Air Pollution from Livestock Farms Is Associated with Airway Obstruction in Neighboring Residents

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Abstract

Rationale: Livestock farm emissions may not only affect respiratory health of farmers but also of neighboring residents.

Objectives: To explore associations between spatial and temporal variation in pollutant emissions from livestock farms and lung function in a general, nonfarming, rural population in the Netherlands.

Methods: We conducted a cross-sectional study in 2,308 adults (age, 20–72 yr). A pulmonary function test was performed measuring prebronchodilator and post-bronchodilator FEV_1, FVC, FEV_1/FVC, and maximum mid-expiratory flow (MMEF). Spatial exposure was assessed as (*1*) number of farms within 500 m and 1,000 m of the home, (*2*) distance to the nearest farm, and (*3*) modeled annual average fine dust emissions from farms within 500 m and 1,000 m of the home address. Temporal exposure was assessed as week-average ambient particulate matter <10 μm in diameter and ammonia (NH_3) concentrations before lung function measurements. Data were analyzed with generalized additive models (smoothing).

Measurements and Main Results: A negative association was found between the number of livestock farms within a 1,000-m buffer from the home address and MMEF, which was more pronounced in participants without atopy. No associations were found with other spatial exposure variables. Week-average particulate matter <10 μm in diameter and NH_3 levels were negatively associated with FEV_1, FEV_1/FVC, and MMEF. In a two-pollutant model, only NH_3 remained associated. A 25-μg/m^3 increase in NH_3 was associated with a 2.22% lower FEV_1 (95% confidence interval, −3.69 to −0.74), FEV_1/FVC of −1.12% (−1.96 to −0.28), and MMEF of −5.67% (−8.80 to −2.55).

Conclusions: Spatial and temporal variation in livestock air pollution emissions are associated with lung function deficits in nonfarming residents.

Keywords: livestock farm; lung function; air pollution; respiratory health; residents

Recent studies have highlighted the large contribution of agriculture to fine particulate matter (PM) air pollution, and the public health impact that may result from agricultural emissions (1–4). In the Netherlands, a small country with one of the highest population densities in the world and one of the highest livestock farm densities, neighboring residents are concerned about potential health risks of farm emissions (5).The air inside livestock farms contains high levels of (organic) dust, which is known to lead to adverse respiratory health effects in those occupationally exposed (6, 7). Livestock farms may also emit air pollutants into the atmosphere, consisting of a mixture of gases, such as ammonia (NH_3)

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At a Glance Commentary

Scientific Knowledge on the Subject: The air inside livestock farms contains high levels of dust and gases, which can affect respiratory health in occupational settings. Several air pollutants are emitted into the atmosphere, including such gases as ammonia, and particulate matter contaminated with (parts of) microorganisms. However, little is known about health risks for neighboring residents that may result from such agricultural emissions.

What This Study Adds to the Field: This large-scale population-based study shows that air pollution from livestock farms is associated with obstructive lung function changes in neighboring residents. We found a negative association between farm density around the home address and lung function. In addition, lung function was lower when measured after weeks with higher ambient ammonia levels. Almost all ammonia emissions result from agricultural activities. Associations were mainly observed with lung function parameters, which are indicative of airway obstruction. Our results indicate that spatial and temporal variation in livestock farm emissions are related to obstructive respiratory effects.

and hydrogen sulfide (H_2S), and PM contaminated with microorganisms and toxins, such as endotoxins: cell-wall components of gram-negative bacteria (8, 9). Raised endotoxin levels were measured up to 200 m downwind from farms (10, 11). NH_3 is an irritant gas that is formed by enzymes in animal waste, and used as a marker for livestock farm emissions (12). NH_3 is also an important precursor of secondary inorganic aerosols (SIA) and highly contributes to atmospheric PM concentrations of, among others, PM <10 μm in diameter (PM_{10}) and PM <2.5 μm in diameter ($PM_{2.5}$), of which especially $PM_{2.5}$ can be transported over great distances (4).

Despite the substantial contribution of livestock farming to ambient air pollution, potential respiratory health risks have been poorly studied. Three longitudinal panel studies have been conducted in the United States. Two were conducted among 51 children with asthma and reported a temporal effect of NH_3 and $PM_{2.5}$ exposure on FEV_1 (12, 13). The other panel study also found a temporal effect of farm-related pollutants on self-reported respiratory symptoms and FEV_1 in 101 adults (14). Two other American studies described spatial associations between residential proximity to livestock farms and self-reported respiratory effects (15, 16).

Studies from Europe have been conducted in Germany and the Netherlands. A cross-sectional German study found a decrease in FEV_1 in adults with more than 12 stables within 500 m of the home address (17), and among subjects exposed to higher annual NH_3 levels (18). In the same area a cross-sectional study among 3,867 children found an association between asthmatic symptoms and modeled endotoxin exposure among children of parents with atopy (19). Conversely, two Dutch studies found inverse associations between livestock farm proximity and asthma and chronic obstructive pulmonary disease (COPD) prevalence using medical records and self-reported data (20, 21). However, patients with COPD reported more symptoms in areas with high farm density (20, 22).

Thus, only a limited number of studies measured pulmonary function in neighboring residents, and most studies focused on spatial variation (e.g., distance to the nearest farm). However, we expect that time-varying exposure to air pollutants resulting from agricultural activities also plays a role. The current study aims to explore associations between proxies of both temporal and spatial variation in air pollution from livestock farms and lung function in a general, nonfarming population of 2,308 adults in the Netherlands. Results presented in this manuscript are part of the Livestock Farming and Neighboring Residents' Health study and have been previously presented as abstracts (23, 24).

