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Review

A systematic review of the public health risks of bioaerosols from intensive farming

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ABSTRACT

Background: Population growth, increasing food demands, and economic efficiency have been major driving forces behind farming intensification over recent decades. However, biological emissions (bioaerosols) from intensified livestock farming may have the potential to impact human health. Bioaerosols from intensive livestock farming have been reported to cause symptoms and/or illnesses in occupational-settings and there is concern about the potential health effects on people who live near the intensive farms. As well as adverse health effects, some potential beneficial effects have been attributed to farm exposures in early life. The aim of the study was to undertake a systematic review to evaluate potential for adverse health outcomes in populations living near intensive livestock farms.

Material and methods: Two electronic databases (PubMed and Scopus) and bibliographies were searched for studies reporting associations between health outcomes and bioaerosol emissions related to intensive farming published between January 1960 and April 2017, including both occupational and community studies. Two authors independently assessed studies for inclusion and extracted data. Risk of bias was assessed using a customized score.

Results: 38 health studies met the inclusion criteria (21 occupational and 1 community study measured bioaerosol concentrations, 16 community studies using a proxy measure for exposure). The majority of occupational studies found a negative impact on respiratory health outcomes and increases in inflammatory biomarkers among farm workers exposed to bioaerosols. Studies investigating the health of communities living near intensive farms had mixed findings. All four studies of asthma in children found increased reported asthma prevalence among children living or attending schools near an intensive farm. Papers principally investigated respiratory and immune system outcomes.

Conclusions: The review indicated a potential impact of intensive farming on childhood respiratory health, based on a small number of studies using self-reported outcomes, but supported by findings from occupational studies. Further research is needed to measure and monitor exposure in community settings and relate this to objectively measured health outcomes.

Abbreviations: AFO, Animal feeding operation; AHR, Airway hyper-responsiveness; ATS, American thoracic society; BAL, Bronchoalveolar lavage; BAT, Best available technique; BPI, Bactericidal permeability-increasing; BREF, Reference document; CAFOs, Concentrated animal feeding operations; CAP, Community-acquired pneumonia; CI, Confidence interval; COPD, Chronic obstructive pulmonary disease; CRP, C-reactive protein; ECP, Eosinophilic cationic protein; EMR, Electronic medical records; ERS, European respiratory society; EU, Endotoxin units; FEF25-75, Forced expiratory flow between 25 and 75%; FEV1, Forced expiratory volume in the first second; FVC, Forced vital capacity; GI, Gastrointestinal; GP, General practitioner; GRADE, Grads of recommendations, assessment, development and evaluation; ICS, Inhaled corticosteroid; IED, Industrial emissions directive; IL, Interleukin; ISAAC, International study of asthma and allergies in childhood; LPS, Lipopolysaccharides; MBL, Mannose-binding lectin; MRC, Medical research council; MOOSE, Meta-analyses and systematic reviews of observational studies; NIHR HPRU, National institute for health research health protection research unit; OR, Odds ratio; PEF, Peak expiratory flow; PHE, Public health England; PM10, Particles with aerodynamic diameter 10 μm or less; PR, Prevalence ratios; RR, Relative risk; RV, Residual volume; SD, Standard deviation; SSLW, Steady state live weight; TLC, Total lung capacity; TLR, Toll-like receptor; TNF, Tumour necrosis factor; VC, Vital capacity; WBC, White blood count; WIBS, Wideband integrated bioaerosol sensor

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1. Introduction

The current world population of 7.5 billion (2017) is set to rise to almost 10 billion by 2056. An increase in the population means more food is required and thus a growing demand for livestock products. In 2010 the Food and Agriculture Organisation of the United Nations estimated that food production will need to increase by 70% by 2050 to cope with population growth (FAO, 2009). With efforts to meet the food demand of an increasing population there has been widespread adoption of more intensive (achieving higher total output per unit of land) farming (or agricultural) practices. These farms hold large numbers of animals (primarily pigs or poultry), often indoors, typically at high densities. Animal farming contributes to air pollution in many ways, emitting odours, gases (ammonia, hydrogen sulfide), particulates, including dust and airborne biological components (bioaerosols), and a complex mixture of volatile organic compounds. Emissions from farms have been linked with a broad range of adverse health effects, including respiratory disorders and gastrointestinal (GI) problems in farm workers (Iversen et al., 2000; Schiffman 1998), and more recently negative health effects have been documented for residents living nearby intensive farms (O'Connor et al., 2010; O'Connor et al., 2017). Livestock exposure has also been associated with zoonotic infectious diseases (such as Q fever) (Dijkstra et al., 2012; Gyuranecz et al., 2014; Halsby et al., 2017). Symptoms of Q fever in humans range from mild to severe and is caused by *Coxiella Burnetii*, a bacterium mostly commonly found in cattle, sheep and goats (Raoult et al., 2005). In keeping with the hygiene hypothesis (see Section 1.3 below) some studies have shown a protective effect of farming exposure against, for example the development of atopic outcomes (Douwes et al., 2003). The ongoing intensification of livestock production, together with recent cases of Q fever reported in the UK (Halsby et al., 2017) and in the Netherlands (Dijkstra et al., 2012) has urged policy-makers and planners to better understand the dispersion and health impacts of the air emissions to the surrounding area. For policy makers to make better, more informed decisions about how to regulate air emissions there is a need to identify the causative agent(s). Dust emitted as a result of farming practices is primarily organic (of a biological nature), and therefore contains bioaerosols (Dungan 2010). Workplace exposures to bioaerosols in other industries (e.g. waste recycling, composting, cotton processing) have been linked to adverse, mainly respiratory, health effects (Douwes et al., 2000; Douwes et al., 2003; Poulsen et al., 1995). A recent systematic review also reported qualitative evidence linking bioaerosol emissions from composting facilities to poor respiratory health in nearby residents (Pearson et al., 2015). Some studies show the presence of bioaerosols at some distance downwind from their source (Fischer et al., 2008; Hryhorczuk et al., 2001). In order to establish and implement appropriate strategies and effective measures to mitigate risk, it is essential that regulatory authorities have access to the most up-to-date and accurate information, and key gaps in knowledge are highlighted to corroborate future research.

1.1. Regulation of intensive farming

There is no uniform international definition of what constitutes an intensive farm and regulation of such facilities varies between countries. European Union member states intensive farming activities are regulated under the Industrial Emissions Directive (IED) 2010/75/EU (European Union, 2010). Under the IED an intensive farm is defined as rearing poultry or pigs in an installation with more than 40,000 places for poultry or 2000 places for production pigs over 30 kg or 750 places for sows, and will require a permit to operate. To prevent, reduce or otherwise manage environmental and health impacts, pig and poultry farms within the European Union are required to use appropriate operational practices known as the Best Available Techniques (BAT), as described in the Reference Document (BREF) (Santonja et al., 2017). While this does set out requirements for meeting dust emission limits that will help to reduce bioaerosol emissions, there are no specific regulatory limits for bioaerosol emissions. Bioaerosol concentrations and emissions are influenced by a number of factors including: design of animal housing and manure collection system; ventilation; temperature; type of feed; feeding and watering techniques; quality of feed raw materials; use of bedding; cleaning of houses to remove dust deposits; and production method, which are addressed in the BREF (Santonja et al., 2017).

European Union member states implement their own local regulations to ensure compliance with the IED. For example, in England permitting arrangements require operators to undertake a site specific bioaerosol risk assessment if an intensive farming operation is within 100 m of a sensitive human receptor (e.g. a residential house or place of work) (Defra, 2016). The Netherlands considered producing a health-based quantitative risk assessment framework for intensive farms and recommended an exposure limit for the general population of 30 endotoxin units (EU) per cubic metre (EU m^{-3}), based on applying a safety factor of three to the occupational limit of 90 EU m^{-3} (Netherlands HCot, 2012). However, it was concluded that, to date, there was insufficient evidence available to set health based regulatory distances between farms and residential areas. At present in the UK, most farmers do not normally monitor and control emissions to air unless specifically required to do so as a result of local complaints (Commission, 2015).

1.2. Bioaerosol exposure

Bioaerosols consist of viable or non-viable airborne microorganisms, their constituent parts and by-products (Douwes et al., 2003). They are ubiquitous in the environment (indoor and outdoor) and can originate from a range of sources, both natural and anthropogenic. In animal houses, major sources of bioaerosols are animals, animal wastes, feed and bedding material (AirQuality, 2012). The continuing increasing trend in farming intensification is therefore likely to increase bioaerosol concentrations and diversity. Bioaerosols can stay suspended in the air for prolonged periods and potentially travel long distances from their source (Nygard et al., 2008), and as a result may pose health effects to nearby communities with elevated exposures.

1.3. Health effects of bioaerosols

Human exposure to bioaerosols has been associated with a range of acute and chronic adverse health effects and diseases. The most commonly reported are respiratory system problems (e.g. rhinitis, asthma, bronchitis and sinusitis), through both atopic and non-atopic allergic mechanisms as well as non-allergic pathways (Douwes et al., 2003). Other health problems reported include GI distress, fatigue, weakness and headache (Douwes et al., 2003). Bioaerosol exposure occurs primarily through inhalation, although ingestion also contributes. A number of studies, focussing mainly on small-scale family farming, have linked bioaerosol emissions to the potentially fatal disease, Farmer's Lung – the prototype of hypersensitivity pneumonitis (HP; also known as extrinsic allergic alveolitis) (Eduard et al., 2012). However, major stumbling blocks in the study of potential health consequences of exposure to bioaerosols in the agricultural setting have been a lack of information on exposure and difficulties in disentangling the effects of bioaerosol emissions from those of other emissions.

A further need to understand better the composition of bioaerosols is indicated by a consideration of particle size. Bioaerosol particles in air can be suspended in air as single cells or spores or as aggregates. Asthma is a disease of the upper airways. Particles ranging from about 4 μm to 10 μm tend to deposit in the upper airways. Many bioaerosol particles, such as fungal spores and pollen, fall within this size range, although others (e.g. bioaerosol aggregates, spore chains) may be larger and as a result likely remain within the nasal cavity.

Overall these challenges and the consequent lack of valid exposure, dose and response data has prevented the establishment of limit values for bioaerosol emissions from farming operations.

While there tends to be a bias towards the presumption of health risks from bioaerosols, the converse – beneficial health effects – may also occur. The hygiene hypothesis, (Stiemsma et al., 2015; Strachan, 1989) a somewhat misleading term (Bloomfield et al., 2016), states that exposure to microbial agents – including those resulting from intensive farming practices – during early life to be beneficial to later health. There is some limited evidence to suggest prevalence of wheeze and asthma was lower among children living in close proximity of an intensive farm (Mirabelli et al., 2006).

A systematic review of potential health effects associated with living in close proximity to an intensive farm (O'Connor et al., 2010) which was recently updated (O'Connor et al., 2017) had inconclusive findings. However, proximity measures are an indirect measure of exposure and it is difficult to determine the potential contribution of bioaerosol emissions on the health of residents near intensive farms. It can also be difficult to disentangle the impact of exposure on health from that of other factors, such as socio-economic status. The aim of this systematic review was to evaluate potential health effects associated with bioaerosol emissions from intensive farming, and provide an unbiased, up-to-date understanding of the bioaerosol risk to residents living near these farms. We included occupational studies to investigate the type of health effects reported in those most highly exposed to bioaerosols, to inform our interpretation of community studies. Our focus was on bioaerosols, so we excluded studies solely related to zoonotic infectious disease e.g. Q fever or gaseous air pollutants e.g. ammonia.

2. Material and methods

A systematic review was conducted, according to Meta-Analyses and Systematic Reviews of Observational Studies (MOOSE) guidelines (Stroup et al., 2000).

2.1. Search strategy

A literature search was conducted across two electronic databases (PubMed and Scopus). Grey literature was identified using internet-wide search engines (Google and Google Scholar). The search string (provided in Appendix A) was reviewed by a project steering group and experts in the field and was used to search within the title and abstract fields of the electronic databases. The search string also included terms associated with waste operations (composting, landfill, etc.) to identify any studies which may have involved a combination of both intensive farming and waste disposal sites. Other papers were identified from prior knowledge, contact with experts in the field and hand searching of the bibliographies of the papers identified from the electronic search. References were downloaded into the referencing software program Endnote (version X8).

2.2. Study selection

After excluding duplicates, the selection of studies from the electronic databases was conducted in two stages; first by titles and abstracts and then by full text. All titles and abstracts were reviewed independently by two reviewers (SR, PD); any discrepancies were resolved by an additional reviewer. Full-text copies of potentially eligible papers were then retrieved and similarly screened for inclusion (SR, PD). To be included in the final analysis, studies had to meet the following inclusion criteria:

- Peer-reviewed articles or published by a recognised institution between January 1960 and April 2017
- Design: Epidemiological studies – experimental and observational
- Type of facility: animal (poultry, pig*) feeding operations (if it was not clear from the description in the paper whether it was an intensive farm, the paper was included)
- Exposure: measured concentrations of bioaerosol components
- Health outcome: respiratory, lung function indices, cardiovascular effects, GI effects
- Population: Workers, residents
- Data analysis: the analysis techniques have been reported
- Language: English and non-English languages

* Papers referring to swine and hog were also identified. Papers did not distinguish between pig, swine and hog. The word "pig" will be used throughout the remainder of the paper.

