Full length article

Residential proximity to livestock animals and mortality from respiratory diseases in The Netherlands: A prospective census-based cohort study

Mariana Simões [a],[*], Nicole Janssen [b], Dick J.J. Heederik [a], Lidwien A.M. Smit [a], Roel Vermeulen [a],[c], Anke Huss [a]

[a] Department Population Health Sciences, Institute for Risk Assessment Sciences (IRAS), Utrecht University, Utrecht, the Netherlands
[b] Centre for Sustainability, Environment and Health (DMG), National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands
[c] Department of Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands

ARTICLE INFO

ABSTRACT

Background: There is increasing evidence of associations between residential proximity to livestock farms and respiratory morbidity, but less is known about potential effects on respiratory mortality among residents.
Objectives: We aimed to assess potential associations between respiratory mortality and residential proximity to (intensive) livestock farming.
Methods: In DUELS, a national census-based cohort, we selected all inhabitants from rural and semi-urban areas of the Netherlands, aged ≥30 years and living at the same address for five years up to baseline (2004). We followed these ~4 million individuals for respiratory mortality (respiratory system diseases, chronic lower respiratory diseases, pneumonia) from 2005 to 2012. We computed the average number of cattle, pigs, chicken, and mink present in 500 m, 1000 m, 1500 m and 2000 m of each individual's residence in the period 1999–2003. Analyses were conducted using Cox proportional hazards regression, adjusting for potential confounders at individual and neighbourhood level.
Results: We found evidence that living up to 2000 m of pig farms was associated with respiratory mortality, namely from chronic lower respiratory diseases, with Hazard Ratios ranging from 1.06 (1.02, 1.10) in people living close to low numbers (<median number of animals) of pigs in 1000 m and 1.18 (1.13, 1.24) in those living near high numbers (≥median) of pigs in 2000 m. We also found indications of higher pneumonia mortality in people living near mink farms.
Conclusion: Our results are in line with previous findings of adverse respiratory effects in people living near livestock farms. Little is known about the physical, chemical, and biological exposures leading to respiratory morbidity and mortality warranting further explorations of air contaminants in the vicinity of livestock farms.

1. Introduction

Livestock farms have been shown to be major sources of zoonotic pathogens and air pollutants including particulate matter, endotoxins, ammonia, volatile organic compounds and greenhouse gases (Cambra-López et al., 2010; Jonges et al., 2015; de Rooij et al., 2017; Schulze et al., 2006; Seedorf et al., 1998; Smit et al., 2012; Winkel et al., 2015). Despite concentrations of these compounds being considerably lower in ambient air compared to inside farms, some studies have shown that residents living near farms are at increased risk of respiratory health effects, such as exacerbation of chronic obstructive pulmonary disease (COPD) and symptoms indicative of asthma (wheezing), decreased lung function, increased respiratory symptoms and pneumonia (Borlée et al., 2015, 2017; van Kersen et al., 2020; Radon et al., 2007; Rasmussen et al., 2017). Heterogeneity of outcome definitions and limited evidence of exposure-response relationships do not allow firm conclusions about causality of exposure to livestock farms' emissions and adverse respiratory outcomes in residents living near farms (O'Connor et al., 2017).

The Netherlands is a densely populated country with a large livestock industry and currently witnesses a debate about the future of intensive animal farming, namely regarding loss of biodiversity due to nitrogen deposition, sustainability of farming practices, animal welfare, and possible adverse public health effects (Eijrond et al., 2019). Particularly effects on the health of residents living near (intensive)

livestock farms have received considerable attention in recent years in the Netherlands after the emergence of antimicrobial resistant bacteria (MRSA and ESBLs) starting in 2005, the Q fever epidemic of 2007–2010, and SARS-CoV-2 outbreaks in mink farms in 2020 (Maassen et al., 2016; de Neeling et al., 2007; Oreshkova et al., 2020; Munnink et al., 2021; Overdevest et al., 2011). Several studies conducted after the Q-fever epidemic consistently showed increased risks for pneumonia in people living near goat farms and, to a lesser extent, poultry farms, although the exact causal mechanisms are still under investigation (Freidl et al., 2017; Kalkowska et al., 2018; Smit et al., 2012, 2017). These studies also showed that people living near livestock farms had poorer lung function and higher risk of COPD exacerbations, while, in contrast, a lower prevalence of asthma, allergies, and COPD was observed (Borlée et al., 2015; van Dijk et al., 2016). Respiratory problems were weakly associated with living in the vicinity of cattle, pigs and mink (Borlée et al., 2015, 2017; Smit et al., 2014). Most of these studies focused on incidence of respiratory diseases and symptoms using predominantly data from general practitioners in two rural regions of the Netherlands where density of intensive farming is high. To the best of our knowledge, no studies have investigated associations between respiratory diseases mortality and proximity to livestock farms at a nationwide level.

In this paper, we aimed to investigate the association between living up to 2000 m of cattle, pigs, chicken, and mink farms and mortality due to respiratory system diseases in general, and chronic lower respiratory diseases and pneumonia specifically. Using historical data on the location of farms and registry data, we followed the entire rural Dutch population for respiratory mortality from 2005 to 2012.

2. Methods

2.1. Study population

The Dutch Environmental Longitudinal Study (DUELS) is an administrative cohort that includes all inhabitants aged 30 years or older on 01-01-2004 and registered in the Dutch population registry (GBA – Gemeentelijke Basisadministratie Persoonsgegevens); registration in GBA is mandatory in the Netherlands. The cohort was built integrating data from several databases from Statistics Netherlands (Centraal Bureau voor de Statistiek, CBS) including mortality, individual characteristics, residential history, and neighbourhood characteristics. In this study, we excluded persons who lived within 2000 m of the border with Germany or Belgium (for whom we were unable to compute the livestock specific exposure reliably), persons who changed address in the five years prior to enrolment, and persons living in the more urbanized areas of the Netherlands ($\geq$1500 addresses per km^2, at neighbourhood level, since urban populations rarely live in proximity to livestock farms and differ in lifestyle and living environment factors compared to the more rural populations) (Fig. 1).

