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Acute respiratory effects of livestock-related air pollution in a panel of COPD patients

Warner van Kersen[a], Marieke Oldenwening[a], Bernadette Aalders[b], Lizan D. Bloemsma[a], Floor Borlée[a], Dick Heederik[a], Lidwien A.M. Smit[a,*]

[a] Institute for Risk Assessment Sciences, Utrecht University, 3584 CM Utrecht, the Netherlands
[b] Netherlands Expertise Centre for Occupational Respiratory Disorders, Utrecht, the Netherlands

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ABSTRACT

Living close to livestock farms has been associated with increased symptoms in patients with chronic obstructive pulmonary disease (COPD). The causes of these effects are still poorly understood. This panel study attempts to assess the acute effects of livestock-related air pollution in patients with COPD living in an area with intensive livestock farming in the Netherlands.

Between February 2015 and July 2016, 82 participants took spirometry measurements twice daily (morning and evening) during a 3-month period, resulting in 12,672 FEV_1 and PEF records. Participants also kept a diary on respiratory symptoms as well as livestock-related odor annoyance. Daily average ammonia (NH_3) (a proxy for livestock-related air pollution) and fine particulate matter (PM_{10}) levels were collected from monitoring stations in the area. Lung function was analyzed as decrements of > 10% and > 20% from their median as well as absolute values. Self-reported odor annoyance was analyzed as a dichotomous variable. All analyses were done using generalized estimated equations. We adjusted for humidity, temperature, linear trend, and took multiple testing into account.

We found an odds ratio of 1.14 95%CI [1.05; 1.25] for decrements > 20% in morning FEV_1 per interquartile range (12 μg/m^3) increase in NH_3 concentration (lag 2). Odor annoyance was negatively associated with evening PEF (−4.46 l/min 95%CI [−7.59; −1.33]). Sensitivity analyses showed a stronger effect in participants with worse baseline lung function. No associations with symptoms were found.

Our results show acute effects of livestock-related air pollution on lung function in COPD patients living in close proximity to livestock farms.

1. Introduction

Several studies on the effects of air pollution in patients with chronic obstructive pulmonary disease (COPD) have reported an increase in morbidity and mortality, emergency room visits, exacerbations and hospitalization rates (Halbert et al., 2006; Li et al., 2016). These studies have mainly been conducted in COPD patients living in urban areas. However, in rural areas with intensive livestock farming, there is emerging evidence of health effects due to air pollution episodes, especially resulting from primary particulate matter and ammonia (NH_3) emissions as well as NH_3-related reaction products (secondary inorganic particles) (Hristov, 2011). A recent study in the Netherlands showed that week-average NH_3 levels before lung function measurements were associated with lung function deficits in 2308 nonfarming residents, suggesting that acute respiratory effects may occur due to temporally elevated NH_3 levels (Borlée et al., 2017a).

Evidence for a relationship between livestock-related air pollutants and acute respiratory effects has also been found in multiple longitudinal panel studies amongst agricultural communities in the United States. In 2011, a study performed in North Carolina found that fine particulate matter with a diameter up to 2.5 μm ($PM_{2.5}$) was associated with a decline in the forced expiratory volume in one second (FEV_1) in healthy volunteers near swine feeding operations (Schinasi et al., 2011). A study published in 2015 reported similar associations amongst asthmatic school-aged children in rural Washington State. Both increasing asthma morbidity and decrements in FEV_1 were associated with week average $PM_{2.5}$ (Loftus et al., 2015a). Later that year in the same area and cohort, an increase in NH_3 concentration was reported to be associated with decrements in FEV_1 (Loftus et al., 2015b). Besides effects from $PM_{2.5}$ and NH_3, associations between livestock odor

* Corresponding author at: Institute for Risk Assessment Sciences, Yalelaan 2, 3584 CM Utrecht, the Netherlands.
E-mail address: l.a.smit@uu.nl (L.A.M. Smit).

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annoyance and respiratory symptoms have also been reported (Hooiveld et al., 2015; Schinasi et al., 2011).

A cross-sectional German study has shown a lower FEV_1 in subjects exposed to higher annual (livestock farm emitted) NH_3 levels (Schulze et al., 2011). A similar spatial association between the number of stables in a 500m buffer around the home address and a lower FEV_1 was found in adults (Radon et al., 2007). In several epidemiological and experimental studies, COPD patients appeared to be the most susceptible group for livestock farm exposures, showing increases in respiratory symptoms, exacerbations and inflammatory responses (Borlée et al., 2017a, 2015; Harting et al., 2012; van Dijk et al., 2016).