Studies were excluded from further review if:

- They did not contain original data (e.g. review papers, editorials and commentaries were excluded). However, reference lists from the identified original articles and reviews were screened to identify any other potential relevant studies.
- Design: Animal (*in vivo*) and *in vitro* studies
- Exposure: odour, ammonia
- Health outcome: Papers only dealing with mental health (e.g. depression, anxiety, distress), zoonotic infectious diseases** (e.g. Q fever) and/or unspecified physical/mental health (e.g. feeling unwell)
- The article did not have an abstract or the full text of the article is not available
- They did not have both an exposure and health outcome measure

**But included papers related to respiratory infections that also include mention of Q fever.

2.3. Data extraction

A standardised checklist was used to extract data from studies that met the inclusion criteria. Data collected were: study design, study setting, study population, exposure assessment, outcome assessment, bioaerosols/pollutants measured. The data extraction was conducted independently by authors (SR, PD).

2.4. Bias assessment

We considered using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) framework for rating the quality of studies included in the review (modified Cochrane), which presents an approach similar to the Cochrane risk of bias assessment tool (Guyatt et al., 2011). However these criteria do not consider exposure assessment, which is an essential component to evaluate these studies. Therefore, we used a quality assessment scoring tool which was developed from Pearson et al. (2015), which was itself previously developed from Shah and Balkhair (2011). This scoring tool, which was originally designed to assess bias from cross-sectional and cohort studies, was adapted to also allow bias to be assessed from experimental and quasi-experimental studies (Appendix B). Two reviewers (AH, PD, SR) independently assessed each study with reported health effects for eight potential sources of bias: study design, selection, responder, confounder, exposure assessment, outcome assessment, sample size and analytical. A third reviewer resolved any disputes (PD, AH). Scores were provided on a scale of 1–4; a score of 4 was given where there was low bias.

3. Results

The study selection process is represented in Fig. 1. After removing duplicates, the search strategies (electronic databases, personal communication) identified 5555 citations. During title and abstract screening, 5488 citations failed to meet the inclusion criteria. The most frequent reasons for exclusion were: did not concern bioaerosols, did

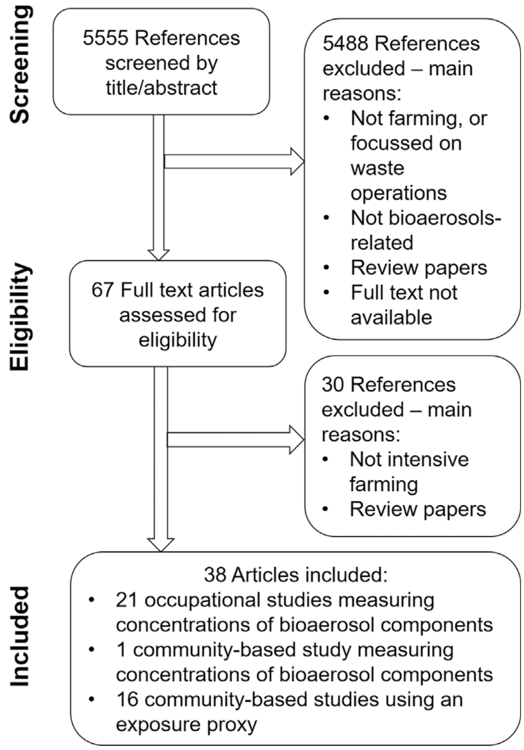

Fig. 1. Flow chart detailing the study selection process.

not publish original research, did not assess the level of exposure and relationship of exposure to outcome, or did not concern farming (for example, considered only composting or waste studies). Of the remaining 67 studies that underwent full text screening, 38 papers were eligible and underwent data extraction. Among the final set of 38 papers, 21 were occupational studies measuring concentrations of bioaerosol components, there was one community-based study measuring concentrations of bioaerosol components, and 16 community-based studies that used a proxy for bioaerosol exposure (e.g. distance from site or estimated concentrations from dispersion modelling). The majority of the studies were located in Europe, particularly the Netherlands and Germany and in the USA. Few studies provided sufficient information for clear decisions on the operation of the farms (i.e. whether intensive livestock farming). Four community-based studies using a proxy for bioaerosol exposure were conducted exclusively on children (Hoopmann et al., 2006; Mirabelli et al., 2006; Pavilonis et al., 2013; Sigurdarson and Kline, 2006); a fifth study (Smit et al., 2012) was conducted on children and adults. The study characteristics of the studies are summarised in Table 1.

The studies identified in this review demonstrated high levels of heterogeneity in study designs, outcome measures and exposure assessment. Therefore, statistical meta-analysis was not justified and narrative and tabular summaries of the exposure characteristics and health effects are presented. We consider occupational and community studies separately.

3.1. Summary of the exposure measures

3.1.1. Occupational studies measuring concentrations of bioaerosol components

All of the 21 occupational studies measuring concentrations of bioaerosol components enumerated endotoxin from measured respiratory, inhalable and/or total airborne dust (eight measured only total airborne dust (Dosman et al., 2006; Eduard et al., 2004; Eduard et al., 2009; Larsson et al., 1992; Palmberg et al., 2002a; Radon et al., 2001; Schiffman et al., 2005), three measured total airborne and respiratory dust (Donham et al., 1989; Donham et al., 2000; Zejda et al., 1994), five measured only inhalable dust (Portengen et al., 2005; Preller et al., 1995; Vogelzang et al., 1997; Vogelzang et al., 1998; Vogelzang et al., 2000), four measured inhalable and respiratory dust (Hoffmann et al., 2005; Palmberg et al., 2004; Sahlander et al., 2010) and one study measured respiratory dust only (Radon et al., 2000; Schinasi et al., 2011)). Although the dust size fraction was not defined in the studies, it is now widely accepted that the inhalable fraction and the respirable fraction includes particles with an aerodynamic diameter $\leq 100\ \mu m$ and $\leq 10\ \mu m$, respectively (Commission, 2002). Only four studies measured total bacteria (Donham et al., 1989; Eduard et al., 2004; Eduard et al., 2009; Radon et al., 2001), the same studies also measured total fungi, of which one also measured *actinomycetes* (Eduard et al., 2009).

The ranges of the different bioaerosol components and particulates extracted from the reviewed literature (if provided) are as follows (note that studies presented results with various units, which have been harmonised below):

- Endotoxin $2.00\ 10^{-2}$ to $7.16\ 10^{11}$ ng m^{-3}
- Total dust/Airborne dust/Personal dust $2.40\ 10^{-2}$ to $2.73\ 10^{10}$ mg m^{-3}
- Inhalable dust $9.70\ 10^{-1}$ to $1.65\ 10^{1}$ mg m^{-3}
- Respirable dust $0.00\ 10^{0}$ to $3.96\ 10^{1}$ mg m^{-3}
- Total bacteria $0.00\ 10^{0}$ to $4.20\ 10^{10}$ CFU m^{-3}
- Total fungi/mould $0.00\ 10^{0}$ to $1.10\ 10^{9}$ CFU m^{-3}

The concentrations of the bioaerosol components and particulates measured in the selected studies were highly variable; measured endotoxin concentrations ranged over 14 orders of magnitude, total bacteria concentrations over 11 orders of magnitude and total fungi/mould over ten orders of magnitude. Total/airborne/personal dust was also highly variable (expanding over 13 orders of magnitude), whereas inhalable dust and respirable dust was less variable, expanding over three and two orders of magnitude respectively.

The majority of studies (n = 18) were conducted on pig farms. One study was conducted on pig and poultry farms (Radon et al., 2001), another study was conducted on just poultry farms (Donham 2000) and two studies were conducted on pastoral farms (including pig and poultry farms but also cattle, sheep, and goat) (Eduard et al., 2004; Eduard et al., 2009). Endotoxin measurements were conducted in farm buildings, during feeding and tending operations, and on the subjects included in the study (personal samples), as highlighted in Fig. 2. Three studies measured endotoxin concentrations in a fixed location in a farm building or during feeding/tending operations (Donham et al., 1989; Schinasi et al., 2011; Zejda et al., 1994). One study (Schiffman et al., 2005) measured endotoxin concentrations in an experimental chamber whereby air from a pig house building was pumped into the chamber to simulate pig house conditions in a controlled environment. The remaining 18 studies measured personal endotoxin exposure (samplers were placed on at least one subject in the study). Table 1 summarises the exposure assessments conducted in each study.

To evaluate whether there were any patterns in the endotoxin concentrations by farming type and sampling location, their average values (mean or median depending on what metric was reported in the study) are presented in Fig. 2 (results for total bacteria and total fungi/moulds are presented in Appendix C).

The results in Fig. 2 indicate that feeding and tending operations at

Table 1
Study characteristics of the studies included in the review.

Author (year)	Study design	Setting	Population/ subjects studied	Exposure assessment	Outcome assessment	Bioaerosols/ pollutants studied
Occupational studies measuring concentrations of bioaerosol components (n = 21)						
Bonlokke et al. (2012)	Quasi-experimental (pre-post shift) study	Pig farms in Canada	23 Pig farmers	Personal filter samplers during working hours in pig houses	Questionnaire, spirometry,inflammatory analysis in blood	Personal dust, endotoxin, carbon dioxide and ammonia
Donham et al. (1989)	Quasi-experimental (pre-post shift) study	30 pig farms in Sweden	Pig farm workers (n = 57) and control farmers (did not work with pigs) (n = 55),	Personal filter samplers. Andersen and filter samplers were also used inside pig confinement buildings	Interview, questionnaire, spirometry	Respirable and total dust, endotoxin, total microorganisms, viable microorganisms, bacteria, moulds, ammonia, carbon dioxide, hydrogen sulfide
Donham et al. (2000)	Quasi-experimental (pre-post shift) study	Poultry farms in USA	Poultry farmers (n = 257)	NIOSH personal dust samplers	Questionnaire, spirometry	Total dust, respirable dust, total endotoxin, respirable endotoxin, ammonia
Dosman et al. (2006)	Experimental study	Pig farms in Canada	20 non-smoking males aged 18–35	Personal filter samplers	Spirometry, inflammatory analysis in, blood and nasal lavage	Personal dust, airborne endotoxin and area samples of ammonia, carbon dioxide and hydrogen sulfide
Eduard et al. (2004)	Cross-sectional study	Farms (including livestock farms) in Norway	2149 farmers	Personal exposures were measured during specific tasks using dust samplers	Questionnaire, allergy testing	Dust, fungal spores, bacteria, endotoxin, ammonia
Eduard et al. (2009)	Cross-sectional study	Farms (including livestock farms) in Norway	4735 farmers	Personal exposures were measured during specific tasks using dust samplers	Questionnaire, spirometry, allergy testing	Dust, fungal spores, actinomycete spores, endotoxins, bacteria, storage mites, glucans, fungal antigens, organic dust, inorganic dust, silica, ammonia, hydrogen sulfide
Hoffmann et al. (2005)	Experimental study	Pig farms in Denmark	16 former farming apprentices (8 cases, 8 controls)	Personal filter samplers during 3 h exposure period in a pig confinement building	Allergy testing, bronchoscopy, inflammatory analysis in blood and bronchoalveolar lavage (BAL), spirometry	Inhalable dust, respirable dust, and endotoxin
Larsson et al. (1992)	Cross-sectional study	Pig farms in Sweden	20 healthy non-smoking pig confinement workers.	Personal filter samplers for 1 h during pig tending and feeding	Interview, spirometry, BAL, bronchial hyperresponsiveness, skin reactivity test	Dust, endotoxin
Palmberg et al. (2002a,b)	Experimental study	Pig farms in Sweden	8 male pig farmers aged 31–54 and 9 healthy volunteers (4 male) aged 18–29	Personal filter samplers worn for the exposure period	Questionnaire, oral temperature, spirometry. methacholine challenge, blood, nasal lavage	Dust, endotoxin
Palmberg et al. (2004)	Quasi-experimental (pre-post exposure) study	Pig farms in Sweden	22 healthy non-smoking volunteers	Personal filter and cyclone samplers for 3 h and nasal air samplers in subject nostrils for 10 min	Self-reported symptoms; BAL, inflammatory analysis in blood, bronchial hyperresponsiveness	Inhalable dust, respirable dust, endotoxin
Portengen et al. (2005)	Case control study	Pig farms in the Netherlands	194 pig farm workers	Personal filter samplers with used once in the summer and once in the winter	Interview, medical examination; blood, spirometry, bronchial hyperresponsiveness	Personal dust, endotoxin
Preller et al. (1995)	Cross-sectional	Pig farms in the Netherlands	194 pig farm workers	Personal filter samplers with used once in the summer and once in the winter	Questionnaire, medical examination, spirometry)	Inhalable dust, endotoxin, personal ammonia
Radon et al. (2000)	Quasi-experimental (pre-post exposure) study	Pig farms in Germany	Pig farmers (n = 100)	Personal filter samplers during feeding periods in the morning and afternoon	Interview, questionnaire, spirometry	Respirable dust, endotoxin, ammonia, carbon dioxide
Radon et al. (2001)	Quasi-experimental (pre-post exposure) study	Pig and poultry farms in Denmark and Switzerland (respectively)	40 Danish pig farmers and 36 Swiss poultry farmers	Personal filter samplers worn during normal farming tasks for a median time of 18 min	Questionnaire, interview, spirometry	Dust, endotoxin, total bacteria, fungi
Sahlander et al. (2010)	Experimental study	Pig farms in Sweden	11 non-smoking pig farmers, 12 non-farming, 12 non-farming, non-smoking controls	Personal filter samplers were worn by 1–2 subjects during each exposure occasion	Inflammatory analysis in blood	Dust, endotoxin
Schiffman et al. (2005)	Experimental study	Controlled exposure chamber and a pig confinement facility, USA	48 healthy adult volunteers aged 19–49 (half male, half female)	Subjects were exposed for one hour in an experimental chamber; once to diluted pig confinement air, once to filtered	Vital signs, spirometry, nasal lavage, saliva	Endotoxin, total suspended particulates, ammonia, odour and hydrogen sulfide

