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Increased respiratory symptoms in COPD patients living in the vicinity of livestock farms

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ABSTRACT

Several studies have investigated the effect of livestock farm emissions on the respiratory health of local residents, but results are inconsistent. This study aims to explore associations between the presence of livestock farms and respiratory health in an area of high-density livestock farming in the Netherlands. We focused especially on associations between farm exposures and respiratory symptoms within subgroups of potentially susceptible patients with a pre-existing lung disease.

In total, 14875 adults (response rate 53.4%) completed a questionnaire concerning respiratory health, smoking habits and personal characteristics. Different indicators of livestock farm exposures relative to the home address were computed using a geographic information system.

Prevalence of chronic obstructive pulmonary disease (COPD) and asthma was lower among residents living within 100 m of a farm (OR 0.47, 95% CI 0.24–0.91 and OR 0.65, 95% CI 0.45–0.93, respectively). However, >11 farms in 1000 m compared to fewer than four farms in 1000 m (fourth quartile *versus* first quartile) was associated with wheezing among COPD patients (OR 1.71, 95% CI 1.01–2.89). Using general practitioners' electronic medical records, we demonstrated that selection bias did not affect the observed associations.

Our data suggest a protective effect of livestock farm emissions on the respiratory health of residents. Nonetheless, COPD patients living near livestock farms reported more respiratory symptoms, suggesting an increased risk of exacerbations.

INTRODUCTION

Intensive livestock production is associated with environmental impacts and public health issues on a global scale [1]. Concerns about emerging antibiotic resistance and outbreaks of zoonotic diseases, such as avian influenza [2] and Q fever [3] have drawn attention to various risks to human health that may result from livestock farms near residential areas. Neighbouring residents can potentially be exposed to dust, infectious agents, microbial toxic agents (endotoxins), allergens and irritant gases such as ammonia and hydrogen sulfide emitted by livestock farms [1]. Various studies have measured elevated levels of livestock farm-related agents in the vicinity of stables, especially downwind [4–8].

Exposure to endotoxins, cell-wall fragments of Gram-negative bacteria, has been associated with pro-inflammatory responses and adverse respiratory health effects [9]. Paradoxically, a farm childhood is associated with a lower prevalence of asthma and atopy [10, 11]. Higher and more diverse environmental exposures to microbial components seem to play a role in this protective effect on IgE-mediated asthma and allergies [12, 13].

Two ecological studies reported a higher prevalence of wheezing and physician-diagnosed asthma among children and adolescents attending schools near confined swine-feeding operations [14, 15]. However, Elliot et al. [16] found a lower frequency of asthma in schoolchildren associated with higher community-level livestock farm exposures. Studies on the effect of livestock farm exposures assessed at the individual level are scarce. In a cross-sectional study in 565 children from Iowa (USA), a higher environmental exposure to animal feeding operations was associated with asthma outcomes [17]. A panel study among 101 nonsmoking adults in North Carolina (USA) showed that self-reported hog odour and measured air pollutants were associated with acute physical symptoms [18]. In a rural area of Germany, living within 500 m of >12 animal houses was a predictor of self-reported wheeze and decreased forced expiratory volume in 1 s [19]. Conversely, a Dutch study found mostly inverse associations between the presence of livestock near the home address and asthma, allergic rhinitis and chronic obstructive pulmonary disease (COPD), based on 92 548 electronic medical records (EMRs) from general practitioners (GPs) [20]. However, a comparison of the EMRs of patients in rural Dutch areas with high and low densities of livestock farms suggested more airway infections, cough and pneumonia among asthma and COPD patients in areas with high livestock densities, which could be indicative of an increased risk of exacerbations [8]. Indeed, patients with pre-existing respiratory diseases seem to respond with a greater intensity to air pollution from livestock farms in experimental studies [21, 22]. Therefore, we hypothesise that livestock farm emissions may particularly affect potentially susceptible patients with a pre-existing lung disease. The number of studies on the effect of (individually estimated) livestock farm exposure on respiratory health of local residents are limited and results are inconsistent. We performed a survey based on a large sample size, with a validated and widely used questionnaire to assess respiratory health, which enabled us to explore respiratory diseases and self-reported respiratory symptoms. Our aim was to 1) investigate associations between livestock farm exposures and respiratory health in residents; and 2) focus especially on associations between livestock farm exposures and self-reported respiratory symptoms within subgroups of potentially susceptible patients. Since subjects were recruited via GPs, we had the unique opportunity to investigate selective response by comparing the EMRs of responders and nonresponders. This research is part of the VGO (Farming and Neighbouring Residents' Health) study.

