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

Christos Baliatsas [a,*], Floor Borlée [a,b], Christel E. van Dijk [a], Baukje van der Star [a], Jan-Paul Zock [a], Lidwien A.M. Smit [b], Peter Spreeuwenberg [a], Dick Heederik [b], C. Joris Yzermans [a]

[a] Netherlands Institute for Health Services Research (NIVEL), Utrecht, The Netherlands
[b] Institute for Risk Assessment Sciences (IRAS), Utrecht University, Utrecht, The Netherlands

ARTICLE INFO

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.

© 2017 Elsevier GmbH. All rights reserved.

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.,

* Corresponding author at: Netherlands Institute for Health Services Research (NIVEL), Otterstraat 118–124, 3513 CR Utrecht, The Netherlands.
E-mail address: c.baliatsas@nivel.nl (C. Baliatsas).

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).

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

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 (%)	
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[‡]	
Within 500 m	0.0001–0.31
Within 1000 m	0.1–2.8
IQR weighted ammonia (NH3) emission[‡]	
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
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.
[‡] g*year-1*m-2.

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).

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)
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.

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 Tables 2–5 . 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.

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

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

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)
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 problems	1.87 (0.41–8.51)	0.95 (0.48–1.87)	0.91 (0.42–1.99)	0.42 (0.09–1.89)	1.71 (0.58–5.05)
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.

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

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).

Comorbidity	Modeled emissions from farms			
	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 (0.52–1.37)	1.03 (0.77–1.38)	0.85 (0.53–1.37)	1.04 (0.73–1.48)
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)
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.

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.

Acknowledgements

References

Agusti, A., MacNee, W., Donaldson, K., Cosio, M., 2003. Hypothesis: does COPD have an autoimmune component? Thorax 58, 832–834.

Agusti, A., Sobradillo, P., Celli, B., 2011a. Addressing the complexity of chronic obstructive pulmonary disease: from phenotypes and biomarkers to scale-free networks, systems biology, and P4 medicine. Am. J. Respir. Crit. Care Med. 183, 1129–1137.

Agusti, A., Hedner, J., Marin, J.M., Barbé, F., Cazzola, M., Rennard, S., 2011b. Night-time symptoms: a forgotten dimension of COPD. Eur. Respir. Rev. 20, 183–194.

Barnes, P.J., Celli, B.R., 2009. Systemic manifestations and comorbidities of COPD. Eur. Respir. J. 33, 1165–1185.

Barrecheguren, M., Esquinas, C., Miravitlles, M., 2015. The asthma-chronic obstructive pulmonary disease overlap syndrome (ACOS): opportunities and challenges. Curr. Opin. Pulm. Med. 21, 74–79.

Borlée, F., Yzermans, C., van Dijk, C., Heederik, D., Smit, L., 2015. Increased respiratory symptoms in COPD patients living in the vicinity of livestock farms. Eur. Respir. J. 46, 1605–1614.

Campagna, D., Kathman, S.J., Pierson, R., et al., 2004. Ambient hydrogen sulfide, total reduced sulfur, and hospital visits for respiratory diseases in northeast Nebraska, 1998–2000. J. Exposure Anal. Environ. Epidemiol. 14, 180–187.

Eder, W., von Mutius, E., 2004. Hygiene hypothesis and endotoxin: what is the evidence? Curr. Opin. Allergy Clin. Immunol. 4, 113–117.

Franssen, F.M., Rochester, C.L., 2014. Comorbidities in patients with COPD and pulmonary rehabilitation: do they matter? Eur. Respir. Rev. 23, 131–141.

Frei, R., Roduit, C., Bieli, C., Loeliger, S., Waser, M., Scheynius, A., Von Mutius, E., 2014. Expression of genes related to anti-inflammatory pathways are modified among farmers' children. PLoS One 9, e91097.

Gibson, P.G., Simpson, J.L., 2009. The overlap syndrome of asthma and COPD: what are its features and how important is it? Thorax 64, 728–735.

