–1.25)
L_{den} >48 dB	838	1.19 (1.06–1.36)	1.14 (1.01–1.29)	1.12 (0.98–1.27)
L_{den} >53 dB	584	1.41 (1.18–1.68)	1.32 (1.11–1.58)	1.28 (1.07–1.54)
L_{den} (categorical)				
Low (<48 dB)	139	Ref.	Ref.	Ref.
Medium (48–53 dB)	254	1.34 (1.09–1.65)	1.31 (1.07–1.61)	1.29 (1.05–1.59)
High (>53 dB)	584	1.39 (1.15–1.67)	1.33 (1.11–1.61)	1.29 (1.07–1.56)

Estimates are presented as hazard ratios with 95% confidence intervals based on interquartile range increases for $PM_{2.5}$ (6.26 μg·m^{-3}), PM_{10} (7.01 μg·m^{-3}), NO_2 (8.19 μg·m^{-3}) and NO_x (12.17 μg·m^{-3}) and per 10 dB increase for L_{den}. COPD: chronic obstructive pulmonary disease; $PM_{2.5}$: particulate matter with an aerodynamic diameter <2.5 μm; PM_{10}: particulate matter with an aerodynamic diameter <10 μm; NO_2: nitrogen dioxide; NO_x: nitrogen oxide; L: road traffic noise estimated as the equivalent A-weighted sound pressure level at the most exposed residential facade of all buildings; L_{den}: overall weighted 24-h traffic noise. [#]: the current European air quality limit values are 25 μg·m^{-3} for $PM_{2.5}$ and 40 μg·m^{-3} for NO_2, and the current World Health Organization environmental noise guideline limit value for the European region for exposure to outdoor road traffic noise is 53 dB; [¶]: Model 1 was adjusted for age (time axis), year of baseline (1993/1999) and calendar year of follow-up (strata one year); [+]: Model 2 was further adjusted for smoking (status, duration and intensity); [§]: Model 3 was further adjusted for body mass index (category), marital status, occupational status and leisure time physical activity status.

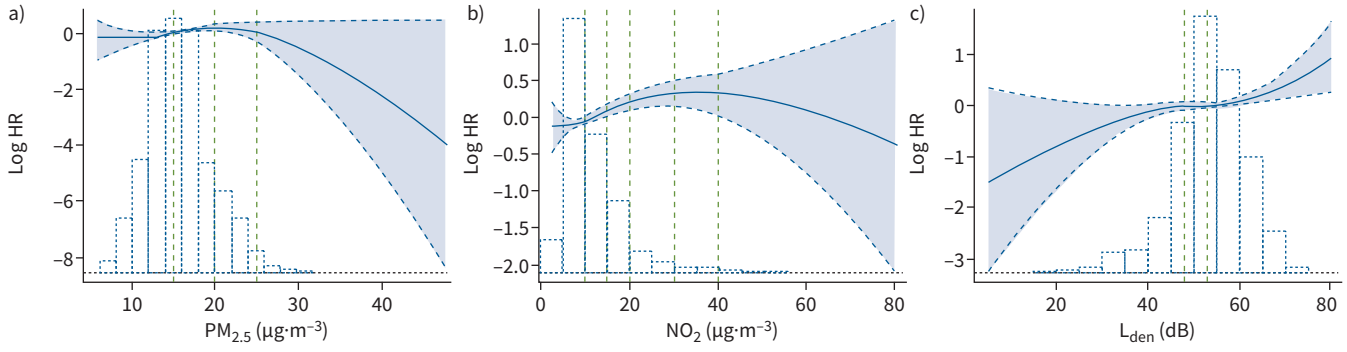

FIGURE 2 Natural cubic splines with three degrees of freedom of the associations between 3-year moving average exposures to a) particulate matter with an aerodynamic diameter <2.5 μm ($PM_{2.5}$), b) nitrogen dioxide (NO_2) and c) overall weighted 24-h traffic noise (L_{den}) and chronic obstructive pulmonary disease (COPD) incidence in the Danish Nurse Cohort. The curve results were based on Model 3. Blue solid lines indicate log hazard ratio values and dashed lines indicate their 95% confidence intervals. Green dashed lines indicate the cut-off values for $PM_{2.5}$ (25, 20 and 15 μg·m^{-3}), NO_2 (40, 30 and 20 μg·m^{-3}) and L_{den} (53 and 48 dB). The histograms show the distributions of 3-year moving averages of $PM_{2.5}$, NO_2 and L_{den}.

