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Risk of exacerbations in COPD and asthma patients living in the neighbourhood of livestock farms: Observational study using longitudinal data

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ABSTRACT

Objective: Living in an area with a high density of livestock farms has been associated with adverse respiratory health effects in some studies. As patients with COPD and asthma already have a compromised respiratory function and chronic airway inflammation, they are expected to be at increased risk for adverse respiratory health effects. The objective of this study was to assess the association between livestock exposure and exacerbations in COPD and asthma.
Methods: 899 COPD and 2546 asthma patients from 15 general practices in a rural area with a high livestock density and 933 COPD and 2310 asthma patients from 15 practices in a control area in the Netherlands were included. Occurrence of exacerbations was based on the pharmaceutical treatment of exacerbations in COPD and asthma patients using 2006–2012 prescription data of electronic medical records. Farm exposure was assessed by comparing the study area with the control area, and with individual exposure estimates in the study area using Geographic Information System data.
Results: The exacerbation rate was higher in the study area compared with the control area in COPD (IRR: 1.28; 95%CI: 1.06–1.55), but not in asthma patients (IRR: 0.87; 95%CI: 0.72–1.05). In general, individual exposure estimates in the study area were not associated with exacerbations. COPD patients living within a 500 m radius of up to12,499 chickens had a 36% higher exacerbation rate (IRR: 1.36; 95%CI: 1.03–1.79).
Conclusions: Living in an area with a high livestock density is a risk factor for exacerbations in COPD patients. The environmental exposure responsible for this increased risk remains to be elucidated.
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1. Introduction

The expansion of (concentrated) livestock farms has created concerns with regard to the health of residents living in the proximity of livestock farms worldwide (Smit et al., 2012; Heederik and Yzermans, 2011). Livestock farms emit several compounds, including pro-inflammatory microbial agents such as endotoxins, and infectious agents such as bacteria, fungi and viruses. In addition, particulate matter (PM), ammonia, hydrogen sulphide (H_2S), and volatile organic compounds are being emitted (Dungan, 2010). General population studies investigating exposure to livestock and respiratory health symptoms at the individual level showed an increased prevalence of 'wheezing', 'difficulty with breathing' and lower lung function with higher livestock exposure (Radon et al., 2007; Schinasi et al., 2011; Schulze et al., 2011). Although these respiratory symptoms are more often seen in respiratory disease, the evidence regarding an association between livestock exposure and prevalence of respiratory diseases such as asthma and COPD is inconclusive (Radon et al., 2007; Smit et al., 2014; Pavilonis et al., 2013). Chronic obstructive pulmonary disease (COPD) and asthma are respiratory diseases characterised by a compromised respiratory function and chronic airway inflammation. Therefore, patients with COPD or asthma could be at increased risk of the harmful effects of livestock exposure.

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Patients with respiratory conditions seem to respond to a greater extent to livestock exposure. Harting et al. (2012) showed that patients with COPD responded to *ex vivo* stimulation with swine dust extract to a greater extent than healthy volunteers. Sigurdarson et al. (2004) found a decreased lung function and increased bronchial hyper-responsiveness in asthma patients experimentally exposed to endotoxin-rich grain dust, whereas healthy controls were not affected. In addition, previous studies showed that particularly vulnerable populations, such as patients with respiratory diseases, showed adverse health effects (*e.g.* lung function, respiratory symptoms) of exposure to PM10 and endotoxins (Lawson et al., 2011; Boezen et al., 1999). Borlée et al. (2015) showed more wheezing among COPD patients who were more exposed to livestock farms. In addition, Portengen et al. (2005) showed a stronger association between endotoxin exposure and airway hyperresponsiveness for sensitised pig farmers compared with nonsensitised pig farmers.

Increased respiratory health risks of livestock exposure in COPD and asthma patients may also have consequences for the occurrence of exacerbations in these patients. Exacerbations are defined as 'worsening of the patient's condition, from the stable state and beyond normal day-to-day variations that is acute in onset and may warrant additional treatment in a patient' (Burge and Wedzicha, 2003; Reddel et al., 2009). Exacerbations are associated with increased morbidity and mortality, accelerated decline in lung function, reduced health status, and increased health care costs (O'Byrne et al., 2009; Halpin et al., 2012; Soler-Cataluña et al., 2005). To our knowledge, associations between livestock exposure and exacerbations in asthma and COPD patients have not been addressed previously.

The present study investigated the association between livestock exposure and exacerbations among COPD and asthma patients in an area with a high density of livestock farms in the Dutch provinces of Noord-Brabant and Limburg.

2. Methods

2.1. Study design

An observational study was undertaken to explore the association between exposure from livestock farms and exacerbations in COPD and asthma patients, and was part of the VGO study (Dutch acronym for Farming and Neighbouring Residents' Health). Data from 2006–2012 were used from the electronic medical records (EMRs) of general practices that participated in the NIVEL Primary Care Database (PCD) (Verheij, 2014). The NIVEL PCD contains longitudinal data at the patient level in terms of contacts, morbidity, prescriptions and referrals, with limited annual changes in practice composition. Prescription data were classified according to the Anatomical Therapeutic and Chemical (ATC) classification (WHO, 1996), and morbidity was coded by using the International Classification of Primary Care (ICPC) scheme (Lamberts and Wood, 1987). Each Dutch inhabitant is obligatorily listed in just one general practice, and GPs act as gatekeepers for specialised, secondary health care. For this study, data were used from practices located in a rural area with a high density of livestock farms in the Netherlands (study area) and from practices located in a rural area with a much lower density of livestock farms (control area). For example, in 59% of the postal code areas of the general practices in the study area one or more concentrated animal feeding operations (livestock farms with for example more than 120,000 laying hens, more than 250 dairy cows or more than 7500 finishing pigs) were located, compared to 5% in the control area. Especially, poultry and swine were more common in the study area. We included data from 15 out of 32 participating general practices in the study area and 15 out of 23 general pratices in the control area that passed a number of checks regarding the quality and completeness of data on morbidity and prescriptions for three consecutive years. Lack of good quality morbidity data was the main reason for exclusion.

The study was carried out according to Dutch legislation on privacy and the Code of Conduct for Medical Research, as described previously (Smit et al., 2014; Borlée et al., 2015). In short, privacy was ensured by keeping medical information and address records (only available for study area) separated at all times, by using a Trusted Third Party. The researchers received information about patients' age, gender, medical information and about the individual livestock exposure (rounded at 10 animals or 10 m) based on the address records. Dutch law allows the use of EMR for research purposes under certain conditions. According to this legislation, neither obtaining informed consent from patients nor approval by a medical ethics committee is obligatory for this type of observational studies containing no directly identifiable data (Dutch Civil Law, Article 7:458).