To the best of our knowledge, the acute effects of livestock-related air pollution have not yet been investigated in patients with COPD, while one can hypothesize that the adverse respiratory effects described in healthy individuals will be more pronounced in this susceptible subgroup. The aim of this prospective panel study is therefore to assess the acute respiratory health effects of short-term exposure to NH_3, particulate matter < 10 µm in diameter (PM_{10}) and livestock farm odor in patients with COPD in a livestock-dense area in the Netherlands.

2. Materials and methods

2.1. Study population and design

Study participants were selected from the cross-sectional Dutch 'Livestock farming and neighboring residents' health' study (VGO) population, of which the design and selection process have been described in detail (Borlée et al., 2015). Briefly, this general population sample was recruited from a questionnaire survey conducted among patients of 27 general practitioners. Out of the 14,882 participating adults (aged 18–70 years), 2494 non-farming residents underwent medical examination in 2014–2015 (Borlée et al., 2017b). The medical examination included a lung function test and an extensive health questionnaire. Participants with COPD (n = 213), who produced a good quality lung function test according to ATS/ERS criteria, were invited by mail to participate in this panel study, of which 117 agreed to participate (response 55%). Subjects who reported to be current smokers (n = 27) were *a priori* excluded to avoid effect modification by tobacco smoke exposure. To investigate whether the effect of livestock-related air pollution differs for participants with different COPD definitions, we selected participants falling within one of the following three categories: (1) a post-bronchodilator (BD) measurement of FEV_1/FVC below the lower limit of normal or below 0.7 (Global Initiative for Chronic Obstructive Lung Disease); (2) a pre-BD measurement of FEV_1/FVC below 0.7 and wheezing, dyspnea or shortness of breath; (3) self-reported COPD, defined as a positive answer to the question: 'Have you ever been told by a doctor that you had COPD or emphysema?' (Borlée et al., 2017b). Eight participants did not complete the study, or were excluded from data analysis because of current smoking at the time of the panel study. This resulted in a study population of 82 participants with COPD, see supplementary figure 1 for a flowchart of the selection procedure. The study protocol (no. 13/533) was approved by the Medical Ethical Committee of the University Medical Centre Utrecht. All participants signed informed consent.

2.2. Data collection

Over a three month period, participants were asked to conduct morning and evening peak expiratory flow (PEF) and FEV_1 measurements, and to fill out an online diary on farm odor annoyance, medication use and respiratory symptoms (Appendix A). Measurements were performed after waking or before going to bed in order test the hypothesis that most exposure occurs overnight. Data collection started after an initial home visit by a fieldworker who explained the use of the spirometer (Asma-1 Monitor, Vitalograph, Buckingham, UK) and online diary. Instructions included taking measurements in an upright position and before taking medication. Participants were visited again after approximately six weeks to monitor their compliance, and one last time at the end of the study. The same fieldworker (M.O.) conducted all visits in this study. During each visit, an additional health questionnaire was completed and spirometry measurements were performed to monitor health status and spirometer use. The correlation between the mean FEV_1 measured by participants using the Asma-1 monitor and their baseline FEV_1 measured by spirometry during the earlier medical examination (according to GOLD initiative standards) (Borlée et al., 2017b) was found to be > 0.9. The data collection period lasted 491 days between February 15th 2015 and June 20th 2016. On average, individuals were observed in this study for 90 days (± 16) with a maximum of 20 participants enrolled simultaneously.

We distinguished morning and evening spirometry measurements based on a cut-off time at 13:00. Measurements between 00:00 and 01:59 were considered evening measurements that belonged to the previous day. Occasional measurements between 02:00 and 04:00 were evaluated individually based on the measurement pattern of that participant. Data completeness for the diary, morning and evening spirometry was 94.4%, 86.3% and 84.8%, respectively. The average time of measurement was 08:38 (± 01:22) in the morning and 20:59 (± 02:16) in the evening. In total, participants collected 12,673 good quality (best of three successful attempts) PEF and FEV_1 records.

2.3. Air pollution exposure

Average daily ambient levels of NH_3 and PM_{10} were obtained from the Dutch Air Quality Monitoring Network (National Institute for Public Health and the Environment, n.d.). Daily levels were computed using the mean from two measurement stations. The distance between the stations and the participants' home addresses ranged from 2 km to 40 km with an average of 23 km. Additionally, participants recorded daily livestock-related odor annoyance on a scale from 0 to 10 as a proxy for livestock exposure, with a higher score indicating more odor annoyance. We obtained data on daily ambient temperature and relative humidity from a weather station close to the study area, at the courtesy of the Royal Netherlands Meteorological Institute (KNMI).

