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Health conditions in rural areas with high livestock density: Analysis of seven consecutive years☆

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A B S T R A C T

Previous studies investigating health conditions of individuals living near livestock farms generally assessed short time windows. We aimed to take time-specific differences into account and to compare the prevalence of various health conditions over seven consecutive years. The sample consisted of 156,690 individuals registered in 33 general practices in a (rural) area with a high livestock density and 101,015 patients from 23 practices in other (control) areas in the Netherlands. Prevalence of health conditions were assessed using 2007–2013 electronic health record (EHR) data. Two methods were employed to assess exposure: 1) Comparisons between the study and control areas in relation to health problems, 2) Use of individual estimates of livestock exposure (in the study area) based on Geographic Information System (GIS) data. A higher prevalence of chronic bronchitis/bronchiectasis, lower respiratory tract infections and vertiginous syndrome and lower prevalence of respiratory symptoms and emphysema/COPD was found in the study area compared with the control area. A shorter distance to the nearest farm was associated with a lower prevalence of upper respiratory tract infections, respiratory symptoms, asthma, COPD/emphysema, allergic rhinitis, depression, eczema, vertiginous syndrome, dizziness and gastrointestinal infections. Especially exposure to cattle was associated with less health conditions. Living within 500m of mink farms was associated with increased chronic enteritis/ulcerative colitis. Livestock-related exposures did not seem to be an environmental risk factor for the occurrence of health conditions. Nevertheless, lower respiratory tract infections, chronic bronchitis and vertiginous syndrome were more common in the area with a high livestock density. The association between exposure to minks and chronic enteritis/ulcerative colitis remains to be elucidated.

1. Introduction

The increased risk to develop upper and lower respiratory diseases such as rhinitis, sinusitis and chronic obstructive pulmonary disease (COPD) due to occupational exposure to air pollutants in livestock farms has long been acknowledged (May et al., 2012). Livestock farm air is known to contain increased levels of various compounds that could elicit adverse health effects, such as bacteria, viruses, endotoxins, particular matter (PM) and ammonia (Dungan, 2010). For example, endotoxin concentrations in livestock stables have shown to provoke inflammatory effects in numerous studies (May et al., 2012).

More recently, the potential health risks of living in the neighbourhood of (large) livestock farms has received increasing attention. This is mainly due to health concerns of nearby residents of large, intensive livestock farms, which increasingly characterize animal production. Although information regarding exposure type and levels in the proximity of livestock farms is limited (Dungan, 2010), several studies have investigated health effects in residents living in the neighbourhood of livestock farms, not necessarily intensive livestock farms.

Most of the studies were conducted in North Carolina with one

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of the world's highest concentrations of large swine farms mainly located in low income, African-American communities. Comparisons between regions with and without a high density of swine farms showed increased respiratory symptoms including physician-diagnosed asthma in children, gastrointestinal symptoms, weakness, dizziness, fainting, headaches, irritating symptoms as burning eyes, negative mood and lower quality of life (Schiffman et al., 1995; Thu et al., 1997; Wing and Wolf, 2000; Bullers, 2005; Mirabelli et al., 2006). A panel study in this area showed changes in daily activities (Wing et al., 2008), increased respiratory and irritation symptoms, stress, negative mood and blood pressure with especially reporting of odour and to a lesser degree for H_2S and hardly with PM10 and endotoxin exposure (Horton et al., 2009; Schinasi et al., 2011; Wing et al., 2013). In addition, an indication for decreased forced expiratory volume in one second (FEV_1) with increased $PM_{2.5}$ was found (Schinasi et al., 2011). Two studies in Iowa, one comparing school children with and without exposure to a large swine farm and the other using individual estimates for exposure, showed increased prevalence of asthma (Sigurdarson and Kline, 2006; Pavilonis et al., 2013). Another study in Michigan showed increased Campylobacter jejuni enteritis in counties with a high poultry density (Potter et al., 2002). A study conducted around a large swine farm outside Ottawa, Canada showed no differences in respiratory symptoms, but reduced quality of life and increased prevalence of depression in residents living closer to this farm (Villeneuve et al., 2009). Two ecological studies in agricultural municipalities in Quebec showed more acute gastroenteritis hospitalization in children with increasing poultry density (Febriani et al., 2009), but no association between swine and cattle density and diarrhea in adults (St-Pierre et al., 2009). Two ecological study in Ontario showed increased Shiga toxin-producing Escherichia coli (STEC); associated with among others diarrhea and hemolytic uremic syndrome (HUS) infections in areas with a higher ratio of beef cattle number to human population (Michel et al., 1999; Valcour et al., 2002).

