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Comorbidity and coexisting symptoms and infections presented in general practice by COPD patients: Does livestock density in the residential environment play a role?

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ABSTRACT

Objectives: Patients with chronic obstructive pulmonary disease (COPD) constitute a potentially susceptible group towards environmental exposures such as livestock farm emissions, given their compromised respiratory health status. The primary aim of this study was to examine the association between livestock exposure and comorbidities and coexisting symptoms and infections in COPD patients.

Methods: Data were collected from 1828 COPD patients (without co-occurring asthma) registered in 23 general practices and living in a rural area with a high livestock density. Prevalence of comorbid diseases/disorders and coexisting symptoms/infections were based on electronic health records from the year 2012. Various indicators of individual exposure to livestock were estimated based on residential addresses, using a geographic information system.

Results: At least one comorbid disorder was present in 69% of the COPD patients (especially cardiac disorders and depression, while 49% had at least one coexisting symptom and/or infection (especially upper respiratory tract infections, respiratory symptoms and pneumonia). Half of the COPD-patients resided less than 500 m of the nearest farm. Some positive as well as inverse associations were found between the examined outcomes and exposure estimates, although not consistent.

Conclusions: Despite the high prevalence of coexisting chronic and acute conditions presented in primary care by in COPD patients, this investigation found no convincing evidence for an association with livestock exposure estimates. There is a need for a replication of the present findings in studies with a longitudinal design, on different groups of potentially susceptible patients. Future research should also elucidate the biological plausibility of possible protective effects of exposure.

1. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a complex, multifactorial condition characterized by progressive airflow limitation (Agusti *et al*., 2011a ; Barnes and Celli, 2009). Cigarette smoking, air pollution, occupational exposures and viral infections have been identified as important risk factors (Roth, 2008). COPD has an adverse impact on all aspects of health-related quality of life (van Manen et al., 2003). It is a leading hospitalization cause in adults, especially of older age (Mannino, 2002) and the associated mortality is expected to increase dramatically in the years to come (Mathers and Loncar, 2006).

Co-morbid diseases such as hypertension, cardiovascular conditions and depression and coexisting symptoms or infections such as sleep problems and respiratory infections are highly prevalent among COPD patients (Van Ede *et al*., 1999; Wongsurakiat *et al*., 2004; Rodríguez-Roisin and Soriano, 2008; Agusti *et al*., 2011b ; Miłkowska-Dymanowska *et al*., 2015) and have a major contribution to the severity of the disease (Van Manen *et al*., 2001 ; Vestbo *et al*., 2013). Coexisting conditions can occur independently, or as a direct or indirect consequence of COPD (Agusti *et al*., 2003 ; Houghton, 2013). A large body of evidence suggests that comorbid disorders and coexisting symptoms constitute important determinants of functional impairment, prolonged hospitalization, unfavorable prognosis and increased healthcare costs in patients with COPD (McDaid et al., 2013; Franssen and Rochester, 2014).

Respiratory diseases in general have been associated with exposure to environmental pollutants such as fine airborne particles (PM10) and endotoxins (MacNee and Donaldson, 2003 ; Strak *et al*., 2012). Livestock farms are a relevant source of these components, the increasing expansion of which, has amplified concerns regarding potential health effects especially among people living in their vicinity (Heederik and Ijzermans, 2011; Smit *et al*., 2012 ; Hooiveld *et al*., 2015). Recent evidence highlighting pathologic features of vulnerable groups, in particular patients with COPD, seem to be more conclusive. Harting et al. (2010) demonstrated that whole blood cells of COPD patients were more prone to release markers of systemic inflammation upon stimulation with swine dust extract compared to their healthy counterparts. Borlée et al. (2015) showed that COPD patients exposed to livestock farms reported more respiratory symptoms. Furthermore, it was recently shown that living in an area with a high livestock density may be a risk factor for exacerbations in COPD patients (Van Dijk et al., 2016). However, epidemiological research on respiratory susceptible groups exposed to livestock remains scarce.

To further elucidate possible environmental determinants of morbidity and symptomatology in patients with respiratory diseases, the present study focused on patients with COPD living in an area with a high density of livestock farms. Using a large and reliable primary care database, the primary aims were to: 1) determine the prevalence of comorbid diseases/disorders and coexisting symptoms and infections in patients with COPD and 2) explore the association between livestock farm exposures and multiple comorbidities as well as symptoms and infections in this patient group.