METHODS

Study population

A cross-sectional study was conducted among residents living in the eastern part of the province of Noord-Brabant and the northern part of the province of Limburg, a highly populated rural area in the Netherlands with a high density of livestock farms. In the Netherlands, every resident is obliged to be on the list of just one GP, who acts as a gatekeeper to secondary care. Therefore, all Dutch inhabitants can be reached by using the patient lists of GPs. Residents were selected by a two-stage selection procedure. First, GPs located in the study area in 2012 were selected on predefined registration quality criteria as described earlier [23] and were asked to collaborate in the study. In total, 24 GPs met these criteria and 21 agreed to participate. In the second stage of the selection procedure, patients from the selected GP practices were invited to participate in the study if they met the following inclusion criteria: 1) living in the eastern part of Noord-Brabant or the northern part of Limburg; 2) inhabitant of a municipality with <30 000 residents; and 3) aged 18–70 years. Of the eligible patients, one person per home address was randomly selected. In total, 28 163 subjects received a questionnaire. The questionnaires were accompanied by a letter from the GP that stated the name and birthday of the selected subject to ensure that the selected person would complete the questionnaire. Figure 1 presents a flow chart of the selection procedure of the study population. Questionnaires for 294 subjects were undeliverable, and were subtracted from the total number of invited patients. The total number of responders was 14 882, resulting in a response of 53.4%. Analyses were conducted on 12 117 responders, after excluding farmers (those who reported to be living or working on a farm) and subjects who lived at their home address for <1 year, since we assumed that their exposure period was too short.

[FIGURE 1]

Questionnaire

The questionnaires were sent in November 2012. After 2 weeks, a reminder was sent. The two-page questionnaire contained questions on respiratory health, smoking habits, age, sex, whether subjects were living or working on a farm and the number of years living in their current home. Questions on respiratory health were adopted from the European Community Respiratory Health Survey (ECRHS)-III screening questionnaire [24] (online supplementary table S1).

Exposures to livestock farms

Exposure to livestock farms was computed for each subject. Information on farm characteristics in the study area was derived from the provincial databases of mandatory environmental licences for keeping livestock in 2012. These databases contain data on number and type of animals, geographic coordinates of farms and estimated fine dust emissions from each farm per year on the basis of farm type and number of animals. Addresses of subjects were geocoded. Distances between the home address and all livestock farms within 500 m and 1000 m radii were determined using a geographic information system (ArcGis 10.1; Esri, Redlands, CA, USA). The following farm exposure variables were studied for each subject: 1) distance (m) to the nearest farm (continuous variable and quartiles (Q)); 2) total number of farms within 500 m and 1000 m (quartiles); 3) presence of a specific livestock farm type within 500 m and 1000 m (pigs, poultry, cattle, goats and mink) (binary variables); and 4) inverse-distance weighted fine dust emissions from all farms within 500 m and 1000 m (continuous variables) as described previously [20], and in the online supplementary methods S1.

Nonresponse analysis

To study potential selection bias, age, sex, morbidity data and farm exposure estimates of responders and nonresponders were compared in subjects with EMR and exposure data available (fig. 1). EMRs were available through the GPs, who all participated in the Netherlands Institute for Health Services Research primary care database and agreed to participate in the study [25]. EMRs contain data at the patient level. The International Classification of Primary Care (ICPC) [26] was used to define asthma, COPD and allergic rhinitis for responders and nonresponders. Chronic diseases asthma (R96) and COPD (R91 or R95), were defined as ≥1 ICPC code found in the 2010–2012 EMRs. Allergic rhinitis (R97) was defined as ≥1 ICPC code found in 2011–2012.

Data analysis

Data were analysed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 3.0.2 (www.r-project.org).

First, we investigated selective response to the questionnaire, and to what extent risk estimates were biased as a result of self-selection. Multiple logistic regression was used to analyse whether a response to the questionnaire (dependent variable) was associated with livestock farm exposure estimates and morbidity data based on EMRs, with adjustment for age and sex (independent variables). Furthermore, we compared associations between different exposure estimates and asthma, COPD and nasal allergies (from EMRs) in the total "source" population, in all responders (including farmers) and in responders excluding farmers.

Logistic regression models were used to explore associations between farm exposure estimates (independent variables) and self-reported COPD, current asthma and nasal allergies (dependent variables) in responders. Analyses were adjusted for age, sex and smoking habits (never-smoker, ex-smoker or current smoker). The presence of a farm animal species was adjusted for the presence of other farm animal species. We expected a negligible effect of the GPs on self-reported outcomes, and therefore we decided not to adjust for clustering across practices. Moreover, results obtained by generalised estimating equations (exchangeable correlation and clustering by practice) were very similar to analyses that were not adjusted for clustering.

Analyses of current asthma were stratified by nasal allergies (as a proxy for atopy) to assess the effect of exposure on "atopic" and "nonatopic" asthma [27]. Separate analyses were undertaken for susceptible subgroups: individuals with self-reported COPD, current asthma or nasal allergies. In addition, associations between farm exposure estimates and the use of inhaled corticosteroids (ICS) in COPD patients were studied. COPD is a progressive illness which develops most often in people aged ≥40 years. We assumed that reported COPD diagnosis was more reliable in patients who reported an age of ≥40 years at diagnosis. In a sensitivity analysis, only subjects who were aged ≥40 years at COPD diagnosis were included.