(*continued on next page*)

Table 1 (*continued*)

Author (year)	Study design	Setting	Population/ subjects studied	Exposure assessment	Outcome assessment	Bioaerosols/ pollutants studied
Vogelzang et al. (1997)	Cross-sectional study	Pig farmers in the Netherlands	196 pig farmers	Personal samplers during a work shift (average 8.3 h)	Questionnaire; bronchial hyperresponsiveness	Dust, ammonia, endotoxin
Vogelzang et al. (1998)	Prospective cohort	Pig farmers in the Netherlands	171 pig farm workers	Personal samplers during a work shift (average 8.3 h)	Questionnaire, medical examination, spirometry	Inhalable dust, endotoxin
Vogelzang et al. (2000)	Prospective cohort	Pig farmers in the Netherlands	Pig farm workers (n = 200) and controls (n = 199)	Personal samplers during a work shift (average 8.3 h), conducted on one day in the summer and one day in the winter	Questionnaire, bronchial hyperresponsiveness	Inhalable dust, endotoxin, ammonia
Zejda et al. (1994)	Cross-sectional study	Pig farmers in Canada	Pig farm workers (n = 54)	Filter samplers were positioned in a location near to the centre of the pig building	Questionnaire, spirometry	Dust, endotoxin, carbon dioxide, ammonia
Community-based studies measuring concentrations of bioaerosol components (n = 1)						
Schinasi et al. (2011)	Quasi-experimental (panel) study	Communities living within 1.5 miles of pig operations in USA	Residents of 16 eastern North Carolina communities	Partisol plus sampler located centrally within each community for 12 h	Self-reported symptom diary; self-measured spirometry	Hydrogen sulfide, Particles with aerodynamic diameter 10 µm or less (PM_{10}), $PM_{2.5}$, $PM_{2.5–10}$, endotoxin
Community-based studies using proxy measures for exposure (n = 16)						
Borlee et al. (2015)	Cross-sectional study	Residents living near pig, poultry, cattle, goat and mink farms in the Netherlands	14,875 adults	Distance from nearest farm is used as an exposure proxy (included dwellings within 1 km of a farm)	Questionnaires, Chronic Obstructive Pulmonary Diseases (COPD), asthma and allergic rhinitis prevalence	None
Bullers (2005)	Cross-sectional study	Resident group living near pig farms, and a control resident group in the USA	nearby residents(n = 48), controls (n = 34)	Resident group living near pig farms were compared to a control group (not living near pig farms)	Interviews	None
Hooiveld et al. (2016)	Cross-sectional study	Residents living near pig, poultry, cattle and goat farms in the Netherlands	197,096 (n = 119,036 high-level exposed and n = 78,060 low-level exposed)	Numbers and type of Concentrated Animal Feeding Operations (CAFOs) located in the same postal areas as the study population was identified (exact location of the farm was not available)	Morbidity data from electronic medical records. 1-year prevalence rates for atopic disease, respiratory infections, gastrointestinal infections, and other infectious disease (includes Q fever)	None
Hoopmann et al. (2006)	Cross-sectional study	5–6 year old school children in Germany	7943 5–6 year old school children	Modelled annual average bioaerosol concentration at residential addresses within 2 km of a livestock farm Also used parents' 'guesstimated' distance to nearest farm	Questionnaire (all children). Blood IgE and SE1 (subsample of 891 children)	None
Huijskens et al. (2016)	Case-control study	Persons attending emergency ward of two hospitals, Netherlands	Cases: Aged 18 or over with suspected Community-Acquired Pneumonia (CAP) (n = 400) Controls: Aged 18 or over with abdominal symptoms or chest pain (n = 1096)	Distance from patients' home address and all animal farms within 1 km (presence of farms; yes/no, if yes, total number of farms)	Emergency ward records of patients with suspected CAP (cases) and abdominal symptoms or chest pain (controls) Cases and controls were matched 1:3 within a 5-year age range	None
Mirabelli et al. (2006)	Cross-sectional study	12–14 year old school children, North Carolina (USA)	Children reporting complete data for all asthma survey variables of interest (58,169 children from 265 schools)	(1) Distance between school and nearest pig CAFO housing at least 250 animals and using a liquid waste management system (2) number, type and weight of animals (steady state live weight; SSLW) within 3 miles (3) weighted SSLW based on distance to nearest CAFO	Questionnaire	None
Pavilonis et al. (2013)	Cross-sectional study	Children living in rural areas in Keokuk county, Iowa, USA	565 children (0–17 years)	Calculated relative environmental exposure using an inverse square law calculated using area of the pig	Questionnaire	None

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Table 1 (*continued*)

Author (year)	Study design	Setting	Population/ subjects studied	Exposure assessment	Outcome assessment	Bioaerosols/ pollutants studied
				animal feeding operation (AFO), distance between residence and pig AFO, and percentage of time the wind was blowing < 4 m/s from the AFO to the home		
Radon et al. (2005)	Cross-sectional study	Non-farming residents from four municipalities in Germany	6937 adults aged 18–44 with no prior professional or personal contact with agriculture	Number of livestock houses within 500 m of subjects' residence	Questionnaire (all). Specific IgE, spirometry, methacholine challenge (subset of 2812)	None
Radon et al. (2007)	Cross-sectional study	Residents (18–44 years) from four rural towns in northwest Germany	3131 residents with farm contact (first three years of childhood and/or at the time of the study. 2425 residents with no farm contact	(1) Defined by self-reported level of odour-annoyance on a four point scale (2) Number of CAFOs within 500 m of participants' homes	Questionnaire (all). Blood samples, spirometry, and methacholine bronchial challenge (subset of 2571)	None
Sigurdarson and Kline (2006)	Cross-sectional study	Children attending one of two schools in Iowa, USA. Study school located approx. 800 m from pig CAFO. Control school over 16 km from a CAFO	Study school (n = 116) and control school (n = 456) students in kindergarten through to fifth grade (assumed aged 5–11)	Comparing the study school with the control school	Questionnaire	None
Smit et al. (2012)	Cross-sectional study	Adult and child neighbouring residents of livestock farms in the Netherlands	70,142 adults aged 18–70 (68,989 controls and 1153 cases (702 with pneumonia and 432 with an 'other infectious disease' and 19 with both pneumonia and 'other infectious disease')) and 22,406 children aged 0–17 (22,134 controls and 272 cases (221 with pneumonia, 51 with 'other infectious disease' and 1 with both pneumonia and 'other infectious disease'))	Distance between residential address and all animal farms within 1 km, and distance between residential address and goat farms within 5 km	Electronic medical records from general practices for pneumonia and Q fever	None
Smit et al. (2014)	Cross-sectional study (and a case control study on a subset)	As per Smit et al. (2012)	As per Smit et al. (2012)	(1) Distance to nearest farm (quartiles) from residential address (2) binary indicator of presence of farms within 500 m and 1000 m of residential address (3) total number of farms within 500 m and 1000 m of residential address (4) binary indicator of presence of a specific farm type within 500 m and 1000 m of residential address (5) PM_{10} emissions from farms within 500 m and 1000 m of residential address, using estimated (modelled) PM_{10} for each farm to create an emissions factor.	Electronic medical records from general practices for asthma, COPD and allergic rhinitis (all). Questionnaire (subset of 758 cases and 1519 controls)	None
Thu et al. (1997)	Cross-sectional method development study	Cases: Residents living within two miles of a pig farm. Controls: rural residents not living near livestock operations	Cases: 10 eligible households (n = 19 individuals). Controls: Nine eligible households (n = 18 individuals)	Comparing the control area with the study area	Questionnaire	None
van Dijk et al. (2016a)	Cross-sectional study	Residents living in rural areas of the Netherlands with high density	Study area, 899 COPD patients and 2546 asthma. Control area,	(1) Comparing the control area with the study area	Electronic medical records from general practices for exacerbations of asthma and	None

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Table 1 (*continued*)

Author (year)	Study design	Setting	Population/ subjects studied	Exposure assessment	Outcome assessment	Bioaerosols/ pollutants studied
		of livestock farms (study area) and lower density of livestock farms (control area).	933 COPD patients and 2310 asthma patients	(2) using individual exposure estimates in the study area of	COPD (all) Forced Vital Capacity (FVC) and Forced Expiratory Volumn in the first second (FEV_1) measurements in a subset of 551 COPD patients (from both the study and control areas)	
van Dijk et al. (2016b)	Cross-sectional study	As per Smit et al. (2012)	A subset of 1519 control patients (described in Smit et al., 2014) completed a questionnaire; 531 had no missing data	With respect to residential address:	Questionnaire and General practice electronic medical records	None
Wing and Wolf (2000)	Cross-sectional study	Residents of three communities; one within 2 miles of a pig farm, one within 2 miles of two cattle farms, and a third control community situated in a rural area at least two miles away from a livestock operation, in North Carolina, USA	155 households (n = 105 in the study area (50 from the cattle farm community, 55 from the pig farm community and n = 50 from the control area)). Excluded persons believed to be farmers.	Comparing the two study areas to the control area	Questionnaire and household interviews	None

pig farms result in higher endotoxin concentrations than personal samples and samples taken in buildings. However these are reported from a single study (Larsson et al., 1992), who reported concentrations in non-standard units (ng/cu mm). Although the units were converted to ng m^{-3} to facilitate comparisons between studies, the conversion resulted in unusually high endotoxin concentrations compared with other studies. With this exception, Fig. 2 shows that there was no clear pattern on where the highest endotoxin concentrations were observed. Fig. 2 also highlights the large variation in endotoxin concentrations, and high variability within the same study

It was difficult to compare bioaerosol and particulate measurements in the studies, due to the different measurement techniques used, and units presented. Furthermore, measurements were often performed over short time periods. Background concentrations, which are particularly important when trying to interpret values at the lower end of exposure (Fig. 2), were not provided.

3.1.2. Community-based studies measuring concentrations of bioaerosol components

Only one study where bioaerosol concentrations were measured was conducted in a community setting (Schinasi et al., 2011). In this study air pollution monitors were located in a central location in 16 communities (it is not stated in the paper how far from an intensive farm these sampling locations are). Endotoxin was assayed from 12-h $PM_{2.5-10}$ samples whereby estimates of exposure were made with a time-weighted average of the concentrations during the 12 h prior to outdoor exposure. The mean average endotoxin concentrations (converted from the original EU mg^{-1} values reported) values were measured in 12 communities and are presented in Fig. 2. Endotoxin concentrations in this study were comparable to those at the lower end of the range of exposures for occupational studies (minimum mean 20.06 (standard deviation (SD) ± 8.36) – maximum mean 87.55 (SD ± 74.80)), but background values were not available.

3.1.3. Community-based studies using proxy measures for exposure

16 of the 17 community-based studies did not directly measure bioaerosol concentrations. Instead a proxy for exposure was used to assess health outcomes in relation to intensive farming sites. Proxy measures do not give a direct indication of bioaerosol exposure, and any observed health effects may not be directly due to increased bioaerosol exposure as a result of intensive farming, and may be the result of another pollutant and/or source or scenario. The proxies used are summarised in Table 1 and varied in levels of reliability, including:

- Living in a study area (e.g. homes or schools near intensive farms) compared with a control area (e.g. an area of similar population characteristics, located away from intensive farms) (Bullers, 2005; Sigurdarson and Kline, 2006; Thu et al., 1997; van Dijk et al., 2016a; Wing and Wolf, 2000)
- The number of farms and/or animals (sometimes stratified into farm/animal type) within the area (Hooiveld et al., 2016; Radon et al., 2005; Radon et al., 2007; Smit et al., 2014; van Dijk et al., 2016b)
- Distance from farm (Borlee et al., 2015; Huijskens et al., 2016; Mirabelli et al., 2006; Pavilonis et al., 2013; Smit et al., 2012; Smit et al., 2014). Pavilonis et al. (2013) also considered the percentage of time that the wind was blowing from the farm
- Inverse distance weighted PM_{10} (particles with aerodynamic diameter 10 µm or less) as an exposure proxy for bioaerosols (van Dijk et al., 2016b).
- Using dispersion models to estimate concentrations. Hoopmann et al. (2006) used a Lagrange particle model to model bioaerosol concentrations. Smit et al. (2014) used modelled PM_{10} as a proxy for bioaerosols.
- Self-reported odour level (Radon et al., 2007).