2. Methods

2.1. Study design

The present cross-sectional investigation was conducted within the framework of the VGO (Farming and Neighbouring Residents' Health) study (Van Dijk et al., 2016). Health data were based on electronic health records (EHRs) of 23 general practices participating in the NIVEL Primary Care Database (PCD) (Verheij, 2015). Diagnosed (co)morbidity and registered symptoms were coded following the International Classification of Primary Care (ICPC) (Lamberts and Wood, 1987). It is obligatory for Dutch citizens to be registered in one general practice. General practitioners (GPs) are gatekeepers for secondary health care and the population registered in family practice can be used as the denominator in epidemiological studies.

Data were collected from practices located in a rural area with a high density of livestock farms in the Netherlands (eastern part of the province of Noord-Brabant and the northern part of the province of Limburg). About 95% of the sample in the present study were living within 1000 m from an animal feeding operation. Details regarding the design of the study are described elsewhere (Borlée *et al*., 2015 ; Van Dijk *et al*., 2016).

2.2. Study population & health data extraction

For the primary analysis, COPD (ICPC codes: R91 or R95) patients without asthma (R96) were included, aged ≥40 years (n = 1828). Patients with at least three consecutive years of GP-registered data were considered eligible for inclusion. Since the study was focused on neighbouring residents, patients likely living or working on a farm (distance between home address and centroid of livestock farm stables <50 m) were excluded. A previous study in the same area in the Netherlands found that 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 (Van Dijk et al., 2016).

Prevalence rates (estimated for the year 2012) were based on episodes of care and their construction was based on all records with an ICPC code in the EHRs of general practices. ICPC codes are categorized into acute conditions, long lasting reversible conditions and chronic irreversible conditions. For each ICPC category a different symptom-free period is adopted that determines whether two ICPC records belong to the same episode. For acute conditions, a symptom-free period of 8 weeks is defined. This means that an episode of care is "closed" when no similar ICPC code is found within that specific time-frame. For long lasting reversible conditions a symptom-free period of one or two years is used, while no symptom-free period is defined for irreversible conditions (which means that the episodes will not be closed).

Selection of relevant comorbidities and coexisting symptoms and infections (Table 1) was based on the relevant literature (Van Ede *et al*., 1999; Rodríguez-Roisin and Soriano, 2008; Agusti *et al*., 2011b ; Miłkowska-Dymanowska *et al*., 2015).

[TABLE 1]

2.3. Exposure assessment

Individual exposure estimates were available for the year 2012. Information on farm characteristics was extracted from provincial databases of mandatory environmental licenses for keeping livestock ("Bestand Veehouderij Bedrijven" https://bvb.brabant.nl/). These databases contain data on number and type of animals, geographic coordinates of farms and estimated fine dust and ammonia emissions from each farm per year on the basis of farm type and number of animals. For the individual exposure estimates, the residential addresses of the eligible patients were geocoded and distance between home addresses and livestock farms was determined using a geographic information system (ArcGis 9.3.1, Esri, Redlands, CA). Incomplete data on addresses were excluded from the analyses. Based on the approach of recent studies (Smit *et al*., 2014; Borlée *et al*., 2015 ; van Dijk *et al*., 2017) the following exposure variables were considered: 1) distance (in meters) from patient's residency to the nearest farm (binary variables, 50–250 m and 250–500 m versus >500 m as reference category); 2) presence of different farm animals (mink, poultry, pigs, goats and cattle) within 500 m and 1000 m (binary); and 4) inverse-distance weighted fine dust (PM10) and ammonia (NH3) emissions (g*year-1*m-2) from all livestock farms within 500 m and 1000 m (continuous variables). Weighted fine dust and ammonia emissions were log-transformed to reduce skewness and also rescaled using interquartile range (IQR; distance between the 25th and 75th percentiles). The selection of cut-off points was also based on previous studies showing differences in health effects among subjects living in the vicinity of livestock farms (Radon et al., 2007).

2.4. Ethical aspects

The NIVEL PCD complies with the Dutch Data Protection Authority. Data were treated according to national data protection regulations, while medical information and address records were kept separated with the contribution of an Institute (IVZ, Houten, The Netherlands) acting as a "Trusted Third Party". The protocol of the VGO study was approved by the Medical Ethical Committee of the University Medical Centre Utrecht.

2.5. Data analysis

Considering the hierarchical structure of the data, associations between exposure and binary and ordinal outcome variables were investigated by means of multilevel logistic and Poisson regression analyses respectively. A two-level multilevel structure was used, in which the observations were clustered within general practices. Associations were analyzed separately for each exposure variable. Analyses were adjusted for gender and age (including a quadratic term to allow for a potential non-linear trend between age and morbidity). For each investigated association, Odds ratios (OR) or incidence rate ratios (IRR) and 99% confidence intervals (CI) were computed.