Methods

Study Population and Design

A questionnaire survey was conducted among patients of 21 general practitioner practices resulting in 14,875 participating adults (53.4% response) from the general population as described previously (20). Subjects who were working or living on a farm (n = 712; 4.8%) were excluded. Questionnaire respondents who were willing to participate in a follow-up study were eligible for a medical examination (n = 8,714). Based on their home addresses, 12 temporary research centers were established (Figure 1). Between March 2014 and February 2015, all participants living within a distance of approximately 10 km of a temporary research center (n = 7,180) were invited to the nearest research center for medical examination, which resulted in 2,494 participants (response, 34.7%) (25). Nonresponse was analyzed by comparing characteristics and associations between respiratory health indicators and livestock exposure in different population subsets. The study protocol (no. 13/533) was approved by the Medical Ethical Committee of the University Medical Centre Utrecht. All 2,494 participants signed informed consent.

Medical Examination

Population characteristics were collected with an extended questionnaire. Atopy was defined as the presence of specific serum IgE antibodies to one or more common allergens (house dust mite, grass, cat, and dog) and/or a total IgE higher than 100 IU/ml (26). Bronchodilator (BD) spirometry (pre-BD and post-BD) was conducted. FEV_1, FVC, FEV_1/FVC, and maximum mid-expiratory flow (MMEF) were expressed as percentage predicted based on the Global Lung Function Initiative 2012 reference Equations (27). COPD was defined as a post-BD measurement of FEV_1/FVC below the lower limit of normal and/or a post-BD measurement of FEV_1/FVC less than 0.70 (Global Initiative for Chronic Obstructive Lung Disease) (25).

Spatial and Temporal Livestock Farm Exposure Proxies

An aim of the current study is to replicate the association between farm density around the home and lung function in German adults (17). In addition, other spatial and temporal exposure proxies were considered. The following spatial livestock farm exposure proxies were studied for each subject: (*1*) total number of farms within 500 and 1,000 m; (*2*) distance in meters to the nearest farm (general and specific animal farms: pigs, poultry, cattle, goats,

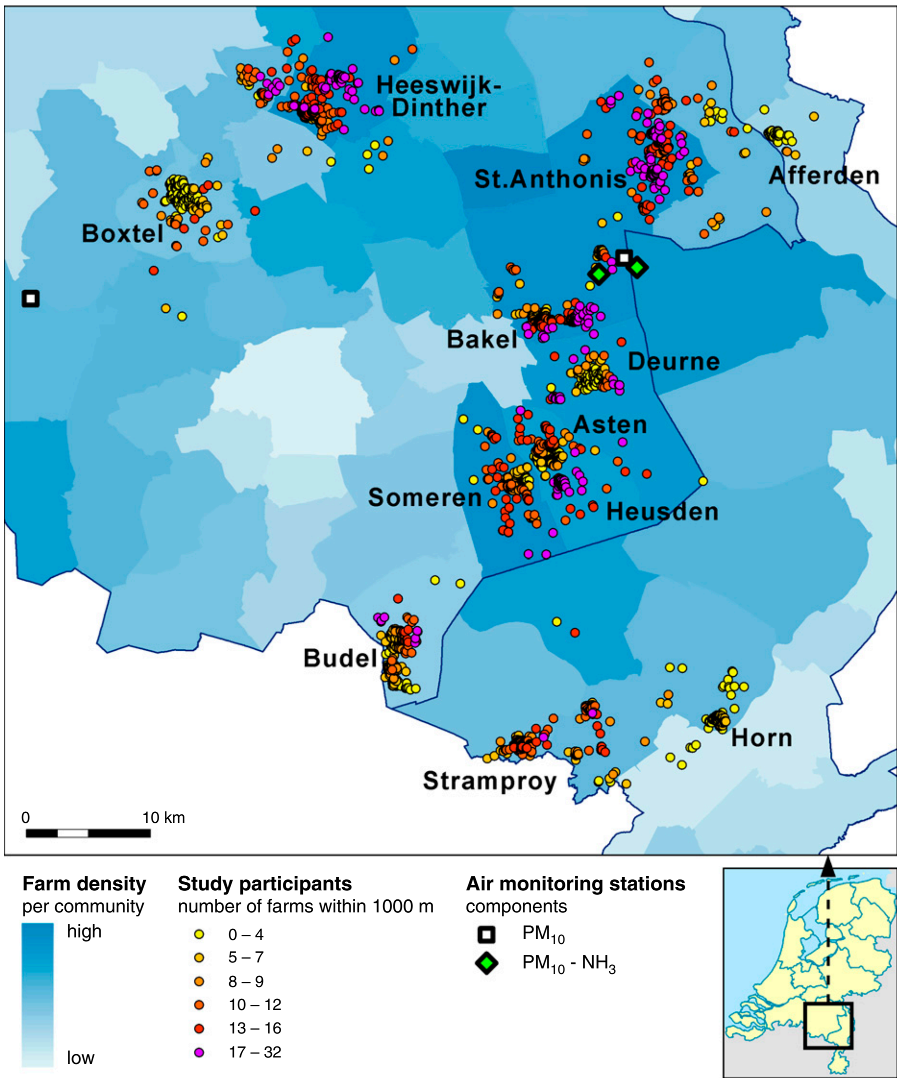

Figure 1. Map of the study area. PM_{10} = particulate matter < 10 μm in diameter.

and mink); and (*3*) inverse-distance weighted fine dust emissions from all farms within 500 m and 1,000 m, as described previously (21). Ambient NH_3 and PM_{10} levels before the spirometry measurement were studied as temporal exposure proxies. Average daily ambient NH_3 and PM_{10} levels were obtained from air monitoring stations located in the study area, which are part of the Dutch Air Quality Monitoring Network (28).