The shape of the relationships between wheeze and exposure variables within susceptible subgroups was studied using a penalised regression spline using the (default) "thin plate" basis as implemented in the mgcv (mixed generalised additive model computation vehicle) R package. Selection of smoothing parameters was based on the unbiased risk estimator criterion (a scaled version of the Akaike information criterion).

Ethical aspects

Patients' privacy was ensured as described previously [20]. In short, medical information and address records were kept separate at all times by using a trusted third party. The VGO study protocol was approved by the medical ethical committee of the University Medical Centre Utrecht (Utrecht, the Netherlands).

RESULTS

Nonresponse analysis

Characteristics of responders and nonresponders are summarised in table 1. Responders were older than nonresponders (mean age 50.4 *versus* 42.8 years) and women were more often willing to participate. Responders lived closer to livestock farms than nonresponders (mean distance to the nearest farm 475 *versus* 498 m), the mean number of farms within 1000 m was higher for responders (8.1 *versus* 7.4) and responders were more often living near specific farm animals. Although the prevalence of GP-registered COPD was slightly higher among responders, an inverse association was found with being a responder (OR 0.81, 95% CI 0.69–0.96) after adjustment for age and sex. GP-registered allergic rhinitis was positively associated with being a responder after adjusting for age and sex (OR 1.28, 95% CI 1.14–1.44). Overall, selection bias did not seem to affect associations between different farm exposure estimates and morbidity based on EMR data (online supplementary table S2). All associations in the total invited ("source") population and in the responder populations (including and excluding farmers) showed a similar magnitude, with overlapping confidence intervals, and had a similar direction.

Associations between livestock farm exposures and respiratory outcomes

The prevalence of self-reported asthma, COPD and nasal allergies (table 2) were higher than that based on EMR (table 1). Associations between the covariates (age, sex and smoking) and COPD, asthma and nasal allergies showed expected patterns (table 2). Several indicators of livestock farm exposures were inversely associated with current asthma and COPD; minor associations were found with nasal allergies (table 2). Adjustment for age, sex, smoking and the presence of specific farm animals did not change the results (unadjusted data not shown). Participants living very close to a farm (<290 m, Q4) had significantly lower odds for current asthma, COPD and nasal allergies compared to participants living >640 m (Q1) from the nearest farm. A statistically significant test-for-trend was found between the quartiles of the minimal distance to the nearest farms and current asthma, COPD and nasal allergies. The presence of a livestock farm within 100 m of the home address was significantly negatively associated with COPD (OR 0.71, 95% CI 0.51–0.98) and current asthma (OR 0.65, 95% CI 0.45–0.93). Analysis of specific animals around the home address showed inverse associations between the presence of pigs within 500 m and the presence of goats within 1000 m and current asthma.

When analyses of current asthma were stratified by nasal allergies (as a proxy for atopy) a positive association was found for presence of poultry at 500 m and atopic asthma (online supplementary table S3). However, the presence of mink at 500 m and goats at 1000 m showed negative associations with atopic asthma. Nonatopic asthma was only significantly negatively associated with the presence of pigs within 500 m.

Associations of livestock farm exposure and respiratory symptoms within susceptible subgroups

Wheezing among COPD patients was positively associated with several indicators of livestock farm exposures (table 3). Living at 290–450 m (Q3) and 450–640 m (Q2) from the nearest farm compared to living >640 m (Q1, reference) from a farm was significantly associated with current wheeze in COPD patients (Q3 OR 1.65, 95% CI 1.05–2.59; Q2 OR 2.17, 95% CI 1.32–3.57). The spline in figure 2 illustrates a nonlinear association between a decreasing probability of wheezing when living ≥500 m from a farm. Living in an area with a high density of livestock farms (>11 farms within 1000 m, Q4) was also associated with more wheezing in COPD patients (OR 1.71, 95% CI 1.01–2.89; table 3). No associations were observed between livestock farm exposure variables and wheezing within current asthma and nasal allergy patients.

[FIGURE 2][TABLE 3]

The presence of at least one cattle farm within 500 m was significantly associated with an increased OR for usage of ICS (OR 1.50, 95% CI 1.01–2.23) (online supplementary table S4). In addition, a positive nonsignificant association with usage of ICS was found among COPD patients with >11 farms within 1000 m of the home address (Q4) compared with fewer than four farms (Q1), but a significant association was seen with >12 farms within 1000 m (OR 1.71, 95% CI 1.08–2.71, result not shown).