A p-value of <0.01 was considered statistically significant, to control for multiple testing. Analyses were carried out using STATA version 13.0 (StataCorp LP, College Station, TX, USA).

3. Results

3.1. Demographic and exposure characteristics

Characteristics of the study sample are presented in Table 1. Patients were more likely to be men and were on average 69 years of age. At least one comorbid disorder was present in 69% of the COPD patients while about 49% of the patients had at least one coexisting symptom/infection. Almost half of the sample lived ≤500 m from an animal farm. Furthermore, patients were frequently living within 500 m of farms with domestic pigs (23.5%) and cattle (34.7%). Corresponding rates were higher within a kilometer (Table 1).

3.2. Exposure–outcome associations

Results of the primary analyses are shown in Table 2, Table 3, Table 4 ; Table 5. Presence within 500 m of domestic pigs was significantly associated with a higher prevalence of rheumatoid arthritis (Table 3). Regarding coexisting symptoms and infections, analyses showed a significant association between ammonia emissions within 500 m and allergic rhinitis (Table 5). No other significant positive exposure-outcome associations were observed.

[TABLE 2][TABLE 3][TABLE 4][TABLE 5]

Analyses also yielded some inverse associations, suggesting potential protective effects of exposure in relation to total comorbidity rates and respiratory symptoms (Table 2, Table 3, Table 4 ; Table 5).

4. Discussion

The current study investigated the association between livestock exposure and comorbidity and coexisting symptoms and infections among COPD patients living in an area with high livestock density. In line with the broader literature on clinical profile of COPD (Rodríguez-Roisin and Soriano, 2008 ; Miłkowska-Dymanowska *et al*., 2015), we found several comorbid and concurrent conditions in patients with COPD within the study period. More specifically, at least one comorbid disorder was diagnosed by the GP in the majrity of the patients, while about half of them visited their GP for at least one coexisting symptom and/or infection. Rheumatoid arthritis was the only comorbid condition significantly associated with livestock exposure, specifically with presence of pigs within 500m. An explanatory mechanism for this association is currently unknown and the limited existing evidence is inconclusive and based mainly on occupational exposures. (Li *et al*., 2008 ; Parks *et al*., 2016). The general lack of associations observed in the present study is in line with the study of van Dijk et al., on patients with COPD (2016). Although that study showed a significantly lower exacerbation rate in control areas, individual exposure estimates were not associated with exacerbations among patients living in a rural area with high livestock density (Van Dijk et al., 2016).
Regarding coexisting symptoms and infections, analyses yielded a statistically significant association between allergic rhinitis and ammonia emissions within 500m, while there also seemed to be a trend for an association with PM10 within 500m. Although evidence on health effects of ammonia on COPD patients living in the vicinity of livestock is scarce, there is indication for adverse effects of ammonia on lung function in respiratory vulnerable subgroups (Loftus et al., 2015). It is also

possible that ammonia is not the primary cause of such effects, but a marker of other pollutants, potentially associated with respiratory infections (Campagna *et al*., 2004 ; Heederik *et al*., 2007; Loftus et al., 2015).
In relation to the rest of the examined symptoms and infections no positive associations were found. This is in contrast with recent findings that self-reported symptoms such as wheezing were associated with estimates of livestock farm exposures in a sample of COPD patients (Borlée et al., 2015). This difference might be at least partly explained by the fact that we used registry-based data instead of a questionnaire. One might argue that symptoms presented to a GP are (perceived to be) more severe and/or may last longer. When statistical significance was set at the 0.05 level several more positive significant associations were found between exposure and outcomes such as dizziness/vertigo, sleep problems and memory/concentration problems (data not shown). However, these analyses do not take into account multiple testing and thus the possibility of false positive associations is high. Future studies should investigate whether the effects of livestock exposure on morbidity and symptomatic reactions are more pronounced among respiratory patients with other clinical phenotypes such as the Asthma and COPD Overlap Syndrome (ACOS) (Gibson and Simpson, 2009). A growing body of evidence suggests that ACOS patients have higher exacerbation rates, more respiratory symptoms and higher disease burden and can have different treatment responses compared to patients with COPD alone (Hardin *et al*., 2011 ; Barrecheguren *et al*., 2015).
In the present study, some inverse associations were also found, suggesting potential protective effects of livestock exposure. These were observed in relation to total comorbidity rates and respiratory symptoms. Although such associations are in principle counterintuitive, especially when it comes to susceptible groups, they have been documented in other recent studies as well (Smit *et al*., 2014; Borlée *et al*., 2015 ; Van Dijk *et al*., 2016). Based on the so-called "hygiene hypothesis', people living in rural areas and being exposed to livestock at an early age are less prone to allergies related to the respiratory system, because of the role of infections and microbial products such as endotoxins in immunizing against allergic and autoimmune diseases (Eder and von Mutius, 2004; Von Mutius and Radon, 2008 ; Frei *et al*., 2014). An alternative explanation might be that people living nearby livestock farms are generally healthier and/or represent a population group with different health and illness behavior patterns.