TABLE 4 Associations in two-pollutant models between 3-year moving average exposures to $PM_{2.5}$, NO_2 and L_{den} and COPD incidence in main and subset analyses in the Danish Nurse Cohort

Exposures[#]	Cases n	Model 3[¶] HR (95% CI)	Model 3[¶] + $PM_{2.5}$ HR (95% CI)	Model 3[¶] + NO_2 HR (95% CI)	Model 3[¶] + L_{den} HR (95% CI)
$PM_{2.5}$	977	1.19 (1.01–1.41)	–[+]	0.96 (0.77–1.20)	1.08 (0.91–1.30)
NO_2	977	1.13 (1.05–1.20)	1.14 (1.04–1.25)	–[+]	1.08 (0.99–1.18)
$PM_{2.5}$					
<25 μg·m^{-3}	971	1.28 (1.07–1.53)	–[+]	1.02 (0.81–1.28)	1.16 (0.96–1.41)
<20 μg·m^{-3}	873	1.41 (1.13–1.77)	–[+]	1.09 (0.83–1.43)	1.30 (1.03–1.65)
<15 μg·m^{-3}	460	1.04 (0.68–1.60)	–[+]	0.88 (0.54–1.42)	0.97 (0.62–1.52)
NO_2					
<40 μg·m^{-3}	963	1.26 (1.10–1.45)	1.17 (1.06–1.29)	–[+]	1.12 (1.01–1.24)
<30 μg·m^{-3}	932	1.36 (1.15–1.62)	1.19 (1.06–1.35)	–[+]	1.15 (1.01–1.31)
<20 μg·m^{-3}	856	1.45 (1.15–1.83)	1.22 (1.03–1.43)	–[+]	1.17 (0.98–1.39)
<15 μg·m^{-3}	714	1.26 (1.03–1.55)	1.27 (1.02–1.59)	1.26 (1.03–1.55)	1.22 (0.97–1.55)
<10 μg·m^{-3}	451	1.09 (0.66–1.78)	1.24 (0.73–2.12)	1.09 (0.67–1.79)	1.01 (0.59–1.72)
L_{den}					
All levels	977	1.15 (1.06–1.25)	1.13 (1.03–1.24)	1.08 (0.98–1.21)	–[+]
L_{den}>48 dB	838	1.12 (0.98–1.27)	1.07 (0.93–1.23)	0.99 (0.84–1.17)	–[+]
L_{den}>53 dB	584	1.28 (1.07–1.54)	1.21 (0.99–1.47)	1.13 (0.90–1.42)	–[+]
L_{den}					
Low (<48 dB)	139	Ref.	Ref.	Ref.	–[+]
Medium (48–53 dB)	254	1.29 (1.05–1.59)	1.27 (1.03–1.57)	1.25 (1.02–1.54)	–[+]
High (>53 dB)	584	1.29 (1.07–1.56)	1.24 (1.03–1.51)	1.16 (0.94–1.42)	–[+]