Studies conducted in a rural area in the Netherlands with high density of livestock farms showed decreased prevalence of asthma, allergic rhinitis and COPD with increased exposure to livestock measured as PM10 emission, presence of (specific) farm animals within 500 m radius from home, and distance to nearest farm (Smit et al., 2014; Borlée et al., 2015). An increased prevalence of pneumonia was found in residents living within 1 km from poultry (Smit et al., 2012). Another study in the same area showed increased reporting of anxiousness, sadness and respiratory and gastrointestinal symptoms in residents reporting odour annoyance (Hooiveld et al., 2015). Three studies conducted in a German area with a high density of livestock farms, especially swine and poultry, showed decreased quality of life, increased prevalence of wheezing without a cold, asthma and allergic rhinitis with increased odour annoyance, but no difference in sensitization, bronchial hyperresponsiveness and FEV_1 values (Radon et al., 2004, 2007). In addition, increased wheezing without a cold and decreased FEV_1 values in residents in the proximity of >12 farms within 500m was found and decreased FEV_1 with increased ammonia exposure (Radon et al., 2007; Schulze et al., 2011). In school children, modeled individual endotoxin levels were associated with increased asthma in children with atopic parents (Hoopmann et al., 2006). An ecological study conducted in France showed a higher incidence of HUS in children with increased dairy cattle density and the ratio of calves to children within districts (Haus-Cheymol et al., 2006).

In general, these studies indicate increased respiratory, gastrointestinal, irritation, neurological and stress/psychological symptoms with increased livestock exposure, but some studies show protective effects (Smit et al., 2014; Borlée et al., 2015). Most negative health effects are found with increased odour or odour annoyance, and these effects are to a lesser extent found for more objective measures of livestock exposure. The use of various estimates for livestock exposure complicates a direct comparison of results. To reduce the potential influence of time-specific differences and different livestock exposure estimates, the objective of the present study was to compare prevalence of various health conditions over a period of seven years using different methods to estimate livestock exposure.

2. Materials and methods

2.1. Research design and study population

This was an observational study analysing differences in the prevalence of respiratory, gastrointestinal, neurological, dermatological and psychological symptoms and diseases with livestock exposure between 2007 and 2013. This research was conducted within the framework of the "VGO" project ("Farming and Neighbouring Residents' Health"). Data was obtained from electronic health records (EHRs) of general practices in the Primary Care Database (PCD) of the Netherlands Institute for Health Services Research (NIVEL) (Verheij, 2014) Morbidity is registered following the International Classification of Primary Care (ICPC) (Lamberts and Wood, 1987). All Dutch inhabitants are obligatory listed in a general practice and GPs act as gatekeepers for specialized, secondary health care. Therefore, the EHR kept by GPs provides a complete picture of people's health. For this study, data was used from practices located in a rural area with a high density of livestock farms in the Netherlands (study area - general practices outside the larger cities in the eastern part of the province of Noord-Brabant and the northern part of the province of Limburg) and practices located in other rural areas in the Netherlands with a substantially lower livestock farm density (control area) (van Dijk et al., 2016), particularly in the provinces of Noord-Holland, Zuid-Holland, Utrecht, Gelderland, Zeeland, Overijssel and Groningen. In 2013 for instance, based on the current data, ≥ 1 large intensive livestock farms were located in 59% of the postal code area of the general practices in the study area, compared to 5% in the control area (only information available about large intensive livestock farms). Also smaller livestock farms, especially poultry and swine farms, are more common in the study area. In the selected area(s) there were no other known major landscape features that could affect residents' health. Inclusion criteria for practices were i) availability of morbidity data in the NIVEL PCD in the reporting year and one or two previous years, ii) minimum of 46 weeks of registration and iii) ICPC code registration in at least 70% of the consultations in the reporting year. In addition, for practices with one previous year one of the criteria ii and iii needed to be fulfilled and for practices with two previous years one of the criteria ii and iii needed to be fulfilled twice. As at least one previous year of data was needed to estimate prevalence rates, and as 2006–2013 data were available, we reported for the years 2007 until 2013. Table 1 shows the included practices and patients per year.

2.2. Ethics

The NIVEL PCD complies with the regulations of the Dutch Data Protection Authority and the Dutch law regarding use of health data for epidemiological research purposes (Dutch Civil Law, Article 7:458). Medical information as well as address records were kept separated at all times by using a Trusted Third Party (Stichting Informatie Voorziening Zorg, Houten). The VGO study protocol was approved by the Medical Ethical Committee of the University Medical Centre Utrecht.

Table 1
Included general practices per year.