2.4. Statistical analysis

Relationships between morning and evening PEF and FEV_1, symptoms and (livestock-related) air pollution exposure were analyzed using generalized estimated equations (GEE) assuming a first order autoregressive (AR1) correlation structure. The AR1 assumption that correlation between observations decreases with time logically fits our dataset with numerous observations per subject better than an exchangeable correlation structure. We included air pollution exposure from the same day (lag 0), the previous day (lag 1) or two days before (lag 2) the lung function measurements. Both single- and two-pollutant models were explored. Besides symptoms (wheezing, cold or flu, shortness of breath in rest) and absolute lung function values, decreases in PEF or FEV_1 values from an individual's median value greater than 10% and 20% were analyzed as more clinically relevant dichotomous response variables (Hoek et al., 1998). All models were adjusted for daily mean ambient temperature, relative humidity and day-in-study (linear trend). Sensitivity analyses were conducted to investigate the effect of the different COPD definitions as well as effects introduced by differences in active participants grouped by year in the study period (2015/2016). Model estimates are expressed per interquartile range increase (IQR) in NH_3 and PM_{10}. To limit the influence of differences in odor perception, odor annoyance scores were dichotomized before analysis. Therefore, the estimates for those models are expressed as changes on days with odor annoyance, compared to days without odor annoyance. All analyses were performed in R version 3.5.1 using the package Geepack ("The R Package geepack for Generalized Estimating Equations | Højsgaard | Journal of Statistical Software," n.d.). Model p-

Table 1
Study population characteristics per COPD definition.

Characteristics	COPD definition 1	2	3
n	43	22	17
Age, yr	60.8 ± 9.7	63.5 ± 5.4	60.4 ± 7.4
Female	15 (34.9)	9 (40.9)	11 (64.7)
BMI*	27.3 ± 5.3	28.0 ± 3.7	26.1 ± 4.0
Former smoker	32 (74.4)	15 (68.2)	10 (58.8)
Pack-years[†]	15.5 ± 15.2	9.0 ± 10.5	12.2 ± 15.3
Education level			
Low	10 (23.3)	5 (22.7)	5 (29.4)
Medium	24 (55.8)	10 (45.5)	4 (23.5)
High	9 (20.9)	7 (31.8)	8 (47.1)
Lung function characteristics			
Pre-BD measurement % predicted			
FEV_1	71.3 ± 17.4	80.8 ± 12.4	100.7 ± 14.0
FVC	96.9 ± 17.5	96.1 ± 15.8	105.8 ± 15.2
FEV_1/FVC	72.8 ± 10.0	84.0 ± 6.1	95.0 ± 7.3
Post-BD measurement % predicted			
FEV_1	75.7 ± 17.4	87.7 ± 13.4	105.8 ± 12.5
FVC	99.0 ± 16.0	99.5 ± 17.3	108.4 ± 14.1
FEV_1/FVC	75.8 ± 10.7	88.1 ± 4.6	97.6 ± 8.3
Coughing most days	14 (32.6)	7 (33.3)	10 (58.8)
Phlegm most days	11 (26.8)	6 (30.0)	9 (52.9)
Wheezing most days	21 (48.8)	19 (86.4)	8 (47.1)
Nasal allergies	14 (32.6)	12 (54.5)	7 (41.2)
Farms within 1 km from home address	12 ± 8	11 ± 7	10 ± 6
Distance to closest farm, m	429 ± 251	393 ± 226	512 ± 347

Definition of abbreviations: BD = bronchodilator; BMI = body mass index; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; PEF = peak expiratory flow. Data are presented as mean ± SD or n (%). Education levels: low—lower secondary school or less; medium—intermediate vocational education or upper secondary school; high—higher vocational education or university. *BMI = mass(kg)/(height (m))^2. [†]Mean pack-years for former smokers.
COPD definitions: 1—a post-BD measurement of FEV_1/FVC below the lower limit of normal or below 0.7 (Global Initiative for Chronic Obstructive Lung Disease); 2—a pre-BD measurement of FEV_1/FVC below 0.7 and wheezing, dyspnea or shortness of breath; 3—self reported, defined as a positive answer to the question: 'Have you ever been told by a doctor that you had chronic obstructive pulmonary disease or emphysema?'(Borlée et al., 2017b). Participants in group 2 did not meet criteria for group 1, participants in group 3 did not meet criteria for group 1 and 2.

values were corrected for multiple testing using the Benjamini–Hochberg procedure with a false discovery rate of 10% (Benjamini and Hochberg, 1995).