Statistical Analysis

Relationships between spirometry variables and livestock farm exposure variables (spatial and temporal) were studied using a penalized regression spline using the (default) "thin plate" basis as implemented in the mixed generalized additive model computation vehicle R package. Based on the results of the spline analyses, exposure cutoff values were chosen for further analyses. Multiple linear regression analyses were used to study associations between these dichotomized exposure variables and spirometry values. For all these analyses pre-BD spirometry values were used. These models were adjusted for smoking habits, living on a farm during childhood, and growing up in the study area. Multicollinearity between confounders was checked with Spearman rank correlation and variance inflation factors.

Sensitivity analyses were conducted to investigate the effect of spirometry technician, influenza-season, humidity, temperature, and traffic-related air pollution at the home address of NO_2, $PM_{2.5}$, and $PM_{2.5}$ absorbance (soot) using land use regression models from the ESCAPE (European Study of Cohorts for Air Pollution Effects) project (29, 30). In addition, analyses were stratified for atopy, COPD (based on spirometry [Global Initiative for Chronic Obstructive Lung Disease and/or lower limit of normal]), asthma, and smoking habits and interaction between these groups and exposure variables was tested.

More details on the study methodology are provided in the online supplement.

Results

Study Population Characteristics

The medical examination was conducted in 2,494 persons aged 20–72 years, including more females (54.6%) than males (Table 1). In total, 837 individuals (33.6%) reported a farm childhood and 1,871 (75.0%) were born in the study area. Only subjects with lung function measurements with sufficient quality were included in the analyses, which resulted in 2,308 pre-BD measurements and 2,169 post-BD measurements. Based on spirometry results we found indication of reversibility in 4.1% and COPD in 10.9% of all participants.

Nonresponse Analysis

Differences in personal characteristics of different population subsets were found (e.g., age, sex, self-reported morbidity, distance to farms) indicating that selection-bias could have played a role (Table 2; *see* online supplement). However, associations between farm exposure estimates and respiratory morbidity based on self-reported data in different population subsets (the source population, the population that participated in the questionnaire survey, the population invited for the medical examination, and the population that participated in the medical examination) showed similar associations, in terms of direction and magnitude, with overlapping confidence intervals (CIs) (*see* Table E3 in the online supplement).

Association between Spatial Variation in Livestock Exposure and Lung Function

Farms located in the study area are a mix of small farms with relatively few animals to large farms with thousands of animals (*see* Table E1). Smoothed plots suggested a nonlinear negative association between

Table 1. General Characteristics of the Study Population

Characteristics	Total Population (*n* = *2,494*)
Age, yr	54.7 ± 11.0
Female	1,363 (54.6)
BMI*	27.1 ± 4.3
Never smoker	1,122 (45.0)
Ever smoker	1,112 (44.6)
Current smoker	252 (10.1)
Pack-years†	18.1 ± 17.9
Education level	
Low	607 (24.3)
Medium	1,112 (44.6)
High	746 (29.9)
Farm childhood	837 (33.6)
Grown up in study area	1,871 (75.0)
Lung function characteristics	
Pre-BD measurement % predicted (n = 2,308)‡	
FEV_1	99.0 ± 15.4
FVC	102.9 ± 13.0
FEV_1/FVC	95.7 ± 8.7
MMEF	93.5 ± 32.8
Post-BD measurement % predicted (n = 2,169)‡	
FEV_1	102.0 ± 14.5
FVC	102.9 ± 12.6
FEV_1/FVC	98.7 ± 8.4
MMEF	105.9 ± 35.1
Health characteristics (n = 2,037‡, and subjects with atopy measurement n = 2,443)	
Reversibility§	83 (4.1)
COPD‖	222 (10.9)
Atopy	727 (29.8)

Definition of abbreviations: BD = bronchodilator; BMI = body mass index; COPD = chronic obstructive pulmonary disease; MMEF = maximum mid-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 education or university.
*BMI = mass (kg)/(height [m])^2.
†Mean pack-years for subjects who ever smoked.
‡Lung function measurements with quality C or better. Reversibility and COPD were analyzed in subjects with before and after measurements with a sufficient quality (n = 2,037).
§Reversibility: a post-BD measurement with >12% increase or >400 ml.
‖COPD: a post-BD measurement of FEV_1/FVC below the lower limit of normal and/or a post-BD measurement of FEV_1/FVC <0.70 (Global Initiative for Chronic Obstructive Lung Disease).

the number of farms in a 1,000-m radius and FEV_1, FEV_1/FVC, and MMEF (Figure 2). The association was statistically significant for MMEF. No clear association was found for FVC, indicating that in particular obstructive lung function changes occurred. No associations were found with farm density for specific animal species or with the other spatial exposure proxies including distance to the nearest farm (general and specific animal farms) and modeled annual average fine dust emissions from farms within 500 m and 1,000 m. Spirometry results expressed as *z* scores showed minimal differences compared with results presented as % predicted values (*see* Figure E1). Adjustment for week-average NH_3 and PM_{10} levels at the time of the medical evaluation resulted in only minor changes of the association between farm density and lung function (*dashed* and *dotted lines* in Figure 2).