2.2. Study population

COPD and asthma patients were included only when they had at least three consecutive years of data. The first year was used to define COPD and asthma and to include only prevalent cases. Asthma was defined as two or more morbidity or prescription records with an indication for asthma (ICPC: R96); COPD was defined as R91 (chronic bronchitis) or R95 (pulmonary emphysema/COPD). As we were interested in neighbouring residents, we excluded patients who had a high likelihood to be living on a farm (distance between home address and livestock farm <50 m – information only available for study area) and therefore could confound the association between livestock exposure and exacerbations.

In addition, patients with a history of lung malignancy and patients for whom no reference period without an exacerbation could be defined (see below) were excluded. For COPD patients, patients aged ≤40 years were excluded, as were those with a concurrent diagnosis of asthma. Patients with asthma aged <6 years were excluded, as asthma can only be diagnosed from six years of age according to the Dutch guidelines (Bindels et al., 2014), and asthma patients with a concurrent diagnosis of COPD were also excluded. The group of patients with both COPD and asthma was too small to be included as a separate patient group. In total, 899 COPD patients with 2456 patient-years and 2546 asthma patients with 8387 patient-years were included in the study area, and 933 COPD patients with 2667 patient-years and 2310 asthma patients with 7200 patient-years were included in the control area (see Fig. 1 for flow chart). Patient-years were the unit of analyses in this study. For 551 (30%) of the included 1832 COPD patients, at least one measurement result of post-bronchodilator FEV_1 and FVC was available. Of these patients, 451 (81.9%) had a FEV_1/FVC ratio <70%.

2.3. Exacerbations

Exacerbations were defined based on pharmaco-therapeutic treatment information of exacerbations in COPD and asthma patients: (i) a prescription of a systemic glucocorticosteroid; (ii) a prescription of an antimicrobial agent (COPD only); (iii) a temporary increase in the dose of a short-acting bronchodilator (short-acting β2-agonist (SABA) and/or short-acting anticholinergic (SAAC)) or (iv) temporary treatment with a short-acting bronchodilator or a combination of short-acting bronchodilators (Smeele et al., 2007; Geijer et al., 2007; Evensen, 2010).

We calculated the number of exacerbations per patient-year. Each patient-year was divided into thirteen periods of four weeks in which the presence of an exacerbation was established. In Fig. 2

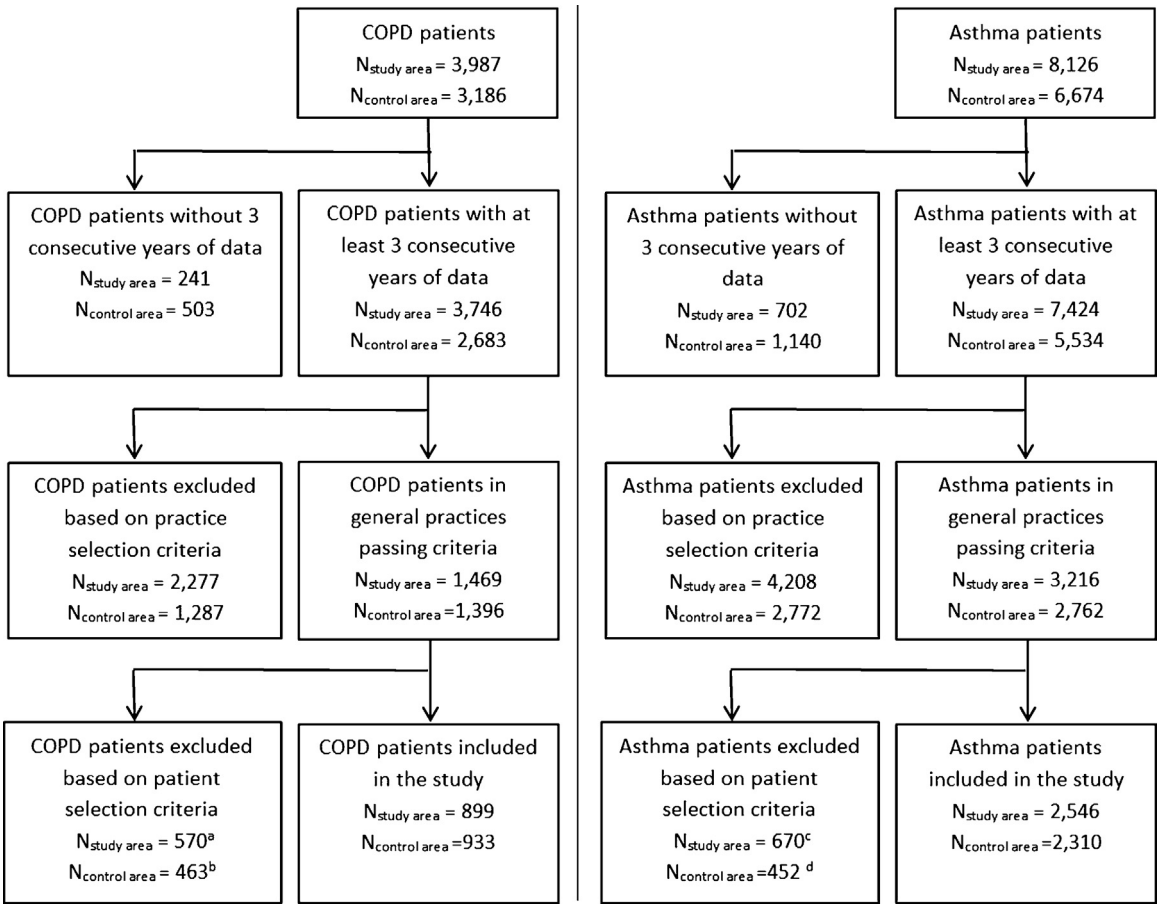

Fig. 1. Flow chart of patient selection. [a] Excluded based on age ($N=50$), no reference period without an exacerbation ($N=38$), concurrent diagnosis of asthma ($N=438$), history of lung malignancy ($N=49$) and distance between home address and livestock farm <50 m ($N=33$); [b]excluded based on age ($N=50$), no reference period without an exacerbation ($N=41$), concurrent diagnosis of COPD ($N=345$), and history of lung malignancy ($N=61$); [c]excluded based on age ($N=126$), no reference period without an exacerbation ($N=9$), concurrent diagnosis of COPD ($N=438$), history of lung malignancy ($N=17$) and distance between home address and livestock farm <50 m ($N=113$); [d] excluded based on age ($N=19$), no reference period without an exacerbation ($N=17$), concurrent diagnosis of COPD ($N=345$), and history of lung malignancy ($N=19$).