	Rural area with high livestock density (study area)				Rural area with a low livestock density (control area)	
	Analyses comparison study area with control area		Analyses individual exposure estimates		Analyses comparison study area with control area	
	Practices	Patients	Practices	Patients	Practices	Patients
2007	15	66,109	14	51,363	15	56,860
2008	15	64,858	15	59,106	16	55,563
2009	22	93,053	22	87,433	21	73,709
2010	22	95,501	22	90,435	21	74,251
2011	24	99,256	24	93,916	19	62,674
2012	27	110,728	27	104,708	22	75,391
2013	27	116,539	27	107,241	16	62,858
All years	33	156,690	32	132,077	23	101,015

2.3. Prevalence and incidence of symptoms and diseases

Prevalence estimates are based on care episodes. The construction of episodes was based on all records with an ICPC code in the EHR of general practices. These were available from episode records constructed by GPs themselves, morbidity and medication prescription records. As mentioned previously, two or three consecutive years of data were used. ICPC codes are divided into three categories: I) acute conditions (e.g. acute bronchitis, infectious conjunctivitis), ii) long lasting reversible conditions (e.g. depression, allergic rhinitis), and iii) chronic irreversible conditions (e.g. COPD, chronic enteritis/ulcerative colitis). For each ICPC category a different symptom-free period is adopted. The symptom-free period is a period that determines whether two ICPC records belong to the same episode. For acute conditions, a symptom-free period of eight weeks is defined. This means that a care episodes is closed after eight weeks when no similar ICPC code is found within eight weeks. For long lasting reversible conditions a symptom-free period of one or two years is used, depending on the specific condition. For chronic irreversible conditions no symptom-free period is defined, which means that the episodes will not be closed. The prevalence is the number of patients with a condition, both incident and prevalent cases, divided by the total practice population. As the prevalence of chronic conditions are highly dependent on the number of previous years (not all chronically ill patient visit the general practice yearly), we only reported prevalence rates for the years 2008 until 2013. For this study, we focused on health conditions that have been associated or are likely to be associated with livestock exposure (ICPC code): lower respiratory tract infections (R81-R83), pneumonia (R81), upper respiratory tract infections (R74-R78), respiratory symptoms (R02, R03 & R05), asthma (R96), chronic bronchitis/bronchiectasis (R91 – 40 years and older), emphysema/COPD (R95 – 40 years and older), pneumonia (R81), allergic rhinitis (R97), depression (P03 & P76), constitutional eczema (S87), vertiginous syndrome (H82), vertigo/dizziness (N17), gastro-intestinal infections (D73), chronic enteritis/ulcerative colitis (D94).

2.4. Livestock farm exposure

Exposure to farms was estimated on the basis of comparisons between the study area and the control area and also with the employment of individual exposure proxies in the study area. Information regarding characteristics of the farms (geographic location, animal type and number) in the study area was extracted from provincial databases of mandatory environmental licences for keeping livestock (https://bvb.brabant.nl/). These included data on number and type of animals, geographic coordinates of farms and annual estimates of fine dust emissions from farm. For the individual exposures estimates patients' residential addresses were geocoded, and the distance between home addresses and farms was estimated using a geographic information system (ArcGis 9.3.1, Esri, Redlands, CA). Full addresses were not available for all patients, and patients with incomplete address records were excluded from the analyses (see Table 1). The following individual farm exposure variables were considered: 1) distance to nearest farm (continuous variable); 2) distance to nearest farm with a specific type of farm animal (continuous variable); 3) presence of one or more farms within 500 m from the home address; 4) the number of farms within 500 m, 5) the presence of a specific farm animals within 500 m, and 6) inverse-distance weighted PM10 emission from all farms within 500 m (see for detailed description modelling PM10 emission (Smit et al., 2014). 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). Individual exposure estimates were available for the years 2009 and 2012. For patients in the years 2007–2010, exposure data from 2009 was used, while 2012 exposure data was used for patients in the years 2011–2013. Comparisons between exposure 2009 and 2012 exposure data shows less livestock farms 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. Statistical analysis

To investigate whether prevalence of health conditions differed with livestock exposure, logistic multilevel regression analyses were conducted using MLwiN 2.30 (PQL, 1st order). Multilevel analyses were carried out given the hierarchical structure of the data (patient years nested within patients and patients nested within general practices). The dependent variable in all analyses was the prevalence. The independent variable was the livestock exposure estimate. Analyses were adjusted for age (polynomial) and gender. Differences in the prevalence of health conditions were estimated for all years together and for each year separately. Multilevel analyses were estimated with a random intercept with on practice level variances for each year and on patient level variances and covariances for each year (model 1). If it was not possible to estimate this model, a model was used with one variance on practice level for all years together (model 2). If also model 2 was not possible, the covariances on patient level were estimated between two consecutive years only (model 3). If we could not estimate model 3, a model was used with only variances on patient level (model 4). If also model 4 was not possible, a model with one variance on patient level for all years together was estimated (model 5). Descriptive tables and figures were standardised to the age and gender distribution of the Dutch population using population data from Statistics Netherlands (Statistics Netherlands, 2015). To correct for multiple testing, the significance level was set at $p < 0.01$.

3. Results

3.1. Patient characteristics

Characteristics of the patients in the study and control area are shown in appendix I. Mean age varied between 39.5 and 42.0 years in the study area, and 39.1 and 41.4 years in the control area. Patients in the study area were slightly but significantly older compared with patients in the control area. Gender did not differ between the two areas. Patients in the study area were frequently living within 500 m of stables with cattle (42%), swine (29%), poultry (13%), and sheep (11%). Patients were less often living within 500 m of stables with goats (2%) and minks (2%) (Table 2).