Based on the shape of the splines, a cutoff value of 17 farms or more was chosen to compare so-called hotspot areas with a high farm density, with lower farm density areas. This cutoff value was based on a visual inspection of the smoothed plots; around 17 farms within 1,000 m, there is a turning point where the % predicted value is lower than the % predicted value at 0 farms. In total 11.3% participants lived in a hotspot and they had a 4.5% lower MMEF (95% CI, −8.64 to −0.36), and a 1.86% lower FEV_1 (95% CI, −3.80 to 0.09) than participants from lower farm density areas. Adjustment for spirometry technician, influenza-season, humidity, temperature, and traffic-related air pollution (NO_2, $PM_{2.5}$, and soot) had minor effects on the association between lung function and hotspot (*see* sensitivity analyses in Figure E2). No association between living in a hotspot and lung function was observed when patients with COPD were removed from the analyses. Associations were also stronger when analyses were restricted to subgroups of subjects without atopy and ever smokers.

A significant interaction was observed between atopy and hotspot in models with lung function variables FEV_1/FVC and MMEF ($P < 0.05$), indicating significantly different associations between living in a hotspot and lung function among subjects without and with atopy. Minor changes were observed when atopy was defined as specific serum IgE to one or more common allergens (instead of the combination specific serum IgE and/or total IgE >100 IU/ml): associations were still stronger when analyses were restricted to subjects without atopy and (borderline) significant interaction was observed between atopy and hotspot in FEV_1/FVC and MMEF models (results not shown).

Association between Temporal Variation in Livestock Exposure and Lung Function

During the period the medical survey took place, ambient NH_3 levels ranged from 1.6 to 52.5 μg/m^3 (week-average values) (Figure 3) with a median NH_3 level of 16.3 μg/m^3. Higher NH_3 peaks were observed in spring and summer compared with autumn and winter, most likely as a result of manure spreading. Ambient PM_{10} levels ranged from 9.6 to 54.0 μg/m^3 (week-average values) (Figure 3) with a median PM_{10} level of 18.9 μg/m^3. Correlation between week-average NH_3 and PM_{10} levels was moderately strong (Pearson $r = 0.64$). Smoothed plots indicated negative linear associations between all lung function variables and week-average NH_3 level before the lung function measurement (Figure 4). Significant associations were found for FEV_1, FEV_1/FVC, and MMEF, which are indicators of airway obstruction. Other lags for NH_3 (lag 0–2 d) resulted generally in weaker, but often statistically significant, associations (*see* Figure E3A). Adjustment for farm density around the home address did not change the association between lung function and NH_3 (Figure 4). Spirometry results expressed as *z* scores

Table 2. Comparison of Characteristics of Consenting versus Nonconsenting Subjects

	Agreed to be Contacted for Follow-up Study			Participated in Medical Examination		
	Yes	No	Adjusted OR (95% CI)	Yes	No	Adjusted OR (95% CI)
Subjects, n	8,714	5,449		2,494	4,686	
Age, mean (SD), yr*	51.1 (12.9)	49.8 (13.9)	**1.07 (1.04–1.10)**	54.7 (11.0)	49.1 (13.3)	**1.49 (1.43–1.56)**
Female, %	53.0	54.7	0.94 (0.88–1.00)	54.6	52.2	**1.20 (1.08–1.32)**
Never smoker, %	45.5	49.1	1	45.0	46.4	1
Ever smoker, %	38.8	31.4	**1.28 (1.18–1.38)**	44.6	35.7	**1.20 (1.08–1.33)**
Current smoker, %	15.4	17.4	0.94 (0.86–1.04)	10.1	17.7	0.97 (0.86–1.08)
Self-reported morbidity, %						
Current asthma	5.9	4.3	**1.46 (1.24–1.71)**	4.9	5.9	0.94 (0.75–1.18)
Ever asthma	7.7	6.3	**1.29 (1.12–1.48)**	6.3	8.0	0.90 (0.74–1.10)
COPD	4.7	4.0	1.14 (0.96–1.35)	5.1	4.3	1.03 (0.81–1.30)
Nasal allergies	24.3	19.0	**1.42 (1.30–1.54)**	24.6	23.7	**1.15 (1.02–1.30)**
Morbidity based on EMR						
Subject complete EMR, n	6,859	4,390		1,936	3,443	
Asthma (ICPC R96), %	7.2	6.1	**1.21 (1.03–1.41)**	5.9	6.9	0.88 (0.69–1.12)
COPD (ICPC R91 and/or R95), %	3.7	3.3	1.05 (0.85–1.30)	3.6	3.4	0.80 (0.59–1.10)
Allergic rhinitis (ICPC R97), %	7.1	5.4	**1.40 (1.19–1.65)**	6.9	6.9	1.18 (0.95–1.50)
Exposure						
Mean (SD) distance to the nearest farm, m						
Any farm†	487 (277)	493 (271)	0.99 (0.98–1.00)	439 (257)	486 (278)	**0.94 (0.92–0.95)**
Pig farm†	767 (369)	775 (765)	0.99 (0.98–1.00)	692 (346)	763 (354)	**0.94 (0.93–0.95)**
Poultry farm†	955 (456)	967 (457)	**0.99 (0.99–1.00)**	874 (409)	909 (413)	**0.98 (0.97–0.99)**
Cattle farm†	587 (315)	598 (311)	**0.99 (0.98–1.00)**	503 (273)	552 (284)	**0.94 (0.92–0.95)**
Goat farm†	1,648 (473)	1,642 (474)	1.00 (0.99–1.01)	1,602 (504)	1,635 (481)	**0.98 (0.97–0.99)**
Mink farm†	1,848 (370)	1,841 (381)	1.00 (0.99–1.01)	1,794 (426)	1,847 (370)	**0.96 (0.95–0.98)**
Mean (SD) number of livestock farms						
Within 500 m radius	1.5 (1.9)	1.4 (1.8)	**1.03 (1.01–1.05)**	1.8 (2.1)	1.5 (1.8)	**1.10 (1.07–1.13)**
Within 1,000 m radius	7.9 (5.5)	7.9 (5.6)	1.00 (0.99–1.01)	9.3 (5.9)	8.1 (5.6)	**1.04 (1.03–1.05)**
Modeled fine dust emission, median, $g \cdot yr^{-1} \cdot m^{-2}$						
Weighted fine dust emission from farms within 500 m‡	0.02	0.01	**1.01 (1.00–1.02)**	0.07	0.02	**1.04 (1.03–1.05)**
Weighted fine dust emission from farms within 1,000 m‡	1.17	1.18	1.00 (0.99–1.02)	1.83	1.33	**1.08 (1.06–1.10)**

