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Proximity to livestock farms and exposure to livestock-related particulate matter are associated with lower probability of medication dispensing for obstructive airway diseases

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ABSTRACT

Objectives: The aim of this study is to assess whether medication use for obstructive airway diseases is associated with environmental exposure to livestock farms. Previous studies in the Netherlands at a regional level suggested that asthma and chronic obstructive pulmonary disease (COPD) are less prevalent among persons living near livestock farms.

Methods: A nationwide population-based cross-sectional study was conducted among 7,735,491 persons, with data on the dispensing of drugs for obstructive airway diseases in the Netherlands in 2016. Exposure was based on distances between home addresses and farms and on modelled atmospheric particulate matter (PM_{10}) concentrations from livestock farms. Data were analysed for different regions by logistic regression analyses and adjusted for several individual-level variables, as well as modelled PM_{10} concentration of non-farm-related air pollution. Results for individual regions were subsequently pooled in meta-analyses.

Results: The probability of medication for asthma or COPD being dispensed to adults and children was lower with decreasing distance of their homes to livestock farms, particularly cattle and poultry farms. Increased concentrations of PM_{10} from cattle were associated with less dispensing of medications for asthma or COPD, as well (meta-analysis OR for 10th-90th percentile increase in concentration of PM_{10} from cattle farms, 95%CI: 0.92, 0.86–0.97 for adults). However, increased concentrations of PM_{10} from non-farm sources were positively associated (meta-analysis OR for 10th-90th percentile increase in PM_{10}-concentration, 95%CI: 1.29, 1.09–1.52 for adults).

Conclusions: The results show that the probability of dispensing medication for asthma or COPD is inversely associated with proximity to livestock farms and modelled exposure to livestock-related PM_{10} in multiple regions within the Netherlands. This finding implies a notable prevented risk: under the assumption of absence of livestock farms in the Netherlands, an estimated 2%–5% more persons (an increase in tens of thousands) in rural areas would receive asthma or COPD medication.

1. Introduction

Previous research in the Netherlands suggests that persons living in the vicinity of livestock farms are less likely to have asthma or chronic obstructive pulmonary disease (COPD) (Borlée et al., 2015; de Rooij et al., 2019; Smit et al., 2014). The reduced asthma prevalence may be explained by more diverse microbial exposures in livestock-farming areas, leading to a reduced risk for development of allergic

Abbreviations: COPD, chronic obstructive pulmonary disease; GCN, large-scale concentration-maps the Netherlands [grootschalige concentratie-kaarten Nederland]; PAF, population-attributable fraction; PM, particulate matter; SES, socio-economic status.

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sensitization (von Mutius, 2016). This explanation is largely based on studies in children growing up on livestock farms (Ege et al., 2011; Riedler et al., 2001), who tend to have a lower risk of atopic asthma and allergies. A lower atopy prevalence was also recently found among Dutch adults living in the vicinity of livestock farms (Borlée et al., 2018). In contrast, no biologically plausible explanation could be provided for the reduced prevalence of COPD in the vicinity of livestock farms (Smit et al., 2014). Furthermore, while prevalence was lower close to farms, the frequency of exacerbations among patients with COPD was higher and pulmonary function was lower, particularly with higher livestock-related air pollution levels (Borlée et al., 2015, 2017; van Dijk et al., 2016a; van Kersen et al., 2020).

In countries other than the Netherlands, evidence is mixed regarding a protective effect of living in the vicinity of livestock farms (Casey et al., 2015; Douglas et al., 2018; Kauffmann et al., 2002; Schultz et al., 2019). Studies among farmers themselves are also inconclusive, as some have shown a protective effect with increased farming exposure, whereas others have indicated a higher risk of asthma with increasing farming exposures, particularly for non-atopic asthma (Wunschel and Poole, 2016). Studies among farmers generally have shown an increased prevalence of COPD compared to those in non-farmers, which is attributed to long-term dust exposure (Fontana et al., 2017; Guillien et al., 2019).

In previous research in the Netherlands on associations between asthma and COPD in relation to proximity to livestock farms, several measures of exposure were used, including nearest distances to several types of animal farms and particulate matter (PM) emissions from these farms (Smit et al., 2014). Recently, such exposure measures were extended with modelled concentrations of PM and endotoxins, which is a constituent of organic PM (de Rooij et al., 2019). Such modelled concentrations take into account the proximity to multiple farms and may better approximate the exposures behind the previously observed associations that are currently unknown.

The previous studies focussed on a study population of 92,548 persons (22,406 children; 70,142 adults) living in a livestock-dense area in the southeast of Netherlands and a subset of that population (Borlée et al., 2015; de Rooij et al., 2019; Smit et al., 2014). This region may not be representative of other regions in the Netherlands, because it differs in the density of livestock farms and has relatively higher particulate matter concentrations.[1] This follows from the relatively larger contribution of the agricultural sector in this area besides for instance traffic sources and a relatively high contribution from abroad (with industry and traffic being the most important contributors).

Hence, previous research may be complemented by studies including the entire Netherlands, with a larger study population and modelled PM concentrations as an additional measure of exposure besides distance to the nearest livestock farm. The use of nationwide available data on medication dispensing for asthma and COPD allows full coverage of the Netherlands. Therefore, the aim of this study is to investigate the association between medication dispensing for asthma and COPD and environmental exposure related to livestock farms in the Netherlands.

2. Material and methods

2.1. Study population

The basis of our study population was the Dutch population (16, 670, 000 individuals), with available data on anonymized address locations (key register for addresses and buildings: BAG), individual-level variables, and medication of all persons that were reimbursed by their statutory basic medical insurance.[2] Medication data covered the calendar year 2016. Persons were included if they were registered as living in the Netherlands on 01-01-2015 and had been living at the same home address for at least two years prior to that date. This and several other selection criteria are listed in Table S1, together with the excluded number of persons. Persons with data missing in either the address locations dataset or individual-level variables were excluded. Also, persons were excluded who lived in districts[3] that included houses within 2 km of the border with Belgium or Germany, as emissions of and distances to foreign livestock farms could not be accounted for in the analysis. Persons living in residential care homes were excluded, because of uncertainty whether their medication use is always registered through insurance. Two criteria were defined to exclude persons likely to be occupationally exposed to livestock: persons that lived at the same address as a farm registered in the farm location data and those that were registered as working in the livestock sector.[4] Lastly, persons living in urban agglomerations[5] were excluded.