Average prevalence of included health conditions is shown in Table 3 for the study and control area. Upper respiratory tract infections were the most common health condition with a prevalence of 115.5 and 134.8 per 1000 patients on average in the study and control area respectively. Also respiratory symptoms (75.3 *versus* 83.3 per 1000 patients), allergic rhinitis (50.6 *versus* 56.1 per 1000 patients) and asthma (49.8 *versus* 53.3 per 1000 patients) had a relatively high prevalence (see Table 4).

3.2. Differences in prevalence rate between area with high and low livestock density

The annual prevalence of lower respiratory tract infections (including pneumonia) was, in general, significantly higher in the study area, with an OR of 1.37 (99%CI:1.06–1.75) for all years combined. Upper respiratory tract infections seem to be more common in the control area, although the difference was non-significant in most years. Chronic bronchitis/bronchiectasis is more prevalent in the study area (all years together: OR 1.74; 99%CI: 1.15–2.62). On the other hand, the prevalence of emphysema/COPD

Table 3
Average prevalence of health conditions per 1000 patients in the study (646,044 patients years) and control area (461,306), 2007–2013.[a]

	Average prevalence 2007–2013	
	Study area	Control area
Lower respiratory tract infections	19.7	14.6
Upper respiratory tracts infections	115.5	134.8
Respiratory symptoms	75.3	83.3
Asthma	49.8	53.3
Chronic bronchitis/bronchiectasis[b]	9.2	5.3
Emphysema/COPD[b]	42.6	47.1
Pneumonia	16.3	11.9
Allergic rhinitis	50.6	56.1
Depression	35.8	40.4
Constitutional eczema	36.8	31.5
Vertiginous syndrome	19.3	15.4
Vertigo/dizziness	14.6	15.3
Gastro-intestinal infections	13.2	13.3
Chronic enteritis/ulcerative colitis	4.9	4.0

[a] For chronic conditions average prevalence 2008–2013, 579,935 patient years in the study area and 404,446 patient years in the control area.
[b] Prevalence per 1000 for patients 40 years and older.

Table 2
Livestock farm exposure in the study population (594,202 patient years), 2007–2013.

Characteristic	Study area
Individual exposure estimates	
Distance weighted PM10 emission from farms within 500 m, g y^{-1} m^{-2} (GM (IQR))	0.0240 (0.0001–1.3000)
One or more farms within 500 m, n (%)	331,558 (55.8)
Livestock farms within 500 m, nr (mean (SD))	1.5 (2.0)
Presence of livestock within 500 m, n (%)	
Cattle	249,249 (42.0)
Swine	173,697 (29.2)
Poultry	79,361 (13.4)
Goats	11,360 (1.9)
Sheep	66,846 (11.3)
Minks	10,551 (1.8)
Distance to nearest (m, GM (IQR))	
Livestock farm	460 (290–660)
Farm with cattle	510 (360–810)
Farm with swine	612 (460–920)
Farm with poultry	877 (670–1300)
Farm with goats	1520 (1300–2000)
Farm with sheep	922 (680–1380)
Farm with minks (m, GM (10th perc – 90th perc)	1748 (1210–2000)
Distance to nearest, n (%)	
Swine	
<530 m	195,907 (33.0)
530–800 m	193,154 (32.5)
<800 m	205,141 (34.5)
Poultry	
<770 m	195,911 (33.0)
770–1170 m	195,951 (33.0)
>1170 m	202,340 (34.1)
Cattle	
<430 m	193,912 (32.6)
430–710 m	201,745 (34.0)
>710 m	198,545 (33.4)
Goats	
<1510 m	197,165 (33.2)
1510–1990 m	114,677 (19.3)
>1990 m	282,360 (47.5)
Sheep	
<790 m	194,005 (32.7)
790–1230 m	198,846 (33.5)
>1230 m	201,351 (33.9)
Minks	
<1990 m	145,098 (42.4)
>1990 m	449,104 (75.6)

GM: geometric mean; IQR: interquartile range.

Table 4
Difference in prevalence of various symptoms and diseases between population in study area and control area, 2007–2013.

