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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.,

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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

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