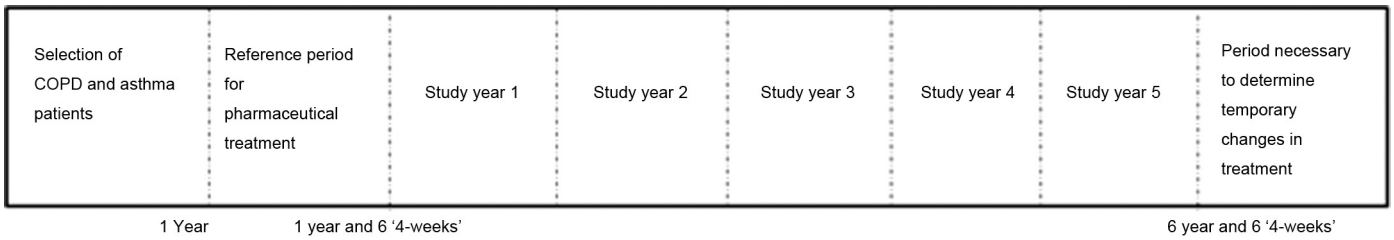

Fig. 2. Example of selection period of COPD/asthma, reference period for pharmaceutical treatment, study period and period necessary to determine temporary change in treatment with short-acting bronchodilators for patients with seven consecutive years of data.

an example is shown for seven years of data. The first six periods of each patient in the second year of data (first year used to define COPD and asthma) were used as a reference period as our definition of exacerbation included a temporary change in the dose of or treatment with short-acting bronchodilators; the last seven periods of each patient were excluded, as these were necessary to determine whether changes in treatment with short-acting bronchodilators were really temporary, and to return the number of patient-years into round years. Only the time in the reference period without an exacerbation (no prescription of antimicrobial agents or systemic glucocorticosteroid) was used. For 79 COPD and 26 asthma patients, no exacerbation-free period could be defined within the reference period, and these patients were excluded. As patients need time to recover from an exacerbation and the pharmaceutical treatment of each exacerbation could last for several 4-week periods, no new exacerbations were defined in the two 4-week periods after the 4-week period with an exacerbation, leading to a maximum of five exacerbations per year. We defined the treatment with short-acting bronchodilators on a 4-week basis based on the prescription pattern of the patients (see Appendix A). A temporary increase in the dose of a short-acting bronchodilator was defined as at least a doubling of the dose of the bronchodilator, followed by at least a halving of this dose within 12 weeks. A temporary treatment with a short-acting bronchodilator or a combination of short-acting bronchodilators was defined as an addition of a short-acting bronchodilator (SABA or SAAC) or addition of another type of short-acting bronchodilator (first 4-week period), with a return in treatment in the following 12 weeks.

As systemic glucocorticosteroids and antimicrobial agents can be prescribed for other indications than asthma and COPD, these medicines were only included if they were accompanied by a respiratory indication (excluding pneumonia – differential diagnosis). The specific indication was known for 76% and 79% of the prescriptions of glucocorticosteroids for COPD and asthma, respectively, and for 83% of the prescriptions of antimicrobial agents. In case of missing indications, we used additional information of patients or general practices (see Appendix A). For 19%/13% of the prescriptions of a short-acting bronchodilator, the defined daily dose (DDD) of the prescription was unknown. We imputed the DDD based on additional information (see Appendix B).

2.4. Exposures from livestock farms

Farm exposure was assessed (1) by comparing the study area with the control area, and (2) by using individual exposure estimates in the study area. Individual exposure estimates were not available for COPD and asthma patients in the control area as we did not have access to information about the residential address of patients in the control area. Data on farm characteristics (geographic location, type and number of animals) in the study area were obtained from the 2009 and 2012 provincial databases of mandatory environmental licences for keeping livestock. Participants' residential addresses were geocoded, and distances between the home address and all livestock farms were calculated using a geographic information system (ArcGis 9.3.1, Esri, Redlands, CA). The following individual farm exposure variables were considered: (1) distance to nearest farm; (2) distance to nearest farm with a specific farm animal (continuous variable and categories); (3) presence of one or more farms within 100 m and 500 m from the home address; and (4) presence and number of specific farm animals (equal groups with at least four percent of patients >0 animals) within 500 m. A distance of 500 m was chosen as a previous study showed differences in respiratory health in subjects living within 500 m of a livestock farm (Radon et al., 2007). As studies on livestock exposure show highest exposure levels of poultry and swine stables, only associations were reported for swine and poultry specifically, although all analyses were adjusted for the presence of cattle, sheep, goats and minks (Seedorf and Hartung, 2000; Cambra-López et al., 2010). For the patient-years from 2007 until 2010, exposure data from 2009 was used, while 2012 exposure data was used for patient-years starting in 2011. Comparisons between exposure 2009 and 2012 exposure data shows less livestock exposure in 2012. For example, the mean distance to nearest farm was in 2009 473 m and in 2012 487 m, and in 2009 the mean number of livestock farms in a radius of 500 m from home was 1.70 in 2009 and 1.57 in 2012.

2.5. Confounders

Analyses were adjusted for age, gender, maintenance treatment with an inhaled corticosteroid (ICS), diagnosis of depression (ICPC P03 or P76) and ischaemic heart disease (coronary heart disease: K74-K76; heart failure: K77; stroke: K89, K90). We adjusted for maintenance treatment with an ICS as it has an anti-inflammatory effect affecting exacerbation risk (Jen et al., 2012). Previous research has shown that exacerbations are more common in patients with depression and with ischaemic heart disease (Campo et al., 2015; Ito et al., 2012), as well as associations between livestock exposure and depression and risk factors of ischaemic heart diseases (Hooiveld et al., 2015; Wing et al., 2013). Smoking status was available from the EMR for only a selective part of the patients and therefore not included in the analyses. Other patient characteristics as the socioeconomic status were not available from the EMR of general practices.

2.6. Statistical analysis

Associations between farm exposure variables and exacerbations were analysed by means of zero-inflated multilevel Poisson regression analyses. Multilevel analyses were conducted as the data was hierarchically structured (patient-years nested within patients and patients nested within general practices). Multilevel analyses adjust for the cluster effect of hierarchically structured data. Variation on patient and the general practice level was estimated with a random intercept only. To adjust for over-dispersion (larger variance than mean; greater proportion of patients without exacerbations), zero-inflated Poisson analyses were performed. Models on the presence of specific livestock were mutually adjusted for the presence of other livestock animals. The distance to the nearest farm was natural log-transformed to adjust for left skewedness. Incidence rate ratios (IRRs) and 95% confidence intervals (CI) for an interquartile range (IQR) increase in exposure were calculated by taking the exponent of regression coefficients and their confidence intervals after multiplying by the interquartile range of log-transformed exposure. We performed several sensitivity analyses and subgroup analyses with regard to the individual exposure estimates: (i) including only patients with no imputed data; (ii) definition of exacerbations with systemic glucocorticosteroid and antimicrobial agents (COPD only); (iii) separate analyses for patients with and without a known allergy (ICPC A12, H71, R97 and S87) within general practice; (iv) only COPD patients with known FEV1/FVC <0.7 (in this case we did not analyse the exposure to specific livestock animals, as the number of patients per group was too small). The shape of possible associations was studied by means of generalised additive models (smoothing) using 'gam' in R-studio (thin plate regression splines).