2.2. Residential proximity to livestock farms

We determined the presence of livestock farms located in the vicinity of residences using the Geographic Information System for Agricultural Holdings (Geografisch Informatiesysteem Agrarische Bedrijven, GIAB) database, which provides spatial information on agricultural land use, namely data on Dutch agricultural holdings, obtained through the annual agricultural census by CBS and the Netherlands Enterprise Agency (RVO). Data on farm type, farm size and average annual numbers per animal group, among others, are linked to the main farm location of each agricultural holding. These data were available for the years 1999 to 2003. For each year we computed the number of cattle, pigs, chicken, and mink present within buffers of 500, 1000, 1500 and 2000 m around each residence in the Netherlands as proxies for farm exposure. We averaged the number of (specific) animals over the exposure period (1999–2003) and categorized the obtained exposure variables into "no animals" (0 animals within a buffer – referent group),
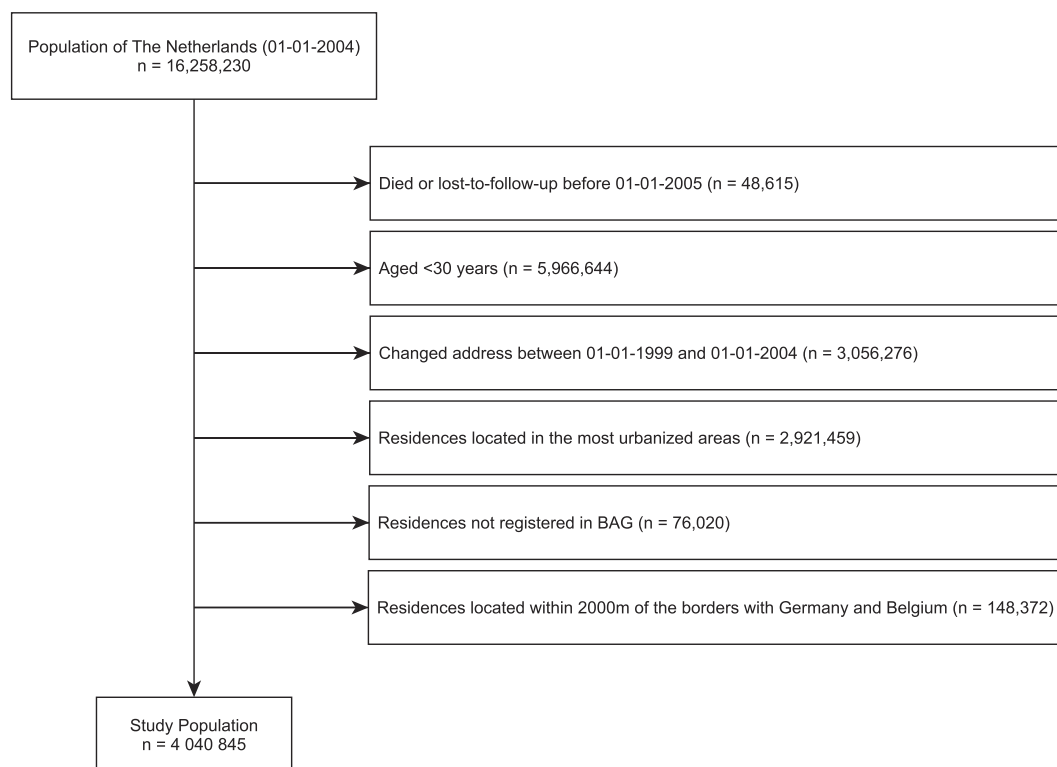

Fig. 1. Flow chart of the study population.
BAG = Basisregistratie Adressen en Gebouwen, the cadastral dataset containing all addresses in the Netherlands used to compute individual residential exposure proxies.

"low" (<median number of animals within a buffer) and "high" (≥median number of animals within a buffer) – see Table S2.1 for cut-off points (medians) of each buffer. The types of farms and buffer sizes were chosen based on results from the "Livestock Farming and Neighbouring Residents' Health" (VGO) project for which some evidence for associations to respiratory health was determined within the abovementioned buffer sizes around residences, namely slightly higher risk of pneumonia in people living near poultry and exacerbation of symptoms and/or more complications in COPD patients living near cattle, pigs, poultry and mink and reduced lung function in people living near livestock in general (Borlée et al., 2015; Freidl et al., 2017; Maassen et al., 2016).

2.3. Cohort follow-up and mortality endpoints

Each individual in the cohort was assigned five years of exposure period, from 01-01-1999 to 31-12-2003. We included a one-year lag period (01-01-2004 to 31-12-2004), to allow for a latency period. Follow-up started on 01-01-2005 and terminated at the end of the follow-up period (31-12-2012), at the time of death or when individuals were lost to follow-up, whichever came first. Data on mortality due to respiratory system diseases (RSD), chronic lower respiratory diseases (CLR) and pneumonia (PNE) were retrieved from the mortality database from CBS, where primary causes of death are classified according to the International Classification of Diseases, 10th revision (ICD-10; Fig. 2) (World Health Organization, 2004). Reliability of causes of death statistics for respiratory diseases was shown to be about 85% in the Netherlands (Harteloh et al., 2010).

2.4. Statistical analysis

We studied the association between respiratory mortality and number of livestock present within our *a priori* defined buffer sizes using age-stratified (one-year age strata) Cox proportional hazards regression, including all considered livestock animal species in the models (Fig. 2). We applied a combination of increasingly adjusted models by adding potential confounders at individual and neighbourhood level and compared residents living within 500, 1000, 1500 and 2000 m from livestock farms ('exposed') to residents that did not have livestock farms within those distances from their residences ('unexposed' – referent group):

- *basic model*, adjusted for sex
- *intermediate model*, basic model further adjusted for origin (based on the mother's country of birth or, if unavailable, father's country of birth), marital status and standardized household income (an individual socioeconomic indicator adjusted for differences in household size and composition)
- *full model*, intermediate model further adjusted for socioeconomic position (SEP) as defined by the SCP (Sociaal en Cultureel Planbureau; a social status score taking into account average income, percentage of people with a low income, percentage of people with a low education and percentage of people not working in a postal code area) (Knol 1998) at four-digit postcode level, urbanization degree at neighbourhood level as defined in the "Wijk- en buurtkaart" (neighbourhood maps) from 1999 and 2003, the proportion of low educated residents in the neighbourhood in 2007 and ambient Particulate Matter < 2.5 μm in diameter (PM$_{2.5}$) and nitrogen dioxide (NO$_2$) levels, as estimated by land use regression models using data for the year 2010 (de Hoogh et al., 2018).

All potential confounders were used as categorical variables (see Table 1 for classes). We also included goat and rabbit farms in all models in the same fashion as our selected types of farms (no animals, <median and > median number of animals) since living near rabbit and goat farms has been reported to be associated with adverse respiratory effects in the Netherlands (Freidl et al., 2017; Jonges et al., 2015; Klous et al., 2018; Maassen et al., 2016; Post et al., 2019; Smit et al., 2012). Nevertheless our exposure assessment for these types of farms presents important limitations that hamper the interpretation of their results. First, there are 40–50 rabbit farms in the Netherlands, and most farms keep just few rabbits, therefore resulting in very few people exposed to rabbit farms. Second, the goat farm industry has seen an important increase between 2000 and 2009, with a doubling of the number of animals and an increasing number of farms. Our exposure (1999–2003) and follow-up (2005–2012) periods encompass, each, part of this rise, resulting in underestimation of "goat exposure", especially during the follow-up period. This is particularly relevant in the context of the large Q fever outbreak of 2007–2010.