3. Results

3.1. Study population

A detailed description of participant characteristics per COPD definition is given in Table 1. Participants were on average 61.4 years old and 43% was female. Ex-smokers made up 70% of the study population with an average smoking history of 13.1 pack-years. Forty-three participants had COPD according to definition 1 (a post-bronchodilator (BD) measurement of FEV_1/FVC below the lower limit of normal or below 0.7). Categories 2 (a pre-BD measurement of FEV_1/FVC below 0.7 and wheezing, dyspnea or shortness of breath) and 3 (self-reported) each held 22 and 17 participants, respectively. Participants had on average 10 livestock farms within 1 km from their homes and the average distance to the nearest farm was 437 m. The study area is characterized by a large number of dairy, pig, and poultry farms as previously described in detail (Borlée et al., 2017b).

3.2. Air pollution exposure and odor annoyance

Fig. 1A shows the daily mean NH_3 and PM_{10} concentrations over the study period. The interquartile ranges for NH_3 and PM_{10} were 12.0 and 11.3 μg/m^3, respectively. A steep increase in NH_3 levels was observed in the Spring of 2016. The proportion of reported odor annoyance is highest in the first half of the entire study period (Fig. 1). This is probably explained by the lower mean number of farms within 1km from the home address amongst participants active in 2016 compared to those in 2015 (−5 farms; 95% CI [−9; −1]).

3.3. Air pollution and lung function

The most consistent associations between air pollutant levels and lung function were found for NH_3 levels (lag 2) and FEV_1 (Table 2). The models for morning FEV_1 decrements (dichotomous) in relation to an IQR increase in NH_3 (lag 2) showed statistically significant odds ratios (OR) 1.06; 95% confidence interval (95%CI) [1.00;1.13] for a 10% decline and 1.14; 95% CI [1.05;1.25] for a > 20% decline (Fig. 2). The association between NH_3 (lag 2) and > 20% decrements in morning FEV_1 remained significant after correction for multiple testing (Supplementary Table 2). The models for NH_3 (lag 2) and evening FEV_1 decrements > 10% followed the same trend with an OR of 1.07, 95%CI [1.01,1.13], while the OR for a > 20% decrement was 0.89, 95%CI [0.88,1.10]. No associations with dichotomized PEF decrements where observed.

For analyses of lung function as a continuous variable, a weak negative association was seen between NH_3 (lag 2) and morning FEV_1 (β = −3.1 ml, 95% CI [−6.9,0.6]) (Table 2). Lag 2 NH_3 also showed weak negative associations with evening FEV_1 and both PEF variables. Lag 0 and Lag 1 NH_3 showed weak effects in both directions. No associations were found between NH_3 levels and respiratory symptoms (Supplementary Figure 2).

A similar but weaker pattern was found for PM_{10}. An OR of 1.11 95%CI [1.01;1.23] was found for decrements of > 10% in morning PEF with an IQR increase in lag0 PM_{10} (Fig. 2). For all lags, PM_{10} showed effects in both directions across the lung function variables. PM_{10} (Lag 1) showed a negative association with evening FEV_1 (β = −4.8 ml, 95% CI [−9.5, −0.2]) (Table 2). None of the associations with PM_{10} were significant after adjustment for multiple testing. Little difference was seen between single- and two-pollutant models (Table 2). PM_{10} showed no effects on symptoms (Supplementary Figure 2).

Models with odor annoyance as an exposure proxy revealed an association between odor annoyance (Lag 0) and evening PEF (β = −4.5 l/min 95%CI [−7.6, −1.3]), which remained statistically significant after adjustment for multiple testing (Table 2). No relation was found between symptoms and odor annoyance.

3.4. Sensitivity analyses

Models with an interaction term between exposure and COPD definition revealed that the described effects are the strongest in participants with COPD definition 1. Participants with COPD definition 1 show an OR of 1.23 95%CI [1.12,1.36] for decrements in FEV_1 > 20% per interquartile range increase of NH_3 (lag 2). For the same relationship, participants with COPD definition 2 and 3 show OR of 0.98 95%CI [0.93,1.03] and 1.13 95%CI [1.01,1.29] respectively (Supplementary Figure 3). Results for the stratified analysis of odor annoyance and evening PEF are shown in Supplementary Table 3.