Prevalence	2007	2008	2009	2010	2011	2012	2013	All years combined
	OR (99%CI)	OR (99%CI)	OR (99%CI)	OR (99%CI)	OR (99%CI)	OR (99%CI)	OR (99%CI)	OR (99%CI)
Lower respiratory tract infections[b,2,3]	**1.54 (1.17–2.04)**	**1.59 (1.21–2.10)**	**1.40 (1.07–1.82)**	**1.36 (1.04–1.77)**	1.16 (0.89–1.51)	1.24 (0.95–1.60)	1.32 (1.02–1.72)	**1.37 (1.06–1.75)**
Upper respiratory tracts infections[a]	0.85 (0.64–1.13)	0.83 (0.63–1.09)	0.82 (0.63–1.06)	0.88 (0.70–1.11)	0.84 (0.69–1.02)	**0.80 (0.66–0.98)**	0.83 (0.68–1.01)	**0.83 (0.76–0.91)**
Respiratory symptoms[a]	0.92 (0.70–1.20)	0.93 (0.69–1.25)	0.90 (0.71–1.15)	0.88 (0.67–1.16)	0.85 (0.64–1.11)	0.91 (0.72–1.16)	0.87 (0.68–1.12)	**0.89 (0.81–0.99)**
Asthma[a]	–	1.03 (0.80–1.31)	0.93 (0.75–1.15)	0.91 (0.74–1.13)	0.92 (0.75–1.13)	0.91 (0.76–1.10)	0.91 (0.72–1.14)	0.93 (0.85–1.03)
Chronic bronchitis/bronchiectasis[b,2]	–	**1.78 (1.15–2.76)**	**1.90 (1.23–2.93)**	**1.87 (1.21–2.88)**	**1.69 (1.10–2.60)**	**1.66 (1.08–2.55)**	**1.55 (1.01–2.39)**	**1.74 (1.15–2.62)**
Emphysema/COPD[a,2,3]	–	**0.84 (0.74–0.96)**	**0.83 (0.76–0.92)**	**0.88 (0.80–0.96)**	**0.92 (0.85–1.00)**	0.94 (0.86–1.02)	0.97 (0.89–1.07)	**0.90 (0.83–0.96)**
Pneumonia[b,1,3]	**1.56 (1.13–2.14)**	**1.55 (1.13–2.13)**	**1.50 (1.11–2.04)**	**1.41 (1.04–1.91)**	1.17 (0.86–1.59)	1.18 (0.87–1.59)	1.28 (0.95–1.73)	**1.37 (1.03–1.83)**
Allergic rhinitis[a,1,2]	0.86 (0.71–1.03)	0.87 (0.75–1.02)	0.90 (0.78–1.04)	0.89 (0.79–1.01)	0.91 (0.82–1.00)	0.90 (0.80–1.02)	0.92 (0.81–1.04)	**0.89 (0.84–0.95)**
Depression[a,1,2]	0.94 (0.76–1.17)	0.94 (0.78–1.14)	0.84 (0.70–1.00)	0.86 (0.73–1.01)	0.88 (0.76–1.02)	0.86 (0.74–1.02)	0.86 (0.72–1.02)	**0.88 (0.81–0.96)**
Constitutional eczema[d,1,2]	–	1.09 (0.84–1.41)	1.18 (0.92–1.53)	1.19 (0.92–1.54)	1.18 (0.91–1.52)	1.18 (0.92–1.53)	1.23 (0.95–1.59)	1.18 (0.92–1.51)
Vertiginous syndrome[a,1,2]	1.08 (0.73–1.61)	1.20 (0.84–1.71)	1.20 (0.90–1.62)	1.22 (0.93–1.58)	**1.28 (1.00–1.63)**	1.27 (0.99–1.62)	**1.52 (1.17–1.98)**	**1.25 (1.10–1.41)**
Vertigo/dizziness[b,1,2]	0.98 (0.72–1.35)	0.92 (0.67–1.26)	1.00 (0.73–1.36)	0.87 (0.64–1.19)	1.00 (0.74–1.36)	0.99 (0.73–1.35)	0.93 (0.68–1.25)	0.96 (0.71–1.28)
Gastro-intestinal infections[c]	0.95 (0.67–1.37)	0.88 (0.62–1.25)	0.95 (0.68–1.35)	1.02 (0.72–1.45)	1.08 (0.76–1.53)	1.16 (0.82–1.63)	0.96 (0.68–1.36)	1.00 (0.72–1.39)
Chronic enteritis/ulcerative colitis[d,1,2]	–	1.09 (0.78–1.53)	1.13 (0.82–1.54)	1.23 (0.90–1.67)	1.33 (0.98–1.82)	1.31 (0.97–1.76)	1.30 (0.97–1.75)	1.23 (0.95–1.58)

[a]Model 1; [b]Model 2; [c]Model 3; [d]Model 4; [e]Model 5; [1]significant linear trend for control area; [2]significant linear trend for study area; [3]significant difference in linear trend between study area and control area.
Models are adjusted for age and gender. Bold type indicates significance ($P < 0.01$).

was significantly lower in the study area in most years, with an OR of 0.90 (99%CI: 0.83–0.96) for all years combined. This difference between the areas seemed to become smaller in the course of time. Also, the prevalence of vertiginous syndrome was higher in the study area, but only statistically significant in 2011 and 2013. Prevalence rate of constitutional eczema were also higher, although not statistically significant. Depression tended to be less common in the study area, although only a statistical significant difference was found for all years combined. The prevalence of other symptoms and diseases did not differ between the two areas, although some differences were statistically significant when all years were combined (e.g. respiratory symptoms and allergic rhinitis).