4.1. Strengths and limitations

Major strengths of the present study are the use of clinically defined outcome variables from general practices, based on a reliable registration system (Okkes et al., 2012), the objective assessment of exposure based on various different estimates and the large sample of patients. Exposure misclassification is expected to be limited since information on livestock farm licenses and health data correspond to the same year.
Among the limitations is the cross-sectional design which does not allow to establish temporal precedence of the examined associations and the fact that analyses were not adjusted for potential confounders such as smoking habits and socioeconomic status. Regarding the latter, however, it has been previously shown that controlling for indicators of socioeconomic status does not change the associations between

livestock exposure and health effects (Smit et al., 2014). Finally, despite that we controlled for multiple testing, the possibility of some false-positive associations cannot be entirely ruled out.

5. Conclusions

Despite the high prevalence of comorbid disorders and coexisting symptoms and infections in patients with COPD, this study showed no convincing evidence for an association between livestock exposure and the examined health outcomes. Considering the frequently observed protective effects in the literature and given between-study heterogeneity, evidence on the effects of non-occupational livestock exposure on health remains inconclusive. Furthermore, it is still unclear which relevant exposure components underlie the health effects and therefore the employment of direct measurements might be necessary. More research is needed to understand these effects in various potentially susceptible groups and determine whether livestock density can be a factor that can influence the natural course of respiratory conditions.

Conflicts of interest

None.

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TABLES AND FIGURES

Table 1. Characteristics of COPD patients (n = 1828) living in an area with high density of livestock farms.

Characteristic	
Demographics	
Female gender (%)	43.8
Mean age in years (SD)	69.2 (11.0)
Exposure	
Distance to the nearest farm (%)	
<250m	14.5
250–500 m	34.8
Presence of farm animals within 500 m (%)	

Characteristic	
Mink	1.0
Poultry	9.6
Pigs	23.5
Goats	1.3
Cattle	34.7
Presence of farm animals within 1000 m (%)	
Mink	4.4
Poultry	47.4
Pigs	75.4
Goats	9.3
Cattle	83.5
IQR weighted fine dust emission[ǂ]	
Within 500 m	0.0001–0.31
Within 1000 m	0.1–2.8
IQR weighted ammonia (NH_3) emission[ǂ]	
Within 500m	0.0001–0.01
Within 1000m	0.004–0.05
Comorbidity (%) & corresponding ICPC codes	
GERD (D84)	5.8
Heart failure (K77)	9.0
Osteoporosis (L95)	6.7
Diabetes mellitus (T90)	16.3
Hyperlipidemia (T93)	8.8
Anxiety (P01, P74)	5.0
Depression (P03, P76)	8.8
Coronary heart disease (K74–K76)	17.4
Lung cancer (R84–R85)	2.3
Hypertension (K86)	31.0
Rheumatoid arthritis (L88)	2.6
Atherosclerosis (K91)	8.3
Total prevalence	68.5
Mean number comorbidities (SD)[a]	1.2 (1.1)
Coexisting symptoms/infections (%) & corresponding ICPC codes	
Pneumonia (R81)	9.2
Sleep problems (P06)	5.5
Memory/Concentration (P20)	3.7
Upper respiratory tract infections (R74–R78)	18.6
Respiratory symptoms (R02, R03, R05)	19.9

Characteristic	
Dizziness/Vertigo (N17)	3.3
Anemia (B80–B82)	6.5
Allergic rhinitis/Hay fever (R97)	3.8
Total prevalence	48.7
Mean number coexisting symptoms/infections (SD)[a]	0.7 (0.87)

Abbreviations: SD, Standard deviation; IQR, Interquartile range; ICPC, International classification of primary care; GERD, Gastro-esophageal reflux disease.

[a] Count variable, expressed in mean score.
ǂ g*year-1*m-2.

Table 2. Association (OR, 99% CI)[a] between the presence of a farm in the home vicinity and primary outcomes among COPD patients (significant associations in bold).