2.2. Health outcome

The health outcome measure was the dispensing of drugs prescribed for obstructive airway diseases in 2016, indicated as a binary variable. Medication for obstructive airway diseases includes both inhalants and drugs for systemic use, which are indicated by an ATC-code (Anatomical Therapeutic Chemical classification: R03) in data collected by the administrative body responsible for Dutch health insurance (CVZ, Zorginstituut Nederland) for risk equalization among insurance companies. These data do not contain information about duration of use or dosage. The data include persons that are eligible to receive medication according to the standard health insurance policy, excluding medication dispensed during hospital admission and in nursing homes but including medication dispensed by outpatient pharmacies and in residential homes for the elderly. Children aged 0–5 years, those aged 6–17 and adults were distinguished, because diagnosis and treatment of asthma are generally different for children under 6 years of age compared to older children and adults, whereas older children will not be occupationally exposed and are less likely to smoke than adults.

2.3. Exposure indicators

Two proxies of environmental exposure related to livestock farms were used: one based on distances of homes to livestock farms in the Netherlands and one based on the modelled particulate matter concentration originating from livestock farms. Both proxies are conceptually related and provide different perspectives on possible exposure. Particulate matter concentration is not only an indicator of exposure to particulate matter but also to other farm-related emissions. Moreover, modelled concentrations, besides accounting for meteorological conditions, implicitly take into account the proximity of addresses to multiple farms of various sizes, whereas the distance-measure used only takes into account the proximity of the nearest farm. Both proxies should have expressed exposure in 2015, which would then indicate exposure of at least one year prior to medication use in 2016.

[1] The yearly produced concentration maps (such as $PM_{2.5}$ and PM_{10}) can be viewed and/or downloaded via links on https://www.rivm.nl/gcn-gdn-kaarten/concentratiekaarten.

[2] "Risicovereveningsbestanden van het College voor Zorgverzekeringen".

[3] Dutch: "wijk"; no administrative unit but statistical unit used by Statistics Netherlands.

[4] Economic activity data collected by Statistics Netherlands: SECSMBIBUS; company classification code (SBI-code): A 014.

[5] The mapping of Statistics Netherlands is used, which defines urban agglomerations as connected areas with urban buildings where most human activities take place, where most jobs are present and where most public facilities are located.

2.4. Distance to livestock farms

Exposure variables based on distances to farms were defined as the distance to the nearest livestock farm in meters, represented by fixed distance intervals (initially 0–500; 500–1000; 1000–1500; 1500–2000; and >2000 m). The distances between the residences and livestock farms, were calculated with ArcGIS (ESRI (Environmental Systems Research Institute), 2011), on the basis of locations of farms (landbouwtelling, Netherlands Enterprise Agency: RVO) and address locations (BAG) from 2015. Only farms with a minimum number of animals were taken into account, as in previous studies (Borlée et al., 2015; Smit et al., 2014) (Table S2), and a distinction was made between livestock farms of any type, as well as by type: cattle, pig, poultry, goat, sheep, and farms with any other animals.

2.5. Modelled particulate matter concentration

The exposure to livestock-related particulate matter up to 10 μm (PM_{10}) was calculated with the OPS (Operational Priority Substances) model (Sauter et al., 2018), which is an atmospheric transport and dispersion model for airborne pollutants. One of the applications of OPS, is the production of annual-averaged maps of concentration and deposition for the Netherlands at a 1 km by 1 km resolution for air quality monitoring purposes (e.g. (RIVM, 2016)) referred to as GCN and GDN maps (Largescale Concentration/Deposition maps of The Netherlands). The model uses Gaussian plumes to describe the relation between an individual source and an individual receptor. The contributions of the individual sources are summed to obtain the total concentration at a certain location or grid cell. It uses trajectories for long-range transport. The long-term version of the model is employed, which is statistical in the sense that calculations are performed for a number of typical meteorological situations (classes) occurring in, for example, a year. The sum of the values per class, weighted according to their relative frequency of occurrence, is the long-term value.

For this study, a resolution of 250 m by 250 m and meteorological conditions of 2015 were used. The PM_{10} emission strengths of point sources of the various farm locations throughout the Netherlands were requested from the Pollutant Release and Transfer Register[6] for the year 2015. These emissions are calculated by multiplying the number of animals per location with animal-specific and housing type-specific emission factors (Vonk et al., 2016). Emissions from abroad were not included for this model exercise. We distinguished between PM_{10} emissions from housing for goats, poultry, cattle, pigs, horses and ponies, donkeys, mink and rabbits; data for sheep were not available. The sum of the concentrations resulting from these emissions is referred to as "livestock-related PM_{10} exposure". This sum does not include secondary inorganic aerosol, which can partly be attributed to ammonia emissions from livestock farms. However, it does not have a role in microbial or other exposures that are of interest in this study. For analyses of specific animal categories, only goats, poultry, cattle, pigs and the combined concentrations from other animals were distinguished.

To improve the dispersion modelling on the local scale, animal category-specific particle size distributions were implemented. These distributions differ from those implemented by default that are used to obtain the large-scale picture of the air quality in the Netherlands. Specification of such distributions is important, as small and light particles are transported over longer distances than larger and heavier particles. The particle-size distributions were determined on the basis of measurement data of Lai et al. (2014) and Winkel et al. (2015) (see Supplementary Methods).

Exposure to PM_{10} from sources other than Dutch livestock farms as well as to secondary inorganic aerosols was determined by subtracting PM_{10} concentrations originating from livestock farms from the total PM_{10} concentration from all sources. These data were retrieved from the standard available annual GCN map for 2015, with meteorological conditions of 2015, emissions of 2014 and a grid, 1 km by 1 km, which includes emissions from all sectors within the Netherlands and abroad, including aggregated emissions from agriculture per country (RIVM, 2016). A comparison of these livestock-related PM_{10} concentrations from GCN maps and the calculations performed for this study showed only small differences, due to differences in resolution of both model grid and emission sources and year of emission data. Further, the subtraction assures that non-livestock PM_{10} concentrations exclude livestock-related emissions that do not originate from housing (e.g., supply of concentrates to farms). The nitrogen dioxide (NO_2) concentration, as another important source of air pollution was directly obtained from the standard available GCN maps.

2.6. Confounding variables

We included individual covariates relevant for studies on respiratory health because they are potential determinants and are available for analysis within a secure environment provided by Statistics Netherlands. Only age, sex, marital status, migration background and household income fulfilled these requirements. Data on sex, age, marital status and migration background originate from registry data (Basisregistratie Personen), and data on household income were compiled by Statistics Netherlands based on information from tax authorities and other sources. In addition, an indicator for neighbourhood socioeconomic status (SES) in 2016, which is derived every 4 years by the Netherlands Institute for Social Research (Knol, 1998), was used. This indicator is constructed on the four-digit postal code level, with each postal code area comprising on average about 4000 inhabitants. It is based on a principal-component analysis of the income level, unemployment rate and education level of the inhabitants of the postal-code area, which is rescaled to 5 categories, with 1 indicating highest and 5 indicating lowest SES.