3. Results

3.1. Patient characteristics

Patient characteristics of COPD and asthma patients in the study and control area are shown in Table 1. COPD patients in the study area were more often male than female (60%), were on average 68 years of age and were often a previous smoker or a current smoker (Table 1). Asthma patients were on average 36 years of age, often had an atopic condition (42%) and were most often lifetime non-smokers (61%). COPD patients in the study area were significantly younger and had a coronary heart disease more often compared with COPD patients in the control area. No statistically significant differences in patient charateristics were found for asthma. COPD and asthma patients in the study area were frequently living within 500 m of stables with swine (COPD/asthma: 23%/29%) and poultry (11%/12%).

3.2. Exacerbations

Almost half of the COPD patients in the study area (46.3%) had one or more exacerbations per year, compared with 39.6% in the control area. The average exacerbation rate for all COPD patients was 0.71 (SD: 0.94) per year in the study area and 0.58 (SD: 0.86) in the control area; for patients with one or more exacerbations, the average exacerbation rate was 1.54 (SD: 0.80)/1.47 (SD: 0.74) per year. Asthma patients had exacerbations less often. Only 16.0% of the asthma patients in the study area had one or more exacerbations per year and 18.3% in the control area. The average exacerbation rate was 0.19 (SD: 0.46) per year in the study area for all asthma patients and 0.22 (SD: 0.50) in the control area;

Table 1
Characteristics of the study population (per patient-year).

Characteristic	Study area		Control area	
	COPD	Asthma	COPD	Asthma
Patients (*n*)	899	2546	933	2310
Patient-years (*n*)	2456	8387	2667	7200
Female gender, *n* (%)	993 (40.4%)	4230 (50.5%)	1253 (47.0%)	3725 (51.7%)
Age (years, mean ± sd)	67.7 (11.1)	36.2 (20.5)	69.6 (11.5)	36.2 (20.4)
Depression, *n* (%)	181 (7.4%)	400 (4.8%)	175 (6.6%)	318 (4.4%)
Atopic symptoms/conditions, *n* (%)	402 (16.4%)	3490 (41.6%)	574 (21.5%)	3229 (44.9%)
Coronary heart disease	688 (28.0%)	396 (4.7%)	658 (24.7%)	288 (4.0%)
Heart failure	357 (14.5%)	95 (1.1%)	448 (16.8%)	95 (1.3%)
History of stroke	299 (12.2%)	191 (2.3%)	287 (10.8%)	132 (1.8%)
Distance to nearest				
Livestock farm (m, GM (IQR))	542 (310–750)	470 (280–640)		
Farm with swine (m, GM (IQR))	742 (520–940)	708 (460–870)		
Farm with poultry (m, GM (IQR))	1024 (740–1280)	1010 (700–1280)		
One or more farms within 100 m	79 (3.2%)	297 (3.5%)		
One or more farms within 500 m, *n* (%)	1183 (48.2%)	5004 (59.7%)		
Presence of livestock within 500 m, *n* (%)				
Swine				
<749	223 (9.1%)	813 (9.7%)		
750–2249	164 (6.7%)	824 (9.8%)		
2250–23,810	170 (6.9)	830 (9.9%)		
Poultry				
<12,499	150 (6.1%)	499 (6.0%)		
12,500–364,940	114 (4.6%)	510 (6.1%)		

GM, geometric mean; IQR, interquartile range.

for patients with at least one exacerbation per year, the average exacerbation rate was and 1.16 (SD: 0.44)/1.20 (SD: 0.47) per year.

3.3. Difference in exacerbations between study and control area

COPD patients in the study area more often had exacerbations compared with COPD patients in the control area (IRR: 1.28; 95%CI: 1.06–1.55). No statistical significant difference in exacerbation rate was found for asthma patients between the study and control area (IRR: 0.87; 95%CI: 0.72–1.05).

3.4. Association between individual exposure to livestock and exacerbations

In general, individual exposure to livestock was not associated with exacerbations in COPD and asthma patients. COPD patients living within a 500 m radius of stables with up to 12,499 chickens had exacerbations more often than patients without poultry exposure (IRR: 1.36; 95%CI: 1.03–1.79; Table 2). However, COPD patients living within a 500 m radius of stables with more than 12,499 chicken did not have a higher exacerbation risk, and also no significant differences were found for the distance to the nearest farm with poultry. Asthma patients living 500–999 m from a farm with poultry had exacerbations more often than patients living 1000 m or further from the nearest farm with poultry (IRR 1.15; 95%CI: 1.00–1.33; Table 2).

The association between exposure to poultry and exacerbations was studied in more detail. Dividing the number of chickens within 500 m into four equal exposure categories (excluding no exposure) showed a fairly equal exacerbations risk for the two lowest categories of poultry in COPD patients, whereas for asthma patients a higher exacerbation risk was found in the category 500–12,499 chickens (Table 3). Also, the smoothed spline in Appendix C illustrates the increased exacerbation risk in COPD patients exposed to a relatively small number of poultry within a 500 m radius from the home address. A forest plot of the association between up to 12,499 chickens in a 500 m radius from home and exacerbations in COPD patients shows homogeneity in the association between general practices (Appendix D).

Table 2
Association of livestock farm exposures and exacerbations in 2456 COPD patient-years and 8387 asthma patient-years in the study area.