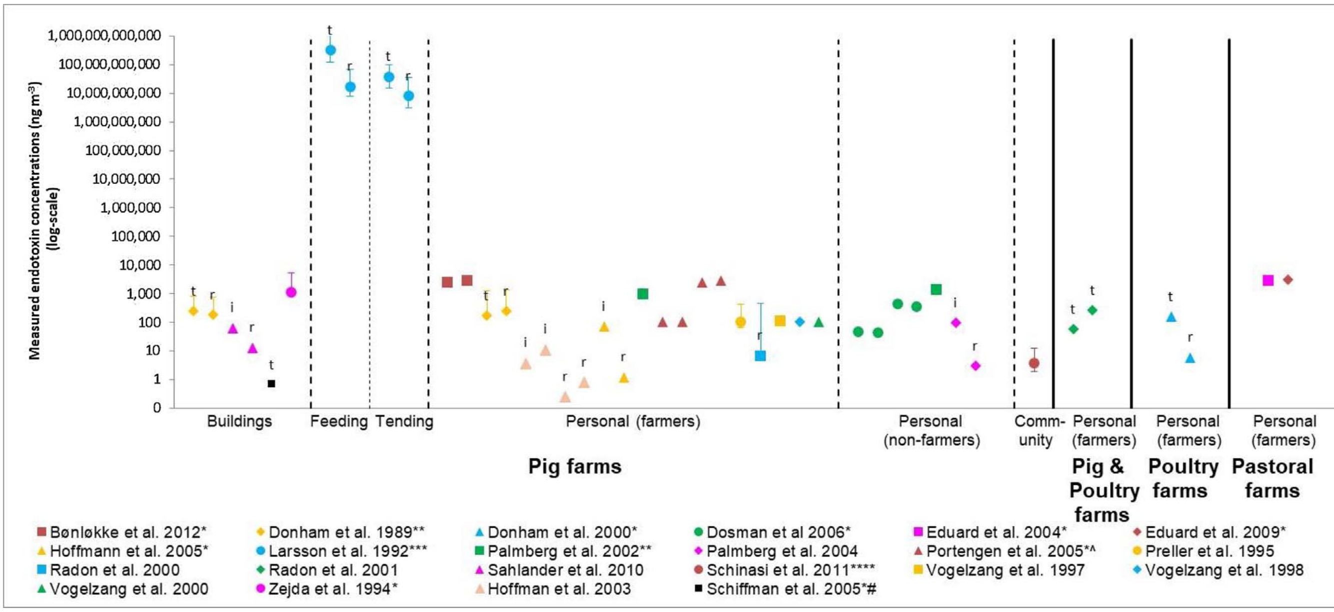

Fig. 2. Mean airborne endotoxin concentrations (median where mean is not reported). Error bars represent the range of values if provided in the study. Labels above the points indicate whether endotoxins were enumerated from total (t), respirable (r), or inhalable (i) dust or were enumerated from nasal (n) samples – if there is not a label above the point, then it is not clear in the study what type of dust endotoxin was enumerated. Note that studies classed as 'pig farms' may also include swine farms. Bioaerosols/pollutants measured in each study are provided in Table 1.

* Units were provided as EU m^{-3} and have been converted to ng m^{-3} on the assumption that 1ng = 10 EU (Commission, 2002)

** Units were provided as μg/m^3 and have been converted to ng m^{-3}

*** Units were provided as ng/cu mm and have been converted to ng m^{-3}

**** Schinasi et al., 2011 referred to concentrations but reported units as EU mg^{-1} which are assumed to be EU mg^{-1} and have been converted to ng mg^{-1} on the assumption that 1ng = 10 EU (Commission, 2002)

^ Portengen et al., 2005 reported endotoxin measurements in ng m^{-3} and EU m^{-3}. Only EU m^{-3} values were converted to ng m^{-3}

Schiffman et al., 2005 was an experimental study whereby air from a pig house was pumped into a chamber. The value reported is the concentration measured within the chamber when simulating pig house conditions

Some studies considered multiple exposure proxies, as summarised in Table 1. The use of exposure proxies is likely to result in exposure misclassification, which can introduce bias. The severity of exposure misclassification depends on the exposure proxy used. For example, using distance from farm as a proxy is more likely to result in a higher level of exposure misclassification than using a dispersion model to estimate pollutant concentrations for example (see also Appendix B).

3.2. Summary of the health measures

3.2.1. Occupational studies measuring concentrations of bioaerosol components

The majority of papers (21 out of 22) that both measured concentrations of bioaerosols and assessed health effects were in occupational groups (i.e. farmers). Of the 21 studies measuring bioaerosol concentrations, eight were cross-sectional in design (Eduard et al., 2004; Eduard et al., 2009; Larsson et al., 1992; Preller et al., 1995; Vogelzang et al., 1997; Zejda et al., 1994), two were also quasi-experimental pre-post exposure studies (Radon et al., 2000; Radon et al., 2001). Six studies were experimental in design (Sahlander et al., 2010; Schiffman et al., 2005), and a further four studies were pre-post exposure, quasi-experimental in design (Bonlokke et al., 2012; Donham et al., 1989; Donham et al., 2000; Palmberg et al., 2004). Two studies were prospective cohorts (Vogelzang et al., 1998; Vogelzang et al., 2000), and one was a case-control study (Portengen et al., 2005). Study designs are summarised in Table 1.

Studies used a wide range of sample sizes, with some as few as 16 workers and some several thousands. A wide range of outcome measures or endpoints were used, but chiefly related to respiratory health and immune system activation. Such measures include both subjective measures (based on self-report, usually questionnaires) and objective measures (based on direct measurement). Most studies contained multiple endpoints to assess the effects of exposure on health. No study showed a significant effect with respect to all the endpoints. However, all of them reported at least one significant finding supporting adverse health effects of occupational exposure to bioaerosols from farms. The statistical significant health outcome associations with bioaerosol exposure are shown in Table 2 and described further in the text below.

3.2.1.1. Lung function and respiratory symptoms. In terms of health outcomes studied most studies reported impaired lung function, especially FEV_1 (forced expiratory volume in the first second), and respiratory symptoms such as coughing, wheezing, chest tightness and shortness of breath in workers exposed to bioaerosols. The exact aetiology remains unclear, but associations were primarily found with inhalable dust and endotoxin exposures. Analyses of Bronchoalveolar Lavage (BAL) fluid and sputum samples revealed the presence of an inflammatory response (increased cellularity and alteration of cytokine milieu) in workers exposed to bioaerosols. Consistent findings were obtained for studies involving intentional and controlled exposures to bioaerosols in healthy, but previously unexposed human volunteers. However, whether these effects remain after cessation of exposure or may lead to long-term effects remains largely unknown. Interestingly, there is some evidence of an inflammatory adaptation, tolerance-like response in chronically exposed farm workers (Sahlander et al., 2010).

Few studies examined interactions. There was insufficient evidence available to determine whether the type of farm (pig or poultry) influenced interactions between health and bioaerosol exposures. Few studies found evidence of effect modification by factors, such as sex, age, smoking status and co-morbidity. However, Preller et al. (1995) showed stronger associations between occupational exposures to bioaerosols and adverse health outcomes among subjects with a history of chronic respiratory health problems. A slightly increased risk was also observed with increasing duration of work (Radon et al., 2000).

3.2.1.2. Asthma. Only one study reported an association between occupational exposure to bioaerosols and increased risk of non-atopic asthma (Eduard et al., 2004). Among the bioaerosol components measured, elevations of fungal spores and endotoxin showed the strongest associations with disease. However, in the same study these exposures were negatively associated with atopic asthma, suggesting possible protective effects.

3.2.1.3. Chronic bronchitis. Studies of occupational exposure to bioaerosols and chronic bronchitis showed mixed results, with some studies showing no association (Radon et al., 2001) and positive findings in other studies (Donham et al., 1989; Eduard et al., 2009; Zejda et al., 1994). Positive associations were principally with endotoxin and bacteria. Analyses stratified by duration of employment did not indicate a consistency of results among those employed the longest (Donham et al., 1989; Eduard et al., 2009).

3.2.2. Community-based studies measuring concentrations of bioaerosol components

There was only one study of health outcomes related to environmental bioaerosol exposure from intensive farming in a community setting (Schinasi et al., 2011). This study was quasi-experimental in design. This study did report a 10 EU mg^{-1} increase in endotoxin to be associated with increased log odds of sore throat (0.10 ± 0.05), chest tightness (0.09 ± 0.04) and nausea (0.10 ± 0.05). However the study used a sample size of 101 and relied upon self-reported measures of health. Also, this study did not statistically adjust their analyses to account for socio-economic status, which has been shown to affect how individuals assess their health status.

3.2.3. Community-based studies using a proxy for bioaerosol exposure

All 16 studies were cross-sectional in design with the exception of Huijskens et al. (2016) which was a case control study. Smit et al. (2014) also conducted a case control study in a subset of participants.

In general, the sample size of these studies was larger than those measuring bioaerosol concentrations in the workplace. Most studies have relied on clinical data extracted from general practitioner (GP) electronic medical records. The included studies were very heterogeneous in study population and outcomes measured. Of the 16 included studies, four of these studies were explicitly concerned with children (Hoopmann et al., 2006; Mirabelli et al., 2006; Pavilonis et al., 2013; Sigurdarson and Kline 2006). The findings of studies that examined the relation between proximity to livestock farms and adverse health outcomes are summarised in Table 2.

3.2.3.1. Lung function and respiratory symptoms. Three of the sixteen studies reported protective associations with respiratory health (Borlee et al., 2015; Smit et al., 2014; van Dijk et al., 2016b), while the others have reported adverse associations although these were not necessarily consistent across studies. Studies relying on self-reported chronic respiratory syndromes, such as wheezing, pulmonary function and use of respiratory medicine, found higher risks among residents living closer to livestock farms (Bullers, 2005; Mirabelli et al., 2006; Radon et al., 2005; Radon et al., 2007; Thu et al. 1997; van Dijk et al., 2016b; Wing and Wolf, 2000). The three studies finding protective associations used electronic medical records from GP practices (Borlee et al., 2015; Smit et al., 2014; van Dijk et al., 2016b) – all these studies were based in The Netherlands and used the same study population. Only a few studies adjusted for the presence of other types of farm animals. Of note, van Dijk and colleagues found a higher prevalence of respiratory conditions on GP registers among residents living within 500 m from a poultry farm with > 14,000 birds (Relative Risk (RR):1.09; 95% Cl:1.00–1.18) (van Dijk et al., 2016b). However, in the same study the presence of pig farms within a 500 m radius of the home address was associated with a decreased prevalence of respiratory conditions (RR: 0.89; 95% Confidence Interval (Cl): 0.83–0.95) (van Dijk et al., 2016b). Adjusting for education level (used as a proxy for socio-economic status) did not significantly alter these associations. Smit et al. (2012) reported increased pneumonia incidence to be associated with the presence of poultry within 1 km in adults (Odds Ratio (OR): 1.25; Cl: 1.06–1.47). However in general, other investigators looking at pneumonia or other infectious diseases (such as Q fever) have found associations only for goats, which are known to be one of the main carriers of Q fever (Hooiveld et al., 2016; Huijskens et al., 2016).

3.2.3.2. Asthma. Although most of the studies found no association of distance to nearest pig or poultry farm and asthma in adulthood, some reported statistically significant inverse (protective) correlations (Borlee et al., 2015). Indeed, the presence of a livestock farm with 100 m of the home address was significantly negatively associated with current asthma (OR 0.65, 95% Cl 0.45–0.93). Stratification by atopic status indicated a positive association for presence of poultry at 500 m and atopic asthma (Borlee et al., 2015). However, the presence of pigs at 500 m showed negative associations with non-atopic asthma (Borlee et al., 2015). Interestingly, all four studies (three in USA, one in Germany) involving children yielded modest but consistent evidence supporting increased self-reported asthma rates among those children living or attending schools located within close vicinity (e.g. 500 m) of an intensive farm (Hoopmann et al., 2006; Mirabelli et al., 2006; Pavilonis et al., 2013; Sigurdarson and Kline 2006). Of note, the Hoopmann study used modelled endotoxin as exposure measure, but significant associations with asthma symptoms were only seen in children with atopic parents.

3.2.3.3. Chronic bronchitis. Only three of the included studies specifically mentioned assessing the effect of living in the vicinity (e.g. 100–500 m) of livestock farms on new-onset or exacerbation of COPD (Borlee et al., 2015; Smit et al., 2014; van Dijk et al., 2016a). The study by Borlee et al. (2015) found the presence of a livestock farm within 100 m of the home address to be significantly negatively associated with COPD (OR 0.71, 95% Cl: 0.51–0.98). However, when analysis was stratified to those with COPD, there was an increasing probability of wheezing among COPD patients when living < 500 m from a farm (Borlee et al., 2015). Increased symptom reporting associated with livestock farm exposures in COPD patients has also been reported by van Dijk and colleagues (van Dijk et al., 2016a). Interestingly, this study showed COPD patients living within a 500 m radius of stables with the lowest poultry densities (up to 12,499), but not higher poultry densities (> 12,499), had exacerbations more often than patients without poultry exposure (van Dijk et al., 2016a).

Table 2
Summary of health outcomes. Non-significant findings are not reported.