2.7. Data privacy regime

Data were analysed within the secure environment provided by Statistics Netherlands, where researchers had access to information on the individual level but not to directly identifiable information such as address locations. No data used outside this secure environment contained information with which individuals could be identified. Exposure variables were calculated outside the secure environment and linked to a general address code (BAG), which was then re-coded by Statistics Netherlands and linked to the health outcome and associated demographic and socioeconomic variables under study.

2.8. Analyses

Logistic regression analyses were conducted separately for 14 regions with different agricultural characteristics as defined by Statistics Netherlands (Dutch: groepen van landbouwgebieden, Fig. 1). Such separate analyses were performed because of computational limitations that hampered the joint analysis of 7.7 million individuals. Separate analyses were performed for each distance-exposure variable and PM_{10}-exposure variable, and results were combined across the 14 regions in meta-analyses. Analyses were conducted separately for children and adults with three different levels of adjustment: personal-level adjustment models included, in addition to the exposure variable, sex, age, marital status (not for children), migration background and household income; fully adjusted models included, in addition to these variables,

[6] www.emissieregistratie.nl. (Pollutant Release and Transfer Register). The Pollutant Release and Transfer Register is responsible for collecting, processing, managing, registering and reporting emission data, so that the Netherlands can meet (inter)national obligations in the field of emission reporting. Emission registration is a cooperative program between various parties; the management and control of emission registration is the responsibility of RIVM.

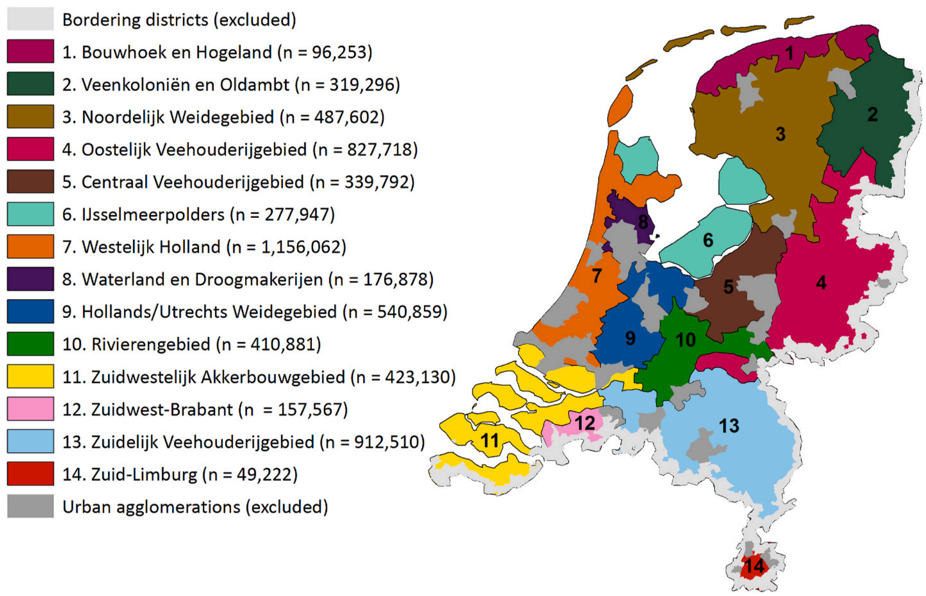

Fig. 1. Specific regions in the Netherlands are shown. The numbers refer to those regions as noted in the manuscript, their Dutch names and number of adults living in the region within brackets. Dark grey indicates the urban agglomerations; light grey indicates the areas close to the border from which inhabitants were excluded.

SES of the postal code area and exposure to non-livestock PM_{10} and NO_2; mutually adjusted models included all animal categories simultaneously, as well as all other covariables. Distance-exposure and livestock-related PM_{10}-exposure variables were not adjusted for each other as this may lead to over-adjustment. Logistic regression analyses were performed with the glm function of the stats package in R (R Core Team). For PM_{10}-exposure analyses, random effects meta-analyses were performed with the metafor package in R (Viechtbauer, 2010). For distance-based exposure analyses, multivariate random effects meta-analyses were performed by including covariance matrices of the distance-categories in the mvmeta package in R (Gasparrini, 2018) to account for the covariance of distance categories. Heterogeneity between regions was assessed with the I^2-statistic.

Models based on distance-based exposure variables, included distance intervals of 500 m (0–500; 500–1000; 1000–1500; 1500–2000 and > 2000 m). For the exposure variables "distance to nearest livestock farm" and "distance to nearest cattle farm", the interval "1500–2000 m" was not included because of the low number of persons living further than 2000 m from cattle farms in some regions; hence, the largest distance category for these variables was ">1500 m". For the mutually adjusted model based on distance variables, the distance intervals were refined by first making a model including distance intervals of 500 m. Because with this model most effects were observed within 1000 m, a new model was made including distance intervals of 250 m (0–250; 250–500; 500–750; 750–1000 and > 1000 m). When high variance within a distance interval or little difference between adjacent distance intervals was observed, distance intervals were merged, keeping a minimum of three distance intervals per animal category.

2.9. Sensitivity analyses

Several types of sensitivity analyses concerning the analytical model, health outcome, exposure and selection of the study population were performed. Sensitivity analyses were compared to fully adjusted analyses. Sensitivity to the analytical model was studied by running multilevel analyses in which the district (Dutch: "wijk"[3]) was included as random effect as a proxy to adjust for potential differences in medication prescription practices between general practitioners and for differences between districts that could not be explained by the other covariables (van de Kassteele et al., 2017). The GLIMMIX procedure in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for these multilevel analyses.

The health outcome in the main analyses concerns the prevalence of medication dispensing in 2016, thus assuming a consistent relation between exposure and health outcome over time. To distinguish new prescriptions from such a prevalence measure, incidence measures of medication dispensing were defined with a run-in time of either 2 or 5 years, thus excluding all persons who received medication in 2014 and 2015 or in 2011–2015. A further refinement in health outcome to help distinguishing asthma and COPD is an analysis of a subset of adults younger than 40 years who are unlikely to have COPD.

Sensitivity to the application of different exposure measures was performed by use of a different source of farm location data provided by the Pollutant Release and Transfer Register[6]. Sensitivity to different selection criteria was assessed by performing additional analyses in which persons that moved in the past two years, those that lived close to the border, those that were assumed to be living or working on a farm, or those that lived in urban agglomerations were added to the study population. For the last selection criterion, persons living in urban agglomerations were not included in analyses of the 14 regions, but logistic regression analyses were performed for the entire population in urban agglomerations, the results of which were included as a 15th region in meta-analyses.