Sensitivity analyses

Sensitivity analyses of COPD patients aged ≥40 years at diagnosis (62% of COPD patients, n=344) showed no significant associations between livestock farm exposures and COPD prevalence (online supplementary table S5). However, distance to the nearest farm was still significantly associated with wheezing among COPD patients (290–450 m (Q3) OR 2.18, 95% CI 1.21–3.93) and 450–640 m (Q2) OR 1.89, 95% CI 1.03–3.47). The presence of >11 farms within 1000 m (Q4) was also still associated with wheezing among COPD patients (OR 2.88, 95% CI 1.36–6.11). The association between the presence of cattle within 500 m and usage of ICS among COPD patients was attenuated. However, the positive association between >11 farms within 1000 m and the usage of ICS among COPD patients became significant (OR 2.15, 95% CI 1.02–4.53).

DISCUSSION

We found inverse associations between the proximity to livestock farms and self-reported asthma, COPD and allergic rhinitis among neighbouring residents. This suggests a protective effect of livestock farm exposures on respiratory health. However, current wheezing and usage of ICS among COPD patients were positively associated with indicators of livestock farm exposures. This may indicate an increased risk of exacerbations among COPD patients who have a high exposure to livestock farm emissions.

The inverse associations between livestock farm exposures and respiratory diseases in neighbouring residents confirm the study by Smit *et al*. [20] in 92 548 individuals in the same area using GP EMRs instead of questionnaires. Most studies on proximity to livestock farms show adverse respiratory health effects among neighbouring residents [14–19]. Several studies [15, 16, 18, 28] were performed in North Carolina (USA) where industrial hog farms cause widespread pollution. Farm characteristics and the management of manure in North Carolina [29] differs from our study area, which may result in different exposures. Furthermore, hog farms in North Carolina are clustered in low-income minority communities. Therefore, the results of these studies may not be directly comparable with ours.

An explanation for the protective effect of farms could be migration of people with respiratory health problems from rural areas to urban areas. However, we found that asthma and COPD patients living in close proximity to farms deregistered less frequently from the GP registers (based on EMR data over 4 years (2009–2012)) than asthmatics and COPD patients who live at a greater distance from farms. Moreover, asthma and COPD patients showed a similar relationship between distance from livestock farms and the number of years they had lived at their present address compared with the non-patient population (online supplementary methods S2 and S3 and fig. S1). Together these analyses do not give any indication that selective migration due to respiratory health status might explain the associations observed in this study.

Higher and more diverse environmental exposures to microbial components have been attributed to a protective effect on IgE-mediated allergies and asthma in childhood [11, 30]. The inverse association between livestock farm exposures and COPD prevalence has been observed before by Smit *et al*. [20], who used EMR data. We found moderate agreement (κ 0.58, 95% CI 0.54–0.62) between self-reported COPD and COPD based on EMRs. Although there are some inconsistencies between the COPD definitions, the associations were similar in terms of magnitude and direction. The observed protective effect on COPD is not easily explained. We did not have information on potentially confounding farm exposures in childhood, which could partly explain the observed protective effect on asthma and allergy, and possibly COPD. However, several studies have shown that farm exposures during adulthood may also protect against atopy and allergic asthma [31–33]. In the present study we had to rely on self-reported nasal allergy as a proxy for atopy, which might explain why we did not observe pronounced differences in associations between farm exposures and atopic and nonatopic asthma. The second aim of the present study was to explore respiratory symptoms in susceptible subgroups. We found support for the hypothesis that patients with a chronic lung disease may be more susceptible for livestock farm exposures. Increased symptom reporting associated with several indicators of livestock farm exposures in COPD patients could indicate an elevated risk of exacerbations. We did not find this in adult asthma or nasal allergy patients. In occupational settings, an increased risk of COPD is reported for livestock farmers compared with crop farmers [34], and dust and endotoxin exposure showed a dose–response relationship with COPD in never-smoking animal farmers [35]. Farmers are exposed to much higher levels than non-farming residents, since exposure levels inside stables are considerably higher than outside. However, elevated levels of particles with a 50% cut-off aerodynamic diameter of 10 μm and microbial agents such as endotoxin emitted from stables have been measured 200–250 m downwind of livestock farms [7, 8]. Therefore, increased farm-related air pollution could lead to airway inflammation in neighbouring COPD patients, and might explain the associations we found with wheezing and usage of ICS.

Furthermore, increased morbidity in individuals with COPD near livestock farms might be explained by environmental exposures to pathogenic micro-organisms from livestock farms, leading to exacerbations with an infectious aetiology [36]. However, infections with specific zoonotic pathogens were not very common in patients with community-acquired pneumonia living in an area with many livestock farms [37]. Nonpathogenic micro-organisms might contribute through their toxins, such as endotoxins, resulting in inflammatory responses [21]. Moreover, Dickson *et al*. [38] suggested that exacerbations of COPD are occasions of respiratory dysbiosis: disorder and dysregulation of the microbial ecosystem of the respiratory tract, coupled with a dysregulated host immune response. It could be speculated that changes in the lung microbiome as a result of long-term environmental exposures could play a role in these adverse respiratory effects as well.