Estimates are presented as hazard ratios with 95% confidence intervals based on interquartile range increases for $PM_{2.5}$ (6.26 μg·m^{-3}) and NO_2 (8.19 μg·m^{-3}), and per 10 dB increase for L_{den}. $PM_{2.5}$: particulate matter with an aerodynamic diameter <2.5 μm; NO_2: nitrogen dioxide; L: road traffic noise estimated as the equivalent A-weighted sound pressure level at the most exposed residential facade of all buildings; L_{den}: overall weighted 24-h traffic noise; COPD: chronic obstructive pulmonary disease. [#]: the current European air quality limit values are 25 μg·m^{-3} for $PM_{2.5}$ and 40 μg·m^{-3} for NO_2, and the current World Health Organization environmental noise guideline limit value for the European region for exposure to outdoor road traffic noise is 53 dB; [¶]: Model 3 was adjusted for age (time axis), year of baseline (1993/1999) and calendar year of follow-up (strata one year), smoking (status, duration and intensity), body mass index (category), marital status, occupational status and leisure time physical activity status; [+]: not applicable in two-pollutant models owing to the high correlation of the two pollutants (above 0.7) or unavailable moving average data above 3 years for $PM_{2.5}$.

indicating very limited confounding impacts by $PM_{2.5}$. The joint HR of all three exposures was similar to that of NO_2 and L_{den} joint exposures (1.15 *versus* 1.17) (figure 3). The joint HRs for different groups of these exposures were all lower than the combined HRs (supplementary table S5). Overall, we observed no indications for multiplicative interaction effects, but antagonistic confounding effects [37], for $PM_{2.5}$, NO_2 and L_{den} exposures on COPD development.

Associations of $PM_{2.5}$, NO_2 and L_{den} with COPD incidence were not modified by any factors examined, and we noted robust associations for all three exposures in never-smokers (supplementary table S6). Associations were slightly weaker, especially for $PM_{2.5}$, when using the 1-year mean exposures of the year before or at cohort baseline (supplementary table S7). Our results were robust to alternative methods for adjustment for calendar year, except for no adjustment for calendar year, which yielded negative associations (supplementary figure S4). Additionally, our results were robust to altering covariates in adjusted models, further adjusting for municipality-level income, using variables identified by DAG models (supplementary figure S5), running analyses without imputed exposure data, and limiting participants without any comorbidities at baseline (supplementary table S8). When we restricted participants to those who did not relocate over the entire follow-up, resulting in the lowest risk for exposure misclassification, similar associations were also observed, but with much wider confidence intervals. These additional analyses are somewhat limited by the loss of statistical power due to almost half of the study population being excluded (supplementary table S8).

Discussion

In this nationwide cohort of female nurses aged >44 years, we found that long-term exposure to ambient air pollution and to road traffic noise were associated with COPD incidence. Associations were most robust for NO_2 and L_{den}, suggesting the relevance of traffic exposure for COPD development.