Comorbidity	**<250 m[b]**	**250–500 m[b]**
GERD	0.46 (0.18–1.2)	0.73 (0.4–1.32)
Heart failure	0.87 (0.42–1.77)	0.86 (0.51–1.45)
Osteoporosis	0.79 (0.36–1.72)	0.77 (0.43–1.37)
Diabetes mellitus	0.94 (0.57–1.55)	0.77 (0.53–1.12)
Hyperlipidemia	1.04 (0.55–2.0)	1.32 (0.81–2.16)
Anxiety	0.69 (0.28–1.68)	0.69 (0.36–1.32)
Depression	0.76 (0.39–1.48)	0.85 (0.52–1.36)
Coronary heart disease	0.64 (0.37–1.1)	0.88 (0.61–1.27)
Lung cancer	0.82 (0.23–2.95)	1.14 (0.48–2.68)
Hypertension	0.89 (0.59–1.34)	1.02 (0.76–1.38)
Rheumatoid arthritis	0.96 (0.29–3.13)	1.48 (0.67–3.3)
Atherosclerosis	0.53 (0.21–1.3)	0.7 (0.38–1.29)
Total prevalence	**0.64 (0.44–0.95)***	0.91 (0.68–1.23)
Number [c]	**0.82 (0.69–0.98)***	0.91 (0.8–1.03)
Coexisting symptoms & infections		
Pneumonia	1.26 (0.68–2.33)	1.39 (0.87–2.21)
Sleep problems	0.85 (0.36–1.99)	1.01 (0.55–1.85)
Memory/Concentration problems	1.22 (0.47–3.2)	1.49 (0.74–3.02)
Upper respiratory tract infections	0.67 (0.41–1.1)	0.81 (0.57–1.15)
Respiratory symptoms	**0.59 (0.36–0.98)***	0.76 (0.54–1.08)

Comorbidity	<250 m[b]	250–500 m[b]
Dizziness/Vertigo	0.62 (0.17–2.17)	1.59 (0.78–3.26)
Anemia	0.69 (0.3–1.61)	0.96 (0.55–1.67)
Allergic rhinitis/Hay fever	1.48 (0.63–3.48)	1.37 (0.7–2.69)
Total prevalence	0.7 (0.48–1.01)	0.93 (0.71–1.22)
Number[c]	0.81 (0.64–1.02)	0.98 (0.84–1.16)

Abbreviations: ORs, Odds ratios; CI, Confidence intervals; COPD, Chronic Obstructive Pulmonary Disease; GERD, Gastro-oesophageal reflux disease. Note.*p < 0.01.

[a] Adjusted for age and gender.
[b] versus >500 m (reference category).
[c] Count variables, incidence rate ratios (IRR) are provided.

Table 3. Association (OR, 99% CI)[a] between presence of farm animals within 500 m and primary outcomes among COPD patients (significant associations in bold).

Presence of farm animals within 500 m (yes/no)					
Comorbidity	**Mink**	**Poultry**	**Pigs**	**Goats**	**Cattle**
GERD	i.n.c.	0.32 (0.08–1.26)	0.88 (0.45–1.71)	0.52 (0.03–7.83)	0.69 (0.38–1.29)
Heart failure	1.27 (0.78–20.8)	0.69 (0.29–1.67)	0.9 (0.5–1.61)	1.61 (0.27–9.51)	1.14 (0.69–1.92)
Osteoporosis	i.n.c.	0.51 (0.18–1.49)	1.1 (0.6–2.02)	0.64 (0.04–9.93)	0.88 (0.5–1.53)
Diabetes mellitus	i.n.c.	0.83 (0.45–1.54)	1.01 (0.67–1.51)	1.22 (0.28–5.39)	0.91 (0.63–1.33)
Hyperlipidemia	i.n.c.	1.00 (0.49–2.06)	1.38 (0.82–2.31)	0.5 (0.07–3.65)	1.15 (0.70–1.87)
Anxiety	i.n.c.	0.5 (0.15–1.7)	0.63 (0.29–1.36)	i.n.c.	0.72 (0.37–1.38)
Depression	i.n.c.	0.44 (0.17–1.17)	0.96 (0.57–1.61)	0.54 (0.04–7.78)	0.86–0.54–1.38)
Coronary heart disease	0.95 (0.17–5.32)	1.17 (0.67–2.04)	0.74 (0.48–1.13)	0.36 (0.05–2.56)	0.98 (0.68–1.42)
Lung cancer	i.n.c.	0.75 (0.16–3.58)	1.17 (0.47–2.93)	3.78 (0.53–26.8)	1.25 (0.55–2.84)
Hypertension	0.57 (0.1–3.09)	0.88 (0.55–1.41)	0.95 (0.68–1.32)	1.91 (0.61–5.97)	1.05 (0.78–1.41)