2.10. Population attributable fractions

Where the odds ratios calculated from logistic regression analyses provided an indication of risk, the population attributable fractions (PAF) provided an indication of the *impact* of a risk factor on the total population; the PAFs took into account both the relative risk of an exposure and the number of persons exposed. Since the number of persons and effect sizes varied by region, the PAFs better reflected the overall impact than the odds ratios (ORs) from meta-analyses. PAFs were calculated using the following equation:

$$PAF = (C_p - C_0) / C_p \quad (1)$$

Here C_p is the predicted number of cases of medication reception in the region under the original data (population), and C_0 is the number of predicted cases based on the model coefficients under the counterfactual situation that no livestock farms were present, i.e., no exposure to livestock-related particulate matter and all distances to the nearest

Table 1
Association between medication dispenses and distance to nearest livestock farms, expressed as odds-ratios (95% confidence interval) from meta-analyses over the 14 regions, for different levels of adjustment.

Adults (>17, n = 6,175,717)	Exposure§	Personal-level adjusted‡	Fully adjusted
Distance to nearest livestock farm (m)			
0–500	29.2% (10–47%)	0.91 (0.87–0.96)***	0.95 (0.91–0.99)**
500–1000	37.6% (19–43%)	0.96 (0.93–0.99)*	0.98 (0.95–1.01)
1000–1500	20.2% (10–29%)	0.99 (0.97–1.00)	0.99 (0.98–1.01)
>1500	13.0% (1–44%)	1	1
Distance to nearest cattle farm (m)			
0–500	20.2% (4–37%)	0.90 (0.85–0.95)***	0.94 (0.90–0.97)***
500–1000	32.9% (10–42%)	0.95 (0.91–0.99)*	0.97 (0.95–1.00)
1000–1500	22.5% (12–30%)	0.98 (0.95–1.01)	0.99 (0.97–1.01)
>1500	24.4% (3–74%)	1	1
Distance to nearest pig farm (m)			
0–500	3.4% (0–11%)	0.93 (0.89–0.97)***	0.95 (0.92–0.98)**
500–1000	10.4% (0–30%)	0.96 (0.92–1.01)	0.99 (0.96–1.02)
1000–1500	13.3% (1–27%)	0.97 (0.92–1.02)	0.99 (0.98–1.01)
1500–2000	12.0% (1–20%)	0.98 (0.96–1.00)	0.99 (0.97–1.01)
>2000	61.1% (16–98%)	1	1
Distance to nearest poultry farm (m)±			
0–500	1.5% (0–6%)	0.91 (0.87–0.95)***	0.92 (0.89–0.95)***
500–1000	5.7% (0–21%)	0.94 (0.90–0.99)*	0.97 (0.94–1.00)*
1000–1500	8.7% (0–26%)	0.98 (0.93–1.02)	1.00 (0.97–1.03)
1500–2000	9.4% (0–21%)	0.99 (0.95–1.03)	1.00 (0.98–1.03)
>2000	74.6% (27–100%)	1	1
Distance to nearest goat farm (m)			
0–500	0.4% (0–1%)	0.88 (0.79–0.98)*	0.91 (0.85–0.99)*
500–1000	1.6% (0–4%)	0.93 (0.88–0.99)*	0.95 (0.90–1.00)*
1000–1500	3.4% (0–8%)	0.95 (0.90–1.00)	0.97 (0.92–1.02)
1500–2000	4.9% (1–15%)	0.94 (0.87–1.01)	0.97 (0.93–1.01)
>2000	89.8% (73–99%)	1	1
Distance to nearest sheep farm (m)			
0–500	8.0% (1–22%)	0.95 (0.89–1.01)	0.98 (0.92–1.04)
500–1000	15.8% (7–34%)	0.97 (0.93–1.02)	0.98 (0.93–1.03)
1000–1500	18.5% (10–28%)	0.97 (0.94–1.01)	0.98 (0.94–1.01)
1500–2000	17.3% (12–28%)	0.99 (0.97–1.01)	0.99 (0.97–1.01)
>2000	40.3% (9–64%)	1	1
Distance to nearest farm with other animals (m)			
0–500	8.1% (2–13%)	0.95 (0.92–0.97)***	0.96 (0.94–0.99)***
500–1000	21.5% (7–29%)	0.97 (0.94–0.99)*	0.98 (0.96–1.00)*
1000–1500	24.2% (12–29%)	0.99 (0.96–1.02)	0.99 (0.97–1.01)
1500–2000	20.2% (14–34%)	1.00 (0.97–1.02)	0.99 (0.97–1.01)
>2000	25.9% (4–66%)	1	1

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
§Exposure: mean percentage of persons living in distance-interval, with lowest and highest exposure over the regions in brackets.
‡Personal-level adjusted: adjusted for age, sex, marital status, household income and migration background.
¶Fully adjusted: adjusted for the same variables as in the personal-level adjusted models as well as for SES-category, NO_2 exposure and exposure to non-livestock-related particulate matter.
±Left out region 8 because of insufficient exposure.

livestock farm in the highest distance category.

Confidence intervals were obtained by simulating 1000 Monte Carlo estimates per region, with a different set of model coefficients for each simulation based on the variance-covariance matrix of the logistic regression model, with use of the mvrnorm function in R from the MASS package (Venables and Ripley, 2002). From these 1000 estimates, 1000 different numbers of predicted cases per region were calculated. The total number of predicted cases was determined by summing the predicted cases over the regions and over age groups. From these 1000 different numbers of predicted cases, PAFs were calculated by equation (1). The 95% confidence interval (CI) is assumed to be the range between the 2.5 and 97.5 percentiles of the 1000 PAFs.

We calculated PAFs for two different sets of models; one set included the distances to nearest farms in six animal categories, and the other set included exposure to animal-type specific particulate matter. Each of the two PAFs was based on summing the number of predicted cases from 42 models for three age groups and 14 regions.

3. Results

3.1. Characteristics of the study population

In total 7,735,491 persons (6,175,717 adults; 1,228,242 children between 6 and 17 years old; 331,532 children under 6) were included; 8,934,509 persons that did not fit the selection criteria were excluded (Table S1). In 2016, 608,173 adults (9.8%), 72,044 children between 6 and 17 (5.9%) and 25,727 children under age 6 (7.8%) received R03 medication (Table S3). In total, 29.2% of the included adults lived within 500 m from any livestock farm, with percentages ranging from 10% to 47% over the regions (Table 1). The median concentration of livestock-related PM_{10} for adults was 0.16 $\mu g/m^3$ (10th-90th percentile: 0.04–0.54 $\mu g/m^3$; Fig. 2), similar to that for children. This particulate matter mostly originated from poultry farms (median: 0.13 $\mu g/m^3$; 10th-90th percentile: 0.03–0.41 $\mu g/m^3$). Concentrations of particulate matter from other types of farms were much lower, with a median for pig farms of 0.019 $\mu g/m^3$ (10th-90th percentile: 0.005–0.10 $\mu g/m^3$), for cattle 0.01 $\mu g/m^3$ (10th-90th percentile: 0.005–0.02) and concentrations for goats lower than 0.002 in 99% of cases. Personal characteristics of the study population can be found in Table S3.