2.5. Sensitivity analyses

We conducted six sensitivity analyses. First, we excluded people who worked in agriculture for at least one year in the period 1999 to 2003, to assess the influence of possible occupational exposure on the estimates. In our administrative cohort, we had no access to more detailed information about occupation other than the sector in which people worked in. The sector "agriculture" encompasses not only farm animal workers but also crop farm workers, fisheries and hunting. Because excluding all
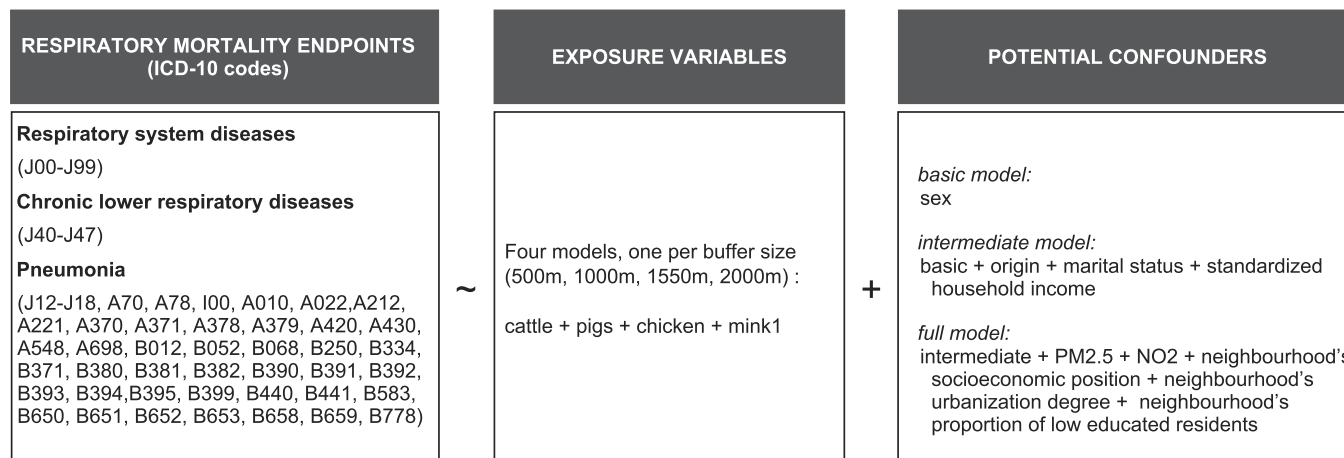
RESPIRATORY MORTALITY ENDPOINTS (ICD-10 codes)	EXPOSURE VARIABLES	POTENTIAL CONFOUNDERS
Respiratory system diseases (J00-J99) **Chronic lower respiratory diseases** (J40-J47) **Pneumonia** (J12-J18, A70, A78, I00, A010, A022,A212, A221, A370, A371, A378, A379, A420, A430, A548, A698, B012, B052, B068, B250, B334, B371, B380, B381, B382, B390, B391, B392, B393, B394,B395, B399, B440, B441, B583, B650, B651, B652, B653, B658, B659, B778)	~ Four models, one per buffer size (500m, 1000m, 1550m, 2000m) : cattle + pigs + chicken + mink1	+ *basic model:* sex *intermediate model:* basic + origin + marital status + standardized household income *full model:* intermediate + PM2.5 + NO2 + neighbourhood's socioeconomic position + neighbourhood's urbanization degree + neighbourhood's proportion of low educated residents

Fig. 2. General framework of the models used in the study.
PM$_{2.5}$ = ambient Particulate Matter < 2.5 μm in diameter, NO$_2$ = ambient nitrogen dioxide.
[1] Exposure variables were categorized into 'none', 'low' (<median number of animals in buffer) and 'high' (≥median number of animals in buffer).

Table 1

Demographic characteristics of the study population and exposed population (at least one livestock animal within 500, 1000, 1500 and 2000 m from the residence), at baseline (2004).

Characteristic	Study Population (N = 4,040,845)	Exposed Population			
		500 m (N = 2,203,650)	1000 m (N = 3,525,961)	1500 m (N = 3,884 771)	2000 m (N = 3,993,150)
Age [mean ± standard deviation]	54.3 ± 13.8	54.1 ± 13.7	54.2 ± 13.8	54.3 ± 13.8	54.3 ± 13.8
Sex [n (%)]					
Female	2,082,912 (51.5%)	1,124,139 (51.0%)	1,812,901 (51.4%)	2,000,863 (51.5%)	2,058,022 (51.5%)
Male	1,957,933 (48.5%)	1,079,511 (49.0%)	1,713,060 (48.6%)	1,883,908 (48.5%)	1,935,128 (48.5%)
Origin [n (%)]					
Dutch	3,688,549 (91.3%)	2,046,999 (92.9%)	3,235,409 (91.8%)	3,553,857 (91.5%)	3,648,072 (91.4%)
Western	278,290 (6.9%)	130,105 (5.9%)	232,409 (6.6%)	262,824 (6.8%)	273,233 (6.8%)
Non-Western	74,006 (1.8%)	26,546 (1.2%)	58,143 (1.6%)	68,090 (1.8%)	71,845 (1.8%)
Civil status [n (%)]					
Married/partner	3,077,930 (76.2%)	1,703,409 (77.3%)	2,699,958 (76.6%)	2,964,955 (76.3%)	3,043,824 (76.2%)
Widowed	328,450 (8.1%)	174,242 (7.9%)	282,552 (8.0%)	314,315 (8.1%)	324,521 (8.1%)
Divorced	222,307 (5.5%)	102,427 (4.6%)	185,796 (5.3%)	209,866 (5.4%)	217,866 (5.5%)
Single	412,060 (10.2%)	223,522 (10.1%)	357,568 (10.1%)	395,541 (10.2%)	406,843 (10.2%)
Unknown	98 (0.0%)	50 (0.0%)	87 (0.0%)	94 (0.0%)	96 (0.0%)
Household income [n (%)]					
<1 percentile	29,409 (0.7%)	19,353 (0.9%)	26,224 (0.7%)	28,375 (0.7%)	29,063 (0.7%)
1-<5 percentile	45,281 (1.1%)	27,663 (1.3%)	39,859 (1.1%)	43,516 (1.1%)	44,680 (1.1%)
5-<10 percentile	89,520 (2.2%)	52,256 (2.4%)	78,591 (2.2%)	86,126 (2.2%)	88,437 (2.2%)
10-<25 percentile	453,406 (11.2%)	249,034 (11.3%)	396,257 (11.2%)	436,811 (11.2%)	448,558 (11.2%)
25-<50 percentile	1,009,797 (25.0%)	543,970 (24.7%)	880,901 (25.0%)	971,012 (25.0%)	998,198 (25.0%)
50-<75 percentile	1,138,095 (28.2%)	617,294 (28.0%)	995,349 (28.2%)	1,094,677 (28.2%)	1,124,407 (28.2%)
75-<90 percentile	748,297 (18.5%)	408,160 (18.5%)	654,468 (18.6%)	720,239 (18.5%)	739,377 (18.5%)
90-<95 percentile	261,202 (6.5%)	142,363 (6.5%)	227,208 (6.4%)	250,803 (6.5%)	258,034 (6.5%)
95-<99 percentile	207,369 (5.1%)	112,008 (5.1%)	177,933 (5.0%)	198,043 (5.1%)	204,653 (5.1%)
99–100 percentile	54,102 (1.3%)	29,430 (1.3%)	45,621 (1.3%)	51,107 (1.3%)	53,467 (1.3%)
Unknown	4,367 (0.1%)	2,119 (0.1%)	3,550 (0.1%)	4,062 (0.1%)	4,276 (0.1%)
Socioeconomic position [n (%)]					
1st quintile	298,062 (7.4%)	115,141 (5.2%)	232,868 (6.6%)	277,870 (7.2%)	292,719 (7.3%)
2nd quintile	769,701 (19.0%)	387,401 (17.6%)	653,861 (18.5%)	732,784 (18.9%)	760,863 (19.1%)
3rd quintile	1,070,146 (26.5%)	636,141 (28.9%)	966,907 (27.4%)	1,044,219 (26.9%)	1,063,152 (26.6%)
4th quintile	1,082,734 (26.8%)	663,151 (30.1%)	975,373 (27.7%)	1,042,292 (26.8%)	1,066,287 (26.7%)
5th quintile	791,645 (19.6%)	377,745 (17.1%)	669,472 (19.0%)	759,409 (19.5%)	781,771 (19.6%)
Unknown	28,557 (0.7%)	24,071 (1.1%)	27,480 (0.8%)	28,197 (0.7%)	28,358 (0.7%)
Urbanization degree [n (%)]					
<500 addresses per km^2	1,366,905 (33.8%)	1,048,318 (47.6%)	1,307,841 (37.1%)	1,351,076 (34.8%)	1,362,100 (34.1%)
500–1000 addresses per km^2	1,361,141 (33.7%)	455,184 (20.7%)	1,040,593 (29.5%)	1,253,290 (32.3%)	1,324,294 (33.2%)
1000–1500 addresses per km^2	1,312,799 (32.5%)	700,148 (31.8%)	1,177,527 (33.4%)	1,280,405 (33.0%)	1,306,756 (32.7%)
Proportion of people with low education [n (%)]					
1st quintile	544,598 (13.5%)	257,759 (11.7%)	451,699 (12.8%)	517,145 (13.3%)	536,404 (13.4%)
2nd quintile	888,532 (22.0%)	493,668 (22.4%)	786,101 (22.3%)	853,556 (22.0%)	874,482 (21.9%)
3rd quintile	969,472 (24.0%)	546,933 (24.8%)	857,073 (24.3%)	940,832 (24.2%)	963,065 (24.1%)
4th quintile	921,454 (22.8%)	515,918 (23.4%)	814,439 (23.1%)	891,406 (22.9%)	912,901 (22.9%)
5th quintile	715,681 (17.7%)	388,857 (17.6%)	615,723 (17.5%)	680,797 (17.5%)	705,203 (17.7%)
Unknown	1,108 (0.0%)	515 (0.0%)	926 (0.0%)	1,035 (0.0%)	1,095 (0.0%)
Mean concentration of nitrogen dioxide (NO_2), μg/m^3 [n (%)]					
1st quartile [7.27,26.9]	1,704,937 (42.2%)	1,106,561 (50.2%)	1,540,337 (43.7%)	1,656,606 (42.6%)	1,693,048 (42.4%)
2nd quartile (26.9,31.7]	1,390,917 (34.4%)	732,236 (33.2%)	1,215,605 (34.5%)	1,331,406 (34.3%)	1,367,766 (34.3%)
3rd quartile (31.7,36.6]	793,081 (19.6%)	309,628 (14.1%)	657,190 (18.6%)	757,547 (19.5%)	783,600 (19.6%)
4th quartile(36.6,93]	126,416 (3.1%)	39,881 (1.8%)	90,747 (2.6%)	114,723 (3.0%)	123,438 (3.1%)
Unknown	25,494 (0.6%)	15,344 (0.7%)	22,082 (0.6%)	24,489 (0.6%)	25,298 (0.6%)
Mean concentration of fine particulate matter ($PM_{2.5}$), μg/m^3 [n (%)]					
1st quartile [8.57,15.4]	1,319,422 (32.7%)	713,768 (32.4%)	1,097,988 (31.1%)	1,244,281 (32.0%)	1,295,899 (32.5%)
2nd quartile (15.4,16.5]	892,046 (22.1%)	517,181 (23.5%)	783,213 (22.2%)	855,853 (22.0%)	880,305 (22.0%)
3rd quartile (16.5,17.4]	836,048 (20.7%)	484,008 (22.0%)	753,564 (21.4%)	814,429 (21.0%)	827,862 (20.7%)
4th quartile (17.4,20.8]	967,835 (24.0%)	473,349 (21.5%)	869,114 (24.6%)	945,719 (24.3%)	963,786 (24.1%)
Unknown	25,494 (0.6%)	15,344 (0.7%)	22,082 (0.6%)	24,489 (0.6%)	25,298 (0.6%)