Hardin, M., Silverman, E.K., Barr, R.G., Hansel, N.H., Schroeder, J.D., Make, B.J., et al., 2011. The clinical features of overlap between COPD and asthma. Respir. Res. 12, 127.

Harting, J.R., Gleason, A., Romberger, D.J., Von Essen, S.G., Qiu, F., Alexis, N., Poole, J.A., 2010. Chronic obstructive pulmonary disease patients have greater systemic responsiveness to ex vivo stimulation with swine dust extract and its components versus healthy volunteers. J. Toxicol. Environ. Health Part A 75, 1456–1470.

Heederik, D.J.J., Ijzermans, C.J., 2011. Potential Effects of Intensive Livestock Farming on Neighboring Residents' Health. IRAS, Utrecht University, NIVEL, RIVM, Utrecht.

Heederik, D., Sigsgaard, T., Thorne, P.S., et al., 2007. Health effects of airborne exposures from concentrated animal feeding operations. Environ. Health Perspect. 115, 298–302.

Hooiveld, M., van Dijk, C.E., van der Sman-de Beer, F., Smit, L.A., Vogelaar, M., Wouters, I.M., Yzermans, CJ, 2015. Odour annoyance in the neighbourhood of livestock farming-perceived health and health care seeking behaviour. Ann. Agric. Environ. Med., 22.

Houghton, A.M., 2013. Mechanistic links between COPD and lung cancer. Nat. Rev. Cancer 13, 233–245.

Lamberts, H., Wood, H., 1987. The International Classification of Primary Care. Oxford University Press, Oxford.

Li, X., Sundquist, J., Sundquist, K., 2008. Socioeconomic and occupational risk factors for rheumatoid arthritis: a nationwide study based on hospitalizations in Sweden. J. Rheumatol. 35, 986–991.

Loftus, C., Yost, M., Sampson, P., et al., 2015. Ambient Ammonia Exposures in an Agricultural Community and Pediatric Asthma Morbidity. Epidemiology 26, 794–801.

MacNee, W., Donaldson, K., 2003. Mechanism of lung injury caused by PM10 and ultrafine particles with special reference to COPD. Eur. Respir. J. 21, 47s–51s.

Mannino, D.M., 2002. COPD: epidemiology, prevalence, morbidity and mortality, and disease heterogeneity. CHEST J. 121, 121S–126S.

Mathers, C.D., Loncar, D., 2006. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. 3, e442.

McDaid, O., Hanly, M.J., Richardson, K., Kee, F., Kenny, R.A., Savva, G.M., 2013. The effect of multiple chronic conditions on self-rated health, disability and quality of life among the older populations of Northern Ireland and the Republic of Ireland: a comparison of two nationally representative cross-sectional surveys. BMJ Open 3, e002571.

Miłkowska-Dymanowska, J., Białas, A.J., Zalewska-Janowska, A., Górski, P., Piotrowski, W.J., 2015. Underrecognized comorbidities of chronic obstructive pulmonary disease. Int. J. Chron. Obstruct. Pulmon. Dis. 10, 1331.

Okkes, I.M., Oskam, S.K., Lamberts, H., 2012. The probability of specific diagnoses for patients presenting with common symptoms to Dutch family physicians. J. Fam. Pract. 51, 31–36.

Parks, C.G., Hoppin, J.A., DeRoos, A.J., Costenbader, K.H., Alavanja, M.C., Sandler, D.P., 2016. Rheumatoid arthritis in agricultural health study spouses: associations with pesticides and other farm exposures. Environ. Health Perspect. 124 (11), 1728, http://dx.doi.org/10.1289/ehp129.

Radon, K., Schulze, A., Ehrenstein, V., et al., 2007. Environmental exposure to confined animal feeding operations and respiratory health of neighboring residents. Epidemiology 18, 300–308.