3.2. Association with distance variables

Proximity to livestock farms was associated with lower R03 medication dispensing in 2016 for adults in personal-level adjusted and fully adjusted analyses, with a pooled odds ratio (OR) of 0.95 (95% confidence interval [CI]: 0.91–0.99) for living within 500 m of a livestock farm, compared to living further than 1500 m away (Table 1). Such an association was also found for children between ages 6 and 17 years, but no significant association was found for younger children (Table S4).

Also, proximity to the nearest cattle, poultry, pig, or goat farm or farm with other animals (except sheep) was significantly associated with lower R03 medication dispensing in meta-analyses among adults (Table 1). Yet, after mutually adjusting for different animal categories, associations remained significant only for cattle and poultry (Table 2). For both cattle and poultry farms, lower R03 medication dispensing with decreasing distance was apparent in multiple regions across the Netherlands (Fig. 3; Fig. S2). Such negative associations were also found in several regions for other animal categories, yet none of these associations remained statistically significant in the meta-analyses (Fig. S3-6). Significantly positive associations were found for distances to the nearest sheep farm and nearest pig farm for some regions, but in other regions significantly negative associations were found (Fig. S3,S5).

The value of I^2 for meta-analyses of mutually adjusted regression outcomes was 67%–94% across animal categories, indicating considerable heterogeneity, which may be driven by the small confidence intervals for some regions. Importantly, regions with fewer than 20% of persons living within 500 m of a cattle farm (2,6,7,8,11,12) tend to have the lowest ORs for small distances (Fig. 3).

In children, significantly negative associations with proximity to cattle farms were found in meta-analyses of mutually adjusted models, as well (Table S5). Meta-analyses for children also showed decreasing medication dispensing with decreasing distance in several other animal categories, but this was not consistently significant across age groups and analysis types (Table S4-5). Proximity of young children (0–5) to sheep appeared positively associated with medication dispensing, yet significant only when mutually adjusted for proximity to other animals (Table S4-5).

3.3. Association with particulate matter exposure

A weak non-significant negative association was found between receipt of R03 medication in 2016 and exposure to PM_{10} from all livestock farms combined (Table 3). Exposure to PM_{10} from cattle farms was significantly negatively associated with receipt of R03 medication in multiple regions across the Netherlands and in a meta-analysis (OR from meta-analysis of mutually adjusted models: 0.92; 95% CI: 0.86–0.97; I^2 = 97%; Table 3; Fig. 4). The I^2 value indicates considerable heterogeneity across regions, as seen in Fig. 4. In regions with relatively low average cattle-PM_{10} concentrations (2,6,7,11, 12, 14), estimates were generally lower than in regions with higher concentrations (Figs. 2 and 4). For poultry, in some regions significantly negative associations were found as well, but meta-analyses results were not significant (Fig. S6). For pigs and goats, both significantly negative and positive associations were found in individual regions (Fig. S8,9), with positive but not significant associations from meta-analyses for both children and adults (Table 3, Table S6). PM_{10} from sources other than livestock farms was positively associated with receipt of R03 medication in several regions and in a meta-analysis, but only for adults (Table 3, Table S6; Fig. S10). Calculated heterogeneity across regions was considerable, ranging from 52% to 97% across animal categories.

3.4. Sensitivity analyses

3.4.1. Sensitivity to model formulation

Inclusion of district as a random effect in multilevel models gave similar results as the single-level model, although coefficients varied between the models (Table S7,8).

3.4.2. Sensitivity to health outcome

Results of inclusion of a run-in time of either two or five years were similar to results of no inclusion of a run-in time. However, somewhat larger effect sizes were found for the distance to the nearest pig farm, whereas the association with pig-related particulate matter turned significantly negative (Table S9,11). The number of cases included for a run-in time of two years was 116,449 (21 per 1000) and for five years 83,952 (16 per 1000). Only inclusion of adults less than 40 years of age or older persons had a limited effect on the estimates, yet for adults less than 40, the positive association between medication dispensing and particulate matter from non-livestock sources was not significant (Table S10,11).

3.4.3. Sensitivity to exposure variables and selection criteria

Results were hardly sensitive to the use of different farm location data or different selection criteria: not excluding persons that moved in 2014 or 2015 or those living close to the border, excluding persons living in a district within five km from the border, or including those that were expected to live on a farm (Table S12,13). Including urban agglomerations as a 15th region also had little effect on meta-analysis

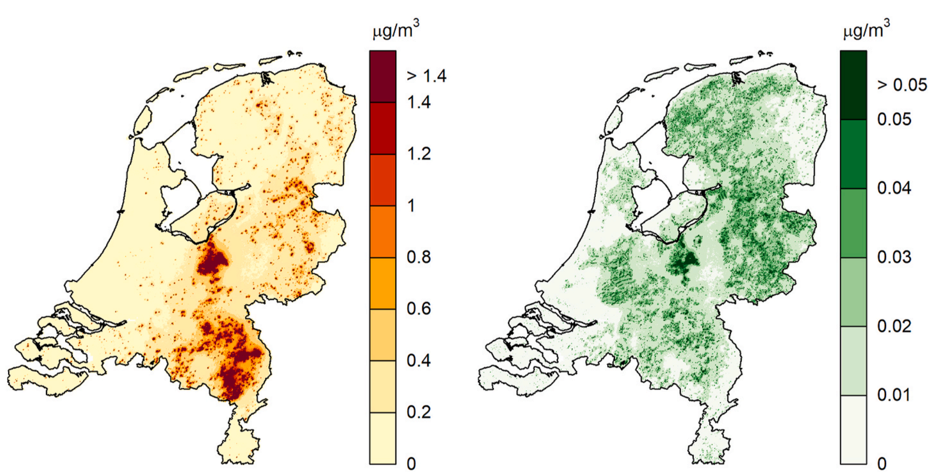

Fig. 2. Modelled particulate matter concentration from all livestock farms (left) and cattle farms (right). The pattern of total livestock-related particulate matter concentrations is driven by emissions from poultry farms (Fig. S1A). Fig. S1 also shows modelled particulate matter concentrations from pig, goat, and other livestock farms.

Table 2
Association between medication dispenses and distance to nearest livestock farms, expressed as odds-ratios (95% confidence interval) from a meta-analysis over the 14 regions of models in which exposures related to different animal categories were mutually adjusted for each other.