persons working in this sector would result in excluding many people that would probably not be farm animal workers we decided to include all in our main analysis and conduct a sensitivity analysis excluding agricultural workers. Second, we restricted analyses to people living in neighbourhoods with less than 1000 addresses per km2 to assess potential bias from a semi-urban environment. Third, we combined the two previous sensitivity analyses, since most farmers will live in the more rural areas and in or near farms. Fourth, we reran analyses using redefined exposure variables' categories, where we assigned a zero if the farm had less than a minimum number of animals, as done previously in the VGO study (Supplementary material, S1), so not to assign people living near stables with only a few hobby animals or a farm with an obsolete licence with a few animals contributing to the "exposed" categories. Fifth, we conducted an analysis including only people residing in the regions of east of Noord-Brabant and the North of Limburg, the two regions covered in the VGO project due to their high animal density and where it was shown to exist associations between residential proximity to livestock and respiratory problems. With this sensitivity analysis, we aimed to compare results of our nationwide main analysis to results obtained when including only people living in these regions. Sixth, for completeness, we ran analyses including equines (horses and donkeys), sheep, and other poultry (mainly turkey and ducks) since data was available, although we had no prior reason for investigation. Furthermore, because (intensive) livestock farming is a regional activity in the Netherlands, we conducted stratified analyses by the four major socio-economic regions (according to the Nomenclature des Unités Territoriales Statistiques, NUTS1), followed by a random effects meta-analysis to assess heterogeneity (I^2 statistic) of regional estimates. Finally, to identify potential residual bias we conducted negative control

analyses using colon cancer, bladder cancer, liver cirrhosis and alcoholic liver disease mortality as the endpoints. These mortality endpoints are strongly associated to smoking and/or other unhealthy lifestyle behaviours, namely alcohol consumption, but unlikely related to environmental pollution from livestock farming (Malhotra et al., 2016; Saginala et al., 2020; Sheron, 2016; Stoffel and Murphy, 2020). For completeness, we also explored associations to 'all cause' and 'non-accidental' mortality.

2.6. Software

The geospatial assignment of exposure variables was conducted in R version 3.6.1 (2019-07-05), using the "sf" and "rgdal" packages. Statistical analyses were performed in R version 3.6.2 (2019-12-12), within a secured remote access environment of CBS.

3. Results

We included 4,040,845 persons in our analyses, of which a total of 412,532 (10.2%) participants died, including 40,131 (1.0%) from RSD, 19,054 (0.5%) from CLR and 15,189 (0.4%) from PNE during follow-up (2005–2012). In this study population there were 26,309 (0.7%) persons lost to follow-up. There were 2,203,650 (54.5%), 3,525,961 (87.3%), 3,884,771 (96.1%) and 3,993,150 (98.8%) people exposed to at least on type of animal in the 500, 1000, 1500 and 2000 m buffer, respectively. We observed few unexposed persons in the larger buffers for the most ubiquitous types of farms in the Netherlands (namely cattle, S2). Table 1 describes the demographic characteristics of the study population and the exposed population within each buffer. A table reporting the number

Table 2

Associations between living within 500, 1000, 1500 and 2000 m from livestock animals and mortality due to Respiratory system diseases, Chronic lower respiratory diseases and Pneumonia. Results are presented as Hazard Ratios (HR) and its corresponding 95% Confidence Interval (95% CI) and P value (full model).