3.3. Prevalence differences with individual livestock exposure estimates

The associations between individual livestock exposure estimates and the prevalence of health conditions are shown in detail in appendix II. In Table 5 the odds ratios for all years together are shown for associations that were consistently statistically significant over the years. Overall, individual livestock exposure was associated with lower prevalence of upper respiratory tract infections, respiratory symptoms, asthma, COPD/emphysema, allergic rhinitis, depression, eczema, vertiginous syndrome, dizziness and gastrointestinal infections. For example, residents living within 500 m of one or more farms had an odds ratio of 0.93 (95% CI:0.90–0.96) to have had an upper respiratory infection and an odds ratio of 0.86 (95%CI:0.80–0.93) to have had a gastro-intestinal infections. Also a larger distance to the nearest farm (and therefore lower exposure) was associated with a higher prevalence of these health conditions and diseases. Especially exposure to cattle was associated with less health conditions. For instance, residents living within 500 m of a farm with cattle had a lower odds of having had respiratory symptoms (OR: 0.93; 95CI: 0.89–0.97) and depression (OR:0.90; 95%CI: 0.84–0.97). In general, individual livestock exposure was not associated with lower respiratory infections, chronic bronchitis/bronchiectasis, pneumonia and constitutional eczema. Exposure to mink farms was associated with increased chronic enteritis/ulcerative colitis.

The distance to nearest farms with minks (less exposure) was associated with a lower prevalence of chronic enteritis/ulcerative colitis (OR: 0.80; 95%CI: 0.73–0.87) and also living within <1990 m was associated with a higher prevalence compared with living >1990 m from mink farms (OR: 1.31; 95%CI:1.11–1.55).

Additional analyses with farm exposure within four-digit postal code areas in the study area also showed mainly lower prevalence of health condition with increased livestock exposure (years 2009–2013; analyses available under request).

4. Discussion

4.1. Primary findings

Comparison between the study and control area showed more lower respiratory tract infections, chronic bronchitis/bronchiectasis and vertiginous syndrome in the study area, and less respiratory symptoms and emphysema/COPD. Results of the individual exposure estimates did not fully support these findings, but also did not show reverse associations. The analyses with individual exposure estimates showed protective associations with various health conditions, including several respiratory conditions, conditions of the gastrointestinal tract and neurological conditions. Especially individual exposure to cattle was associated with a lower prevalence of health conditions. In addition more chronic enteritis/ulcerative colitis was found with increased exposure to mink farms in

Table 5a
Consistent statistically significant differences in prevalence (all years together) of various symptoms and diseases by various individual livestock exposure estimates, 2007/8–2013.[a]

	Lower respiratory tract infections	Upper respiratory tract infections	Respiratory symptoms	Asthma	Chronic bronchitis/ bronchiectasis	Emphysema/COPD	Pneumonia	Allergic rhinitis
	OR (99%CI)	OR (99%CI)	OR (99%CI)	OR (99%CI)		OR (99%CI)	OR (99%CI)	OR (99%CI)
PM10 Emission from farms within 500 m		**0.98 (0.98–0.99)**	**0.98 (0.97–0.98)**	**0.99 (0.98–1.00)**		**0.98 (0.97–1.00)**		**0.98 (0.97–0.99)**
One or more farms within 500 m		**0.93 (0.90–0.96)**	**0.90 (0.87–0.94)**	**0.94 (0.90–0.99)**		**0.90 (0.83–0.97)**		**0.93 (0.89–0.98)**
Number of cattle within 500 m		**0.97 (0.97–0.98)**	**0.97 (0.96–0.98)**	**0.98 (0.96–0.99)**		**0.96 (0.94–0.99)**		**0.97 (0.95–0.98)**
Presence of cattle within 500 m			**0.93 (0.89–0.97)**	**0.94 (0.89–0.99)**		**0.88 (0.81–0.96)**		
Distance to the nearest								
Farm[b]		**1.06 (1.04–1.09)**	**1.09 (1.06–1.11)**	**1.06 (1.03–1.09)**		**1.12 (1.06–1.18)**		**1.08 (1.04–1.11)**
farm with swine[b]						**1.06 (1.01–1.11)**		
farm with poultry[b]								
farm with cattle[b]		**1.04 (1.02–1.07)**	**1.07 (1.04–1.10)**	**1.04 (1.00–1.09)**		**1.12 (1.06–1.18)**		
farm with sheep[b]								
farm with minks[a]								
Distance to nearest farm[a]								
Poultry (ref > 1170 m)								
<770 m								
Cattle (ref > 710 m)								
<430 m		**0.92 (0.88–0.96)**	**0.88 (0.83–0.93)**	**0.92 (0.85–0.98)**		**0.86 (0.77–0.96)**	**0.87 (0.79–0.97)**	**0.92 (0.85–0.99)**
430–710 m								
Sheep (ref > 1230 m)								
790–1230 m	**1.11 (1.02–1.21)**					**1.11 (1.01–1.21)**		
Minks (ref > 1990 m)								
<1990 m								

[a] Statistically significant in at least 2 separate years and all years together.
[b] OR and 95%CI for an IQR increase in log-transformed exposure. IQR for ln(distance farm, m) = 0.82, corresponding to a 2.28-fold increase (exp0.82) for non-transformed values.

the study area. This association was also found in the comparison between the study and control area, but was not statistically significant probably explained by the low prevalence and the relatively low number of minks farms in the study area.