A sensitivity analysis, using models stratified over study year, showed that the association between lung function and NH_3 (lag 2) is strongest in 2016. Similarly, the effect of PM_{10} (lag 1) on evening FEV_1 was slightly more pronounced in 2016 compared to 2015. (Supplementary Table 1)

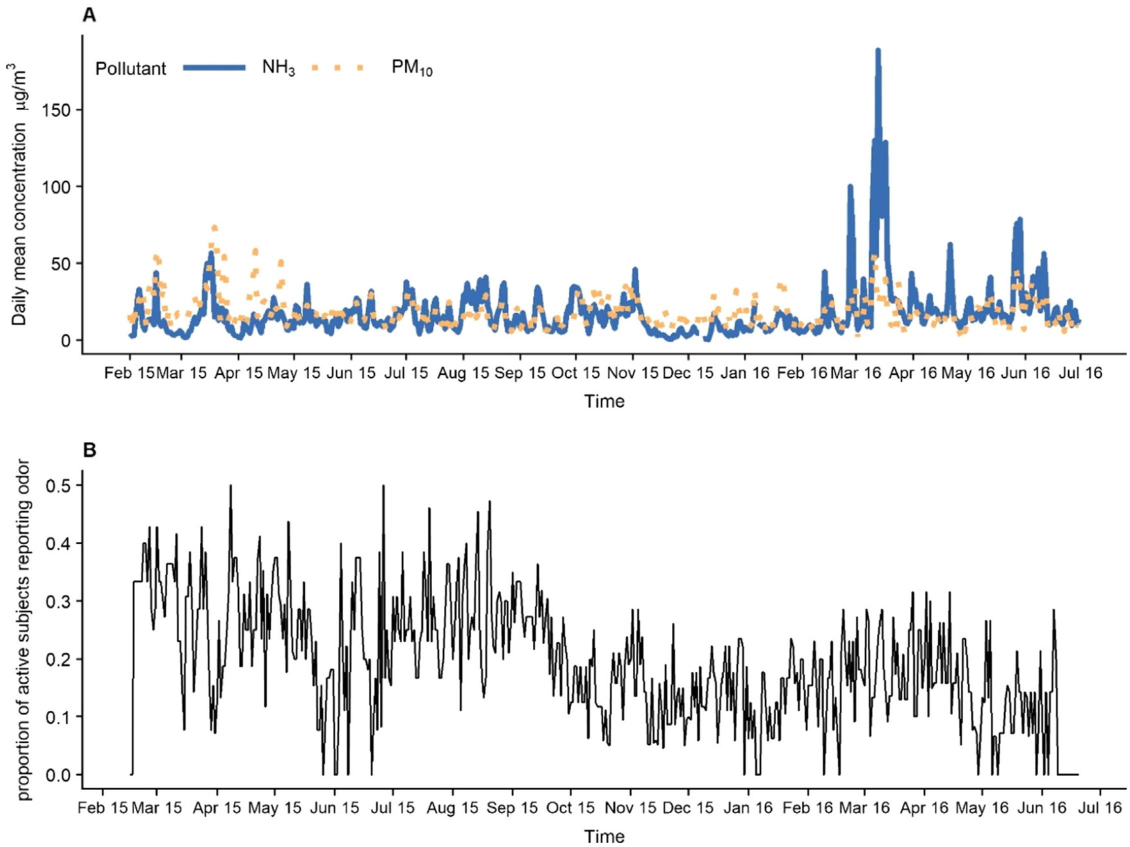

Fig. 1. A: Daily mean NH3 and PM10 concentration over the study period (February 2015-June 2016); B: The proportion of active subjects reporting livestock odor over the study period. Participants collected data for 90 days with a maximum of 20 active participants at a time.

Table 2
Associations between air pollutant levels, livestock odor annoyance and lung function.