The medical information available for nonresponders is a unique feature of the VGO study, and enabled us to compare characteristics of nonresponders and responders. We were able to demonstrate that selection bias did not affect associations between farm exposures and respiratory disease, which was available for invited subjects through the EMRs. The prevalence of self-reported asthma, COPD and nasal allergies (table 2) was higher than that based on EMRs. In particular, the prevalence of current asthma was higher than might be expected in a rural setting. Both methods have their advantages and disadvantages, but estimation of respiratory symptom prevalence by the ECRHS questionnaire is a more commonly used method in epidemiological studies. Misclassification of individual exposure estimates is likely to be limited because we used information on livestock farm licences from the same year in which the questionnaires were collected. We did not take into account the influence of wind direction on exposure. The average wind direction in the Netherlands is south-westerly, but the wind speed and direction varies across the year. Therefore we do not expect that wind direction will greatly influence these results. More refined exposure assessment approaches are under development, which take into account meteorological circumstances, and will be deployed in subsequent phases of this study.

Individual exposure estimates were calculated based on the home address and most people do not spend 24 h a day at home. However, in Europe, adults spend the majority of their time indoors at home (56–66%) [39]. Therefore the home address should be a good and convenient predictor to estimate exposure. It could be argued that an analysis in retired participants would lead to more accurate exposure estimates, leading to less attenuation bias. However, a sensitivity analysis in those aged >65 years did not yield different odds ratios (data not shown).

This is an explorative study, involving multiple exposure variables. The results should be interpreted with caution, given the number of tests performed. Nevertheless, the observed positive and negative trends seem to be consistent across several exposure variables.

In conclusion, we found an inverse association between different indicators of livestock farm exposure from livestock farms and self-reported current asthma and COPD among neighbouring residents. This suggests a protective effect from livestock farm emissions, possibly explained by higher and more diverse environmental exposures to microbial components. However, current wheezing and usage of ICS among COPD patients was positively associated with several indicators of livestock farm exposures, suggesting an increased risk of exacerbations in a susceptible group.

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Footnotes

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FIGURE AND TABLE

FIGURE 1 : Flow chart of the data collection. Data for the nonresponse analysis included subjects with data available on exposure. When comparing electronic medical records (EMRs), only subjects with data available on EMRs were included. Data for the questionnaire analysis included subjects with data available on exposure, who were not living or working on a farm and who had lived >1 year in their current home.

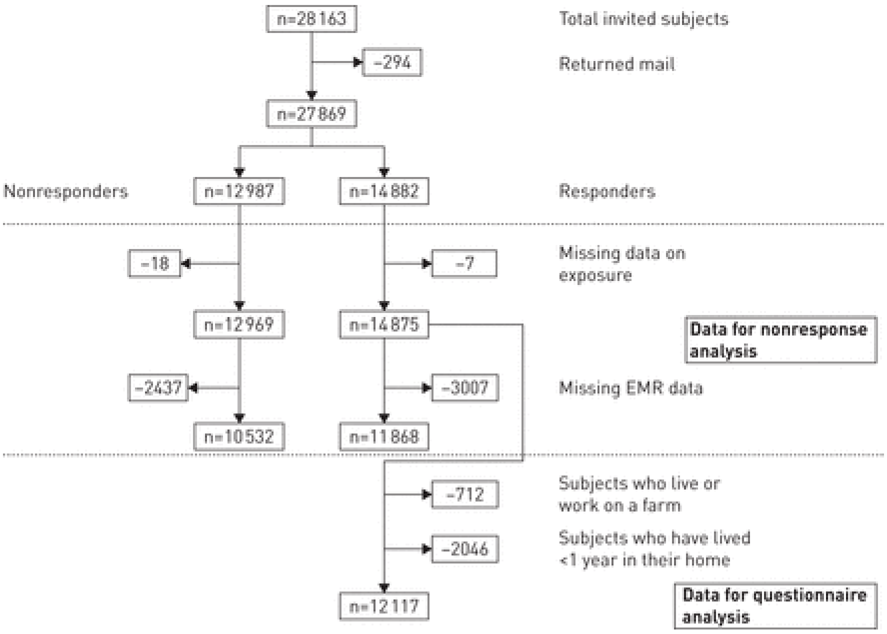

TABLE 1 Comparison of characteristics of responders and nonresponders on exposure variables and electronic medical records (EMRs)