Author (year)	Health outcomes assessed	Significant findings	Comments
Occupational studies measuring concentrations of bioaerosol components (n = 21)			
Bonlokke et al. (2012)	Respiratory health history was assessed in adults via an interview administered questionnaire. Underwent spirometry (FVC, FEV_1, FEV_1/FVC ratio, Forced Expiratory Flow between 25 and 75%($FEF_{25–75}$)) nasal lavage, exhaled breath condensate analysis (pH & IL-8). Blood sampling (cellular analysis, CD14, CD62L, bactericidal/permeability-increasing (BPI) protein & several cytokines)	Some loss of adaptation during time off work that causes greater effects on respiratory function & the immune system when returning to work. Loss of adaptation not complete (suggested by absence of cross-shift burst in Tumor Necrosis Factor (TNF))	Took diurnal variation into account
		FVC decreased 3.1% over the work shift after the period of respirator use whereas it showed no cross-shift decline after the unprotected period	Repeated measurement of the workers at the same time of day – reduces confounding
		Cross-shift increase in blood neutrophils ($p < 0.0001$) with a greater cross-shift increase after the respirator use period ($p = 0.01$). Cross-shift increase in IL-6 ($p < 0.0001$) with a greater cross-shift increase after the respirator use period	Lack of proper absence period from work
		Plasma concentration of BPI protein decline over the work shift after the respirator use period but not after the unprotected work	Small sample size
Donham et al. (1989)	Acute and chronic respiratory symptoms were assessed via interview/questionnaire	Cases reported significantly ($p \leq 0.05$) higher frequencies of cough and chest colds compared to controls.	Standardised questionnaire used to assess chronic respiratory symptoms.
	Cases also completed spirometry (FVC, FEV_1, FEF_{50}. FEF_{75}) and provided blood samples (serum tested for antibodies to suspected environmental allergens) before and after work period.	There were significant relationships between personal respirable dust exposure and cough in non-smokers ($p = 0.04$) and fever episodes in smokers ($p = 0.0001$) and number of airborne mould spores and work-related chest tightness ($p = 0.0009$) and dyspnoea ($p < 0.001$) in non-smokers.	Small study of 57 pig workers and 55 controls, with limited adjustment for confounders
		Chronic bronchitis symptoms were more common among pig workers than controls and were related to the number of years working with pig, which is supported by significant relation of years at work to baseline FEF_{75} ($p \leq 0.05$).	Short term study and does not assess long-term effects of bioaerosol exposure to health.
		There is a significant dose-response relationship (PR > F 0.004) between ΔFEV_1 and endotoxin concentrations in non-smokers.	
Donham et al. (2000)	Respiratory symptoms were assessed by standardised questionnaire	Poultry work status was significantly associated with a work shift decline in FEV_1 (1.10% in poultry workers and 0.02% in controls) and $FEF_{25–75}$ (1.50% decline in poultry workers and 2.10% increase in controls) after adjusting for smoking status.	Additional questions were added to assess occupational and exposure histories.
	Pre- and post- work pulmonary function tests (FEV_1, $FEF_{25–75}$)	Weak but statistically significant correlations between $FEF_{25–75}$ decline with total dust ($r = 0.275$, $p = 0.0001$) and endotoxin ($r = 0.201$, $p = 0.0020$)	Have assessed dose-response relationships and estimated threshold values.
		Generally strong trends of increasing odds ratios for lung function decline relative to increasing exposure quartiles, which were statistically significant for 3% and 5% cross-shift declines in FEV_1 and 3%, 5% and 10% cross-shift decline in $FEF_{25–75}$.	
Dosman et al. (2006)	Spirometry (FVC, FEV_1, FEV_1/FVC ratio, $FEF_{25–75}$) nasal lavage, and blood sampling at the start and end of each day (cross-shift) after the start of each exposure day. IL-6 and IL-8 were analysed in nasal lavage and blood samples.	% change in pulmonary function test variables (FEV_1) at high-level endotoxin and dust exposure were significantly greater in those who were "more responsive" than in those who were "less responsive"	Small sample size. Subjects were exposed for short periods of time (5 h). Therefore only acute effects could be assessed. The study population may not be representative of a typical farming population.
	Individuals categorised into "more responsive" and "less responsive" based on FEV_1 shift reduction following high endotoxin exposure	Most of the inflammatory markers were in the direction of greater response among those who were "more responsive" than among those who were "less responsive". At conditions of low exposure there was significantly greater response in total White Blood Cell (WBC) ($p < 0.05$) and in lymphocyte count ($p < 0.05$) among those who were "more responsive" compared to those who were "less responsive". At high exposure there were significantly greater numbers of nasal lavage cells ($p < 0.05$) among those who were "more responsive"	Subjects exposed to a complex ambient environment in the pig barn that included not only endotoxin but also dust and a variety of gases such as ammonia

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Table 2 (*continued*)

Author (year)	Health outcomes assessed	Significant findings	Comments
Eduard et al. (2004)	Spirometric testing, collection of blood samples (IgE with multiple radioallergosorbent tests (RAST) for respiratory allergens) and a questionnaire on asthma.	Non-atopic asthma prevalence was higher in livestock farmers with more than one type of livestock than arable farmers (Odd Ratio (OR) 1.80, 95% Confidence intervals (CI) 1.10-3.20). Atopic asthma was less prevalent in farmers with more than one type of livestock compared to arable farmers (OR 0.32, 95% CI 0.11-0.97).	Large study involving 8482 farmers, 1614 of which were tested for atopy.
	Statistical analysis for atopy testing	Asthma prevalence was significantly higher in cattle farmers (OR 1.80 95% CI 1.10-2.80) and pig farmers (OR 1.60 95% CI 1.00-2.50) Models with one agent showed significant positive associations in a dose-dependent way between non-atopic asthma and fungal spores/endotoxin; same agents were negatively associated with atopic asthma (also in a dose-dependent manner). Models with two exposure variables indicated that exposure to fungal spores was more strongly associated with atopic asthma than endotoxins and ammonia	No comparison group so not possible to assess differences in prevalence of asthma in farmers and the general population
Eduard et al. (2009)	Atopy was assessed based on answers to a questionnaire (subset from Eduard et al., 2004)	Chronic bronchitis and COPD was more common in livestock farmers than in crop farmers (OR 1.9 95% CI 1.4-2.6 and OR 1.4 95% CI 1.1–1.7-respectively). Chronic bronchitis was significantly ($p < 0.05$) associated with all types of livestock farming (OR 1.6-2.3), and COPD with significant elevated risks in dairy farmers (OR 1.395% CI 1.0-1.7) and farmers with two or more types of livestock (OR 1.4-1.5).	Large study involving 4735 farmers.
		FEV_1 was significantly lower in livestock farmers compared to arable farmers (–41 ml 95% CI −75– −7 ml) and in farmers with two or more types of livestock (−81– −52 ml).FVC and FEV_1 were negatively associated with farming duration. COPD, chronic bronchitis and FEV_1 were significantly associated with exposure to endotoxin, bacteria, and fungal spores	Cross-sectional study and does not assess long-term effects of exposure. Likely misclassification of exposure levels, however, this is likely to be small as exposure study performed during a 5-year period & all seasons, limiting the influence of temporal variations The study included a large number of different exposures, allowing the study of the effects of a wider range of potentially causal agents. However, due to high correlations leading to multicollinearity, the study of independent effects of specific biological agents was not possible.
Hoffmann et al. (2005)	Examined at baseline, three times during 3hr exposure (after each hour), and at 1, 3, 9 and 21 h after exposure	Significant correlations between C3d and respirable dust after start of exposure ($r > 0.543$, $p < 0.030$). C3d was significantly higher in atopics than non-atopics (33.2 mU/l vs 26.0 mU/l $p = 0.043$), and there was a significant increase in plasma C3 in atopic participants from baseline to two hours post exposure (4.39 µmol/l to 4.93 µmol/l $p = 0.010$)	Short-term (1 day exposure). Long-term exposure affects not accounted for, nor was any potential long-lasting health outcomes (e.g. beyond 21 h after exposure)
	Skin prick test (to test for common and work-place related allergy), bronchoscopy at baseline and 21 h after exposure, Bronchoalveolar lavage (21 h after exposure), 8 blood samples taken throughout exposure day (baseline, once per hour during exposure, 1,3, 9 and 21 h after exposure) blood analysed for Eosinophilic cationic protein (ECP), C3, α_1-AT, C-reactive protein (CRP), α_1-AG, C3d, fibronectin, SP-D, Mannose-binding lectin (MBL), α_2-M, spirometry at baseline and after 3 h exposure period.	Plasma C3, fibrinogen and α_1-AG peaked 1 and 6 h after exposure start. Mannan-bingin lectin, CRP and α_1-antiitrypsin peaked after 2 h.	
		Only SP-D, α_2-M and fibronectin were detected in BAL. Spirometric measurements did not vary during exposure Acute exposure leads to a weak inflammatory response	
	Subjects examined 1 week before, during and 1 day after the exposure, and followed until 2 weeks after exposure.	Total indices for erythema, oedema, secretions and friability increased significantly 1 day after exposure, compared to baseline values ($p < 0.006$). BAL IL-6 increased significantly 1 day after exposure, compared to baseline ($p = 0.001$)	Reduction of serum TNF- α suggested induction of endotoxin tolerance
	Underwent bronchoscopy − visual analogue scale (0–3); indices of erythema, oedema, secretions, friability and cough; nasal lavage, and blood IL-6 and TNF-α were analysed in nasal lavage and blood samples.	Serum IL-6 was elevated 3–12 h after exposure start ($p < 0.001$) and returned to pre-exposure values after 24 h. Serum TNF- α decreased within 3 h after the start of exposure, reaching a minimum level after 6 h and remaining decreased for 2 weeks ($p < 0.006$).	Small sample size. Subjects were exposed for short periods of time (3 h) therefore only acute effects could be assessed. The study population may not be representative of a typical farming population. Subjects exposed to a complex ambient environment in the pig barn that included not only endotoxin (also no correlation between endotoxin exposure levels, Lipopolysaccharides (LPS) and reduction in serum TNF-α)

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Table 2 (*continued*)

Author (year)	Health outcomes assessed	Significant findings	Comments
Larsson et al. (1992)	Airway symptoms (cough, phlegm, nasal obstruction, throat irritation) assessed by standardised questionnaire	There were significant elevations in BAL fluid total cell concentrations ($p < 0.05$), neutrophil granulocytes ($p < 0.001$), albumin ($p < 0.01$), hyaluronan ($p < 0.01$) and fibronectin ($p < 0.001$) in farmers in comparison to the reference group. In the percentage of total cell count, neutrophils were significantly higher ($p < 0.01$) in farmers than the reference group (and subsequently alveolar macrophages were significantly lower ($p < 0.05$) in the farmers than the reference group).	Small study involving more invasive biomonitoring in farmers in comparison with different control groups.
	Lung function (Total Lung Capacity (TLC), Residual volumn (RV), Peak expiratory flow (PEF), FEV_1) before, during and after shift (Farmers and a reference group of 20 males) Bronchial methacholine challenge (11 non-exposed females) BAL fluid (25 healthy non-farmers) Blood samples (skin prick tests for gel-enzyme-linked immunosorbent assay analyses) (25 non-farmers (ten of the serum samples also acted as controls for precipitin analysis))	The amount of antibodies in skin prick tests were higher with regard to pig dander, pig dust and pig food in farmers than the reference group ($p < 0.001$).	
Palmberg et al. (2002)	Symptoms of headache, chills, mental fatigue and muscle pain assessed by questionnaire.	FEV_1 decreased significantly by 8.1% in non-farmers	Small study of 17 individuals, not all confounders adjusted for, no measure of exposures
	Spirometry (Vital Capacity (VC), FEV_1 PEF)	Bronchial responsiveness increased, more in non-farmers than farmers	Acute exposure to a pig confinement facility caused airway and systemic effects, with less marked effects in farmers, potentially due to adaptation.
	Methacholine challenge	0.6 ° increase of temperature in farmers but not non-farmers.	Findings are likely to relate to endotoxin exposures.
	Nasal lavage (pre-post) & bloods (sequential) for: differential cell counts; Cytokine IL6 (blood), IL8 and lavage	Increases in blood leucocytes esp. granulocytes after exposure	Unclear relevance to community exposures
	Temperature	Increase in IL6 in serum – higher in non-farmers than farmers	
	Symptoms	9-fold increase in cells in nasal lavage in non-farmers but not farmers, but both groups had increase in neutrophils and IL8 and albumin	
Palmberg et al. (2004)	Spirometry (VC, FEV_1, PEF), bronchial methacholine challenge, nasal lavage, and blood sampling 1 week prior and 7 h after the start of exposure.	In the group without respiratory protection, symptoms such as shivering ($p < 0.01$), headache ($p < 0.05$), and malaise ($p < 0.01$) increased after exposure, whereas only shivering ($p < 0.05$) increased in the group with respiratory protection.	Small sample size. Subjects were exposed for short periods of time (3 h) with no repeat measurements. Therefore only acute effects could be assessed. The study population may not be representative of a typical farming population.
	IL-6 and IL-8 analysed in nasal lavage and blood samples.	FEV_1 decreased significantly by 4–5% in both groups following exposure and PEF decreased significantly after exposure in the group without respiratory protection (from 560 to 520, $p < 0.01$)	However study was not to assess overall respiratory health in comparison to exposure, but was an experimental study to assess respiratory protection effectiveness. Unclear relevance to community effects.
	Body temperature	Bronchial responsiveness to methacholine increased significantly in both groups ($p < 0.05$) Total cell concentrations in nasal lavage fluid increased significantly in both groups (and significantly more in the group without respiratory protection $p < 0.05$) due to an increase in neutrophilic granulocytes ($p < 0.01$ without protection, $p = 0.06$ with protection). IL-6 ($p < 0.01$) and IL-8 ($p < 0.001$) significantly increased in subjects without respiratory protection Leukocytes in blood increased in concentration significantly in the group without respiratory protection ($p < 0.01$) due to an increase of neutrophilic granulocytes	
Portengen et al. (2005)	Symptoms assessed based on answers to a questionnaire	Airway hyperresponsiveness was strongly associated with case-control status (OR 4.1, 95% CI 2.0–8.5)	Relatively small study including 81 cases and 81 controls. Confounding by differences in lifestyle and childhood exposure thought unlikely as all subjects were full-time pig farmers from same geographic area and were likely to have been born on a farm. Unclear relevance to community effects. The cross-sectional design of the study makes it impossible to say whether the low prevalence of atopy in highly exposed farmers is a consequence of a reduced incidence or an increased remission of sensitization. Does consider dose-response relationship

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Table 2 (*continued*)