Presence of farm animals within 500 m (yes/no)					
Comorbidity	**Mink**	**Poultry**	**Pigs**	**Goats**	**Cattle**
Rheumatoid arthritis	2.54 (0.16–39.8)	0.41 (0.06–2.72)	**2.21 (1.01–4.87)***	i.n.c.	1.11 (0.5–2.48)
Atherosclerosis	0.99 (0.15–6.62)	0.97 (0.38–2.48)	0.86 (0.44–1.68)	0.87 (0.08–9.68)	0.93 (0.51–1.7)
Total prevalence	0.26 (0.07–1.03)	**0.54 (0.35–0.84)****	0.9 (0.65–1.24)	1.21 (0.33–4.38)	0.99 (0.74–1.32)
Number[b]	0.51 (0.23–1.14)	0.83 (0.68–1.02)	0.97 (0.85–1.12)	0.97 (0.59–1.6)	0.97 (0.86–1.1)
Coexisting symptoms & infections					
Pneumonia	0.64 (0.04–9.72)	0.9 (0.43–1.89)	0.98 (0.58–1.64)	1.69 (0.37–7.61)	1.24 (0.78–1.97)
Sleep problems	1.36 (0.09–21.1)	1.05 (0.42–2.61)	0.68 (0.33–1.41)	2.12 (0.29–15.6)	1.09 (0.6–1.99)
Memory/Concentration problems	3.05 (0.19–48.9)	1.39 (0.5–3.89)	1.44 (0.69–3.02)	1.01 (0.06–15.6)	1.23 (0.61–2.48)
Upper respiratory tract infections	1.55 (0.34–7.08)	0.75 (0.42–1.33)	0.68 (0.45–1.01)	1.3 (0.34–4.98)	0.79 (0.56–1.13)
Respiratory symptoms	0.62 (0.08–4.54)	0.69 (0.39–1.22)	0.79 (0.54–1.17)	0.43 (0.06–3.02)	0.72 (0.5–1.02)
Dizziness/Vertigo	5.12 (0.62–42.1)	0.89 (0.26–3.07)	1.28 (0.59–2.79)	i.n.c.	1.04 (0.5–2.16)
Anemia	3.26 (0.42–24.9)	1.12 (0.48–2.58)	0.64 (0.32–1.26)	0.74 (0.05–11.1)	0.83 (0.46–1.5)
Allergic rhinitis/Hay fever	1.41 (0.08–22.8)	1.76 (0.72–4.26)	1.77 (0.89–3.5)	1.25 (0.08–18.4)	1.19 (0.61–2.32)
Total prevalence	1.05 (0.29–3.74)	0.86 (0.56–1.32)	0.81 (0.6–1.09)	1.05 (0.34–3.22)	0.86 (0.65–1.13)
Number[b]	1.32 (0.65–2.7)	0.91 (0.71–1.18)	0.88 (0.73–1.05)	1.04 (0.54–2.02)	0.92 (0.78–1.08)

Abbreviations: ORs, Odds ratios; CI, Confidence intervals; COPD, Chronic Obstructive Pulmonary Disease; GERD, Gastro-esophageal reflux disease; i.n.c, Insufficient number of cases. Note. *p < 0.01; **p < 0.001.

[a] Adjusted for age and gender.
[b] Count variables, incidence rate ratios (IRR) are provided.

Table 4. Association (OR, 99% CI)[a] between presence of farm animals within 1000 m and primary outcomes among COPD patients.