	Responders	Nonresponders	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Subjects n	14 875	12 969		
Age years#	50.4±13.3	42.8±13.6	**1.51 (1.48–1.53)**	**1.52 (1.49–1.54)**
Female	53.2	45.4	**1.48 (1.41–1.55)**	**1.54 (1.47–1.62)**
Exposure				
Distance to the nearest farm m¶	475±281	498±287	**0.97 (0.96–0.98)**	**0.97 (0.96–0.98)**
Number of livestock farms				
Within 500 m	1.5±1.9	1.4±1.8	**1.03 (1.02–1.05)**	**1.04 (1.02–1.05)**
Within 1000 m	8.1±5.7	7.4±5.4	**1.02 (1.02–1.03)**	**1.02 (1.02–1.03)**
Presence of farm animals within 500 m				
Pigs	25.1	23.0	**1.12 (1.06–1.19)**	**1.09 (1.02–1.17)**
Poultry	15.7	14.9	1.06 (0.99–1.13)	1.03 (0.95–1.11)
Cattle	44.5	41.3	**1.14 (1.09–1.19)**	**1.10 (1.04–1.16)**
Goats	1.7	1.3	**1.27 (1.05–1.55)**	1.16 (0.94–1.44)
Mink	1.7	1.6	1.06 (0.88–1.27)	1.03 (0.85–1.25)
Presence of farm animals within 1000 m				
Pigs	74.7	71.6	**1.17 (1.11–1.24)**	**1.11 (1.04–1.19)**
Poultry	59.0	55.5	**1.15 (1.10–1.21)**	**1.09 (1.04–1.16)**
Cattle	89.2	87.4	**1.20 (1.12–1.29)**	1.06 (0.97–1.16)
Goats	10.1	8.1	**1.27 (1.17–1.38)**	**1.23 (1.12–1.34)**
Mink	7.1	6.9	1.04 (0.95–1.14)	0.99 (0.89–1.09)
Modelled fine dust emission				
Weighted fine dust emission from farms within 500 m median+	0.03	0.01	**1.13 (1.08–1.17)**	**1.14 (1.09–1.20)**
Weighted fine dust emission from farms within 1000 m median+	1.30	1.10	**1.10 (1.08–1.13)**	**1.12 (1.09–1.15)**
EMRs				
Subjects included with complete EMR data n	11 868	10 532		
Asthma (ICPC R96)	6.8	6.6	1.03 (0.93–1.15)	1.06 (0.95–1.18)
COPD (ICPC R95 or R91)	3.4	2.7	**1.30 (1.11–1.52)**	**0.81 (0.69–0.96)**
Allergic rhinitis (ICPC R97)	6.3	5.8	1.08 (0.97–1.21)	**1.28 (1.14–1.44)**

Data are presented as mean±SD or %, unless otherwise stated. OR (95% CI) were adjusted for age and sex. The likelihood of being a responder is modelled for different characteristics with logistic regression The presence of farm animals was also adjusted for the presence of other types of farm animals. Bold type indicates statistical significance ($p<0.05$). ICPC: International Classification of Primary Care; COPD: chronic obstructive pulmonary disease. #: OR (95% CI) for an increase per 10 years; ¶: OR (95% CI) for an increase per 100 m; +: OR (95% CI) for an interquartile range (IQR) increase in log-transformed exposure. IQR for ln (fine dust) for farms within 500 m 7.54 $g \cdot year^{-1} \cdot m^{-2}$, corresponding to a 1881-fold increase (exposure 7.54) for nontransformed values and IQR for ln (fine dust) for farms within 1000 m 3.08 $g \cdot year^{-1} \cdot m^{-2}$, corresponding to a 22-fold increase for nontransformed values.

TABLE 2 : Associations of livestock farm exposures and chronic obstructive pulmonary disease (COPD), current asthma and nasal allergies in 12 117 questionnaire responders