Despite the unknown exposure levels most previous studies showed increased respiratory, gastrointestinal, irritation, neurological and stress/psychological symptoms with increased livestock exposure (Schinasi et al., 2011; Radon et al., 2007; Pavilonis et al., 2013; Hooiveld et al., 2015). In contrast, our analyses with individual livestock exposure estimates showed predominantly protective associations between livestock exposure and various health conditions. Recent studies in the same area of the Netherlands also found protective association with farm exposure on atopic diseases (e.g. asthma, allergic rhinitis) (Smit et al., 2014; Borlée et al., 2015; van Dijk et al., 2016). The lower prevalence of asthma and allergy among farmers' children living close to farms has been linked to higher endotoxin levels and diversity of microbial components in the farm environment, which might reduce allergic sensitization (Von Ehrenstein et al., 2000; Leynaert et al., 2001; Riedler et al., 2001; Portengen et al., 2002; Ege et al., 2011). In line with this, a number of studies has demonstrated a protective effect of microbial exposures against outcomes such as atopy and allergic asthma (Kauffmann et al., 2002; Eduard et al., 2004; Smit et al., 2008, 2010). However, it does not explain the protective association between livestock exposure and COPD, depression, gastrointestinal infections, upper respiratory infections and vertigo/dizziness.

Other explanations for the protective association of other health conditions may be migration of people with health problems from rural areas with high livestock exposure or confounding by risk factors. Previous research has shown that people living in the vicinity of livestock generally experience better health, in accordance with the lower prevalence of various health conditions (van Dijk et al., 2016).

Living in the neighbourhood of minks was associated with a higher prevalence of chronic enteritis/ulcerative colitis. These associations had not been found previously in the literature. Gastrointestinal disorders are common in farms with minks (Rattenborg et al., 1999; Englund et al., 2002). These disorders are characterised by diarrhea for several days that affect the general condition (Rattenborg et al., 1999). Infection of astrovirus has shown to be associated with pre-weaning diarrhea in minks. In an outbreak of gastrointestinal illness of unknown etiology in a child care centre in Virginia, multiple sequences with limited identity to known astroviruses were identified. Phylogenetic analysis showed that this virus, AstV-VA2 was most closely related to mink and ovine astroviruses (Finkbeiner et al., 2009). A link to mink farming was not made and needs to be addressed in future research.

Increased lower respiratory tract infection, especially pneumonia, was also found in previous studies (Smit et al., 2012; Hooiveld et al., 2016). Smit et al. showed increased prevalence of pneumonia in residents living within 1 km from poultry, and Hooiveld et al. showed increased prevalence of pneumonia in postal code areas with more concentrated animal feeding operations in 2009. The present study found an increased prevalence in the study area compared with the control area, but did not find a higher prevalence with increased exposure to poultry or other livestock. It might be the case that the case-control comparison enabled a better exposure contrast compared to the individual estimates. Another reason for a lack of association between exposure to poultry and pneumonia could be the Q-fever outbreak in

Table 5b
Consistent statistically significant differences in prevalence (all years together) of various symptoms and diseases by various individual livestock. exposure estimates, 2007/8–2013.[a]

	Depression	Constitutional eczema	Vertiginous syndrome	Vertigo/dizziness	Gastro-intestinal infections	Chronic enteritis/ulcerative colitis
	OR (99%CI)	OR (99%CI)	OR (99%CI)	OR (99%CI)	OR (99%CI)	OR (99%CI)
PM10 Emission from farms within 500 m					**0.97 (0.95–0.98)**	
One or more farms within 500 m	**0.88 (0.83–0.93)**			**0.88 (0.82–0.95)**	**0.86 (0.80–0.93)**	
Number of farms within 500 m	**0.96 (0.94–0.98)**			**0.96 (0.94–0.98)**	**0.95 (0.93–0.97)**	
Presence of cattle within 500 m	**0.90 (0.84–0.97)**					
Distance to the nearest						
Farm[b]	**1.11 (1.07–1.15)**	**1.05 (1.01–1.09)**	**1.06 (1.01–1.11)**	**1.10 (1.05–1.16)**	**1.13 (1.08–1.19)**	
farm with swine[b]						
farm with poultry[b]			**1.06 (1.01–1.11)**			
farm with cattle[b]	**1.10 (1.04–1.15)**		**1.05 (1.00–1.10)**			
farm with sheep[b]			**1.05 (1.00–1.10)**			
farm with minks[a]						**0.80 (0.73–0.87)**
Distance to nearest farm						
Poultry (ref > 1170 m)						
<770 m	**0.90 (0.83–0.97)**					
Cattle (ref > 710 m)						
<430 m	**0.83 (0.76–0.90)**				**0.79 (0.71–0.89)**	**0.76 (0.65–0.88)**
430–710 m	**0.88 (0.81–0.95)**					**0.80 (0.70–0.91)**
Sheep (ref > 1230 m)						
790–1230 m	**1.08 (1.01–1.16)**					
Minks (ref > 1990 m)						
<1990 m						**1.31 (1.11–1.55)**