Type animal	Buffer size	Category	Respiratory System Diseases		Chronic Lower Respiratory Diseases		Pneumonia	
			HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Cattle	500 m	low	1.01 (0.98, 1.03)	0.521	0.99 (0.96, 1.03)	0.618	1.04 (1.00, 1.08)	0.081
		high	1.02 (0.99, 1.05)	0.277	0.99 (0.94, 1.03)	0.518	1.05 (1.00, 1.10)	0.045
	1000 m	low	0.99 (0.96, 1.02)	0.589	0.97 (0.93, 1.02)	0.235	0.99 (0.95, 1.04)	0.741
		high	1.01 (0.97, 1.04)	0.630	1.01 (0.96, 1.06)	0.645	0.99 (0.94, 1.04)	0.692
	1500 m	low	0.97 (0.93, 1.02)	0.217	0.89 (0.84, 0.95)	2.2e-04	1.06 (0.99, 1.14)	0.114
		high	1.00 (0.96, 1.05)	0.866	0.91 (0.85, 0.97)	0.007	1.09 (1.00, 1.18)	0.038
	2000 m	low	0.92 (0.86, 0.99)	0.020	0.84 (0.76, 0.93)	6.8e-04	0.99 (0.88, 1.11)	0.858
		high	0.97 (0.90, 1.04)	0.363	0.86 (0.77, 0.95)	0.004	1.06 (0.94, 1.20)	0.312
Pigs	500 m	low	1.05 (1.01, 1.09)	0.018	1.02 (0.97, 1.08)	0.407	1.11 (1.05, 1.18)	5.5e-04
		high	1.03 (0.99, 1.07)	0.158	1.08 (1.02, 1.14)	0.011	1.04 (0.97, 1.11)	0.300
	1000 m	low	1.04 (1.01, 1.07)	0.006	1.06 (1.02, 1.10)	0.006	1.03 (0.99, 1.08)	0.171
		high	1.08 (1.05, 1.11)	1.5e-06	1.09 (1.04, 1.14)	1.7e-04	1.08 (1.03, 1.14)	0.002
	1500 m	low	1.07 (1.04, 1.10)	5.8e-07	1.08 (1.04, 1.12)	3.0e-05	1.04 (1.00, 1.08)	0.061
		high	1.12 (1.08, 1.15)	1.9e-12	1.16 (1.11, 1.21)	1.3e-10	1.07 (1.02, 1.13)	0.005
	2000 m	low	1.06 (1.03, 1.09)	1.9e-05	1.09 (1.04, 1.13)	4.3e-05	1.01 (0.97, 1.06)	0.567
		high	1.11 (1.07, 1.15)	5.6e-10	1.18 (1.13, 1.24)	5.0e-12	1.03 (0.98, 1.09)	0.230
Chicken	500 m	low	0.98 (0.94, 1.02)	0.275	0.98 (0.93, 1.04)	0.574	0.96 (0.91, 1.02)	0.236
		high	1.04 (1.00, 1.08)	0.031	1.01 (0.96, 1.07)	0.705	1.04 (0.98, 1.11)	0.209
	1000 m	low	1.00 (0.97, 1.02)	0.848	1.00 (0.96, 1.04)	0.965	1.01 (0.97, 1.06)	0.528
		high	1.02 (1.00, 1.05)	0.098	1.01 (0.97, 1.05)	0.636	1.04 (1.00, 1.09)	0.061
	1500 m	low	1.00 (0.97, 1.03)	0.994	1.00 (0.96, 1.04)	0.943	1.01 (0.97, 1.05)	0.764
		high	1.01 (0.98, 1.04)	0.490	1.01 (0.97, 1.05)	0.562	1.02 (0.98, 1.07)	0.349
	2000 m	low	1.00 (0.97, 1.03)	0.841	0.99 (0.94, 1.04)	0.630	1.01 (0.96, 1.06)	0.732
		high	1.03 (1.00, 1.07)	0.053	1.04 (0.99, 1.10)	0.094	1.03 (0.97, 1.08)	0.362
Mink	500 m	low	1.04 (0.83, 1.30)	0.731	0.85 (0.60, 1.20)	0.356	1.30 (0.94, 1.80)	0.109
		high	0.92 (0.76, 1.12)	0.426	0.93 (0.70, 1.23)	0.601	0.97 (0.71, 1.33)	0.870
	1000 m	low	0.99 (0.89, 1.10)	0.821	0.99 (0.85, 1.16)	0.927	0.97 (0.82, 1.15)	0.744
		high	1.01 (0.90, 1.12)	0.921	0.95 (0.81, 1.11)	0.493	1.11 (0.94, 1.31)	0.211
	1500 m	low	1.01 (0.94, 1.08)	0.785	1.00 (0.91, 1.11)	0.942	1.01 (0.90, 1.13)	0.889
		high	1.06 (0.99, 1.14)	0.121	0.97 (0.87, 1.08)	0.593	1.20 (1.08, 1.34)	0.001
	2000 m	low	1.01 (0.95, 1.06)	0.797	1.00 (0.93, 1.08)	0.954	1.02 (0.93, 1.11)	0.731
		high	1.06 (1.00, 1.12)	0.049	0.98 (0.90, 1.06)	0.549	1.20 (1.10, 1.31)	2.3e-05

Models were adjusted for: sex, origin, marital status, standardized household income, neighbourhood's socioeconomic position, urbanization degree at neighbourhood level, proportion of low educated residents in the neighbourhood, ambient particulate matter < 2.5 μm in diameter ($PM_{2.5}$) levels and ambient nitrogen dioxide (NO_2) levels. Models were also adjusted for the presence of goats and rabbits. The referent category are those with zero animals in the respective buffer.

of (un)exposed people for each mortality endpoint status can be found in S2.

People living near pigs presented consistently higher risk for all mortality endpoints (RSP, CLR and PNE) across the four buffers (Table 2). We saw no clear pattern indicating that living near cattle, chicken, or mink was associated with these mortality endpoints. Nevertheless, we observed some elevated risk estimates of PNE in people living near a high number of cattle in the 500 m and 1500 m and 2000 m buffers, accompanied by a lower risk of CLR in the two larger buffers in both exposure categories. People living within 1500 and 2000 m of a high number of mink showed higher risk for PNE. In general, estimates obtained in the main analyses were robust to sensitivity analyses (S4), except for the analysis in the VGO areas where we observe weak, absent or even inverse associations compared to the main analysis. Stratified analysis showed that, generally, heterogeneity of the regional estimates was not high ($I^2 < 75\%$) (S5). The negative control analyses showed no associations between colon cancer, bladder cancer, liver cirrhosis, and alcoholic liver disease mortality and residential proximity to livestock animals (S6).

4. Discussion

We investigated the association between living near livestock animals and mortality from respiratory system diseases, chronic lower respiratory diseases and pneumonia using a national administrative cohort. We found higher risk of mortality due to all three respiratory endpoints in people living near farms raising pigs, observing Hazard Ratios above unity consistently across all buffer sizes and a tendency for increasing risks in people living in proximity to higher as compared to lower animal counts. In addition, generally homogeneous results across the Netherlands were observed. There was no clear evidence of associations for the other animals, although several increased risk estimates also emerged for associations between living near cattle and mink farms and risk of PNE mortality.

We conducted a nationwide prospective census-based cohort study using a large non-urban study population of over 4 million individuals for which we objectively assessed individual proxies for livestock farm exposure and included all major groups of animals raised in the Netherlands. By including the entire rural and semi-urban Dutch population aged $\geq$ 30 years, not only did we preclude recall and selection bias for the exposure, outcome and considered confounders, but we also conducted, to the best of our knowledge, the largest study on the topic to date. Additionally, most studies on this topic have focused on short-term exposures or have a cross-sectional design. Our long exposure and follow-up periods allowed the study of long-term exposure and potential respiratory health effects.