Exposure	COPD IRR (95%CI)	Asthma IRR (95%CI)
Distance to nearest		
Farm[#]	1.01 (0.91–1.12)	1.05 (0.96–1.15)
Farm with swine[#]	1.00 (0.90–1.12)	0.98 (0.90–1.08)
Farm with poultry[#]	0.97 (0.90–1.05)	0.95 (0.88–1.03)
One or more farms within 100 m	0.96 (0.64–1.42)	1.05 (0.74–1.49)
One or more farms within 500 m	0.99 (0.85–1.14)	0.91 (0.79–1.05)
Distance to nearest farm		
Swine (ref = 1000 m or further)		
<250 m	0.91 (0.60–1.38)	0.94 (0.68–1.31)
250–499 m	0.89 (0.68–1.17)	0.87 (0.69–1.10)
500–999 m	0.91 (0.75–1.10)	0.90 (0.75–1.09)
Poultry (ref = 1000 m or further)		
<250 m	0.99 (0.67–1.47)	1.01 (0.69–1.46)
250–499 m	1.29 (0.97–1.71)	1.07 (0.83–1.38)
500–999 m	1.00 (0.85–1.18)	**1.15 (1.00–1.33)**
Presence of livestock within 500 m		
Swine (ref = 0)		
<749	1.00 (0.77–1.30)	0.98 (0.78–1.22)
750–2249	1.11 (0.82–1.49)	0.89 (0.71–1.12)
2250 – 23,810	0.99 (0.73–1.35)	0.89 (0.69–1.15)
Poultry (ref = 0)		
<12,499	**1.36 (1.03–1.79)**	1.13 (0.87–1.47)
12,500–364,940	0.84 (0.60–1.18)	0.84 (0.63–1.13)

Incidence rate ratios (IRRs) and 95%CI were adjusted for age, gender, maintenance treatment with ICS, depression, ischaemic heart disease and the presence of other types of livestock animals.
Bold font: significant at p = 0.05 level.

[#] IRR and 95%CI for an IQR increase in log-transformed exposure. IQR for ln(distance farm, m) for COPD patients = 0.88, corresponding to a 2.42-fold increase ($\exp^{0.88}$) for non-transformed values, IQR for ln(distance farm with swine, m) for COPD patients = 0.59, corresponding to a 1.81-fold increase ($\exp^{0.59}$) for non-transformed values, IQR for ln(distance farm with poultry, m) for COPD patients = 0.55, corresponding to a 1.73-fold increase ($\exp^{0.55}$) for non-transformed values, IQR for ln(distance farm, m) for asthma patients = 0.83, corresponding to a 2.29-fold increase ($\exp^{0.83}$) for non-transformed values, IQR for ln(distance farm with swine, m) for asthma patients = 0.64, corresponding to a 1.89-fold increase ($\exp^{0.64}$) for non-transformed values, and IQR for ln(distance farm with poultry, m) for asthma patients = 0.60, corresponding to a 1.83-fold increase ($\exp^{0.60}$) for non-transformed values.

Table 3
Association of poultry exposures within 500 m from home address and exacerbations in 2458 COPD patient-years and 8387 asthma patient-years in the study area.[#]

Exposure	COPD IRR (95%CI)	Asthma IRR (95%CI)
Poultry (ref = 0)		
<499	1.33 (0.88–2.00)	**0.63 (0.41–0.98)**
500–12,499	1.38 (0.98–1.95)	**1.58 (1.14–2.18)**
12,500–43,999	0.78 (0.50–1.22)	0.70 (0.48–1.03)
44,000–364,940	0.90 (0.58–1.41)	1.02 (0.69–1.50)

Bold font: significant at p = 0.05 level.

[#] Incidence rate ratios (IRRs) and 95%CI were adjusted for age, gender, maintenance treatment with ICS, depression, ischaemic heart disease and the presence of other types of livestock animals.

3.5. Subgroup and sensitivity analyses

All subgroup and sensitivity analyses are shown in Appendix E. Analyses showed fairly similar results for both asthma and COPD patients. For COPD patients, including only exacerbations based on prescriptions of systemic glucocorticosteroid and antimicrobial agents showed a lower exacerbation rate in patients living 250–499 m from the nearest farm with swine compared with COPD patients living 1000 m or further away from the nearest farm with swine (IRR: 0.72; 95%CI: 0.53–0.99). For asthma patients, differences were found between patients with and without a known allergy. Living closer to a farm with swine was associated with less exacerbations in patients without a known allergy. The association between exposure to poultry and exacerbation risk also differed between patients with and without a known allergy. For asthma patients without a known allergy, increased exacerbation risk was found for increased exposure to poultry, although none of these associations reached statistical significance (Appendix E).

4. Discussion

We hypothesised a higher exacerbation rate in COPD and asthma patients with increased exposure to livestock farming. For asthma patients, no association was found between livestock exposure and the exacerbation rate. For COPD patients in a rural area with a high density of livestock farms, we did find an increased exacerbation risk compared with a control area. However, we hardly found any association between individual livestock exposure estimates and the exacerbation rate. Only COPD patients living within 500 m of a relatively small number of poultry were at an increased exacerbation risk.

Although several studies have shown increased respiratory symptoms with increased livestock exposure (Radon et al., 2007; Schinasi et al., 2011; Schulze et al., 2006), information on exposure levels of microbial agents or irritant gases and particulate matter in the vicinity of livestock farms is, in general, scarce and shows large exposure variability (Dungan, 2010). As a result, it is uncertain which components could have caused these health effects, as our study did not include direct measurements of exposure. COPD and asthma patients have shown to respond to a greater extent to *ex vivo* stimulation with swine dust or endotoxin-rich grain dust (Harting et al., 2012; Sigurdarson et al., 2004). It might be that the exposure levels are too low to elicit an exacerbation, although other studies have found differences in respiratory health within a distance of 500 m (Radon et al., 2007). Exposure levels are dependent on various factors. Emission of compounds from livestock farms to the environment is dependent on, among others, the type of livestock animal and animal housing systems (*e.g.* natural or mechanic ventilation), number of animals and meteorological influences (Banhazi et al., 2008; Just et al., 2009). Dispersal of compounds from livestock farms is, in addition to emission rates, also dependent on wind velocity and direction, and vegetation (Dungan, 2010). These factors may have differed in our study area compared with previous studies. Also, our individual livestock exposure estimates did not include the number of animals and exact distance to farms in one model, which may explain the absence of clear associations. In addition, in the study area only few people lived at larger distances from livestock farms, which could explain why we did find differences in exacerbation rate between the study and control area, but not with individual exposure estimates within the study area.