Definition of abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; EMR = electronic medical records; ICPC = International Classification of Primary Care; OR = odds ratio.
The likelihood of agreeing to follow-up and of being a participant is modeled for different characteristics with logistic regression. OR (95% CI) adjusted for age, sex, and smoking habits. Bold type indicates statistical significance ($P < 0.05$). In total, 14,163 subjects responded to the short questionnaire (20), of whom 8,714 agreed to be contacted for a follow-up study and 5,449 did not agree to be contacted. In total, 7,180 subjects were invited for a medical examination, of whom 2,494 participated and 4,686 were invited but did not participate.
*OR (95% CI) for an increase per 10 years.
†OR (95% CI) for an increase per 100 m.
‡OR (95% CI) for an unit increase in log-transformed exposure.

showed minimal differences compared with results presented as % predicted values (*see* Figure E4). Smoothed plots showed similar negative linear associations between all lung function variables and week-average PM_{10} (*see* Figure E5). However, in a two-pollutant model, only NH_3 remained associated with lung function (Figure 4; *see* Figures E5 and E6).

Linear regression analyses showed that a change in week-average NH_3 levels between the P10 and P90 (25.1 $\mu g/m^3$) was associated with a difference in FEV_1 of −2.22 (95% CI, −3.69 to −0.74), FVC of −1.07 (95% CI, −2.33 to 0.20), FEV_1/FVC of −1.12 (95% CI, −1.96 to −0.28), and MMEF of −5.67 (95% CI, −8.80 to −2.55). Adjustment for lung function technician, influenza-season, humidity, and temperature had minor effects on the association between week-average NH_3 and lung function (*see* sensitivity analyses in Figure E6). When analyses were restricted to subjects without atopy, or ever smokers, associations became stronger. However, no significant interaction terms between atopy or smoking status and week-average NH_3 levels were observed. When atopy was defined as specific serum IgE to one or more common allergens (instead of the combination: specific serum IgE and/or total IgE >100 IU/ml), associations restricted to subject without atopy were still stronger compared with the total population (results not shown). Minor changes were observed when patients with COPD were removed.

Discussion

This large-scale population-based study shows that emissions from livestock farms are associated with a reduced lung function level of inhabitants of a rural area with high