While access to registry data allowed for the advantages described above, use of these data was accompanied by disadvantages regarding obtaining detailed information about outcomes, exposure and potential confounders. First, we are unable to identify the specific causes of respiratory diseases underlying death. We only included primary causes of death, leading to possible outcome misclassification if people died from other causes but had concomitant respiratory conditions. Second, we could not adjust for behavioural or lifestyle factors and relevant risk factors for respiratory mortality endpoints such as active or passive smoking, body mass index (BMI), nutrition, indoor air pollution and underlying comorbidities. Nevertheless, there is no reason to assume that any residual confounding would be present only for the association found between living close to pig farms and respiratory mortality, and not with the other types of animals. Furthermore, our negative control analyses show no indication for strong confounding by smoking and poor lifestyle behaviours, although the potential for some residual confounding cannot be completely dismissed. Of note, other studies on residential proximity to livestock farms and respiratory outcomes conducted in the Netherlands where some of the abovementioned confounders were taken into account showed no appreciable changes in the

estimates when compared to more parsimonious models controlling only for age and sex (Freidl et al., 2017; Smit et al., 2014). Third, uncertainty about exposure could have resulted in exposure misclassification. Our geographical data on farms pertained to the address of the farm's company which may not correspond to the location where animals were held. This is unlikely an issue for animals such as pigs, chicken, and mink that usually stay in barns/coops, often close to the farmers' home address. However, different housing systems are used for dairy and beef (veal calves) cattle. According to CBS, most dairy cattle had access to outdoor pastures during grazing season in 1997 in the Netherlands (CBS, 1997), while beef cattle is mainly raised indoors. In the Netherlands, sheep are also typically managed in grazing systems and equines (horses) usually have high mobility due to their use in sports; uncertainty about the location of these animals also hampers the interpretation of the results of the sensitivity analyses where we included them (S4). Overall, however, high uncertainty of location information of a specific animal type would mean that the absence of statistically increased risks does not preclude that such risks may exist. We did not define a cut-off for the minimum number of animals a farm should have, thus exploring the effect living near a relatively (very) low number of livestock animals. This may have introduced some exposure misclassification if people lived near a few hobby animals or obsolete licences with a few animals in the "low exposed" group. Still, for comparison, we provide the VGO cut-offs and conducted a sensitivity analysis using these cut-offs, observing that our main findings and conclusions remained unchanged (S1 and S3). Moreover, livestock farming is a ubiquitous activity in the Netherlands resulting in lack of exposure contrasts, especially in the larger buffers. Spatial analysis and adjustment for other types of livestock farming than the one of interest was further complicated by the fact that some types of animals are more predominant in some regions. Nevertheless, our stratified analyses by region showed no indication that the results were influenced by big heterogeneity between these regions, although meta-analytical risk estimates were slightly attenuated (S5). Sensitivity analyses focused on the VGO project study area revealed clear attenuation of HRs towards unity. In this region, most people lived in close proximity to pig farms resulting in reduced exposure contrasts. We observed that there were both somewhat more cases among unexposed and somewhat fewer cases among the exposed in the VGO area as compared to the whole country. In combination, this hampered the interpretation of the results of a sensitivity analysis limited to a smaller regional unit. Stratified analysis by region showed that heterogeneity was overall low.

Our results suggest increased risks of CLR (which is dominated by COPD, S2.4) in residents living close to pigs. Several previous studies have shown negative associations between residential proximity to farms and COPD, which conflicts with what was shown in studies conducted among farmers (de Rooij et al., 2019; Smit et al., 2014). A possible explanation could be that these studies were cross sectional, a design not best suited to study the relationship between long term exposures and chronic diseases. Studies among farmers have indeed shown a higher risk of developing COPD, especially in cattle, poultry and pig farmers, probably due to long-term exposure to indoor air contaminants (Fontana et al., 2017; Guillien et al., 2019).

We observed indications of reduced risks of CLR mortality and increased risks of PNE mortality in people living near cattle. Although a recent study, also conducted in the Netherlands, showed a decreased risks for asthma and COPD prescriptions, especially among people living near cattle (Post et al., 2021), because we were unable to distinguish dairy and beef cattle in our proxy, estimates obtained for cattle are difficult to interpret. While previous studies reported several adverse respiratory effects in people living near poultry farms, we did not find a clear pattern indicating higher risk of respiratory mortality in people living near chicken, which could be related to the difference in outcomes explored (mortality vs symptoms/diagnosis) (Freidl et al., 2017; Kalkowska et al., 2018; Maassen et al., 2016; Smit et al., 2012, 2017). We also observed an indication for higher risk of PNE in people living within

1500 m and 2000 m of mink farms. Note that mink farming is banned from the Netherlands as of January 2021.

Although research shows that living near rabbit and goat farms can be associated with adverse respiratory effects and we did include their presence in the models (Tables S4), we refrained from interpreting the results, for reasons outlined in the Methods section. That our results show no evidence of an association between living near goat farms and increased pneumonia mortality may be related to the underestimation of the number of goats in the follow-up period and is in contrast to the clear increase in the risk of having pneumonia in people living near goat farms, even after the epidemic, as reported by several studies (Freidl et al., 2017; Jonges et al., 2015; Klous et al., 2018; Maassen et al., 2016; Post et al., 2019; Smit et al., 2012).

Despite our data showing that lower animal counts (possibly related to smaller farms) were not more frequently located closer to residences than very high animal counts (possibly related to larger farms), we observed that some HRs were, counterintuitively, higher in the low category compared to the high category. These results could be possibly explained by differences in type of housing system, type ventilation systems and hygiene practices affecting emissions rates, reinforcing the importance of using quantitative exposure information. In fact, most studies so far, including this one, have used exposure proxies for farm emissions, such as distance and number of farms/animals near residences, which can be prone to ecological fallacies. Because we did not perform direct measurements of exposure nor did we have access to information on animal housing systems and other farming practices that can influence emissions, it remains unclear which compounds emitted by animal farming are responsible for the effects seen. Possible underlying exposures include endotoxins and pathogenic infectious agents as well as particulate matter, reactive nitrogen gases and volatile organic compounds, all shown to have deleterious effects on health (Maassen et al., 2016). Recently, a study conducted in the Netherlands found that livestock specific biological components of particulate include induce inflammatory responses in human cells, suggesting that farm emissions can indeed contribute to airway diseases in humans (Liu et al., 2019). Given the lack of validated countrywide exposure assessment models that could be applied to the exposure period of this study, we were unable to determine the spread these emissions across the four buffer distances we considered. Fortunately, work on such models has been developed in more recent years. A model to quantify national agricultural emissions such as ammonia, methane, particulate matter and carbon dioxide has been used for the Netherlands since 2011 (the National Emission Model for Agriculture, NEMA) (Velthof et al., 2012). Furthermore, De Rooij, et al., have done extensive work on improving modelling of farm related exposures. They quantified residential exposure to livestock farms' emissions in the Dutch agricultural setting by developing land use regression and dispersion models, analogue to traffic related air pollution models, to predict endotoxin exposure at residential addresses (de Rooij et al., 2018, 2019). This work has demonstrated that predicted PM_{10} and endotoxin concentrations are well, if not better, suited for individual exposure assessment. Because these models rely on data collected in a later time period than that assessed by us, they are unsuited to be applied to the period of this study (1999–2003). De Rooij's models were furthermore developed in a specific region of the Netherlands and may be unfit for application to the whole country. Still, they constitute a valuable tool to evaluate associations in more detail in the future.

5. Conclusions

In conclusion, this is the first exploratory study conducted in the Netherlands assessing possible associations between residential proximity to (intensive) animal farming and respiratory mortality. We observed an association between residential proximity to pig farms and increased mortality from respiratory diseases, namely COPD and pneumonia and some indications of higher risk of pneumonia in people living near mink. Deeper insights and better guidance towards interventions warrant both additional analyses using improved exposure assessment methodology, using either quantitative molecular techniques or modelled particulate matter and endotoxin residential exposure on a national scale, and identification of the pollutants driving respiratory health effects observed in this and other Dutch studies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2022.107140.

References

Borlée, F., Yzermans, C.J., Aalders, B., Rooijackers, J., Krop, E., Maassen, C.B.M., Schellevis, F., Brunekreef, B., Heederik, D., Smit, L.A.M., 2017. Air Pollution from Livestock Farms Is Associated with Airway Obstruction in Neighboring Residents. Am. J. Respir. Crit. Care Med. 196 (9), 1152–1161.

Borlée, F., Yzermans, C.J., van Dijk, C.E., Heederik, D., Smit, L.A.M., 2015. Increased Respiratory Symptoms in COPD Patients Living in the Vicinity of Livestock Farms. Eur. Respir. J. 46 (6), 1605–1614.