Rodríguez-Roisin, R., Soriano, J.B., 2008. Chronic obstructive pulmonary disease with lung cancer and/or cardiovascular disease. Proc. Am. Thorac. Soc. 5, 842–847.

Roth, M., 2008. Pathogenesis of COPD. Part III. Inflammation in COPD [State of the Art Series. Chronic obstructive pulmonary disease in high-and low-income countries. Int. J. Tuberculosis Lung Dis. 12, 375–380 (Edited by G. Marks and M. Chan-Yeung. Number 3 in the series]).

Smit, L.A., van der Sman-de Beer, F., Opstal-van Winden, A.W., et al., 2012. Q fever and pneumonia in an area with a high livestock density: a large population-based study. PLoS One 7, e38843.

Smit, L.A., Hooiveld, M., van der Sman-de Beer, F., et al., 2014. Air pollution from livestock farms, and asthma, allergic rhinitis and COPD among neighbouring residents. Occup. Environ. Med. 71, 134–140.

Strak, M., Janssen, N.A., Godri, K.J., Gosens, I., Mudway, I.S., Cassee, F.R., Lebret, E., Kelly, F.J., Harrison, R.M., Brunekreef, B., Steenhof, M., 2012. Respiratory health effects of airborne particulate matter: the role of particle size, composition, and oxidative potential-the RAPTES project. Environ. Health Perspect. 120, 1183.

Van Dijk, C.E., Garcia-Aymerich, J., Carsin, A.-E., Smit, L.A.M., Borlée, F., Heederik, D.J., Donker, G.A., Yzermans, C.J., Zock J-, P., 2016. Risk of exacerbations in COPD and asthma patients living in the neighbourhood of livestock farms: observational study using longitudinal data. Int. J. Hyg. Environ. Health, 1–10.

van Dijk, C.E., Zock, J.P., Baliatsas, C., Smit, L.A., Borlée, F., Spreeuwenberg, P., Heederik, D.J., Yzermans, C.J., 2017. Health conditions in rural areas with high livestock density: analysis of seven consecutive years. Environ. Pollut. 222, 374–382.

Van Ede, L., Yzermans, C.J., Brouwer, H.J., 1999. Prevalence of depression in patients with chronic obstructive pulmonary disease: a systematic review. Thorax 54, 688–692.

Van Manen, J.G., Bindels, P.J., Dekker, F.W., Ijzermans, C.J., Bottema, B.J., Van Der Zee, J.S., Schade, E., 2001. Added value of co-morbidity in predicting health-related quality of life in COPD patients. Respir. Med. 95 (496-4).

van Manen, J.G., Bindels, P.J., Dekker, F.W., Bottema, B.J., van der Zee, J.S., Ijzermans, C.J., Schadé, E., 2003. The influence of COPD on health-related quality of life independent of the influence of comorbidity. J. Clin. Epidemiol. 56, 1177–1184.

Verheij RA. NIVEL Zorgregistraties Eerste Lijn: Huisarts. [Netherlands Primary Care Database: General Practitioners]. www.nivel.nl/node/3467 Date last accessed: December 16, 2015. Date last updated: 2014.

Vestbo, J., Anderson, J., Brook, R.D., Calverley, P.M., Celli, B.R., Crim, C., Haumann, B., Martinez, F.J., Yates, J., Newby, D.E., 2013. The study to understand mortality and morbidity in COPD (SUMMIT) study protocol. Eur. Respir. J. 41, 1017–1022.

Von Mutius, E., Radon, K., 2008. Living on a farm: impact on asthma induction and clinical course. Immunol. Allergy Clin. North Am. 28, 631–647.

Wongsurakiat, P., Maranetra, K.N., Wasi, C., Kositanont, U., Dejsomritrutai, W., Charoenratanakul, S., 2004. Acute respiratory illness in patients with COPD and the effectiveness of influenza vaccination: a randomized controlled study. CHEST J. 125, 2011–2020.