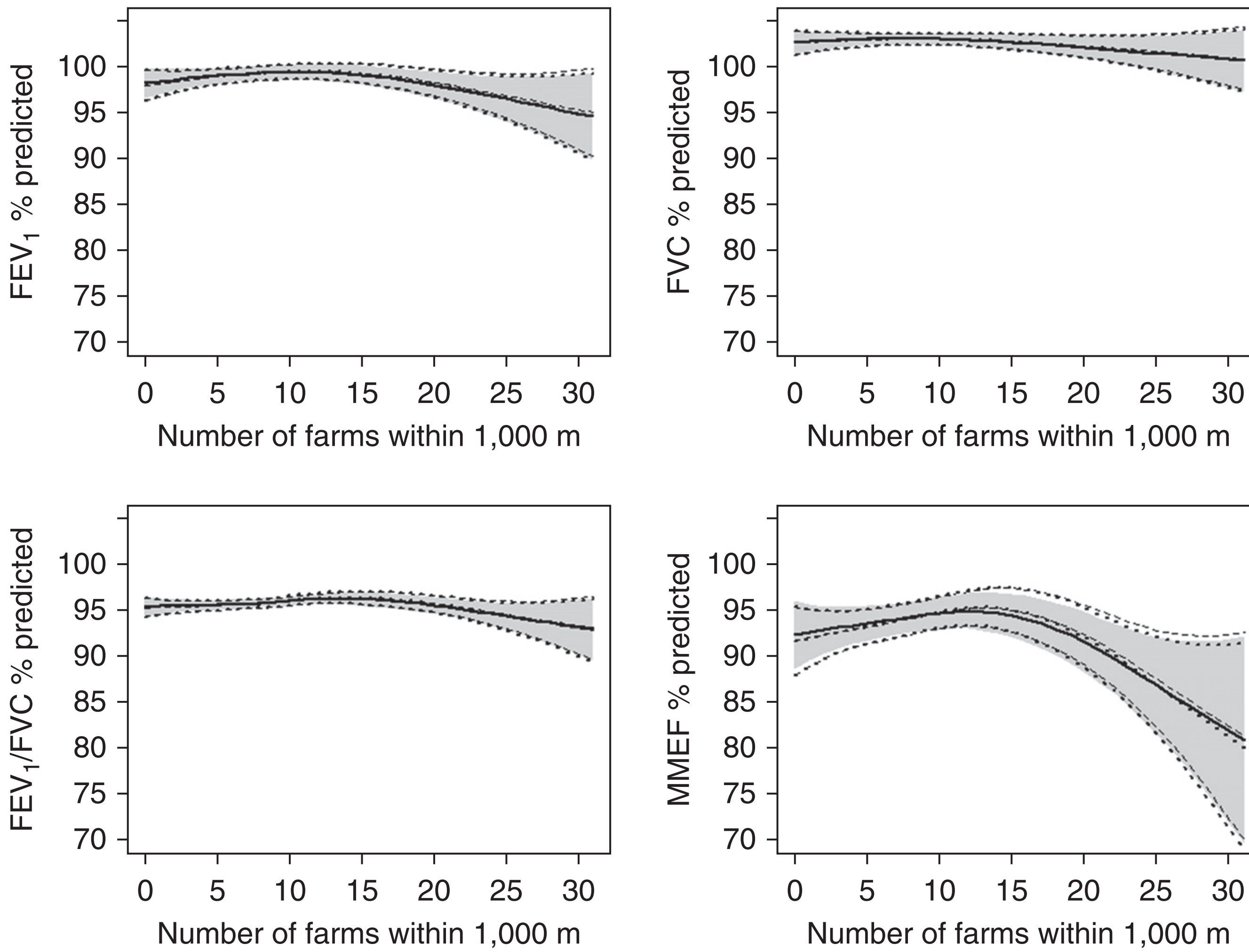

Figure 2. Association between the number of livestock farms within 1,000 m of the home address and lung function in 2,308 residents. Smoothed plots show the association between the number of livestock farms within 1,000 m of the home address and lung function. The *solid lines* show the shape of the smoothed plot, and the *gray shading* reflects the area within the 95% confidence intervals. *P* values of the smooth terms are: FEV_1, 0.116; FVC, 0.347; FEV_1/FVC, 0.114; and maximum mid-expiratory flow (MMEF), 0.045. Adjustment for age, sex, and height was made by calculating % predicted spirometry variables based on Global Lung Function Initiative reference values (27). Associations are also adjusted for smoking habits, being born in the study area, and farm childhood. The *dashed lines* show the results after further adjustment for week-average ambient ammonia (NH_3; $\mu g/m^3$) levels before the lung function test. *Upper* and *lower dashed lines* reflect the upper and lower confidence limits (95%). *P* values of the smooth terms after adjustment for week-average ambient NH_3 levels are: FEV_1, 0.142; FVC, 0.355; FEV_1/FVC, 0.106; and MMEF, 0.051. The *dotted lines* show the models with further adjustment for week-average ambient PM_{10} ($\mu g/m^3$) levels before the lung function test. *Upper* and *lower dotted lines* reflect the upper and lower confidence limits (95%). *P* values of the smooth terms after adjustment for week-average PM_{10} levels are: FEV_1, 0.101; FVC, 0.361; FEV_1/FVC, 0.081; and MMEF, 0.030. PM_{10} = particulate matter <10 μm in diameter.

livestock farming density. Associations were found between lung function and both spatial and temporal livestock exposure estimates. A spatial association was found between the number of livestock farms within 1,000 m and MMEF. A temporal association was found between FEV_1, FEV_1/FVC, and MMEF (three indicators of airway obstruction) and week-average ambient NH_3 levels before the lung function measurements. Mutual adjustment of temporal and spatial effects did not change these associations. Our results indicate that the spatial association was especially apparent in subjects without atopy, whereas the temporal association with NH_3 was observed in the whole population.

To our knowledge, this is the largest study on respiratory health of residents living in close proximity to livestock farms focused on lung function. The combination of both spatial and temporal variation in livestock farm exposure in association with lung function of residents from the general population has not been explored before. Another strength of the current study was the detailed medical information available for nonresponders, enabling a detailed nonresponse analysis. We compared associations between respiratory endpoints using electronic medical records from general practitioners and self-reported respiratory conditions and livestock-related exposure for different subpopulations. A comparison between characteristics of nonresponders and responders of the questionnaire

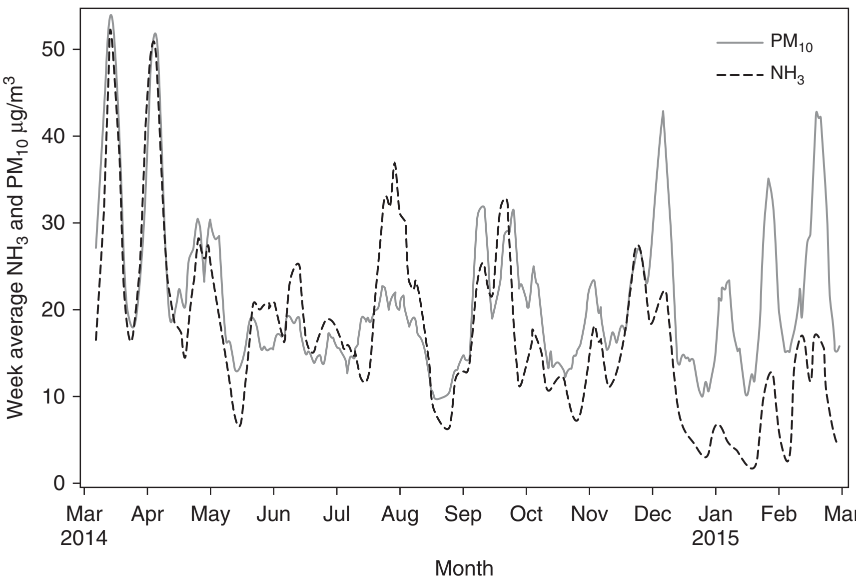

Figure 3. Week-average ambient ammonia (NH_3) and PM_{10} ($\mu g/m^3$) levels in the study area. Week-average ambient NH_3 and PM_{10} concentrations were obtained from, respectively, two and four rural background monitoring stations located in the study area, which are part of the Dutch Air Quality Monitoring Network (28). Pearson correlation between week-average ambient NH_3 and PM_{10} levels was $r = 0.64$. PM_{10} = particulate matter <10 μm in diameter.

survey (source-population) was described before and showed differences in personal characteristics between both groups (20). However, both in the previous questionnaire survey and in the present study, selection bias did not seem to affect associations between different farm exposure estimates and prevalence of respiratory morbidity.