Author (year)	Health outcomes assessed	Significant findings	Comments
	Blood samples (IgE and specific IgE antibodies)	No significant association between endotoxin exposure (dichotomized at median level) and specific allergic sensitisation (OR 0.88, 95% CI 0.34–2.30) or increased levels of total IgE (OR 1.2, 95% CI 0.53–2.60). In contrast, when log-transformed exdotoxin exposure was included as a continuous variable, a two-fold increase in exposure and sensitisation was observed (OR 0.44, CI 95% 0.19–0.98) suggesting a significant nonlinear relationship, which was further supported by a broken-stick model	
	Lung function (FEV_1 and airway responsiveness using histamine provocation)	Endotoxin exposure was associated with increased AHR and lower FEV_1 but not with the presence of chronic respiratory symptoms	
		Dose response curves between endotoxin & respiratory symptoms were steeper in sensitised farmers; dose-response risks for endotoxin exposure & respiratory symptoms, Airway Hyper-Responsiveness (AHR) & lung function showed increasing risk with higher endotoxin exposures	
Preller et al. (1995)	Symptoms assessed based on answers to a questionnaire	All lung function variable were lower in farmers with respiratory symptoms than those without ($p < 0.01$) weak association of a decrease in lung function (FVC and FEV_1) with increase of endotoxin exposure ($p < 0.10$) in the entire group of farmers. Exposure-response relations were much stronger in asymptomatic farmers	First known study to examine disinfectant use as a potential respiratory health hazard in pig farmers
	Blood samples (IgE and specific IgE antibodies) Lung function (FEV_1 and airway responsiveness using histamine provocation)		Relatively small sample size and cross sectional in design – does not examine long term effects
Radon et al. (2000)	Respiratory symptoms assessed by questionnaire	There was a significant decrease in lung function after feeding in the morning ($p < 0.05$) but the decrease was not significant in the afternoon.	Small study involving 100 farmers
	Lung function tests before and after pig feeding activities in the morning and afternoon (FVC, FEV_1, $MMEF_{25/75}$)	There was a significant positive correlation between respirable dust and $MMEF_{25/75}$ ($p = 0.009$)	Short term study, no repeat measurements (e.g. to observe seasonal effects)
		Drop in FEV_1 and $MMEF_{25/75}$ in the morning was significantly associated with duration of work as a farmer (indicating dose-response relationship)	Unclear relevance to community health effects
Radon et al. (2001)	Questionnaire and structured interviews assessing respiratory symptoms and chronic bronchitis	Pig farmers had significantly higher lung function results before and after work compared to poultry farmers except for FVC ($p < 0.05$).	Involved a low number of subjects (40 pig and 36 poultry farmers).
	Lung function tests before and after animal feeding (FVC, FEV_1, $MMEF_{25/75}$)	Farmers not complaining of work-related respiratory symptoms had significantly higher results for FEV_1 and maximal (mid-)expiratory flow between 25 and 75% ($MMEF_{25/75}$) ($p < 0.05$) than farmers with symptoms.	Samples from two countries therefore hard to make comparisons between poultry & pig farmers.were analysed blindly by the same person (lung function testing) Results support the need for a prospective cohort study involving a larger number of farmers to estimate the effects of respiratory health in more detail
Sahlander et al. (2010)	Nasal lavage (cellular analysis), and blood cytokines were analysed in nasal lavage and blood samples (unstimulated and LPS-stimulated samples); flow cytometric analysis of Toll-like Receptors (TLR) and cytokines	Pre-exposure:number of circulating neutrophils was higher in farmers ($p = 0.019$) than in controls. The TLR2 expression on blood monocytes was lower in farmers than in non-farming controls ($p = 0.003$); farmers have an increased proportion of IL-13 & IL-4 producing peripheral blood Th cells compared to non-farming controls	Small sample size
		Post-exposure: Peripheral blood concentration of neutrophils increased significantly after exposure (3 h) in the pig barn ($p = 0.01$) & after LPS challenge in all 3 groups	Did not follow post-exposure expression over time
		The proportion of IL-4 & IL-13 producing Th cells increased in non-farming controls ($p < 0.05$) (but not farmers where expression was already high) after pig house exposure & after LPS challenge	Only looks at TLR2 protein expression & not gene level expression
		Serum IL-6 increased in non-farming controls after exposure in the pig house, & was significantly higher than in farmers ($p = 0.010$)	All subjects were non-atopic (verified by skin-prick test)
		TLR2 expression on blood cells following exposures in vivo and stimulation ex vivo is attenuated in farmers compared to non-farming controls 9p = 0.03)	
Schiffman et al. (2005)	Symptoms (physiological and psychological) were evaluated using a visual analogue scale questionnaire	Subjects were more likely to report headaches (4.1 times more likely ($p = 0.001$)), eye irritation (6.1 times more likely ($p = 0.004$)) and nausea (7.8 more times likely ($p = 0.014$)) in the study conditions than the control conditions.	Small sample size

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Table 2 (*continued*)

Author (year)	Health outcomes assessed	Significant findings	Comments
	Measured blood pressure, temperature, heart rate, respiratory rate, spirometry, nasal lavage, total salivary IgA, mood scale, attention and memory.		Study conditions may not be truly representative of conditions experienced on a farm
Vogelzang et al. (1997)	Questionnaires (on respiratory symptoms, atopy and hyper-responsiveness during or after work)	Association with mild bronchial responsiveness were stronger for asthma-like symptoms than COPD-like symptoms, Prevalence of one or more chronic symptoms had a separate association with mild bronchial responsiveness (OR 2.1, CI 1.0-4.7)	Small sample size
	Medical examination	Mild bronchial responsiveness prevalence increased with number of years respondents had worked in pig farming	
	Lung function testing and histamine challenge (FEV_1)	There were statistically significant associations between mild bronchial responsiveness prevalence and use of disinfectants (OR 6.7, CI 1.4–32.8), use of wood-shavings as bedding (OR 13.3, CI 1.3–136.7), use of automated dry feeding (OR 28, CI 1.0–7.8) use of pellets as feeding material (OR 4.8, CI 1.1–21.1) and location of air exhaust (OR 2.7, CI 1.2–6.3)	
Vogelzang et al. (1998)	Questionnaire (on symptoms, including respiratory symptoms, chronic obstructive pulmonary disease, asthma)	Farmers with chronic symptoms had a significantly lower lung function than those without.	State that dust exposure alone is insufficient to predict lung function decline in farmers.
	Medical examination (included an extensive interview)	Decline in FEV_1 and FVC over the three year period was significantly associated with endotoxin exposure ($p = 0.04$, $p = 0.002$ respectively)	More research is needed on the mechanisms by which endotoxin exposure leads to respiratory disease
	Lung function tests (Spriometer; FEV_1, FVC)	FVC was associated with both endotoxin and inhalable dust ($p = 0.03$)	
Vogelzang et al. (2000)	Questionnaire (on symptoms, including respiratory symptoms, chronic obstructive pulmonary disease, asthma)	Increases in bronchial responsiveness in the 3-year period, measured as doubling concentration steps for PC10 were significantly associated with exposure to inhalable dust ($p = 0.05$). Associations were stronger for symptomatic farmers than for those without symptoms.	Some of the observed increase in bronchial responsiveness may have been due to the reduction in FEV_1 (symptomatic farmers had a lower FEV_1 at the start than the asymptomatic farmers and had a larger increase in responsiveness)
	Medical examination (included an extensive interview) Lung function tests (Spriometer; FEV_1) Histamine challenge		
Zejda et al. (1994)	American Thoracic Society questionnaire to assess respiratory symptoms and frequency including chronic bronchitis, chronic cough and chest wheezing.	Symptoms of chronic cough and chronic bronchitis depended significantly on airborne endotoxin concentration. Chronic cough depended significantly on the interaction of endotoxin and other exposure variables ($p < 0.01$), which improved when including interaction variables	Endotoxin measurement were available for 46 workers; small sample size
	Lung function test (Spirometry; FVC, FEV_1, FEV_1/FVC, $FEF_{25–75}$)	Lung function declined with increasing endotoxin exposure, particularly for FVC, which were significantly correlated ($p < 0.05$). FVC was inversely associated with endotoxin concentration ($p = 0.08$)	Variability relating to work site and seasonal effects was significant, which may reflect livestock production cycles Not all confounders were adjusted for
Community-based studies measuring concentrations of bioaerosol components (n = 1)			
Schinasi et al. (2011)	Subjects noted any cough or irritation, and asked to rate the extent they experienced acute respiratory and physical symptoms on an 8 point scale over 12 h.	Associations of acute irritations with 1-h odour and H_2S, but no PM_{10} except for eye and skin irritation.	Only community-based study where both exposure measurements and health data have been collected
	Lung function (FEV_1 PEF)	T-values for beta coefficients from linear conditional fixed-effect models were small for 12-h average concentrations of $PM_{2.5}$, PM_{10}, and endotoxin and lung function, except for PM2.5 and FEV_1, which decreased Chi Squared values were small indicating that exposure measures were poor There were positive associations between symptoms and endotoxin	Repeat measurements were made, but it is still a small sample size, which limits ability of measuring association in sub groups. Also subjects conducted their own tests with limited training, so the results may not be valid.
Community-based studies using proxy measures for exposure (n = 16)			
Borlee et al. (2015)	Questionnaire on respiratory health	Found an inverse association between different indicators of livestock farm exposure and self-reported asthma, COPD, and nasal allergies with individual exposure estimates based on residential address, suggesting a protective effect. There is a positive association between presence of poultry within 500 m and atopic asthma	Community-based study

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Table 2 (*continued*)

Author (year)	Health outcomes assessed	Significant findings	Comments
	Electronic medical records (EMR) defining asthma, COPD and allergic rhinitis	Current wheezing and use of Inhaled corticosteroid (ICS) in COPD patients was positively associated with several exposure indicators, suggesting increased risk of COPD exacerbation in a susceptible group	Used non-objective questionnaire data 'validated' using objective EMR data
Bullers (2005)	Questionnaires and interviews on physical health symptoms (including headache, nausea, wheezing, asthma, cough, phlegm production, aches and pains, chest tightness and skin rash on a frequency scale), and psychological distress.	Independent sample *t*-tests show statistically significant differences between nearby resident group and control group for watery eyes, runny nose, scratchy throat, sputum, cough, popping ears, nausea & vomiting, dizziness, shortness of breath, & wheezing & chest tightness (all increased in resident group compared to control group)	Unable to complete a meaningful analysis on the effects of ethnicity, as the study included predominantly white citizens. Did not use a random sample
Hooiveld et al. (2016)	Electronic medical records (EMR)	Each additional goat CAFO significantly increased odds of unspecified infectious disease and pneumonia. There was a significant association for acute respiratory infections in swine CAFOs for those living near.	Used objective EMR data Cross-sectional analysis. No temporal data Patient characteristic in the High and low exposure groups were similar
Hoopmann et al. (2006)	Standardised questionnaire on asthma symptoms to diagnose asthma. Standardised physical examination and SX-1 tests to detect visible signs of flexural dermatitis (neurodermatitis). Capillary blood was analysed for IgE to differentiate between intrinsic and extrinsic asthma. SE-1 test to detect specific IgE-antibodies for allergens in serum (pollen, from rye, birch, mugwort, *Cladosporium herbarum*, house dust mite, cat hair, dog hair)	There were few statistically significant associations between bioaerosols exposure and asthmatic and allergic symptoms There was an increase in prevalence of asthma symptoms for increased estimated endotoxin concentrations in children with atopic parents (odds ratio: 1.15, $p = 0.016$ per one unit log endotoxin concentrations).	Results indicate that genetic predisposition and early life exposure (e.g. factors such as breast-feeding) are important.
Huijskens et al. (2016)	Throat swabs and blood samples, sputum and urine were tested for respiratory pathogens	CAP; caused by *coxiella burnetii* is associated with the presence of sheep and number of goats within 1 km of a household ($P < 0.05$),	The database of mandatory environmental licenses for keeping livestock does not state the purpose for which the animals were kept (e.g. meat or dairy). Also potential for exposure misclassification as licence data may not be representative of the actual number of animals present on a farm
Mirabelli et al. (2006)	Answered questions about their respiratory symptoms (video based questionnaire (respiratory – included core wheezing questions from the International Study of Asthma & Allergies in Childhood questionnaire), allergies & medications	Adjusted prevalence ratios (PRs) for wheezing were 1.05 (95% Cl:1.00–1.10) & 1.02 (95% Cl:0.94–1.11) for adolescents who did & did not have allergies respectively & attended schools that were located within 3 miles of the nearest swine CAFO	Strength of study is the standardised symptom data
		Adjusted PRs for physician-diagnosed asthma (1.07; 95% Cl:1.01–1.14), medication use (1.07; Cl:1.00–1.15) & physician or emergency department or hospitalization (1.06; 95% Cl:1.00–1.12) & presence of swine CAFO within 3 miles Most associations were slightly higher in adolescents with self-reported allergies; however, the PR for physician-diagnosed asthma was higher among students without (PR: 1.14; 95% Cl:1.01–1.26) compared with those with (PR: 1.06; 95% Cl:0.99–1.12) self-reported allergies	Although the majority of estimates are small in relative terms, the increases are important in absolute terms because of the high prevalence of asthma-related symptoms in this age-group
Pavilonis et al. (2013)	Medical (including respiratory symptoms, asthma status) information was obtained from questionnaires	Children with a larger relative environmental exposure had significantly increased odds of asthma (OR = 1.51, $p = 0.014$) and asthma and medication for wheeze (OR = 1.38, $p = 0.023$). A linear trend was observed when stratifying for exposure quartiles for asthma and medication for wheeze monotonic dose–response Relationship was observed between increasing exposure quartiles and the prevalence of childhood asthma.	Questionnaires were electronic and included questions from validated questionnaires
Radon et al., 2005	Questionnaire including validated questions of respiratory symptoms and diseases.	The prevalence of allergic diseases was higher in the study population compared to urban populations.	Exposure proxy consists of number of animal houses within 500 m only. Unclear why 500 m was chosen.
	Collection of serum (for allergic sensitisation)	Subjects with more than 12 animal houses within 500 m of their home had a higher odds ratio for wheezing (without cold) (OR: 2.7, CI: 1.4–5.4), and decreased FEV_1 (mean 0.26 l), and lower FEV_1/FVC ratio	Objective and non-objective data used.
	Lung function tests (spirometry, (FEV_1, FVC) Methacholine challenge		