Model	FEV_1 morning (ml)			FEV_1 evening (ml)			PEF morning (l/min)			PEF evening (l/min)		
	Estimate	95% CI	q-value	Estimate	95% CI	q-value	Estimate	95% CI	q value	Estimate	95% CI	q-value
Single pollutant (per IQR)												
Lag 0 NH_3	0.88	−3.34; 5.10	0.91	0.70	−2.74; 4.14	0.82	−0.49	−1.39; 0.41	0.56	0.45	−0.46; 1.36	0.61
Lag 0 PM_{10}	−3.12	−8.04; 1.79	0.76	0.92	−4.86; 6.70	0.82	−1.17	−2.38; 0.04	0.41	−0.61	−2.05; 0.83	0.61
Lag 1 NH_3	0.05	−2.58; 2.69	0.97	−1.84	−6.42; 2.74	0.82	−0.34	−1.06; 0.37	0.56	−0.45	−1.49; 0.58	0.61
Lag 1 PM_{10}	1.73	−3.14; 6.60	0.91	−4.88	−9.55; −0.21	0.49	1.04	−0.31; 2.38	0.41	0.97	−0.16; 2.11	0.56
Lag 2 NH_3	−3.14	−6.86; 0.59	0.76	−0.89	−4.07; 2.30	0.82	−0.29	−1.36; 0.77	0.79	−0.16	−0.92; 0.59	0.74
Lag 2 PM_{10}	0.75	−4.01; 5.50	0.91	1.89	−4.28; 8.05	0.82	−0.01	−1.44; 1.42	0.99	0.26	−1.24; 1.75	0.74
Multiple pollutant (per IQR)												
Lag 0 NH_3	1.05	−3.41; 5.52	0.76	0.68	−3.39; 4.75	0.82	−0.41	−1.32; 0.50	0.41	0.62	−0.44; 1.68	0.61
Lag 0 PM_{10}	−3.09	−8.41; 2.22	0.76	−0.19	−7.32; 6.94	0.82	−1.01	−2.35; 0.33	0.41	−0.88	−2.53; 0.76	0.61
Lag 1 NH_3	−0.10	−2.83; 2.63	0.91	−1.52	−7.39; 4.35	0.82	−0.49	−1.21; 0.23	0.41	−0.83	−2.06; 0.39	0.51
Lag 1 PM_{10}	0.85	−4.14; 5.84	0.91	−3.75	−9.12; 1.62	0.82	1.29	−0.16; 2.74	0.41	1.36	0.04; 2.68	0.51
Lag 2 NH_3	−3.24	−7.42; 0.93	0.76	−0.94	−4.57; 2.69	0.82	−0.17	−1.21; 0.86	0.89	−0.26	−1.03; 0.51	0.68
Lag 2 PM_{10}	2.32	−3.32; 7.95	0.76	2.41	−3.77; 8.60	0.82	−0.02	−1.55; 1.51	0.89	0.40	−1.09; 1.90	0.68
Odor annoyance (yes/no)												
Lag 0	−6.45	−18.9; 6.00	0.76	−2.68	−15.49;10.13	0.82	1.04	−2.61; 4.70	0.77	−4.46	−7.59; −1.33	0.06
Lag 1	0.26	−10.76; 11.27	0.96	5.35	−9.71; 20.40	0.76	−0.86	−3.18; 1.45	0.76	1.84	−1.59; 5.26	0.76
Lag 2	3.65	−7.10; 14.40	0.76	−1.40	−15.56; 12.76	0.92	1.10	−1.80; 3.99	0.76	1.84	−1.64; 5.33	0.76

Estimates are expressed as changes in FEV_1/PEF per IQR increase in pollutant concentration or on days with odor annoyance. Sample size is 82. The IQRs for NH_3 and PM_{10} were 12.0 and 11.3 µg/m^3 respectively. Models are corrected for ambient temperature, humidity and linear trend. Multiple pollutant models are further corrected for either NH_3 or PM_{10}. The q value describes the false discovery rate according the Benjamini-Hochberg procedure, a q-value < 0.10 is considered statistically significant.

4. Discussion

Our results show acute effects of livestock-related air pollution on lung function of COPD patients. The described associations with NH_3 are more pronounced compared to those with PM_{10}, which suggests that livestock farm emissions are the driver of the effect. The OR (1.14, 95%CI [1.05;1.25]) we found for the effect of an IQR increase in NH_3-levels (lag 2) on decrements in FEV_1 of > 20% from the individual median, supports the findings of a recent cross-sectional study conducted in the same area amongst 2308 adults. In that study, a 25 µg/m^3