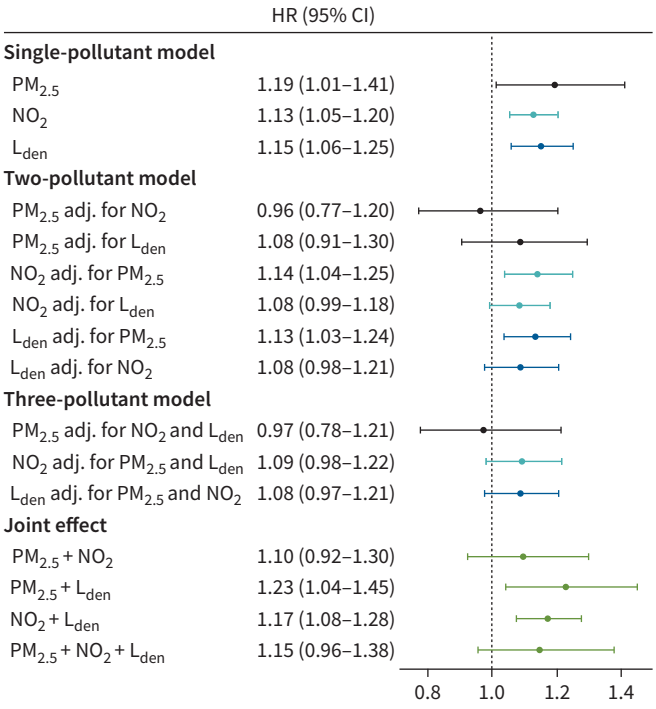

FIGURE 3 Associations of single, mutually adjusted and joint pollutant models between 3-year moving average exposures to particulate matter with an aerodynamic diameter <2.5 µm ($PM_{2.5}$), nitrogen dioxide (NO_2) and overall weighted 24-h traffic noise (L_{den}) and chronic obstructive pulmonary disease (COPD) incidence in the Danish Nurse Cohort. Analyses were based on Model 3. Estimates are presented as hazard ratios with 95% confidence intervals based on interquartile range (IQR) increments for $PM_{2.5}$ (6.26 µg·m^{-3}) and NO_2 (8.19 µg·m^{-3}) and per 10 dB increment for L_{den}.

Our findings of associations between $PM_{2.5}$ and NO_2 with COPD incidence are consistent with several earlier studies [7, 9, 10, 16, 17]. A previous Danish study in 57 053 participants of the Danish Diet, Cancer and Health cohort reported a significant association between NO_2 and COPD incidence using an identical COPD definition as the current study, but with no data on $PM_{2.5}$ [16]. Two cohort studies with $PM_{2.5}$ exposure reported significant associations with COPD incidence, but had no data on NO_2: one conducted in Taiwan with 91 709 participants [9] and another in the USA with 11 million Medicare recipients [7]. The latter, in line with our findings, reported that associations persisted in a subset of participants with $PM_{2.5}$ concentrations <12 µg·m^{-3}, the US limit value [7]. A Canadian cohort study of 1.1 million Toronto residents reported significant independent associations of both $PM_{2.5}$ and NO_2 exposures with COPD incidence [10]. However, the two large population-based cohorts in the USA and Canada did not adjust for smoking, which is an important influence factor for the association between air pollution and COPD [7, 10]. In addition, owing to the typical lack of historical address data in most cohorts, only a few studies had historical air pollution estimates, including the previous Danish study, though only with data on NO_2 [16], and the large Canadian study [10]. A recent large study in three European cohorts found associations between NO_2 and $PM_{2.5}$ and COPD incidence, mostly robust for NO_2, in line with our findings [17]. Overall, our findings add strong support to the evidence that long-term exposure to air pollution contributes to the development of COPD.

The present study is only the second study linking the incidence of COPD to road traffic noise exposure. In a UK cohort study of 211 016 London residents, Carey *et al.* [12] found no association between road traffic noise at night (L_{night}) and COPD incidence. Differences between our results and those of Carey *et al.* can be explained by the differences in road traffic noise exposure models. Our model predicted noise levels with high spatial and time (historical annual estimates since 1970) resolution, at the individual residential address level (1 m^2), while Carey *et al.* assigned road traffic noise at the postcode level (20 m^2), for the single year before the cohort baseline. Carey *et al.* therefore did not account for longer, chronic exposure to noise, and nor for fine, local within-urban variations in noise levels, which may be most relevant for health. Furthermore, Carey *et al.* also failed to detect associations with air pollutants and

COPD, also likely explained by differences (poor resolution) in exposure assessment. A cross-sectional US study found significantly higher risks of prevalent COPD in participants with self-reported occupational noise exposure [39].