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Table 2 (*continued*)

Author (year)	Health outcomes assessed	Significant findings	Comments
Radon et al. (2007)	Questionnaire which included questions on respiratory symptoms. Medical examinations	Number of animal houses was a predictor for self-reported wheeze and decreased FEV_1,	Used both objective and self-reported data
			Assessed potential selection bias, and reduced reporting bias where possible
	Lung function tests (FEV_1) Bronchial methacholine challenge		
Sigurdarson and Kline (2006)	Questionnaire, which included questions on asthma and allergies.	Students attending a school near a CAFO has significant increased odds of being diagnosed with asthma by a physician (OR 5.71, p = 0.004) in comparison to a control school	Response rates were similar in both the case school and control school
Smit et al. (2012)	EMR detailing 'other infectious disease' (which includes Q fever) data from GPs in provinces with a high density of farm animals were collected.	Dose-response relationships were observed between the number of goats within 5 km of home address and pneumonia and other infectious disease (OR 12.03 95% CI 8.79-16.46 comparing fourth to the first quintiles) in adults. Increased pneumonia incidence was associated with the presence of poultry within 1 km in adults (OR 1.25 95% CI 1.06-1.47). There was a strong association between other infectious disease with number of goats (categorised into four quartiles). Odds Ratio = 12.03 (95% confidence interval 8.79–16.46) for quartile with highest number of goats, compared to quartile with lowest number of goats.	Not possible to isolate Q fever as an outcome as this is coded under 'other infectious disease' in the Netherlands
Smit et al. (2014)	EMR data for asthma, COPD and allergic rhinitis from GPs in provinces with a high density of farm animals were collected (as per Smit et al. (2012)).	Statistically significant negative association with farm-related PM10 and all health outcomes. Those living closer to a farm (< 280m) had significantly lower odds of allergic rhinitis and COPD compared with those living further away (> 640m).	Not possible to distinguish between atopic and non-atopic asthma
	A subset of 317 diagnosed with asthma (cases) and 662 with low back pain (controls) answered a questionnaire	The presence of goat, sheep and pig farms were inversely related to health outcomes, whereas the opposite was observed for mink farms.	Use of GP EMR data likely to result in high specificity but a low sensitivity
		Adjustment for confounding did not alter results	
Thu et al. (1997)	Symptoms (physical and psychological), and symptom frequency were assessed in adults via an interview administered questionnaire.	Residents near the swine operation reported higher frequencies of 14 out of the 18 physical symptoms than the control population. Skin rash, muscle aches and fever were reported more frequently among the control group. Physical symptoms in 4 clusters (cluster 1: respiratory symptoms; cluster 2: nausea, weakness, dizziness and fainting; cluster 3: headaches and plugged ears; cluster 4: burning eye, runny nose and throat). Cluster 1, 2 and 3 were significantly greater in swine facility neighbours compared to the control area (p = 0.02, 0.04 and 0.06 respectively). There was no connection between the frequency of reported physical symptoms and distance from the swine facility.	Small study with limited power
		Little evidence to suggest that neighbours of the large-scale swine operation suffer higher rates of anxiety or depression	Relies on questionnaire data
			No exposure measurement − exposure is assumed if residing within 2 mile and higher or lower levels of exposure are not distinguishable Unable to evaluate susceptible groups
van Dijk et al. (2016a)	Electronic Medical Records (EMRs) for 2006–2012 from Asthma and COPD patients aged 7–40 from GP practices located in rural areas with a high density of livestock farms (case area) and lower density of livestock farms (control area)	Individual-level exposure estimates were not associated with exacerbations of asthma or COPD	Performed various sensitivity and subgroup analyses.
		Exacerbation of COPD was higher in areas of high density farming than lower density farming (IRR 1.28 95% CI 1.06–1.55). This was 36% higher for patients living within 500 m of poultry farms with up to 12,499 chickens (IRR 1.36 95% CI 1.03–1.79). This was not observed in asthma patients.	No information on animal housing systems, ventilation and manure handling and spreading systems.
			Unable to distinguish between different severities of asthma and COPD
van Dijk et al. (2016b)	General Practitioner (GP) contacts of 54,777 patients were included: all; respiratory symptoms, respiratory illness, acute respiratory infections.	There were small protective associations with all exposure measures almost all of which were statistically significant except for poultry farms with > 14,000 birds within 500 m with increased risk for respiratory diagnoses of 1.09 (1.00–1.18) and acute respiratory infections 1.17 (1.06–1.29)	Overall negative effect including for PM_{10} emissions except for increased risk of respiratory diagnoses and infections for large poultry farms within 500m

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Table 2 (*continued*)

Author (year)	Health outcomes assessed	Significant findings	Comments
	A random subsample of 1519 who were diagnosed with lower back pain were invited to complete questionnaires on respiratory symptoms including cold/flu, cough, shortness of breath and sore throat	Protective findings were also seen in the subset of self-reported symptoms	Good power from large sample using registry data. Multiple analyses may have increased chance of finding significant results.
			Results may be affected by migration of those affected by farms or differential reporting behaviour by those living in rural areas.
Wing and Wolf (2000)	Symptoms, and symptom frequency were assessed in adults via an interview administered questionnaire.	The average number of symptoms was similar in the three communities. However residents near the hog operation reported more upper respiratory symptoms, more excessive coughing, more gastrointestinal symptoms, and more burning eye. Over half of the hog operation residents said they could not open windows or go outside	Relies on questionnaire data, no objective measures.
			No exposure measurement – exposure is assumed if residing within 2 miles, and higher or lower levels of exposure are not distinguishable Unable to evaluate susceptible groups

3.2.4. Bias assessment

Table 3 presents results of the bias assessment, which was assessed using the tool presented in Appendix B, developed from Pearson et al. (2015), which was itself previously developed from Shah and Balkair (2011). Explanations for the scores agreed for each study are presented in Appendix D. A high score denotes a low risk of bias and a low score denotes a high risk of bias. The highest possible score is 32, and lowest possible score is 8. Overall studies included in this systematic review scored 11–27 (a score of 16–27 for the 21 occupational studies measuring exposure, a score of 19 for the one community study measuring exposure, and a score of 11–25 for the 16 community studies using an exposure proxy).

In general, the occupational studies scored better on study design (as many were experimental or quasi-experimental) and exposure assessment (as measured), but were more prone to selection bias and small sample sizes. A small sample size does not necessarily correspond to low statistical power, but few studies presented sample size calculations. In general community studies had higher sample sizes and were less prone to selection bias, with good or adequate confounder control. However, almost all community studies were cross-sectional in design so it is more difficult to assign effects to farming exposure. Only one community study measured exposure, so studies are prone to bias in exposure misclassification and many relied on self-report of symptoms and respiratory disease, introducing responder bias. Where community studies used general practice medical records for information on health outcomes, details of how the practices were recruited and exclusions from participation were not always present.

The majority of the studies used statistical tests appropriate for the type of question and study design and in general, an adequate description of the methodology used was provided. Comparison (control) groups were not always clearly defined. Nevertheless, the majority of the studies used appropriate methods to adjust for the major confounders, like age, sex, smoking status, socio-economic status and pre-existing medical conditions.

4. Discussion

The increase in the number of intensive farms has led to understandable concerns about bioaerosol emissions from these facilities and any possible resultant adverse health effects. In this systematic review we evaluated the evidence base on the health effects of bioaerosol emissions resulting from intensive farming on both workers and nearby residents. The majority of the studies that measured bioaerosol concentrations were occupational. These studies can provide important insights into a potential etiological role of bioaerosol exposure on human health outcomes at the individual and population level. These studies provided qualitative evidence linking occupational exposure to bioaerosols to respiratory-tract symptoms. However, there was some suggestion that bioaerosol exposures in the workplace may be potentially protective against negative health impacts. This is consistent with bias introduced by the healthy worker effect – a well-known phenomenon in occupational epidemiological studies whereby those suffering health impacts from workplace exposures are more likely to change employment. The community studies typically relied upon proxy exposure measures and reported mixed results in adults, with some studies linking it with adverse self-reported respiratory health and others reporting no effect or even (in studies relying on general practice records) a protective effect. Studies involving children yielded modest but consistent evidence supporting increased self-reported asthma rates among those children living or attending schools located within close vicinity of an intensive farm.

In some studies, the health effects were different according to the type of animal (e.g. pig or poultry). For example, there was an increased risk of respiratory symptoms in residents living within 500 m of a poultry farm but a decrease in those living within 500 m of a pig farm (van Dijk et al., 2016b). However, there were no consistent differences between farm types and more research will be needed before conclusions can be made.

The review showed that occupational endotoxin concentrations inside intensive farms are similar to those levels typically detected at composting facilities – a known source of bioaerosol emissions. A recent systematic review provided qualitative evidence linking bioaerosol emissions from composting facilities to poor respiratory health in workers and nearby residents (Pearson et al., 2015). Different ventilation and air filtration systems are used by farms and as no community studies measured exposure, it is difficult to know how these occupational study measurements might related to community exposures.

Table 3
Risk of bias, scored using the risk of bias tool (Appendix B).

Author (year)	Risk of bias								
	Study design	Selection	Responder	Confounder	Exposure assessment	Outcome assessment	Sample size	Analytical	Total
Occupational studies measuring concentrations of bioaerosol components (n = 21)									
Bonlokke et al. (2012)	3	2	2	2	4	3	1	4	21
Donham et al. (1989)	3	2	1	3	4	3	2	4	22
Donham et al. (2000)	3	3	2	4	4	3	3	4	26
Dosman et al. (2006)	3	2	1	3	4	3	1	3	20
Eduard et al. (2004)	2	3	3	4	4	3	4	4	27
Eduard et al. (2009)	2	3	3	3	3	3	4	4	25
Hoffmann et al. (2005)	3	2	1	3	4	3	1	3	20
Hoffmann et al. (2005)	3	2	1	1	4	3	1	3	18
Larsson et al. (1992)	2	2	2	2	4	3	1	2	18
Palmberg et al. (2002)	3	1	1	2	4	3	1	4	19
Palmberg et al. (2004)	3	1	1	1	4	3	1	2	16
Portengen et al. (2005)	2	3	3	3	3	3	2	4	23
Preller et al. (1995)	2	3	3	2	4	3	2	4	23
Radon et al. (2000)	3	4	4	2	4	3	2	4	26
Radon et al. (2001)	3	4	3	3	4	4	2	4	26
Sahlander et al. (2010)	3	1	1	1	3	3	1	3	16
Schiffman et al. (2005)	3	2	4	4	3	3	1	1	24
Vogelzang et al. (1997)	2	4	2	3	4	3	3	4	25
Vogelzang et al. (1998)	4	4	3	2	4	3	2	4	26
Vogelzang et al. (2000)	4	4	3	2	4	3	2	4	26
Zejda et al. (1994)	2	3	1	3	3	3	2	4	21
Community-based studies measuring concentrations of bioaerosol components (n = 1)									
Schinasi et al. (2011)	3	2	1	2	3	2	2	4	19
Community-based studies using proxy measures for exposure (n = 16)									
Borlee et al. (2015)	2	4	2	3	2	3	4	4	24
Bullers (2005)	2	2	4	3	1	3	1	4	20
Hooiveld et al. (2016)	2	2	1	2	2	2	4	4	19
Hoopmann et al. (2006)	2	3	2	4	3	3	4	4	25
Huijskens et al. (2016)	3	2	4	1	2	3	3	2	20
Mirabelli et al. (2006)	2	4	2	4	2	3	4	4	25
Pavilonis et al. (2013)	2	4	1	4	2	4	3	4	24
Radon et al. (2005)	2	4	2	3	2	3	4	4	24
Radon et al. (2007)	2	4	2	3	2	3	4	4	24
Sigurdarson and Kline (2006)	2	2	2	3	2	3	2	4	20
Smit et al. (2012)	2	4	1	2	2	3	4	4	22
Smit et al. (2014)	2	4	1	4	3	3	4	4	25
Thu et al. (1997)	2	2	1	1	1	2	1	1	11
van Dijk et al. (2016a)	2	4	1	2	2	3	4	4	22
van Dijk et al. (2016b)	2	4	1	2	2	2	4	4	21
Wing and Wolf (2000)	2	3	3	3	1	2	2	4	20

4.1. Limitations

A number of limitations need to be taken into account when interpreting the results from the included studies. The studies were heterogeneous in design and analysis, which limited the possibility to conduct a meta-analysis. Studies measuring bioaerosol concentrations in this review predominantly focussed on endotoxin concentrations. However, bioaerosols are a complex mixture and any potential health effects of other bioaerosol components are not taken into account. Information is currently inadequate to apportion the relative impacts of the different components to observed health effects. Further work needs to be done to determine the potential differential toxicity of the different components. Determining the responsible toxic components in the mix may also result in more effective regulations. Exposure assessment also varied across the included studies – ranging from proxy exposure measures to analysis of bioaerosol constituents using culture-based methods.