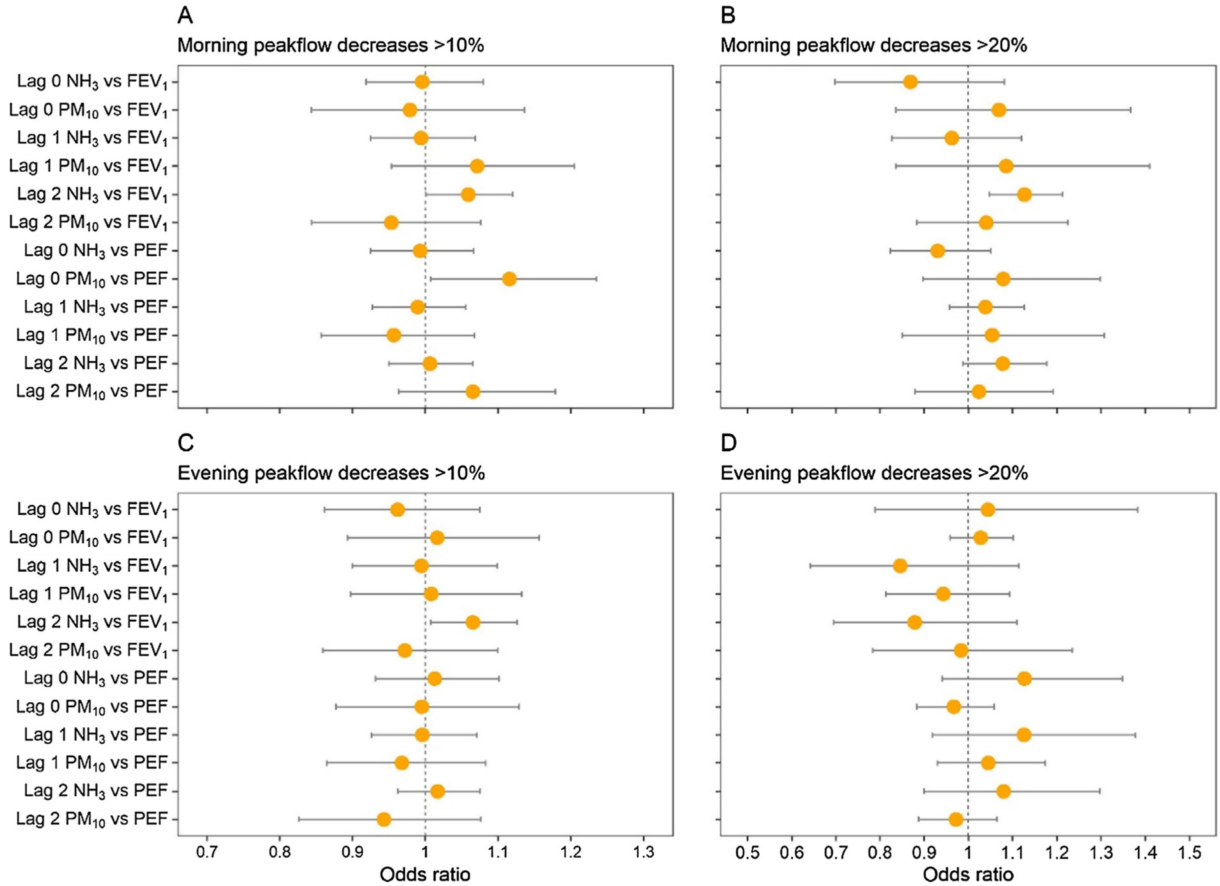

Fig. 2. Effects of an IQR increase in air pollutant levels on (A) morning peak flow decreases > 10% from median; (B) morning peak flow decreases > 20% from median; (C) evening peak flow decreases > 10% from median; and (D) evening peak flow decreases > 20% from median, expressed as odds ratio and 95% confidence interval.

increase in week-average NH_3 was associated with a 2.22% lower FEV_1 (Borlée et al., 2017a). Similarly, two longitudinal panel studies in the United States conducted amongst children with asthma reported acute effects of exposure to NH_3 and $PM_{2.5}$ on FEV_1 (Loftus et al., 2015b,a). Temporal effects of farm-related pollutants on both FEV_1 and self-reported respiratory symptoms were also reported by a third American panel study amongst 101 healthy adults (Schinasi et al., 2011).