We found an increased exacerbation risk in COPD patients living within a 500 m radius from the home of up to 12,499 chickens. A possible association between exacerbations and exposure to poultry is conceivable. Poultry farms have the greatest source strength of, for example, PM10 and probably also microbial factors. These farms emit a wide diversity of microbes, including viruses and gram-negative and gram-positive bacteria, some of which may be pathogenic (Just et al., 2009). Gram-negative and gram-positive bacteria have shown to elicit non-infectious inflammatory effects, which might lead to exacerbations (May et al., 2012). Seedorf and Hartung (2000) showed that respirable endotoxin emission per 500 kg live-weight was highest for poultry, followed by swine and cattle. In addition, Schulze et al. (2006) measured 24-hour levels of endotoxin exposure in the backyards of residents in rural areas with intensive animal production (especially poultry and swine), and showed higher endotoxin levels compared with urban residents. However, although exposure levels were elevated, they were generally below 100 Endotoxin Units/m^3 and very few observations exist of health effect below this level. It is not easy to explain why we find an increased exacerbation risk with up to 12,499 chickens only, and not with 12,500 or more chickens within a 500 m radius. It does not appear that smaller farms with poultry are located closer to COPD patients, as we found only a higher (non-significant) IRR for COPD patients living 250–499 m from the nearest farm with poultry compared with COPD patients living 1000 m or more from the nearest farm. Two potential explanations could be i) differences in animal housing systems or ii) statistical coincidence. Livestock farms with a small number of poultry may have different animal housing systems than larger scale farms. Literature shows that the emission rate of compounds on livestock farms is highly dependent on the animal housing system (Banhazi et al., 2008). The type of ventilation, size of ventilation air inlet, building type and hygiene in stables all affect the emission rate. It might be that especially large-scale livestock farms invest in improved animal housing systems, or that small-scale livestock farms are more often free-range farms with open air runs. Dust levels inside stables are higher in free-range farms compared to farms with cage-housed chickens (Kirychuk et al., 2006; De Boer and Cornelissen, 2002). However, endotoxin levels inside stables have shown to be equal among both types of farms (Kirychuk et al., 2010). Unfortunately, we did not have full information on the various animal housing systems. Future research should incorporate these factors. Statistical coincidence may be another explanation. With a statistical significance threshold of 0.05 as was used in our study, there is a five percent probability that the result has occurred by chance. Replication of this study is necessary to confirm our results.

4.1. Strengths and limitations

The strengths of our study were the objective assessment at the individual level of the presence of livestock farms around the home address, inclusion of the number of various types of livestock in the proximity of residents, and the analyses of exacerbations through the use of EMR data of general practices. However, a number of potential limitations should be considered in our study. First, our study lacked information on animal housing systems, such as ventilation and manure handling systems, and on practices of

land application of manure which could have influenced the emission. Secondly, we only included exacerbations for which patients sought health care or changed their pharmaceutical treatment. However, literature shows that many exacerbations are unreported and may still have an important impact on a patient's health status (Langsetmo et al., 2008). In addition, our definition of exacerbation did not include hospitalisation. As we do not have information on the number of hospitalisations without a previous change in pharmaceutical treatment, it is unknown how many exacerbations were missed. However, the number of exacerbations in COPD patients based on prescription data of EMD of general practices is consistent with the literature (Faganello et al., 2010). The exacerbation rate in asthma patients is slightly lower compared with the literature (Hoskins et al., 2000), probably explained by a different method to determine exacerbations. For asthma patients, a temporary increase in the dose of a short-acting bronchodilator is expected to be an important pharmaceutical treatment of exacerbations. Differences between asthma and COPD patients may exist in the instruction by GPs to increase temporarily inhalers in case of exacerbations without GP intervention. The method using prescription data to determine exacerbations might not be sensitive enough to detect all temporary changes, as the time between two prescription dates is relatively large compared to the period with a temporary increase of a short-acting bronchodilator. In addition, changing in the dose of short-acting bronchodilators could also be due to changes in adherence, and also prescription of a systemic or an antimicrobial agent could have been a rescue pack for future use. Thirdly, in our study population, we could not distinguish between various degrees of severity of COPD or asthma. It might be that exposure to livestock varies with disease severity. Fourthly, COPD was not spirometrically confirmed in all patients. Nevertheless, sensitivity analyses with only the confirmed COPD patients showed fairly similar results. Finally, we did not have information on several potential confounding factors, such as smoking status, occupational exposure and socioeconomic status. A study in the same area showed that living within 500 m of at least one livestock farm was associated with having one or more pets at home and with a higher education level (Smit et al., 2014). Including an indicator for socio-economic status on the level of postal code areas, neighbourhood social status score (composite measure calculated from individual characteristics of neighbourhood residents, *i.e.* mean neighbourhood income, percentage of residents with low-income, percentage of low-educated residents, and percentage of residents without a job), did not change associations between livestock exposure and exacerbations in COPD and asthma. For the study area, questionnaire information on occupational exposure was available for 14,591 of 119,000 residents included in our larger study on EMR data. The questionnaire included a question about living or working on a livestock farm (Borlée et al., 2015). Based on this questionnaire, only 2.6% of the residents were living or working on a livestock farm when subjects who lived within 50 m of a farm were excluded.

5. Conclusions

An increased exacerbation risk was found in COPD patients living in a rural area with a high density of livestock, but we could not explain this difference with various livestock exposure estimates. Only an increased exacerbation risk was found in COPD patients living within 500 m of a relatively small number of poultry. We could not fully explain the difference in the exacerbation risk of COPD patients between up to 12,499 chickens and 12,500–364,940 chickens, but hypothesised a different housing system as a possible agent. The present study did not show differences in exacerbation risk with livestock exposure in asthma patients. More research is needed to understand the association between poultry farm emissions and exacerbation risk in COPD patients.

Conflict of interest

None declared.

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Appendix A. Defining treatment patterns of bronchodilators and ICS

The pattern of treatment was defined for the following medication groups separately:

1. Short-acting β2-agonist (SABA).
2. Short-acting anticholinergic (SAAC).
3. Combination of SABA and SAAC.
4. Inhaled corticosteroids (ICS).
5. Combination of long-acting β2-agonist and ICS.

The pattern of treatment was determined for the whole study period, including the reference period and the last seven periods for each patient (see Fig. 2). The start of a treatment period was defined as:

(i) more than 182 days between prescriptions (only for medication groups 4–5), or
(ii) more days between the two prescription dates than the median difference between two prescriptions plus the difference between the 25th and 75th percentile (with minimum of 21 days), but not when a change in DDD occurred in the same period.

The end of a treatment period was defined as:

- In case of more than one prescription in treatment period: the median time interval between prescription records in the treatment period after last prescription date.
- In case of one prescription in treatment period, patient had previous treatment periods: the median time interval between prescription records of previous treatment period after last prescription date.
- In case of one prescription in treatment period, patient had no previous treatment period: the end date is the start date, and we assume an incidental prescription of the medication.

Based on the treatment periods for the medication groups, the following treatments were defined per period:

- Short-acting β2-agonist (SABA) or short-acting anticholinergic (SAAC).
- SABA & SAAC.
- Inhaled corticosteroids (ICS).

Also, incidental or partial treatment within a 4-week period was considered as the specific treatment.