We present novel results on the association between multiple environmental exposures and the risk of COPD, allowing us to examine possible joint effects of air pollution and road traffic noise for the first time. Weichenthal *et al*. [10] reported significant associations with both $PM_{2.5}$ and NO_2 in two-pollutant models. The only study with noise exposure found no change in HRs for NO_x and $PM_{2.5}$ (traffic sources only) after adjusting for L_{night}, and vice versa [12]. We found robust associations for NO_2 and L_{den} with COPD, independently of $PM_{2.5}$, whereas $PM_{2.5}$ HRs were attenuated to null after adjustment for NO_2 or L_{den}. Because the correlations between $PM_{2.5}$ and NO_2 or L_{den} were moderate or low, we did not interpret the HR changes for the three exposures as merely an artefact due to multicollinearity. However, given that adjustment for modelled NO_2 also adjusted for combustion-related particles from the same sources, we need to be cautious when interpreting the largely attenuated results for $PM_{2.5}$ from mutually adjusted models. Further, differential measurement errors can also complicate the interpretation of multi-pollutant models, because the exposure with the lowest measurement error may show the most consistent association [40]. There were no indications for interaction effects for $PM_{2.5}$, NO_2 and L_{den} exposures on COPD development in our study. More research is needed to discern which exposures or sources are the most relevant for COPD development.

The biological mechanisms behind the progression of COPD due to air pollution are more clearly understood than for noise exposures. Air pollution induces oxidative stress and free radical reactions can activate pulmonary and systemic inflammatory responses that adversely affect lung function, leading to the development of COPD after long-varying exposures of many years [9, 41]. We found that NO_2 could be a more relevant exposure for COPD development than $PM_{2.5}$, implying that NO_2 could have an independent effect on COPD progression, or is merely a proxy of ultrafine particles, which contribute minimally to total $PM_{2.5}$ mass but could contribute significantly to the development of COPD through high pulmonary deposition, oxidative stress and inflammation [42]. The only study with data on ultrafine particles and COPD found that the association between the two attenuated to null after adjustment for NO_2, suggesting a possible direct effect of NO_2 [10]. Compared with air pollution, the biological pathways of noise exposure with COPD are more uncertain because of limited experimental and epidemiological evidence. There are proposed plausible pathways for noise-related COPD development [20], because noise can induce oxidative stress and pulmonary inflammation in the lung, which adversely affect lung function. Noise exposure may activate the hypothalamic–pituitary–adrenal axis and then cause disorders in the immune system, resulting in exacerbation of pre-existing or underlying respiratory disease and increased susceptibility to bronchitis. Noise-related sleep disturbance can adversely affect lifestyles, including an increase in smoking [27], a reduction in leisure time physical activity [28] and an increase in weight and the risk of obesity [29], which are all risk factors for COPD. Furthermore, there is evidence that the changes in emotions, annoyance and anxiety can affect respiratory symptoms, breathing rhythms and lung function, which could be another mechanism by which road traffic noise leads to the development of COPD [43, 44]. More data are needed to link road traffic noise to measured lung function parameters for a better understanding of the mechanisms behind the association between road traffic noise and chronic respiratory disease.

The strengths of our study include objective Danish register data on hospital contacts for COPD, detailed confounder information, fine-scale spatial and temporal assessment of air pollution and noise exposure levels based on complete historical address data for over 40 years, long periods of follow-up and availability of data on road traffic noise. There are also several limitations in our study. COPD under-diagnosis represents one of the main challenges in COPD-related studies. The first hospital contact for COPD is an underestimate of COPD incidence, and is more likely a proxy of disease progression into a more severe stage or exacerbation. We most likely have a low sensitivity, but high specificity, of COPD incidence through using hospital contacts. A study on the validity of COPD diagnosis using the Danish National Patient Register found a high positive predictive value of 92% [45]. Another limitation is that our exposure assessment methods relied on residential addresses and lacked data on working addresses, indoor pollutants and personal activity patterns. Smoking is one of the most important risk factors for COPD, and we adjusted our results for smoking status, intensity and duration at baseline, but not for second-hand smoke exposure, which was not available in this cohort. We did not adjust for individual-level income, which could be an important confounder, because this was not available in the cohort. The information of time-changing covariates was also not available in this study, and the adjusted covariates were from baseline, and might have changed during follow-up.

Conclusions

Our findings provide evidence that long-term exposure to air pollution and to road traffic noise are independently associated with COPD incidence, with traffic likely the most important source. We present novel findings of the relevance of road traffic noise for respiratory health, which needs to be confirmed in future studies.

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