Presence of farm animals within 1000 m (yes/no)					
Comorbidity	**Mink**	**Poultry**	**Pigs**	**Goats**	**Cattle**
GERD	1.97 (0.54–7.16)	0.69 (0.38–1.23)	1.59 (0.78–3.23)	1.08 (0.4–2.88)	1.33 (0.59–2.98)
Heart failure	0.94 (0.27–3.32)	0.99 (0.61–1.61)	0.75 (0.44–1.29)	0.72 (0.29–1.76)	1.4 (0.69–2.82)
Osteoporosis	0.76 (0.18–3.11)	0.95 (0.56–1.62)	1.24 (0.65–2.4)	1.00 (0.4–2.52)	1.23 (0.56–2.68)
Diabetes mellitus	0.81 (0.31–2.11)	0.96 (0.67–1.37)	1.02 (0.68–1.53)	0.64 (0.32–1.3)	0.99 (0.62–1.59)
Hyperlipidemia	1.46 (0.44–4.86)	0.85 (0.52–1.4)	0.86 (0.49–1.53)	1.45 (0.67–3.14)	1.42 (0.66–3.04)
Anxiety	0.95 (0.18–5.08)	1.12 (0.62–2.02)	0.96 (0.49–1.88)	0.44 (0.11–1.78)	0.99 (0.45–2.16)
Depression	0.34 (0.69–1.71)	0.78 (0.5–1.22)	0.69 (0.43–1.12)	0.63 (0.26–1.57)	1.11 (0.6–2.03)
Coronary heart disease	0.87 (0.35–2.13)	1.27 (0.89–1.8)	0.97 (0.65–1.46)	0.85 (0.45–1.61)	1.05 (0.64–1.72)
Lung cancer	2.31 (0.57–9.32)	1.00 (0.45–2.25)	0.52 (0.22–1.27)	0.73 (0.15–3.48)	0.71 (0.26–1.91)
Hypertension	0.93 (0.44–1.97)	0.84 (0.63–1.13)	1.12 (0.8–1.56)	1.26 (0.76–2.09)	1.00 (0.67–1.5)
Rheumatoid arthritis	0.94 (0.13–6.74)	0.95 (0.43–2.07)	1.39 (0.52–3.73)	1.08 (0.3–3.94)	2.17 (0.55–8.6)
Atherosclerosis	1.00 (0.33–3.03)	1.25 (0.73-2.15)	0.75 (0.39–1.44)	0.71 (0.15–3.45)	0.62 (0.26–1.51)
Total prevalence	1.31 (0.66–2.63)	0.82 (0.62–1.09)	0.91 (0.66–1.26)	1.07 (0.65–1.76)	1.17 (0.81–1.68)
Number[b]	0.94 (0.69–1.28)	0.97 (0.86–1.09)	0.97 (0.85–1.12)	0.94 (0.75–1.18)	1.07 (0.9–1.27)
Coexisting symptoms & infections					
Pneumonia	1.29 (0.45–3.69)	1.13 (0.72–1.8)	1.18 (0.69–2.04)	1.16 (0.55–2.48)	1.08 (0.58–2.02)
Sleep problems	1.21 (0.31–4.71)	1.23 (0.7–2.17)	0.88 (0.47–1.66)	0.56 (0.17–1.86)	2.22 (0.85–5.81)
Memory/Concentration	1.87 (0.41–	0.95 (0.48–	0.91 (0.42–	0.42 (0.09–	1.71 (0.58–

	Presence of farm animals within 1000 m (yes/no)				
Comorbidity	**Mink**	**Poultry**	**Pigs**	**Goats**	**Cattle**
problems	8.51)	1.87)	1.99)	1.89)	5.05)
Upper respiratory tract infections	1.29 (0.56–2.95)	0.94 (0.67–1.31)	0.87 (0.6–1.27)	0.9 (0.49–1.62)	1.18 (0.74–1.86)
Respiratory symptoms	0.5 (0.18–1.36)	0.87 (0.62–1.21)	1.04 (0.71–1.52)	0.53 (0.27–1.04)	1.00 (0.64–1.55)
Dizziness/Vertigo	2.69 (0.78–9.35)	1.02 (0.51–2.07)	1.08 (0.47–2.46)	0.47 (0.09–2.31)	1.04 (0.38–2.85)
Anemia	1.55 (0.45–5.4)	0.82 (0.49–1.38)	0.82 (0.46–1.47)	0.68 (0.24–1.93)	0.82 (0.41–1.64)
Allergic rhinitis/Hay fever	0.18 (0.01–3.02)	1.4 (0.73–2.68)	1.27 (0.57–2.85)	0.71 (0.2–2.57)	1.81 (0.62–5.26)
Total prevalence	0.93 (0.48–1.8)	0.95 (0.73–1.24)	0.88 (0.65–1.19)	0.72 (0.45–1.17)	1.26 (0.88–1.81)
Number[b]	1.03 (0.69–1.54)	0.97 (0.83–1.14)	0.98 (0.82–1.17)	0.74 (0.54–1.00)	1.13 (0.91–1.4)

Abbreviations: ORs, Odds ratios; CI, Confidence intervals; COPD, Chronic Obstructive Pulmonary Disease; GERD, Gastro-esophageal reflux disease.

[a] Adjusted for age and gender.
[b] Count variables, incidence rate ratios (IRR) are provided.

Table 5. Association (OR, 99% CI)[a] between fine dust and ammonia emissions from livestock farms and primary outcomes among COPD patients (significant associations in bold).