Odds ratios ORs and 95%CI were adjusted for age and gender and the presence of other types of livestock animals.
IQR for ln(distance farm with swine, m) = 0.9, corresponding to a 2.00-fold increase ($\exp^{0.69}$) for non-transformed values, IQR for ln(distance farm with poultry, m) = 0.66, corresponding to a 1.94-fold increase ($\exp^{0.66}$) for non-transformed values, IQR for ln(distance farm with cattle, m) = 0.81, corresponding to a 2.25-fold increase ($\exp^{0.81}$) for non-transformed values, IQR for ln(distance farm with sheep, m) = 0.71, corresponding to a 2.03-fold increase ($\exp^{0.71}$) for non-transformed values; [$]OR and 95%CI for an increase from the 10th to 90th percentile in log-transformed exposure. 10–90 percentile difference for ln(distance farm with minks, m) = 0.50, corresponding to a 1.65 fold increase ($\exp^{0.50}$). Bold type indicates significance ($P < 0.01$).

[a] Statistically significant in at least 2 separate years and all years together.

[b] OR and 95%CI for an IQR increase in log-transformed exposure. IQR for ln(distance farm, m) = 0.82, corresponding to a 2.28-fold increase ($\exp^{0.82}$) for non-transformed values.

2009. In 2009 a Q fever outbreak occurred which was accompanied with a higher prevalence of pneumonia, which could have biased the associations (Smit et al., 2012). Our study also showed higher non-significant odds ratios in the year 2008 and 2009 for the association between presence of poultry within 500 m and pneumonia and also non-significant odds ratios were found in the year 2009 for the association between presence of poultry within 1000m and pneumonia (not shown; OR: 1,11). Also significant odd ratios were found for the association between presence of goats within 500 m and Q fever in the year 2009 and 2010 (OR: 1.51 and 2.27). However, recent kernel analyses show an increased risk of pneumonia until 1000m after the Q fever outbreak (Maassen et al., 2016).

4.2. Strengths and limitations

This is one of the largest epidemiological studies to date in terms of sample size and the most thorough investigation in terms of outcome assessment to assess the association between livestock exposure and various health conditions in residents living in the neighbourhood of livestock farms.

Important methodological assets of the present study are the use of registry-based health outcomes from general practices which minimizes the risk for selection bias and outcome misclassification and the employment of objective exposure estimates. Furthermore, the availability of precise residential addresses and livestock registrations enabled us to geocode both livestock farms and residents. Several limitations have to be acknowledged. Although the study design provided insight into exposure-outcome patters, it did not allow the establishment of temporal precedence of the investigated associations. Future research should include analyses with areas with alterations in livestock farming to investigate causal relationships. Furthermore, information on factors that can influence exposure levels such as building type and ventilation of farms (Banhazi et al., 2008) was missing. The livestock exposure estimates were not validated with exposure measurements. Although we did not validate our exposure estimates, previous research in the same research area has shown higher endotoxin levels from livestock farms up to 250 m (Heederik and Yzermans, 2011). Another shortcoming was that, analyses were only adjusted for a basic set of confounders (age and gender) and not for smoking habits, socioeconomic status and occupational exposure. Earlier research has shown that adjustment for socioeconomic status did not change the associations between livestock exposure and health outcomes (Smit et al., 2014). Self-reported data on occupational exposure was available for 14,591 residents for the study area (Borlée et al., 2015) and showed that only 2.6% of the residents were living or working on a livestock farm (after exclusion of subjects living within 50 m from a farm). Also, only health conditions were included for which people visit a GP, which could especially have influenced the prevalence of symptoms. Finally, since we carried out a large number of statistical tests, there is some chance for false-positives (Maassen et al., 2016). However, we analysed each year separately and reported consistent findings only.

5. Conclusions

In general, livestock farm exposure did not seem to be an environmental risk factor for the occurrence of various health conditions. A higher prevalence of lower respiratory tract infections was found in the area with a high density of livestock farms, and also chronic enteritis/ulcerative colitis was more common in residents exposed to mink farms. But overall, exposure to livestock exposure was associated with less health conditions. Whether this is due to livestock exposure or other factors remains to be elucidated.

Conflict of interests statement

The authors declare they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.envpol.2016.12.023.

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