Cambra-López, M., Aarnink, A.J.A., Zhao, Y., Calvet, S., Torres, A.G., 2010. Airborne Particulate Matter from Livestock Production Systems: A Review of an Air Pollution Problem. Environ. Pollut. 158 (1), 1–17.

van Dijk, C.E., Garcia-Aymerich, J., Carsin, A.-E., Smit, L.A.M., Borlée, F., Heederik, D.J., Donker, G.A., Yzermans, C.J., Zock, J.-P., 2016. Risk of Exacerbations in COPD and Asthma Patients Living in the Neighbourhood of Livestock Farms: Observational Study Using Longitudinal Data. Int. J. Hyg. Environ. Health 219 (3), 278–287.

Eijrond, V., Claassen, L., van der Giessen, J., Timmermans, D., 2019. Intensive Livestock Farming and Residential Health: Experts' Views. Int. J. Environ. Res. Public Health 16 (19), 3625.

Fontana, L., Lee, S.-J., Capitanelli, I., Re, A., Maniscalco, M., Mauriello, M.C., Iavicoli, I., 2017. Chronic Obstructive Pulmonary Disease in Farmers: A Systematic Review. J. Occup. Environ. Med. 59 (8), 775–788.

Freidl, G.S., Spruijt, I.T., Borlée, F., Smit, L.A.M., van Gageldonk-Lafeber, A.B., Heederik, D.J.J., Yzermans, J., van Dijk, C.E., Maassen, C.B.M., van der Hoek, W., Leroyer, C., 2017. Livestock-Associated Risk Factors for Pneumonia in an Area of Intensive Animal Farming in the Netherlands. PLoS ONE 12 (3), e0174796. https://doi.org/10.1371/journal.pone.0174796.

Guillien, A., Soumagne, T., Dalphin, J.-C., Degano, B., 2019. COPD, Airflow Limitation and Chronic Bronchitis in Farmers: A Systematic Review and Meta-Analysis. Occup. Environ. Med. 76 (1), 58 LP-68.

Harteloh, P., de Bruin, K., Kardaun, J., 2010. The Reliability of Cause-of-Death Coding in The Netherlands. Eur. J. Epidemiol. 25 (8), 531–538.

de Hoogh, K., Chen, J., Gulliver, J., Hoffmann, B., Hertel, O., Ketzel, M., Bauwelinck, M., van Donkelaar, A., Hvidtfeldt, U.A., Katsouyanni, K., Klompmaker, J., Martin, R.V., Samoli, E., Schwartz, P.E., Stafoggia, M., Bellander, T., Strak, M., Wolf, K., Vienneau, D., Brunekreef, B., Hoek, G., 2018. Spatial PM2.5, NO2, O3 and BC Models for Western Europe – Evaluation of Spatiotemporal Stability. Environ. Int. 120, 81–92.

Jonges, M., van Leuken, J., Wouters, I., Koch, G., Meijer, A., Koopmans, M., Yen, H.-L., 2015. Wind-Mediated Spread of Low-Pathogenic Avian Influenza Virus into the Environment during Outbreaks at Commercial Poultry Farms. PLoS ONE 10 (5), e0125401. https://doi.org/10.1371/journal.pone.012540110.1371/journal.pone.0125401.g00110.1371/journal.pone.0125401.g00210.1371/journal.pone.0125401.t001.

Kalkowska, D.A., Boender, G.J., Smit, L.A.M., Baliatsas, C., Yzermans, J., Heederik, D.J. J., Hagenaars, T.J., Loor, J.J., 2018. Associations between Pneumonia and Residential Distance to Livestock Farms over a Five-Year Period in a Large Population-Based Study. PLoS ONE 13 (7), e0200813. https://doi.org/10.1371/journal.pone.020081310.1371/journal.pone.0200813.t00110.1371/journal.pone.0200813.s00110.1371/journal.pone.0200813.s00210.1371/journal.pone.0200813.s003.

van Kersen, W., Oldenwening, M., Aalders, B., Bloemsma, L.D., Borlée, F., Heederik, D., Smit, L.A.M., 2020. Acute Respiratory Effects of Livestock-Related Air Pollution in a Panel of COPD Patients. Environ. Int. 136, 105426. https://doi.org/10.1016/j.envint.2019.105426.

Klous, G., Smit, L.A.M., Freidl, G.S., Borlée, F., van der Hoek, W., IJzermans, C.J., Kretzschmar, M.E.E., Heederik, D.J.J., Coutinho, R.A., Huss, A., 2018. Pneumonia Risk of People Living Close to Goat and Poultry Farms – Taking GPS Derived Mobility Patterns into Account. Environ. Int. 115, 150–160.

Knol, F.A., 1998. Van Hoog Naar Laag, van Laag Naar Hoog: De Sociaal-Ruimtelijke Ontwikkeling van Wijken Tussen 1971–1995 [in Dutch]. Sociaal en Cultureel Planbureau, The Hague.

Liu, D., Mariman, R., Gerlofs-Nijland, M.E., Boere, J.F., Folkerts, G., Cassee, F.R., Pinelli, E., 2019. Microbiome Composition of Airborne Particulate Matter from Livestock Farms and Their Effect on Innate Immune Receptors and Cells. Sci. Total Environ. 688, 1298–1307.

Maassen, K., Smit, L., Wouters, I., van Duijkeren, E., Janse, I., Hagenaars, T., IJzermans, J., van der Hoek, W., Heederik, D., 2016. Veehouderij En Gezondheid Omwonenden (Livestock Farming and the Health of Local Residents).

Malhotra, J., Malvezzi, M., Negri, E., La Vecchia, C., Boffetta, P., 2016. Risk Factors for Lung Cancer Worldwide. Eur. Respiratory J. 48 (3), 889–902.

de Neeling, A.J., van den Broek, M.J.M., Spalburg, E.C., van Santen-Verheuvel, M.G., Dam-Deisz, W.D.C., Boshuizen, H.C., van de Giessen, A.W., van Duijkeren, E., Huijsdens, X.W., 2007. High Prevalence of Methicillin Resistant Staphylococcus Aureus in Pigs. Vet. Microbiol. 122 (3-4), 366–372.

O'Connor, A.M., Auvermann, B.W., Dzikamunhenga, R.S., Glanville, J.M., Higgins, J.P. T., Kirychuk, S.P., Sargeant, J.M., Totton, S.C., Wood, H., Von Essen, S.G., 2017. Updated Systematic Review: Associations between Proximity to Animal Feeding Operations and Health of Individuals in Nearby Communities. Syst. Rev. 6 (1), 86.

Oreshkova, N., Molenaar, R.J., Vreman, S., Harders, F., Oude Munnink, B.B., Hakze-van der Honing, R.W., Gerhards, N., Tolsma, P., Bouwstra, R., Sikkema, R.S., Tacken, M. GJ., de Rooij, M.MT., Weesendorp, E., Engelsma, M.Y., Bruschke, C.JM., Smit, L. AM., Koopmans, M., van der Poel, W.HM., Stegeman, A., 2020. SARS-CoV-2 infection in farmed minks, the Netherlands, April and May 2020. Euro Surveill. Bull. Eur. Sur Les Maladies Transmissibles = European Communicable Disease Bulletin 25 (23). https://doi.org/10.2807/1560-7917.ES.2020.25.23.2001005.