Appendix B. Handling of missing data

Indication for prescription of systemic glucocorticosteroids

For 24% of the prescription of systemic glucocorticosteroids for COPD patients and 21% for asthma patients, indication was not reported. We followed the following steps to impute the indication based on additional information on patients or the practice level (percentage of all prescriptions for COPD and asthma patients):

Step 1: Indication (in morbidity records) in the week before prescription (6.1%/4.1%).
Step 2: Indication (in morbidity records) in the two weeks before prescription (3.2%/2.7%).
Step 3: If patient is always prescribed the systemic glucocorticosteroid for the same indications, use this indication (5.4%/5.8%).
Step 4: In case a systemic glucocorticosteroid (Anatomical Therapeutic and Chemical (ATC) classification level) is in more than 70% of the cases prescribed for respiratory indication or other indication, this indication (respiratory or not) is used for all these prescriptions (8.8%/6.4%).
Step 5: If a prescription is always prescribed for one indication, we assume that it is now also the case (ATC-level) (0.00%/0.22%).
Step 6: In case a systemic glucocorticosteroid (ATC level) is in more than 70% of the cases in a practice prescribed for respiratory indication or other indication, this indication (respiratory or not) is used for all these prescriptions in the practice (0.02%/0.30%).
Step 7: Manually looking into all data of the patients and deciding whether the indication is respiratory or not (0.04%/1.38%).

Indication for prescription of antimicrobial agents

For 17% of prescriptions of antimicrobial agents for COPD patients, indication was not reported. We followed the following steps to impute the indication based on additional information on patients or the practice level (percentage of all prescriptions for patients):

Step 1: If on the same day a systemic glucocorticosteroid was also prescribed, it was imputed to respiratory indication (2.8%).
Step 2: Indication (in morbidity records) in the week before prescription (3.6%).
Step 3: Indication (in morbidity records) in the two weeks before prescription (1.7%).
Step 4: If a patient is always prescribed the antibiotics (ATC-level) for the same indications, this indication is used for all these prescriptions (3.5%).
Step 5: In case an antibiotic (ATC level) is in more than 70% of the cases prescribed for respiratory indication or other indication, this indication (respiratory or not) is used for all these prescriptions (3.9%).
Step 6: In case an antibiotic (ATC level) is in more than 70% of the cases in a practice prescribed for respiratory indication or other indication, this indication (respiratory or not) is used for all these prescriptions in the practice (0.6%).
Step 7: Manually looking into all data of the patients and deciding whether the indication is respiratory or not (0.9%).

Missing defined daily dose (DDD) of the prescriptions of short-acting bronchodilators

For almost every prescription record (99%) in the dataset, a product code is assigned. There are four different product codes in the dataset (GPK, PRK, HPK and ATK). The ATK code represents the article number of the specific package, and of ATK codes the DDD is known (in another national database). For the other codes, it could be that more packages with different DDDs per package are found for one product code. For these product codes, it is not always certain what the exact DDD per package is. For 13% of the prescriptions for asthma patients and 19% of the prescriptions of COPD patients in our study, we did not find a unique combination between the product code and the DDD per prescription package. We followed the following steps to impute the DDD based on additional information (percentage of all prescriptions for patients):

Step 1: If a patient is always prescribed the same DDD (ATC level), then this DDD is used (7.3%/5.9%).
Step 2: Median DDD known for the product code indicating several prescription packages (which were not on a 1:1 base) (10.1%/5.2%).
Step 3: If, in step 1, missing DDDs are always imputed in the same value, then this value is imputed to DDD (0.47%/0.6%).
Step 4: Repetition of step 1 (0.1%/0.3%).
Step 5: In patient with no prescription with a DDD, the average DDD per medication type (ATC-level) is used (0.15%/0.19%).
Step 6: Imputation of the DDD of the previous prescription or, if not available, the DDD of the next prescription (ATC-level) (0.5%/0.4%).

Appendix C. Forest plot association between up to12,499 chickens in a 500 m radius and exacerbations in COPD patients.

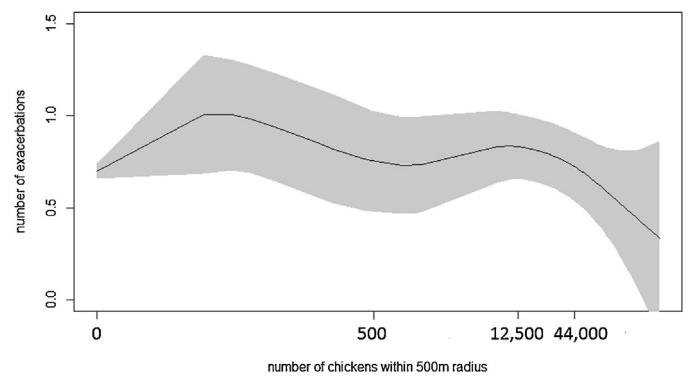

Fig. AIII.1. Forest plot of association between exposure to up to12,499 chickens in a 500 m radius from home address and exacerbations in COPD patients for general practices, with at least five COPD patients exposed. Test for heterogeneity. $p = 0.588$.

Appendix D. Forest plot association between up to 12,499 chickens in a 500 m radius and exacerbations in COPD patients.

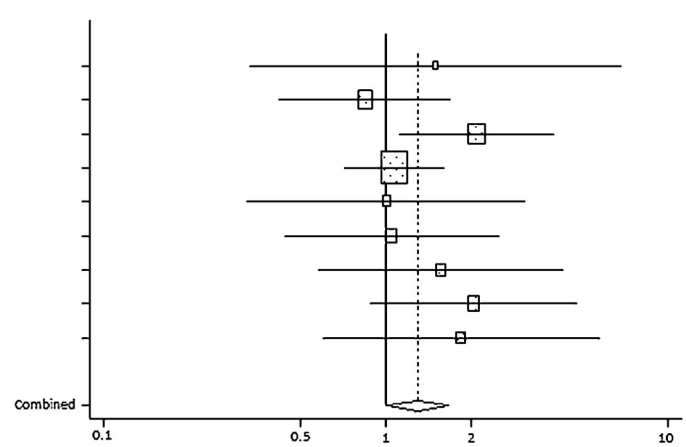

Fig. AIV.1. Forest plot of association between exposure to up to 12,499 chickens in a 500 m radius from home address and exacerbations in COPD patients for general practices, with at least five COPD patients exposed. Test for heterogeneity. $p = 0.588$.

Appendix E. Results of the sensitivity analyses.

Table E.1
Sensitivity analyses of association between livestock farm exposures and exacerbations in COPD patients.