An earlier study in the Netherlands showed that a closer residential distance to one or more livestock farms was associated with wheezing among COPD patients (Borlée et al., 2015). Two American studies also found associations between residential proximity to livestock farms and self-reported respiratory health (Kilburn, 2012; Pavilonis et al., 2013). The association we found between self-reported odor annoyance and a lower evening PEF is another indication for acute effects of livestock farm emissions on lung function. Another Dutch study has shown a positive relationship between modelled odor exposure (based on the presence of livestock farms) and reported odor annoyance, as well as an increase in odor annoyance over the last decade (Boers et al., 2016). A Danish study reported an association between residential exposure to NH_3 and increased respiratory symptoms, mediated by odor annoyance (Blanes-Vidal et al., 2014). Reported odor annoyance did not increase with NH_3 in our study. This is likely due to other (e.g. sulfur) compounds that also contribute to livestock odor (Schiffman et al., 2000). The odor threshold for NH_3 lies between 5 and 53 ppm (Hristov, 2011). The maximum daily mean NH_3 level measured at the central monitor during the study period was 188.6 $\mu g/m^3$ or 0.27 ppm, making it unlikely to be registered as odor annoyance. The steep increase in NH_3 levels measured in the spring of 2016 seems to coincide with the period in which farmers apply most of their manure on agricultural fields. The absence of an increase of similar magnitude in 2015 could be explained by differences in atmospheric conditions. We did not find significant associations between PM_{10} and lung function. In a meta-analysis of panel studies on acute effects of (urban) air pollution among patients with COPD, Bloemsma et al. found a small overall effect of PM_{10} on FEV_1 (−3.38 ml, 95%CI −6.39 to −0.37) with considerable heterogeneity of the outcomes (Bloemsma et al., 2016).

At the core of its design a panel study has repeated measurements on individuals at fixed short time intervals. Its strengths lie in detailed individual participants' data as well as the ability to control for (unmeasured) confounders that are stable over time, because every individual acts as her/his own control. Furthermore the traditional alternative of the registry-based time series does not detect specific health outcomes like (subclinical) changes in lung function and symptoms (Ward and Ayres, 2004).

Our study has a few limitations. First, as in most panel studies, measurement error due to the use of central site monitoring is inevitable. The relatively large population size and long duration of our panel study precluded measuring daily personal air pollutant exposure. However, the correlation between the two monitoring sites was moderate to high (NH_3: 0.53 and PM_{10}: 0.90) and in a panel design one models fluctuations over time instead of spatial differences between participants. Therefore, the impact on the associations is deemed to be low. Selection bias could have influenced the associations with odor annoyance as participants might have joined the study based on their view on livestock farming. However, only 12 out of 82 (14.6%) participants reported that they attribute their health complaints to livestock farms. A recent study, conducted in the population from which our participants were selected, showed that there was no association between lung function and attitude toward livestock farming (Borlée et al., 2019). The mean effects of day-to-day variations in air pollutant concentrations on lung function tend to be small as seen in similar studies (Bloemsma et al., 2016). We do however see a more pronounced effect on large decrements in lung function indicating that there is an especially vulnerable group within our population. Based on the stratified analysis according to COPD definition, participants with COPD defined as fixed airway obstruction showed the strongest association with NH_3 exposure. Given that these participants already have an irreversible airway obstruction, a further > 20% decrement in lung function can be clinically relevant, although we did not detect an increase in reported symptoms. Similar observations were made for the relationship between odor annoyance and evening PEF (Supplementary Table 3). A final point to address is the representativeness of the COPD patients selected from a general population sample. We used different operational definitions of COPD to classify the, mainly mild, COPD patients (Borlée et al., 2017b). COPD is a heterogeneous condition, and, especially in older patients a substantial overlap exists between COPD and asthma making for a complex diagnosis (Wurst et al., 2016). A priori, we hypothesized that the effect of exposure is unlikely to be differential for the different chronic lung disease phenotypes.

Despite livestock farming being indicated as the driver, the exact mechanisms behind the observed associations remain elusive. At the concentrations measured during the present study, it is unlikely that NH_3 is directly responsible for the observed effect. However, the fact that the described associations with NH_3 are more pronounced compared to those with PM_{10} does suggests that livestock farm emissions are the driver of the effect. A possible explanation is that both NH_3 and odor annoyance act as proxies for a complex mixture of air pollutants. The described effect of NH_3 could also be caused by NH_3-related secondary inorganic particles. It was previously found that NH_3 accounts for more than half of the secondary inorganic particles that make up the PM_{10} fraction in the study area (Hendriks et al., 2013). A recent study in China found that reducing livestock NH_3 emissions would be highly effective at reducing these secondary particles (Xu et al., 2018).

4.1. Conclusion

Our longitudinal panel study has shown acute effects of livestock-related air pollutants on the lung function of COPD patients. Our results indicate that the effects of NH_3 exposure are more pronounced in patients with fixed airway obstruction. Our results add to a growing body of evidence showing that agricultural sources of air pollution are of public health relevance.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.105426.

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