	COPD	Current asthma	Nasal allergies
Prevalence n (%)	553 (4.6)	1365 (11.3)	2778 (23.2)
Covariates			
Age increase per 10 years	**1.56 (1.44–1.70)**	**1.06 (1.02–1.12)**	**0.84 (0.81–0.87)**
Sex (reference is male)	1.05 (0.88–1.25)	**1.15 (1.03–1.29)**	1.10 (1.00–1.20)
Ex-smoker	**1.63 (1.32–2.01)**	**1.16 (1.01–1.31)**	**0.82 (0.74–0.90)**
Current smoker	**2.30 (1.78–2.90)**	1.18 (1.00–1.39)	**0.62 (0.54–0.71)**
Exposure			
Presence of livestock farms (yes or no)			
Within 100 m	**0.47 (0.24–0.91)**	**0.65 (0.45–0.93)**	0.78 (0.61–1.00)
Within 500 m	0.91 (0.77–1.09)	0.96 (0.85–1.07)	0.99 (0.91–1.08)
Within 1000 m	**0.71 (0.51–0.98)**	0.84 (0.67–1.06)	0.92 (0.76–1.10)
Presence of farm animals in 500 m (yes or no)			
Pigs	1.01 (0.80–1.26)	**0.84 (0.72–0.97)**	1.02 (0.91–1.13)
Poultry	1.04 (0.80–1.35)	1.17 (0.99–1.38)	1.01 (0.89–1.14)
Cattle	0.91 (0.76–1.11)	0.98 (0.87–1.11)	0.93 (0.85–1.02)
Goats	1.07 (0.51–2.26)	0.90 (0.54–1.48)	1.10 (0.77–1.57)
Mink	0.59 (0.24–1.45)	0.68 (0.39–1.18)	1.34 (0.96–1.88)
Presence of farm animals in 1000 m (yes or no)			
Pigs	0.97 (0.77–1.21)	0.94 (0.81–1.09)	1.03 (0.92–1.15)
Poultry	0.87 (0.72–1.05)	1.02 (0.90–1.15)	0.94 (0.85–1.03)
Cattle	1.01 (0.75–1.37)	1.03 (0.84–1.26)	0.94 (0.81–1.10)
Goats	0.96 (0.69–1.32)	**0.79 (0.64–0.98)**	0.95 (0.82–1.11)
Mink	0.95 (0.66–1.36)	0.99 (0.78–1.25)	0.90 (0.75–1.08)
Distance to the nearest farm (quartiles)			
>640 m	1	1	1
450–640 m	**0.76 (0.60–0.97)**	0.87 (0.75–1.03)	1.03 (0.91–1.17)
290–450 m	0.92 (0.73–1.16)	0.86 (0.73–1.00)	1.02 (0.91–1.15)
<290 m	**0.71 (0.56–0.91)**	**0.83 (0.71–0.98)**	**0.87 (0.77–0.98)**
Test for trend	**0.03**	**0.03**	**0.03**
Number of livestock farms in 1000 m (quartiles)			
<4	1	1	1
4–7	0.96 (0.76–1.21)	1.02 (0.87–1.19)	0.97 (0.87–1.10)
7–11	0.91 (0.72–1.15)	0.97 (0.83–1.13)	0.94 (0.84–1.06)
>11	0.89 (0.69–1.15)	0.95 (0.80–1.12)	0.93 (0.82–1.05)
Test for trend	0.33	0.45	0.19
Modelled fine dust emission from farms			
Log-weighted fine dust emission from farms within 500 m#	0.92 (0.78–1.09)	0.96 (0.86–1.07)	0.98 (0.91–1.07)
Log-weighted fine dust emission from farms within 1000 m#	0.93 (0.85–1.01)	0.96 (0.90–1.02)	0.98 (0.93–1.02)

Data are presented as OR (95% CI), unless otherwise stated. All responders with complete exposure data were included, who did not live or work on a farm and who had lived in their home for >1 year (n=12 117; fig. 1). All OR (95% CI) were adjusted for age, sex and smoking habits. The presence of a type of farm animal was adjusted for the presence of other types of farm animals. Bold type indicates statistical significance ($p<0.05$). Analyses of the influence of covariates on COPD, current asthma and nasal allergies were mutually adjusted. #: OR (95% CI) for an interquartile range (IQR) increase in log-transformed exposure, IQR for ln (fine dust) for farms within 500 m 7.54 $g \cdot year^{-1} \cdot m^{-2}$, corresponding to a 1881-fold increase (exposure 7.54) for nontransformed values and IQR for ln (fine dust) for farms within 1000 m 3.08 $g \cdot year^{-1} \cdot m^{-2}$, corresponding to a 22-fold increase for nontransformed values.

FIGURE 2 : Smoothed plots representing associations of the minimal distance to the nearest farm and wheezing in chronic obstructive pulmonary disease patients; significance of smooth terms p=0.06.