Adults (>17 years of age, n = 6,175,717)	Mutually adjusted§
Distance to nearest cattle farm (m)	
0–250	0.93 (0.91–0.95)***
250–500	0.96 (0.94–0.97)***
500–750	0.97 (0.96–0.99)**
750–1000	0.99 (0.97–1.01)
>1000	1
Distance to nearest pig farm (m)	
0–500	0.99 (0.96–1.02)
500–1000	1.03 (0.99–1.06)
>1000	1
Distance to nearest poultry farm (m)±	
0–250	0.89 (0.82–0.97)**
250–500	0.96 (0.92–0.99)*
500–750	0.96 (0.92–1.00)*
750–1000	0.98 (0.96–1.01)
>1000	1
Distance to nearest goat farm (m)	
0–500	0.95 (0.89–1.00)
500–1000	0.98 (0.95–1.01)
>1000	1
Distance to nearest sheep farm (m)	
0–500	1.01 (0.98–1.05)
500–1000	1.00 (0.98–1.03)
>1000	1
Distance to nearest farm with other animals (m)	
0–250	0.98 (0.96–1.01)
250–500	0.99 (0.97–1.00)
500–1000	0.99 (0.98–1.01)
>1000	1

*p < 0.05, **p < 0.01, ***p < 0.001.
§Mutually adjusted: adjusted for age, sex, marital status, household income, migration background, SES-category, NO_2 exposure, exposure to non-livestock-related particulate matter and for exposure to particulate matter from other animals; all values in this table are the results of the same model.
±Left out region 8 because of insufficient exposure.

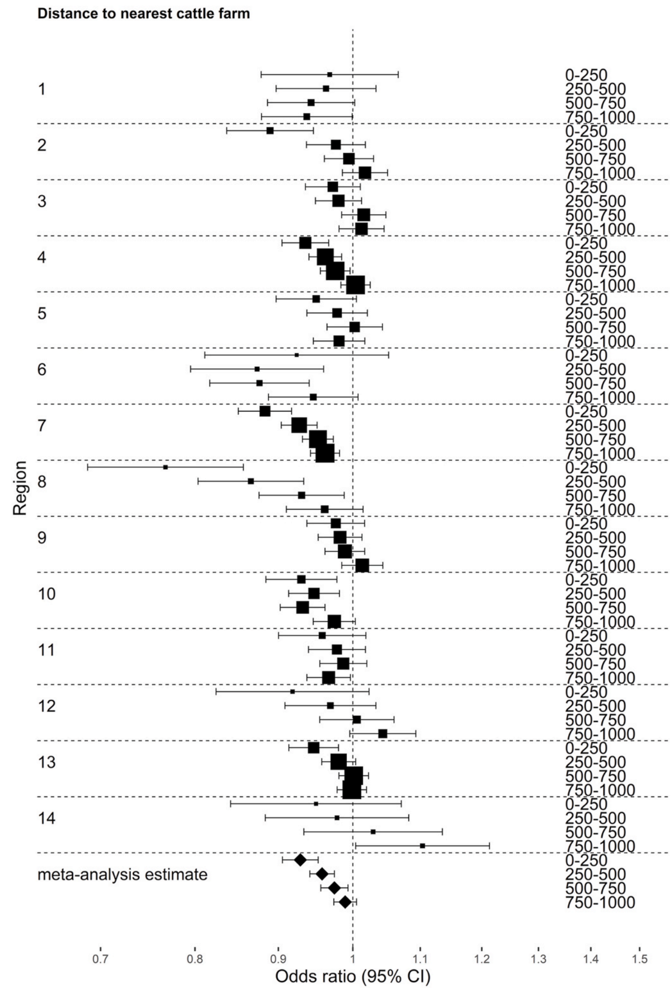

Fig. 3. Forest plot for odds ratios of medication dispensing against distance to nearest cattle farm for mutually adjusted models for adults (adjusted for age, sex, marital status, household income, migration background, socio-economic status, exposure to nitrogen dioxide, distance to nearest poultry farm, distance to nearest pig farm, distance to nearest goat farm, distance to nearest sheep farm, distance to nearest farm with other animals, and exposure to non-livestock-related particulate matter). Regions refer to the regions in Fig. 1, the reference category for all regions is > 1000 m. Meta-analysis summary results can also be found in Table 2.

estimates, but the estimates with pig-related particulate matter turned from non-significantly positive to non-significantly negative when agglomerations were included. Furthermore, associations within urban agglomerations were significantly positive for distance to the nearest sheep farm and for goat-related particulate matter in mutually adjusted analyses (not shown).

3.5. Population attributable fractions

The predicted fraction of persons (adults and children) that receives R03 medication attributable to the presence of livestock farms was −0.016 (95% confidence Interval, CI: -0.013 to −0.019) for a model with distance-based measures and −0.052 (95% CI: -0.045 to −0.059) for a model based on PM_{10}-exposure measures. Hence, on the basis of these models, the number of persons in the study-population receiving R03 medication could increase from 1.6% to 5.2% when no livestock farms were present. Cattle-related exposure contributed most to both estimates, because of both the strength of the associations and the number of persons living close to cattle farms (Fig. 5). The population attributable fraction was positive, assuming no exposure from proximity to sheep farms or from pig-related particulate matter.

4. Discussion

This study shows that environmental exposure to livestock farms is negatively associated with medication dispensing for chronic obstructive airway diseases; persons living close to livestock farms and those with higher modelled exposure to PM_{10} from livestock farms receive less medication than persons living further away and those with lower PM levels. A positive association between medication dispensing and exposure to non-livestock PM_{10} (including secondary inorganic aerosols) was found. The protective association seems most evident for environmental exposure related to cattle farms, for which associations with both distance and PM_{10} remained significant after mutually adjusting for exposure related to other animal categories; such protective association was found to a lesser extent for poultry farms, for which associations were most clear for the distance variables. Results differed per region, but for most regions negative associations were found for distance-based and particulate-matter-based exposure variables and for exposure related to cattle and poultry farms. Such consistency across regions shows that associations are not limited to a previously studied area in the southeast of the Netherlands. Results were only slightly sensitive for the model formulation or use of different selection criteria.

While effect sizes are relatively small, about two-thirds of the Dutch rural population lives within 1 km of a livestock farm (55% including urban agglomerates). Hence, with the assumption that the observed associations are causal, 2%–5% more persons living in rural areas might receive medication for obstructive airway diseases if no livestock farms

Table 3
Association between medication dispenses and livestock-related PM_{10}-exposure, expressed as odds ratios (95% confidence interval) from meta-analyses over the 14 regions, for different levels of adjustment.