The Netherlands is a small country with a high population density in combination with a high livestock farm density. On an area of 41,000 km^2, 17 million people live together with 105 million chickens, 12 million pigs, 4 million cows, 0.5 million goats, and 1 million mink (31). We found an association between lung function and living in areas with more than 17 farms within a 1,000-m radius and designated such areas as hotspots. This cutoff value is based on a data-driven approach, based on a visual inspection of the smoothed plots. This spatial association is consistent with results from a cross-sectional study among residents from a rural area in Germany (Lower Saxony Lung Study) (17): more than 12 stables (fourth quartile) within 500 m of the home address was associated with a lower FEV_1 (−7.4% FEV_1; 95% CI, −14.4 to −0.4) compared with less than five stables within 500 m (first quartile). Annual NH_3 concentrations were measured in the same study area in Germany and the number of farms within 500 m explained 28% of the variability of annual average outdoor NH_3 concentrations (18). Subjects exposed to annual NH_3 levels of 19.7 $\mu g/m^3$ or higher had a lower FEV_1 and FEV_1/FVC (−8.2% FEV_1 and −3.3% FEV_1/FVC compared with subjects exposed to lower NH_3 levels). Both the Lower Saxony Lung Study and the current study found indications for obstructive effects.

We found stronger associations when analyses were restricted to participants without atopy. A significant interaction between atopy and living in a hotspot was observed. Previous studies are inconsistent on the effect of farm exposure in subjects without atopy. A study among children from farming and nonfarming households found a negative (protective) association for atopic wheeze and endotoxin levels in matrass dust, whereas for nonatopic wheeze, there was a positive association (32). Other studies did not demonstrate differences between subject with and without atopy in the effect of endotoxin exposure on respiratory health (33, 34). Contrary, previous studies among farmers showed stronger associations between endotoxin exposure and respiratory health effects for sensitized than for nonsensitized farmers (35, 36). In addition, a German study found a positive association between endotoxin levels and asthmatic symptoms among children of parents with atopy, whereas no association was found among children of parents without atopy (19). Our study also suggested that some of the associations with hotspot exposure were restricted to patients with COPD, who may be especially susceptible to air pollutants (37). This finding is supported by a previous questionnaire study and analysis of medical records in the same study area, showing that patients with COPD living in close proximity to livestock farms reported more wheezing and inhaled corticosteroids usage, and were more often treated for exacerbations (20, 22).

Livestock farm emissions are a complex mixture of bioaerosols, gases, and vapors, many of which are respiratory irritants. One etiologically plausible candidate is endotoxin. Increased endotoxin concentrations have been measured around farms (10, 11). In addition, a larger spatial variation in endotoxin compared with PM_{10} concentrations was observed in ambient air measurements in the same study area and endotoxin concentrations were more strongly predicted by livestock-related characteristics in the environment (38). Previous studies among residents have also found associations between H_2S and eye irritation and respiratory symptoms (14). Guidry and coworkers (8) found spatial and temporal associations between size and distance of upwind livestock farms and H_2S levels. Because of low concentrations of H_2S and strong correlation with other pollutants, Guidry and coworkers (8) argued that health effects can probably not be attributed to H_2S alone, but to a mixture of which H_2S is part of.

Because individuals were subjected to pulmonary function tests on one occasion, but over a study period of a year (between March 2014 and February 2015), we adjusted for week-average air pollution concentrations before each individual's lung function test (39). An association was found between both week-average PM_{10} and NH_3 levels before spirometry and lung function. In a model with mutual adjustment for NH_3 and PM_{10}, the NH_3 association remained (minor change in size of effect) but the association with PM_{10} was no longer observed. Livestock production is the major contributor to ambient NH_3 levels. We evaluated potential