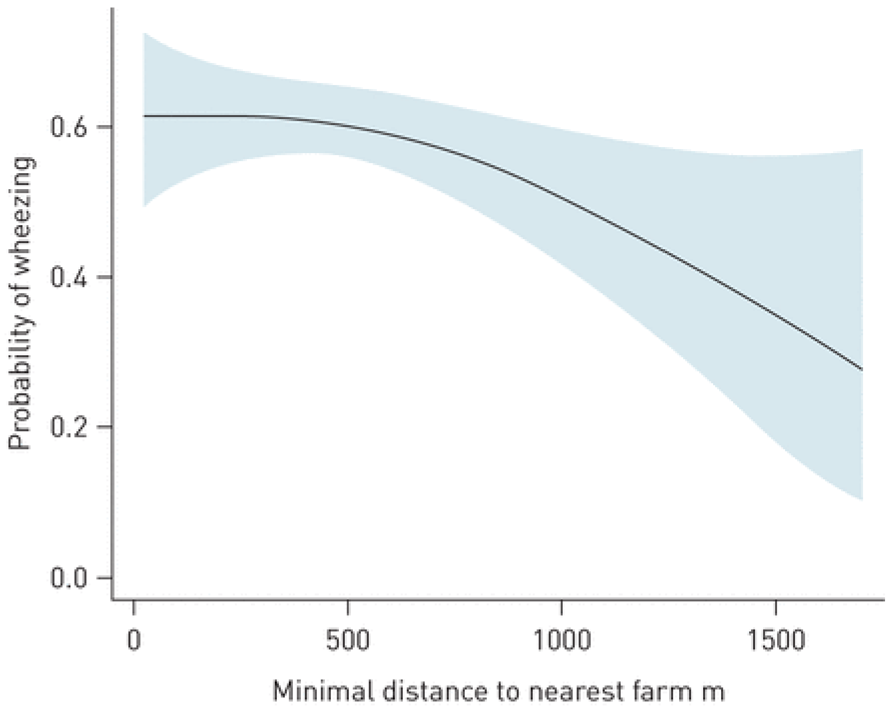

TABLE 3 : Association between livestock farm exposures and current wheeze within subgroups of patients (based on questionnaire)

	Wheezing or whistling on chest in last 12 months		
	COPD	Current asthma	Nasal allergies
Subjects n	322	748	670
Exposure			
Presence of livestock farms			
Within 100 m	0.93 (0.25–3.54)	0.61 (0.30–1.23)	0.80 (0.46–1.37)
Within 500 m	1.35 (0.96–1.91)	0.93 (0.74–1.15)	0.89 (0.74–1.06)
Within 1000 m	1.62 (0.87–3.02)	1.17 (0.76–1.80)	1.07 (0.74–1.55)
Presence of farm animals in 500 m (yes or no)			
Pigs	1.05 (0.66–1.68)	1.08 (0.81–1.44)	0.90 (0.72–1.14)
Poultry	1.30 (0.76–2.23)	1.17 (0.86–1.61)	1.27 (0.99–1.63)
Cattle	1.46 (0.99–2.16)	0.84 (0.67–1.07)	0.88 (0.73–1.07)
Goats	0.69 (0.14–3.40)	0.79 (0.30–2.10)	0.80 (0.38–1.71)
Mink	2.68 (0.27–26.29)	2.05 (0.63–6.65)	0.71 (0.34–1.47)
Presence of farm animals in 1000 m (yes or no)			
Pigs	0.97 (0.60–1.56)	1.04 (0.78–1.39)	0.89 (0.70–1.12)
Poultry	0.96 (0.66–1.39)	0.94 (0.74–1.19)	0.95 (0.79–1.16)
Cattle	1.19 (0.63–2.24)	0.93 (0.62–1.39)	1.02 (0.74–1.39)
Goats	0.99 (0.52–1.88)	1.16 (0.76–1.76)	0.83 (0.60–1.15)
Mink	1.09 (0.53–2.28)	0.88 (0.56–1.39)	1.19 (0.83–1.71)
Distance to the nearest farm (quartiles)			
>640 m	1	1	1
450–640 m	**2.17 (1.32–3.57)**	0.94 (0.69–1.27)	1.14 (0.89–1.46)
290–450 m	**1.65 (1.05–2.59)**	0.88 (0.65–1.19)	0.89 (0.70–1.14)
<290 m	1.45 (0.90–2.35)	0.91 (0.67–1.23)	0.99 (0.77–1.27)
Test for trend	0.14	0.48	0.46
Number of livestock farms in 1000 m (quartiles)			
<4	1	1	1
4–7	0.96 (0.61–1.51)	0.76 (0.57–1.02)	0.96 (0.76–1.22)
7–11	1.01 (0.64–1.59)	0.81 (0.60–1.08)	0.83 (0.65–1.05)
>11	**1.71 (1.01–2.89)**	0.93 (0.67–1.28)	0.90 (0.70–1.15)
Test for trend	0.09	0.58	0.20
Fine dust emission from farms			
Log-weighted fine dust emission from farms within 500 m[#]	1.03 (0.99–1.08)	1.00 (0.97–1.03)	0.99 (0.97–1.01)
Log-weighted fine dust emission from farms within 1000 m[#]	1.01 (0.96–1.07)	0.99 (0.96–1.03)	0.98 (0.95–1.01)

Data are presented as OR (95% CI), unless otherwise stated. OR (95% CI) were adjusted for age, sex and smoking habits. The presence of a type of farm animal is adjusted for the presence of other types of farm animals. Bold type indicates statistical significance ($p<0.05$). #: OR (95% CI) for an interquartile range (IQR) increase in log-transformed exposure. IQR for ln (fine dust) for farms within 500 m 7.54 $g \cdot year^{-1} \cdot m^{-2}$, corresponding to a 1881-fold increase (exposure 7.54) for nontransformed values and IQR for ln (fine dust) for farms within 1000 m 3.08 $g \cdot year^{-1} \cdot m^{-2}$, corresponding to a 22-fold increase for nontransformed values.