Adults (>17, n = 6,175,717)	Personal-level adjusted‡	Fully adjusted	Mutually adjusted§
Livestock-related PM_{10}#	0.98 (0.95–1.02)	0.97 (0.94–1.00)	n.a.
Non-livestock PM_{10}#±	1.27 (1.08–1.49)**	1.27 (1.07–1.51)**	1.29 (1.09–1.52)**
Cattle-related PM_{10}#	0.92 (0.88–0.96)***	0.92 (0.87–0.97)**	0.92 (0.86–0.97)**
Pig-related PM_{10}#	1.40 (0.79–2.47)	1.00 (0.96–1.05)	1.06 (0.99–1.13)
Poultry-related PM_{10}#	0.99 (0.96–1.01)	0.98 (0.95–1.00)	0.99 (0.96–1.02)
Goat-related PM_{10}#	1.00 (0.99–1.01)	1.00 (0.99–1.00)	1.00 (1.00–1.01)
Other animal-related PM_{10}#	0.99 (0.98–1.00)	0.99 (0.98–1.00)	1.00 (0.99–1.00)

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
per 10–90 percentile increase in exposure.
± in fully-adjusted model, adjusted for livestock-related PM_{10}; in Mutually adjusted model adjusted for PM_{10} from animal categories. The estimates correspond to an OR of 1.06 (1.02–1.10) per 1 $\mu g/m^3$ increase.
‡Personal-level adjusted: adjusted for age, sex, marital status, household income and migration background.
¶Fully adjusted: adjusted for the same variables as in the personal-level adjusted models as well as for SES-category, NO_2 exposure and exposure to non-livestock-related particulate matter.
§Mutually adjusted: adjusted for the same variables as in the fully adjusted models as well as for exposure to particulate matter from other animals; all values in this column are the results of the same model.

were present in the Netherlands, which equates to several tens of thousands of persons. The lower bound of this estimate is based on models including the distances to the nearest livestock farms of several types while the upper bound of the estimate is based on models including livestock-related particulate matter. The difference between these estimates may be explained by the inability of the distance to the nearest farm to take into account combined effects of proximity to multiple farms and characteristics such as farm size, which are implicitly accounted for in the modelled livestock-related particulate matter concentrations. The PAFs are in the same order of magnitude as what could be inferred from the odds ratios for asthma and COPD in relation to persons living within 500 m of a livestock farm from the study by Smit et al. (2014). The PAFs that can be calculated from these odds ratios are about −0.053 for COPD and −0.016 for asthma (based on exposure of the entire Dutch population), with a factor 10 uncertainty around these estimates, depending on the assumptions (Post et al., 2020).

Some PAFs appeared to deviate from zero, even though the corresponding null-exposure variables did not show significant associations in meta-analyses. This difference can be explained by a difference in weights of regions between meta-analyses, in which weights are based on standard errors of the estimates, and PAF calculation, in which weights are based on the number of inhabitants of the region. The positive PAFs for pig-related particulate matter and distance to nearest sheep farm and the negative PAFs for distance to nearest pig farm, distance to nearest farm with other animals, and other animal-related particulate matter should thus be interpreted with caution. The inconsistent results between PAFs and meta-analysis results for these animals make such results less strong than results for cattle and poultry farms, for which results are more consistent.

In the present study, no distinction could be made between medication dispensing for asthma and that for COPD. Yet, COPD is generally not diagnosed among persons less than 40 years old, and in adults less than 40 the association between medication dispensing and environmental exposure related to livestock farms was similar to the association among all adults. Moreover, since the associations similar to those in adults were found in children, they likely apply to asthma. Persons 40 years or older receiving R03 medication can have either asthma or COPD, yet analysis in this group showed similar effect sizes compared to analysis in adults younger than 40.

Associations with both proxies used in this study support previous findings in the Netherlands regarding an inverse association between asthma and COPD and proximity to livestock farms that were based on self-reported and general practitioner diagnoses of asthma and COPD

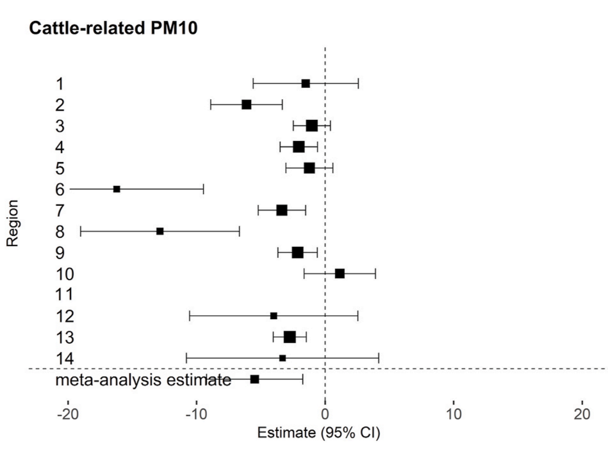

Fig. 4. Forest plot for mutually-adjusted models for the association between medication dispenses and cattle-related PM_{10} exposure among adults (adjusted for age, sex, marital status, household income, migration background, socio-economic status, exposure to nitrogen dioxide, exposure to poultry-related, pig-related, goat-related and other animal-related particulate matter, and exposure to non-livestock-related particulate matter). Regions refer to the regions in Fig. 1. Meta-analysis results can also be found in Table 3.

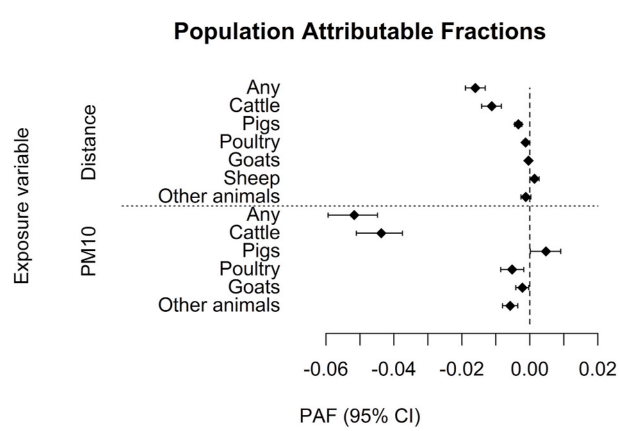

Fig. 5. Population attributable fractions (PAFs) for models with distance to nearest livestock farm as exposure and those with livestock-related PM_{10} as exposure. The exposure variables refer to the counterfactuals in the two sets of 42 mutually adjusted models (14 regions, 3 age groups) from which the PAFs were estimated (mutually adjusted for exposure related to the animal categories, as well as for age, sex, marital status, household income, migration background, socio-economic status, exposure to nitrogen dioxide and exposure to non-livestock-related particulate matter).