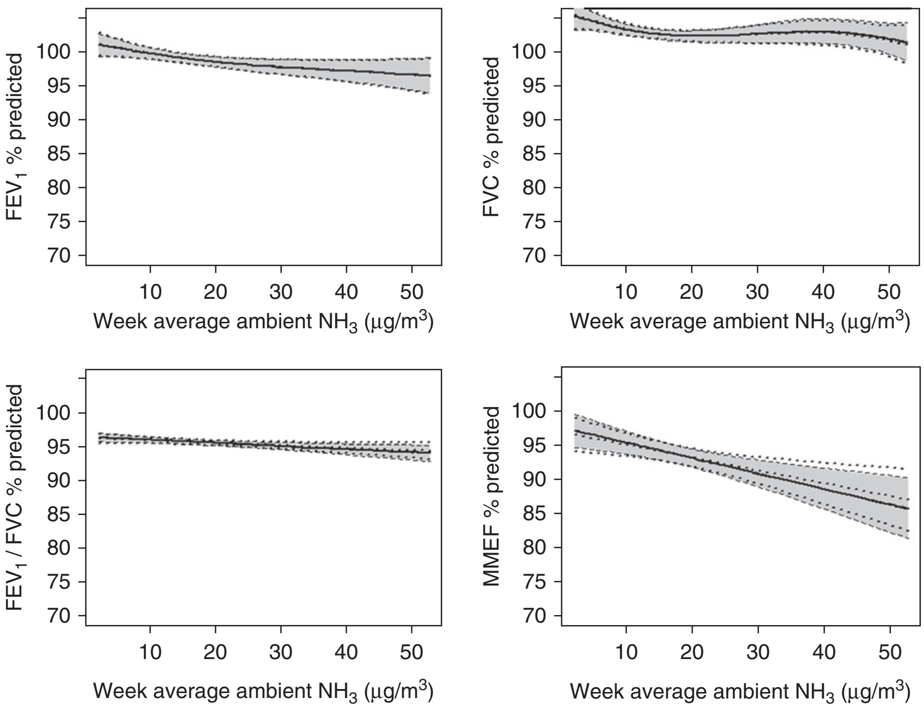

Figure 4. Associations between ambient ammonia (NH_3; μg/m^3) in the week before the lung function test and lung function in 2,308 residents. Smoothed plots show the association between the week-average ambient NH_3 (μg/m^3) levels before the lung function test and lung function. The *solid lines* show the shape of the smoothed plot, the *gray shading* reflects the area within the 95% confidence intervals. *P* values of the smooth terms are: FEV_1, 0.012; FVC, 0.098; FEV_1/FVC, 0.009; and maximum mid-expiratory flow (MMEF), <0.001. Adjustment for age, sex, and height was made by calculating % predicted spirometry variables based on Global Lung Function Initiative reference values (27). Associations are also adjusted for smoking habits, being born in the study area, and farm childhood. The *dashed lines* show the results after further adjustment for spatial exposure: number of farms within 1,000 m of the home address. *Upper* and *lower dashed lines* reflect the upper and lower confidence limits (95%). *P* values of the smooth terms after adjustment for number of farms within 1,000 m are: FEV_1, 0.015; FVC, 0.107; FEV_1/FVC, 0.008; and MMEF, <0.001. The *dotted lines* show the models for further adjustment for week-average ambient PM_{10} (μg/m^3) levels before the lung function test. *Upper* and *lower dotted lines* reflect the upper and lower confidence limits (95%). *P* values of the smooth terms after adjustment for week-average PM_{10} are: FEV_1, 0.101; FVC, 0.133; FEV_1/FVC, 0.196; and MMEF, 0.070. PM_{10} = particulate matter <10 μm in diameter.

confounding by correlated air pollutants and other time-variant variables, such as seasonal effects, but we do not expect that temporal variation in ambient NH_3 levels is associated with other (occupational) exposures or usage of cleaning products. Therefore, we did not consider these variables as potential confounders.

The temporal association with NH_3 levels corresponds to results of Loftus and coworkers (12) who conducted a panel study among 51 children with asthma living in an agricultural region of Washington State, where ammonia levels in ambient air were strongly associated with proximity to farms. Even though Loftus and coworkers (12) used a different study design (panel study with repeated measurements) and a different study population compared with our study, both studies found an association between lung function and agricultural air pollution. A 3.8% (95% CI, 0.2–7.3) decrease of FEV_1 was observed per interquartile range (25 μg/m^3) increase in previous day NH_3 concentration (12). They found a smaller association with $PM_{2.5}$: FEV_1 decreased by 0.9% (95% CI, 1.8–0.0) for an interquartile range increase of previous day $PM_{2.5}$ levels (7.9 μg/m^3) (13).

Because NH_3 is mostly locally generated (40, 41), this suggests that the temporal associations with lung function were mostly driven by locally generated pollutants, represented by NH_3. Considering the ambient NH_3 levels during the study period (median, 16.3 μg/m^3), it is unlikely that NH_3 has a direct effect on respiratory health of residents. The threshold limit value for ammonia in an occupational setting is 25 ppm (1,800 μg/m^3) (42). However, a study among farmers showed a decrease in FEV_1 at levels above 7.5 ppm (43). Nonetheless, it is more plausible that ambient NH_3 levels serve as a marker for airborne emissions from livestock farms and agricultural activities and that the observed decrease in lung function results from exposure to one or more copollutants, including microbial agents, such as endotoxins (9). Another explanation is that ambient NH_3 concentrations are associated with SIA formation. NH_3 reacts in the atmosphere with nitrogen oxides and sulfur dioxide to form solid (particulate) ammonium sulfates and nitrates, which are part of the $PM_{2.5}$ fraction and can penetrate deeply into the lung (4). Secondary particle formation takes time, however, and without further studies of the local atmospheric chemistry we cannot support the likelihood of these transformations happening locally. A recent study from Barcelona suggested that significant SIA formation may take place already on an urban spatial scale (44). More detailed characterization of livestock-associated environmental exposures, including bioaerosol analysis and SIA formation, is needed.

Spatial exposure variables were based on participants' home address, but because most people do not spend 24 hours a day at home, this may lead to exposure misclassification. However, in Europe, adults spend most of their time indoors at home (56–66%) (45), which suggests that home address might be a reasonable proxy for individual exposure. In addition, we did not take into account the influence of wind direction or wind speed on exposure. In the Netherlands, winds are slightly more often from the southwest, but south-westerly winds are also associated with less stable weather conditions favoring larger dispersion of pollutant emissions. As a result, there is usually not much difference between concentrations measured in different directions from a source. Both limitations introduce nondifferential exposure misclassification, leading to an underestimation of the effect of farm exposure. A more comprehensive method to estimate spatial exposure (e.g., with dispersion modeling or even an actual intensive air measurement network) will increase precision of spatial exposure. We have used central site monitoring data to represent temporal NH_3 exposure, which is the usual approach in studies investigating acute effects of air pollution (37). Validation studies have reported moderately high correlations between temporal variations in ambient outdoor concentrations at the home address and at central monitoring sites for both PM and gaseous air pollutants (46, 47).

In conclusion, air pollutant emissions from livestock farms are associated with a reduced lung function level in nonfarming residents of a rural area in the Netherlands. Further research into the impact of emissions from livestock farms, especially on respiratory health of susceptible subgroups (e.g., children, elderly, and respiratory disease patients) is warranted. ■

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