Munnink, O., Bas, B., Sikkema, R.S., Nieuwenhuijse, D.F., Molenaar, R.J., Munger, E., Molenkamp, R., van der Spek, A., Tolsma, P., Rietveld, A., Brouwer, M., Bouwmeester-Vincken, N., Harders, F., Hakze-van, R., der Honing, M.C.A., Wegdam-Blans, R.J., Bouwstra, C.G., van der Eijk, A.A., Velkers, F.C., Smit, L.A.M., Stegeman, A., van der Poel, W.H.M., Koopmans, M.P.G., 2021. Transmission of SARS-CoV-2 on Mink Farms between Humans and Mink and Back to Humans. Science (New York, N.Y.) 371 (6525), 172–177.

Overdevest, I., Willemsen, I., Rijnsburger, M., Eustace, A., Li, X.u., Hawkey, P., Heck, M., Savelkoul, P., Vandenbroucke-Grauls, C., van der Zwaluw, K., Huijsdens, X., Kluytmans, J., 2011. Extended-Spectrum β-Lactamase Genes of Escherichia Coli in Chicken Meat and Humans, The Netherlands. Emerg. Infect. Dis. 17 (7), 1216–1222.

Post, P.M., Hogerwerf, L., Huss, A., Petie, R., Boender, G.J., Baliatsas, C., Lebret, E., Heederik, D., Hagenaars, T.J., IJzermans, C.J., Smit, L.A.M., Lau, E.HY., 2019. Risk of Pneumonia among Residents Living near Goat and Poultry Farms during

2014–2016. PLoS ONE 14 (10), e0223601. https://doi.org/10.1371/journal.pone.0223601.

Post, P.M., Houthuijs, D., Sterk, H.A.M., Marra, M., van de Kassteele, J., van Pul, A., Smit, L.A.M., van der Hoek, W., Lebret, E., Hogerwerf, L., 2021. Proximity to Livestock Farms and Exposure to Livestock-Related Particulate Matter Are Associated with Lower Probability of Medication Dispensing for Obstructive Airway Diseases. Int. J. Hyg. Environ. Health 231, 113651. https://doi.org/10.1016/j.ijheh.2020.113651.

Radon, K., Schulze, A., Ehrenstein, V., van Strien, R.T., Praml, G., Nowak, D., 2007. Environmental Exposure to Confined Animal Feeding Operations and Respiratory Health of Neighboring Residents. Epidemiology 18 (3), 300–308.

Rasmussen, S., Casey, J., Bandeen-Roche, K., Schwartz, B., 2017. Proximity to Industrial Food Animal Production and Asthma Exacerbations in Pennsylvania, 2005–2012. Int. J. Environ. Res. Public Health 14 (4), 362.

de Rooij, M.M.T., Heederik, D.J.J., van Nunen, E.J.H.M., van Schothorst, I.J., Maassen, C. B.M., Hoek, G., Wouters, I.M., 2018. Spatial Variation of Endotoxin Concentrations Measured in Ambient PM10 in a Livestock-Dense Area: Implementation of a Land-Use Regression Approach. Environ. Health Perspect. 126 (1), 017003. https://doi.org/10.1289/EHP2252.

de Rooij, M.M.T., Heederik, D.J.J., Borlée, F., Hoek, G., Wouters, I.M., 2017. Spatial and Temporal Variation in Endotoxin and PM10 Concentrations in Ambient Air in a Livestock Dense Area. Environ. Res. 153, 161–170.

de Rooij, M.M.T., Smit, L.A.M., Erbrink, H.J., Hagenaars, T.J., Hoek, G., Ogink, N.W.M., Winkel, A., Heederik, D.J.J., Wouters, I.M., 2019. Endotoxin and Particulate Matter Emitted by Livestock Farms and Respiratory Health Effects in Neighboring Residents. Environ. Int. 132, 105009. https://doi.org/10.1016/j.envint.2019.105009.

Saginala, K., Barsouk, A., Aluru, J.S., Rawla, P., Padala, S.A., Barsouk, A., 2020. Epidemiology of Bladder Cancer. Med. Sci. (Basel, Switzerland) 8 (1), 15.

Schulze, A., van Strien, R., Ehrenstein, V., Schierl, R., Küchenhoff, H., Radon, K., 2006. Ambient Endotoxin Level in an Area with Intensive Livestock Production. Annals of Agricultural and Environmental Medicine : AAEM 13 (1), 87–91.

Seedorf, J., Hartung, J., Schröder, M., Linkert, K.H., Phillips, V.R., Holden, M.R., Sneath, R.W., Short, J.L., White, R.P., Pedersen, S., Takai, H., Johnsen, J.O., Metz, J. H.M., Groot Koerkamp, P.W.G., Uenk, G.H., Wathes, C.M., 1998. Concentrations and Emissions of Airborne Endotoxins and Microorganisms in Livestock Buildings in Northern Europe. J. Agric. Eng. Res. 70 (1), 97–109.

Sheron, N., 2016. Alcohol and Liver Disease in Europe – Simple Measures Have the Potential to Prevent Tens of Thousands of Premature Deaths. J. Hepatol. 64 (4), 957–967.

Smit, L.A.M., Boender, G.J., de Steenhuijsen, W.A.A., Piters, T.J., Hagenaars, E.G.W., Huijskens, J.W.A., Rossen, M.K., Nodelijk, G., Sanders, E.A.M., Yzermans, J., Bogaert, D., Heederik, D., 2017. Increased Risk of Pneumonia in Residents Living near Poultry Farms: Does the Upper Respiratory Tract Microbiota Play a Role? Pneumonia (Nathan Qld.) 9, 3.

Smit, Lidwien A.M., Hooiveld, Mariëtte, van der Sman-de Beer, Femke, Opstal-van Winden, Annemieke W.J., Beekhuizen, Johan, Wouters, Inge M., Joris Yzermans, C., Heederik, Dick, 2014. Air Pollution from Livestock Farms, and Asthma, Allergic Rhinitis and COPD among Neighbouring Residents. Occupat. Environ. Med. 71(2), 134 LP-140.

Smit, L.A.M., van der Sman-de Beer, F., Opstal-van Winden, A.W.J., Hooiveld, M., Beekhuizen, J., Wouters, I.M., Yzermans, J., Heederik, D., Caylà, J.A., 2012. Q Fever and Pneumonia in an Area with a High Livestock Density: A Large Population-Based Study. PLoS ONE 7 (6), e38843. https://doi.org/10.1371/journal.pone.003884310.1371/journal.pone.0038843.g00110.1371/journal.pone.0038843.g00210.1371/journal.pone.0038843.t00110.1371/journal.pone.0038843.t002.

Statistics Netherlands (CBS), 1997. "Weidegang van Melkvee (Pasture Grazing of Dairy Cattle); Weidegebied 1997-2015." Retrieved December 10, 2020 (https://opendata.cbs.nl/statline/#/CBS/nl/dataset/70736ned/table?ts=1607603670712).

Stoffel, E.M., Murphy, C.C., 2020. Epidemiology and Mechanisms of the Increasing Incidence of Colon and Rectal Cancers in Young Adults. Gastroenterology 158 (2), 341–353.

Velthof, G.L., van Bruggen, C., Groenestein, C.M., de Haan, B.J., Hoogeveen, M.W., Huijsmans, J.F.M., 2012. A Model for Inventory of Ammonia Emissions from Agriculture in the Netherlands. Atmos. Environ. 46, 248–255.

Winkel, Albert, Mosquera, Julio, Groot Koerkamp, Peter W.G., Ogink, Nico W.M., Aarnink, André J.A., 2015. Emissions of Particulate Matter from Animal Houses in the Netherlands. Atmos. Environ. 111, 202–212.

World Health Organization, 2004. ICD-10: International Statistical Classification of Diseases and Related Health Problems: Tenth Revision.