	Modeled emissions from farms			
Comorbidity	**Fine dust (PM10) emission**		**Ammonia (NH3) emission**	
	Within 500 m	**Within 1000 m**	**Within 500 m**	**Within 1000 m**
GERD	0.6 (0.35–1.03)	1.03 (0.76–1.4)	0.62 (0.36–1.05)	0.95 (0.66–1.36)
Heart failure	0.86 (0.55–1.32)	0.92 (0.71–1.18)	0.9 (0.58–1.38)	0.92 (0.68–1.24)
Osteoporosis	0.85 (0.52–	1.03 (0.77–	0.85 (0.53–	1.04 (0.73–

	Modeled emissions from farms			
Comorbidity	**Fine dust (PM10) emission**		**Ammonia (NH3) emission**	
	Within 500 m	**Within 1000 m**	**Within 500 m**	**Within 1000 m**
	1.37)	1.38)	1.37)	1.48)
Diabetes mellitus	0.91 (0.67–1.25)	0.96 (0.8–1.16)	0.89 (0.65–1.21)	0.91 (0.73–1.13)
Hyperlipidemia	1.22 (0.81–1.84)	1.01 (0.77–1.34)	1.2 (0.8–1.79)	0.97 (0.69–1.35)
Anxiety	0.71 (0.41–1.23)	0.95 (0.7–1.29)	0.68 (0.39–1.19)	0.87 (0.6–1.25)
Depression	0.87 (0.58–1.29)	0.9 (0.72–1.12)	0.89 (0.6–1.32)	0.88 (0.67–1.16)
Coronary heart disease	0.84 (0.61–1.15)	0.95 (0.79–1.14)	0.81 (0.59–1.1)	0.9 (0.72–1.12)
Lung cancer	1.04 (0.51–2.14)	0.83 (0.57–1.2)	1.09 (0.54–2.2)	0.85 (0.53–1.36)
Hypertension	0.93 (0.72–1.19)	1.01 (0.87–1.18)	0.93 (0.73–1.2)	1.00 (0.83–1.21)
Rheumatoid arthritis	1.4 (0.72–2.7)	1.34 (0.84–2.14)	1.36 (0.71–2.62)	1.35 (0.8–2.26)
Atherosclerosis	0.78 (0.47–1.27)	0.87 (0.64–1.18)	0.73 (0.45–1.21)	0.84 (0.56–1.25)
Total prevalence	0.84 (0.65–1.07)	0.93 (0.8–1.08)	0.85 (0.66–1.08)	0.92 (0.76–1.1)
Number[b]	0.91 (0.82–1.01)	0.98 (0.92–1.04)	0.91 (0.82–1.01)	0.96 (0.88–1.03)
Coexisting symptoms & infections				
Pneumonia	1.14 (0.77–1.68)	1.05 (0.82–1.35)	1.13 (0.77–1.66)	1.14 (0.85–1.54)
Sleep problems	0.92 (0.55–1.54)	0.99 (0.73–1.34)	1.00 (0.6–1.66)	0.99 (0.69–1.42)
Memory/Concentration problems	1.45 (0.82–2.58)	1.09 (0.75–1.58)	1.42 (0.81–2.5)	1.23 (0.79–1.92)
Upper respiratory tract infections	0.79 (0.59–1.06)	0.95 (0.8–1.13)	0.78 (0.58–1.05)	0.91 (0.74–1.13)
Respiratory symptoms	**0.73 (0.54–0.98)***	0.91 (0.76–1.07)	0.71 (0.53–0.96)	0.87 (0.7–1.07)

	Modeled emissions from farms			
Comorbidity	**Fine dust (PM10) emission**		**Ammonia (NH3) emission**	
	Within 500 m	**Within 1000 m**	**Within 500 m**	**Within 1000 m**
Dizziness/Vertigo	1.26 (0.69–2.32)	1.32 (0.87–2.01)	1.22 (0.67–2.24)	1.37 (0.85–2.19)
Anemia	0.86 (0.53–1.38)	0.83 (0.64–1.07)	0.83 (0.51–1.33)	0.77 (0.57–1.05)
Allergic rhinitis/Hay fever	1.72 (1.00–2.97)	1.33 (0.9–1.97)	**1.73 (1.01–2.96)***	1.42 (0.91–2.22)
Total prevalence	0.87 (0.69–1.1)	0.98 (0.85–1.12)	0.87 (0.69–1.09)	0.97 (0.82–1.15)
Number[b]	0.94 (0.82–1.07)	0.98 (0.9–1.07)	0.93 (0.81–1.07)	0.98 (0.88–1.08)

Abbreviations: ORs, Odds ratios; CI, Confidence intervals; COPD, Chronic Obstructive Pulmonary Disease; GERD, Gastro-esophageal reflux disease. Note.*p < 0.01.

[a]Adjusted for age and gender; OR (99% CI) for an interquartile range (IQR) increase in log-transformed exposure. IQR for ln(fine dust within 500m) = 8.02, IQR for ln(fine dust within 1000m) = 3.33, IQR for ln (ammonia within 500m) = 4.86, IQR for ln (fine dust within 1000m) = 2.59.

[b] Count variables, incidence rate ratios (IRR) are provided.