(Borlée et al., 2015; de Rooij et al., 2019; Smit et al., 2014). The findings therefore support the hypothesis that the inverse association between asthma and residence in the vicinity of livestock farms is caused by more diverse microbial exposure leading to reduced allergic sensitization (Ege et al., 2011; Ehrenstein et al., 2000; von Mutius, 2016). This hygiene hypothesis is not a plausible explanation for an inverse association with COPD, which is currently supported only by previous research in the Netherlands; most studies among farmers show an increased risk of COPD (Fontana et al., 2017; Guillien et al., 2019). The inverse association between medication dispensing for asthma and COPD and livestock-related exposure is not likely explained by a difference between urban and rural areas, because analyses were performed within regions and persons living in urban agglomerations were excluded.

An alternative explanation for fewer occurrences of medication dispensing close to livestock farms are individual differences in healthcare seeking behaviour. In previous research, such healthcare seeking behaviour appeared lower among persons living close to livestock farms but was not affected by distance to general practitioners (van Dijk et al., 2016b). Regional differences in healthcare seeking behaviour are not likely to have driven inverse associations, because these were observed for multiple regions and remained when adjusted for differences at district level in multilevel analyses. Another alternative explanation for the associations is that persons that have asthma or COPD or that are sensitive to such diseases or parents of asthmatic patients may be more inclined to move away from farms. However, this explanation appears in contradiction to sensitivity analyses in which a run-in time was implemented. These analyses suggest that not only prevalent but also new cases of asthma and COPD are inversely associated with livestock-related exposure, which is unlikely if moving is the result of being diagnosed with asthma or COPD.

In contrast to the association with livestock-related particulate matter, the association of medication dispensing for asthma and COPD with non-livestock-related particulate matter was positive. This finding appears to align well with existing evidence of increased or worsening asthma and COPD among persons exposed to air pollution (Salvi and Barnes, 2009; Viegi et al., 2001; World Health Organization, 2013), yet epidemiological evidence for association of incidence and prevalence of asthma and COPD in adults with air pollution exposure is less strong (Atkinson et al., 2015; EPA, 2019; Gowers et al., 2012; Hendryx et al., 2019; Liu et al., 2017; Schikowski et al., 2014). A positive association is biologically plausible, as several mechanisms have been identified by which particulate matter may induce asthma or COPD (Gowers et al., 2012; Schikowski et al., 2014).

Only associations with cattle farms remained significant for both distance and PM_{10}-related variables after mutually adjusting for other animal categories. Cattle farms are the most widely distributed type of farms in the Netherlands, with more than 20% of the study population living within 500 m from such farms. Hence, more persons live close to only a cattle farm and no other farms than live close to other farms but not to a cattle farm. This distribution may have hindered finding associations with other animal categories in mutually adjusted analyses, but makes it unlikely that associations with cattle-specific exposure are affected by correlated proximity to other farms. A significant inverse association between both COPD and asthma and the presence of a cattle farm within 500 m from a home address was also found in a previous study in the Netherlands (Smit et al., 2014), yet in that study the association did not remain significant when adjusted for proximity to other categories of animal farms. Significantly negative associations with proximity to pigs and goats, but not poultry, were also found by Smit et al. (2014) and Borlée et al. (2015), yet they were not consistently significant across studies and asthma and COPD health outcomes. Internationally, in studies on asthma among persons growing up on farms, traditional farms with cattle have been suggested to be an important factor in the protective effect (Illi et al., 2012).

The associations for cattle-related exposures are not likely explained by the amount of PM_{10} emitted from cattle farms, with the 10th-90th percentile interval for cattle-related PM_{10} concentration for adults more than 20 times lower than that of poultry farms and more than 270 times lower than that of the non-livestock PM_{10} concentration. These associations suggest that livestock-related PM_{10} is a proxy that best aligns with an air transmission route. Exposure to air containing molds, bacteria and endotoxins may indeed be a likely route causing a variety of positive and negative respiratory conditions (May et al., 2012; von Mutius and Vercelli, 2010). Besides air exposure, important exposure factors for a protective effect for asthma are consumption of unprocessed milk and contact with straw and animals (Brooks et al., 2013; Wlasiuk and Vercelli, 2012). A possible correlation of such exposure through farm visits with proximity to livestock farms cannot be ruled out, yet most of the persons living on farms should have been excluded from the analyses.

Although the models in this study were adjusted for several covariables, some potentially important confounders were not included. Smoking, for example, is the primary risk factor for COPD (Kohansal et al., 2009; Viegi et al., 2001). We adjusted for several socio-economic factors known to correlate with such behaviour (van de Kassteele et al., 2017), yet we cannot be certain that some bias may be present in the results due to lack of adjustment for lifestyle factors. Small associations between lifestyle factors and general air pollution have previously been shown to influence risk estimates for mortality (Strak et al., 2017).

Other weaknesses of this study are the limited precision in both the health outcome and the exposure measures. The health outcome of medication dispensing for asthma and COPD can be regarded as a proxy for obstructive airway disease, but it may not be as accurate as information on prescriptions or use; it does not provide an indication about the severity of the disease because of lacking information on doses; and it does not provide sufficient information to distinguish between asthma and COPD. Lack of information on the severity of asthma and COPD hindered the investigation of exacerbations among persons with COPD, which were found to be increased among those living close to livestock farms (Borlée et al., 2015; van Dijk et al., 2016a).

Exposure misclassification may have occurred for various reasons. Such misclassification may be particularly large if exposures are not airborne, as airborne exposures aligns best with our exposure proxies. If airborne exposures have a role in the observed associations, misclassification of PM_{10} exposure may still have occurred. Such misclassification may arise, for example, because of exposure at the home address only, since most persons are not at their home address all day. In addition, exposure was determined only on a grid, 250 m by 250 m. Further, assumptions in dispersion modelling may have led to some misclassification. For example, plume rise due to either heat content or momentum was not included, as no general information on source characteristics required for this plume rise is available. Including plume rise has a diluting effect near the source, hence its exclusion may lead to an overestimation of source-specific concentrations, especially close to farms. Among other characteristics such as emission height, standard animal housing characteristics as used for the GCN maps were applied because no detailed database on this exists. The different forms of potential exposure misclassification make it difficult to give an overall estimate about their possible impact. Effects of exposure misclassification on reduction of statistical power is probably not an important issue, given the large number of persons under study.

In conclusion, the results of this study show that medication dispensing for asthma or COPD decreases with decreasing distance to livestock farms or increasing particulate matter exposure from cattle farms, in particular, in multiple regions within the Netherlands. As medication dispensing is likely indicative of prevalence of asthma or COPD, the results suggest an inverse association between asthma or COPD and livestock exposures. On the assumption that this association is causal, the number of persons with asthma or COPD in rural areas might be up to 5% higher with no livestock-related exposure. This number is considerable in view of the more than 700,000 cases we included in this study and hence is a motivation for additional research regarding potential underlying mechanisms. Such research could focus on ruling out alternative explanations such as healthcare seeking behaviour or finding more evidence of the role of microbial exposures in the associations and how such exposure relates to farming practices.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2020.113651.

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