Exposure	Only patients with no imputed data (2078 patient-years) IRR (95%CI)	Definition of exacerbations with systemic glucocorticosteroid and antimicrobial agents (2456 patient-years) IRR (95%CI)	Patients with a known allergy (402 patient-years) IRR (95%CI)	Patients without a known allergy (2054 patient-years) IRR (95%CI)	FEV1/FVC < 0.7 (683 patient-years) IRR (95%CI)
Distance to nearest					
Farm[#]	1.09 (0.97–1.24)	1.02 (0.91–1.15)	1.17 (0.94–1.45)	1.01 (0.90–1.13)	1.11 (0.92–1.33)
Farm with swine[#]	0.98 (0.86–1.11)	1.05 (0.93–1.18)	1.09 (0.88–1.36)	0.98 (0.87–1.11)	0.84 (0.69–1.01)
Farm with poultry[#]	0.97 (0.88–1.07)	0.98 (0.89–1.07)	0.93 (0.78–1.12)	0.99 (0.90–1.08)	0.99 (0.86–1.13)
One or more farms within 100 m	0.69 (0.40–1.19)	1.03 (0.67–1.60)	0.39 (0.15–1.05)	1.07 (0.69–1.66)	0.93 (0.49–1.77)
One or more farms within 500 m	0.93 (0.79–1.10)	0.98 (0.83–1.15)	0.80 (0.58–1.10)	1.01 (0.86–1.18)	0.80 (0.62–1.04)
Distance to nearest farm					
Swine (ref = 1000 m or further)					
<250 m	0.94 (0.57–1.52)	0.79 (0.49–1.26)		0.92 (0.59–1.46)	
250–499 m	0.86 (0.62–1.20)	**0.72 (0.53–0.99)**		0.89 (0.66–1.21)	
500–999 m	0.85 (0.68–1.07)	0.84 (0.68–1.04)		0.93 (0.75–1.14)	
Poultry (ref = 1000 m or further)					
<250 m	1.08 (0.67–1.74)	0.94 (0.61–1.45)		0.94 (0.61–1.45)	
250–499 m	1.21 (0.86–1.71)	1.33 (0.96–1.84)		1.34 (0.98–1.84)	
500–999 m	1.02 (0.84–1.23)	0.99 (0.83–1.20)		0.98 (0.82–1.17)	
Presence of livestock within 500 m					
Swine (ref = 0)					
<749	0.99 (0.72–1.35)	0.88 (0.66–1.19)	–	0.94 (0.70–1.26)	–
750–2249	1.12 (0.79–1.59)	0.96 (0.68–1.37)	–	1.09 (0.79–1.50)	–
2250–23,810	1.12 (0.78–1.59)	0.90 (0.63–1.29)	–	0.98 (0.69–1.38)	–
Poultry (ref = 0)					
<12,499	1.31 (0.93–1.83)	**1.38 (1.01–1.88)**	–	**1.41 (1.04–1.92)**	–
12,500–364,940	0.88 (0.59–1.30)	0.81 (0.56–1.19)	–	0.84 (0.58–1.23)	–

Incidence rate ratios (IRRs) and 95%CI were adjusted for age, gender, maintenance treatment with ICS, depression, ischaemic heart disease and the presence of other types of livestock animals
Bold font: significant at p = 0.05 level.
[#] IRR and 95%CI for an IQR increase in log-transformed exposure. IQR for ln(distance farm, m) for COPD patients = 0.88, corresponding to a 2.42-fold increase ($\exp^{0.88}$) for non-transformed values, IQR for ln(distance farm with swine, m) for COPD patients = 0.59, corresponding to a 1.81-fold increase ($\exp^{0.59}$) for non-transformed values, and IQR for ln(distance farm with poultry, m) for COPD patients = 0.55, corresponding to a 1.73-fold increase ($\exp^{0.55}$) for non-transformed values.

Table E.2
Sensitivity analyses of association between livestock farm exposures and exacerbations in asthma patients.

Exposure	Only patients with no imputed data (7993 patient-years) IRR (95%CI)	Patients with a known allergy (3490 patient-years) IRR (95%CI)	Patients without a known allergy (4897 patient-years) IRR (95%CI)
Distance to nearest			
farm[#]	1.06 (0.96–1.17)	1.01 (0.90–1.13)	1.08 (0.94–1.23)
farm with swine[#]	0.97 (0.88–1.07)	0.96 (0.85–1.08)	0.99 (0.87–1.13)
farm with poultry[#]	0.95 (0.87–1.03)	0.98 (0.88–1.09)	**0.90 (0.80–1.00)**
One or more farms within 100 m	1.11 (0.77–1.62)	1.12 (0.71–1.78)	1.01 (0.60–1.70)
One or more farms within 500 m	0.90 (0.78–1.05)	0.87 (0.72–1.04)	0.97 (0.79–1.19)
Distance to nearest farm			
Swine (ref = 1000 m or further)			
<250 m	1.04 (0.73–1.49)	1.23 (0.79–1.90)	0.72 (0.44–1.18)
250–499 m	0.91 (0.70–1.18)	1.09 (0.79–1.50)	**0.69 (0.49–0.97)**
500–999 m	0.91 (0.74–1.12)	1.11 (0.87–1.42)	**0.75 (0.57–0.99)**
Poultry (ref = 1000 m or further)			
<250 m	1.04 (0.69–1.57)	0.88 (0.51–1.52)	1.36 (0.82–2.27)
250–499 m	1.01 (0.76–1.34)	0.83 (0.59–1.17)	1.39 (0.95–2.03)
500–999 m	1.15 (0.99–1.35)	1.09 (0.90–1.33)	1.19 (0.97–1.45)
Presence of livestock within 500 m			
Swine (ref = 0)			
<749	0.97 (0.76–1.24)	1.01 (0.74–1.39)	0.96 (0.70–1.31)
750–2249	0.95 (0.75–1.21)	0.90 (0.66–1.22)	0.86 (0.61–1.20)
2250 – 23,810	0.92 (0.70–1.21)	0.97 (0.69–1.38)	0.81 (0.55–1.18)
Poultry (ref = 0)			
<12,499	1.09 (0.81–1.46)	1.11 (0.79–1.56)	1.21 (0.81–1.79)
12,500–364,940	0.87 (0.63–1.21)	**0.54 (0.34–0.86)**	1.19 (0.79–1.79)

Incidence rate ratios (IRRs) and 95%CI were adjusted for age, gender, maintenance treatment with ICS, depression, ischaemic heart disease and the presence of other types of livestock animals.
Bold font: significant at p = 0.05 level.
[#] IRR and 95%CI for an IQR increase in log-transformed exposure. IQR for ln(distance farm, m) for asthma patients = 0.83, corresponding to a 2.29-fold increase ($\exp^{0.83}$) for non-transformed values, IQR for ln(distance farm with swine, m) for asthma patients = 0.64, corresponding to a 1.89-fold increase ($\exp^{0.64}$) for non-transformed values, and IQR for ln(distance farm with poultry, m) for asthma patients = 0.60, corresponding to a 1.83-fold increase ($\exp^{0.60}$) for non-transformed values.

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