There was only one community-based study that measured bioaerosol concentrations. The remaining 21 studies were occupational based. Whilst health data on occupationally exposed workers can provide some insight into the toxicity or lack of toxicity of bioaerosol exposures in the general population, caution should be exercised in making any inferences. Workers are typically exposed to the highest airborne levels and the 'healthy worker effect' is a potential source of bias as those affected by exposures may leave farm employment. Furthermore, these studies do not take into account population groups which may be more vulnerable, such as children and the elderly. These studies also do not take into account susceptibilities that may arise in the local population as a result of differences in social and housing factors. Differences in housing quality are known to influence health status and similar factors could also affect susceptibility within the vicinity of intensive farming sites.

For those studies that used an exposure proxy, the majority were cross-sectional in design and therefore it is difficult to determine a temporal relationship between exposure and health outcome.

4.2. Impact

It is hoped that the information provided in this review will assist in the development of risk assessment and limit values in relation to intensive farming. For example, current practices in England require intensive farms to undertake a site specific bioaerosol risk assessment if the farming operation is within 100 m of a sensitive receptor (sensitive receptors include, but are not limited to local residents, schools and elderly housing). However, there has been much debate over the distance required for bioaerosol concentrations to return to background levels. This has been further complicated by the fact that a boundary distance of at least 250 m is currently being recommended by the English Environment Agency in relation to large-scale composting operations. However, the concentration and size distribution of bioaerosols varies with a number of factors (e.g. type of industry, geographical location, weather conditions) so it is difficult, if not impossible to make inferences between composting and intensive farms. The information provided at the time of this review does not provide hard evidence to support a change from the Environment Agency's current permitting guidance of at least 100 m. However, this should be reviewed pending acquisition of further data, which is necessary to address the limitations of those previously described. Also, it should be remembered that in some studies adverse health effects were observed at distances greater than 100 m.

4.3. Recommendations for future work

To address the limitations highlighted above, and gaps in knowledge, studies which incorporate the following are required:

1) More studies are needed with sufficient power to detect the expected effect size. Few studies included details of power calculations, making it difficult to identify which studies were sufficiently powered to detect a meaningful difference. Future studies should include exposed and non-exposed populations, a wider variety of ages (including children and the elderly), males and females, and a variety of current health statuses in both occupational and community studies. As there is evidence of adaptation to bioaerosols (Palmberg et al., 2002b) there also needs to be more studies of naïve populations being exposed to the intensive farming environment, and time needs to be taken into account as a factor.

2) Longer time frames

To determine the effects of chronic and acute exposure, longitudinal studies completed over longer time scales are required. This will determine whether there are healthy worker effects (in occupational settings), innate immunity etc. It will also quantify fluctuations of different bioaerosol components seasonally and potential effects due to climate change.

3) More detailed analysis of exposure

The type and concentration of different bioaerosol components needs to be quantified, and variation due to farming type or practice determined. A greater understanding of bioaerosol dispersal patterns downwind of farms is required to determine safe set back distances. Ideally long-term continuous measurements (e.g. using Wideband Integrated Bioaerosol Sensor (WIBS) technology) are required, combined with molecular analysis methods. The agreement of a standard or best practice monitoring method would also be useful to allow results from multiple studies to be more easily compared. This has recently been implemented in the UK whereby it is recommended that bioaerosol concentrations are monitored according to the M9 technical guidance note (EA, 2017). However, there will be a delay in obtaining a set of more homogenous studies. Also the researchers likely to be using the processes and methods detailed in the M9 technical guidance note are likely to be UK based. Quantification of background concentrations of bioaerosols is needed to help determine which bioaerosol components and concentrations are released as a direct result of intensive farming.

4) Clearer definitions of the health outcomes

While questionnaires can provide rich and useful data about a population, and can be used to assess symptoms, they are prone to reporting and recall bias. Therefore more objective health measurements should be completed (e.g. lung function measurements), combined with biochemical measures (e.g. lymphocyte activation and cytokine analysis).

5) Consideration of confounding factors

An assessment of cofounding effects in the study population such as housing and socioeconomic status.

6) Assessment of mechanisms of action in experimental studies

Experimental work in model systems to determine effects of bioaerosol components without confounding effects and so elucidate those components that have health effects, which can then be specifically focussed on for field studies and interventions.

As indicated above, there is a number of areas which clearly require a need for future research. Initially, however, the focus should be on quantifying exposure and improving understanding of the dose-response relationships in community settings.

5. Conclusions

To conclude, the majority of studies pointed towards a negative impact on health outcomes, particularly respiratory symptoms, among farmers exposed to bioaerosols. Studies investigating the health of communities living near intensive farms were more mixed. Further research is needed to measure and monitor exposure in community settings and relate this to objectively measured health outcomes. However, there was relatively consistent evidence of increased reported asthma among children living or attending schools near an intensive farm.

Acknowledgements

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Appendix A. Search strategy

PubMed Search

(bio-aerosol* OR bioaerosol* OR aerosol* OR microbial OR microorganism OR microorganisms OR allergen* OR dander OR plant fib* OR pollen OR fungi OR fungus OR fungal OR spore* OR conidia OR aspergillus OR alternaria OR penicillin OR cladosporium OR fusarium OR saccharomy* OR mold OR mould OR mycotoxin* OR ("fungal fragments") OR glucan* OR ("volatile organic compounds") OR VOCs OR virus* OR particles OR particulate OR pollutant* OR dust OR bacteria OR bacterial OR bacterium OR endotoxin* OR clostridium OR actinomycetes OR actinobact* OR streptomy*)

AND

(health OR mortality OR morbidity OR admission* OR attendenc* OR lung* OR ("farmer lung") OR ("lung function") OR pulmonary OR respiratory OR inflammation OR inflammatory OR infection OR allergy OR allergies OR allergic OR asthma* OR copd OR ("chronic bronchitis" OR "hay fever") OR rhinitis OR ("hypersensitivity pneumonitis" OR "extrinsic allergic alveolitis") OR ("exhaled NO") OR FEV OR ("peak flow") OR cough OR wheeze OR ("bronchial reactivity" OR "bronchial hyperreactivity" OR "bronchial responsiveness" OR "bronchial hyperresponsiveness") OR cancer OR cancers OR carcinoma* OR heart OR cardiac* OR cardioresp* OR cardiopulmonary OR gastro OR GI OR gastrointestinal OR toxicity)

AND

(((farming OR agriculture)

AND

(intensive OR pig OR hog* OR chicken OR poultry OR swine)) OR composting OR compost OR windrows OR waste OR ("anaerobic digestion") OR landfill)

NOT

(hazardous OR sewage OR incinerat*)

Scopus Search

((((TITLE((bio-aerosol* OR bioaerosol* OR aerosol* OR microbial OR microorganism OR microorganisms)) OR ABS((bio-aerosol* OR bioaerosol* OR aerosol* OR microbial OR microorganism OR microorganisms)))) OR ((TITLE((allergen* OR dander OR plant fib* OR pollen)) OR ABS((allergen* OR dander OR plant fib* OR pollen)))) OR ((TITLE((fungi OR fungus OR fungal OR spore* OR conidia OR aspergillus OR alternaria OR penicillin OR cladosporium OR fusarium OR saccharomy* OR mold OR mould OR mycotoxin* OR ("fungal fragments") OR glucan* OR ("volatile organic compounds") OR vocs)) OR ABS((fungi OR fungus OR fungal OR spore* OR conidia OR aspergillus OR alternaria OR penicillin OR cladosporium OR fusarium OR saccharomy* OR mold OR mould OR mycotoxin* OR ("fungal fragments") OR glucan* OR ("volatile organic compounds") OR vocs)))) OR ((TITLE((virus* OR particles OR particulate OR pollutant* OR dust OR bacteria OR bacterial OR bacterium OR endotoxin* OR clostridium OR actinomycetes OR actinobact* OR streptomy*)) OR ABS((virus* OR particles OR particulate OR pollutant* OR dust OR bacteria OR bacterial OR bacterium OR endotoxin* OR clostridium OR actinomycetes OR actinobact* OR streptomy*)))))

AND

(((TITLE((health OR mortality OR morbidity OR admission* OR attendenc*)) OR ABS((health OR mortality OR morbidity OR admission* OR attendenc*)))) OR ((TITLE((lung* OR ("farmer lung") OR ("lung function") OR pulmonary OR respiratory OR inflammation OR inflammatory OR infection)) OR ABS((lung* OR ("farmer lung") OR ("lung function") OR pulmonary OR respiratory OR inflammation OR inflammatory OR infection)))) OR ((TITLE((allergy OR allergies OR allergic OR asthma* OR copd OR ("chronic bronchitis" OR "hay fever") OR rhinitis OR ("hypersensitivity pneumonitis" OR "extrinsic allergic alveolitis"))) OR ABS((allergy OR allergies OR allergic OR asthma* OR copd OR ("chronic bronchitis" OR "hay fever") OR rhinitis OR ("hypersensitivity pneumonitis" OR "extrinsic allergic alveolitis"))))) OR ((TITLE((("exhaled NO") OR fev OR ("peak flow") OR cough OR wheeze OR ("bronchial reactivity" OR "bronchial hyperreactivity" OR "bronchial responsiveness" OR "bronchial hyperresponsiveness"))) OR ABS((("exhaled no") OR fev OR ("peak flow") OR cough OR wheeze OR ("bronchial reactivity" OR "bronchial hyperreactivity" OR "bronchial responsiveness" OR "bronchial hyperresponsiveness"))))) OR ((TITLE((cancer OR cancers OR carcinoma* OR heart OR cardiac* OR cardioresp* OR cardiopulmonary OR gastro OR gi OR gastrointestinal OR toxicity)) OR ABS((cancer OR cancers OR carcinoma* OR heart OR cardiac* OR cardioresp* OR cardiopulmonary OR gastro OR gi OR gastrointestinal OR toxicity)))))

AND

((TITLE((((farming OR agriculture)

AND

(intensive OR pig OR hog* OR chicken OR poultry OR swine)) OR composting OR compost OR windrows OR waste OR ("anaerobic digestion") OR landfill)) OR ABS((((farming OR agriculture)

AND

(intensive OR pig OR hog* OR chicken OR poultry OR swine)) OR composting OR compost OR windrows OR waste OR ("anaerobic digestion") OR landfill)))))

AND NOT

((TITLE((hazardous OR sewage OR incinerat*)) OR ABS((hazardous OR sewage OR incinerat*))))

Wildcard key:

*retrieves any number of characters, or no characters, after the stem

" " searches for exact terms

Following the original search of both PubMed and Scopus databases, the same search was performed April 2017 to identify any additional papers that had been published in the interim.

Appendix B. Risk of bias assessment tool

The risk of bias scoring tool (Table B1) was used to assess bias in the studies; a higher score indicates a lower risk of bias. The tool was developed from Pearson et al. (2015), which was itself previously developed from Shah and Balkhair (2011). The responder criteria relates to response rate and whether this was adequately described in the article.

Table B1
Risk of bias scoring tool.

Risk of bias	Very low (score of 4)	Low (score of 3)	Moderate (score of 2)	High (score of 1)
Study design	Prospective cohort OR fully experimental with controlled exposure	Retrospective cohort OR	Cross-sectional OR	Case-series OR
		Case-control OR experimental such as pre-post shift, panel study, chamber study without full control over exposure levels	Ecological	Case-studies
Selection	Clear selection criteria, appropriate to study aim and design	Selection criteria not fully explained, appropriate to study aim and design OR all available participants selected	Unclear if selection criteria appropriate to study aim. Unclear if sample is representative of population under study. Minimal details of selection criteria reported	Selection criteria not explained. Sample potentially not representative of population under study
Responder	> 90% response and follow-up. Reasons for loss to follow-up explained and investigated	> 70% response and follow-up. Reasons for loss to follow-up explained and investigated	> 50% response and follow-up. Reasons for loss to follow-up explained and investigated	Response or follow-up rate not reported OR 50% or lower response and follow-up OR Reasons for loss to follow-up not fully investigated or explained OR Unclear GP response rates where GP practice data was used
Confounders	Confounders identified and important confounders controlled for or accounted for in other ways (e.g. matched or excluded or randomisation). Conduct sensitivity analyses and/or test for interactions	Confounders identified and important confounders adjusted for, or accounted for in other ways (e.g. matched or excluded or randomisation)	Confounders identified but some important confounders not adjusted for or otherwise accounted for	Most important confounders not adjusted for OR no information given about confounders
Exposure assessment	Direct personal sampling of subjects and controls for studied bioaerosols over adequate time period. Standard or recognised methodology or non-standard methods explained	Direct ambient monitoring of studied bioaerosols over adequate time period on-site Standard methodology or non-standard methods explained OR exposure modelling using sample, meteorological and source term input data to create exposure bands	On-site ambient sampling over inadequate time period or at limited number of representative sites OR distance from source used as proxy, with appropriate exposure bands but no modelling OR number of animal facilities within a specified radius	No exposure measures, or poor or non-standard sampling methods. Exposures predicted from concentrations sampled at other sites or times OR distance from source used as proxy with unsuitable exposure bands OR odour only
Outcome assessment	Direct questioning with standardised questions (e.g. ATS, ERS, ISAAC) and blinding of interviewer. Standardised clinical examination with blinding of clinician to exposures	Direct questioning with standardised questions but without interviewer blinding to exposures. Standardised clinical examination without blinding of clinician to exposures. Use of records of standardised routine examinations	Use of records of non-standardised clinical examinations. Direct questioning but questions not described or not standardised	Assessment from open-ended or leading questions. Non-standardised clinical examination
Sample size	Sample size calculations. Adequate sample size (> 1000) OR a smaller sample size (201–1000) if there is a clear justification	No sample size calculation performed but all available participants studied (201–1000) OR a smaller sample size is used (50–200) if there is clear justification	No sample size calculations. Small sample size (50–200) OR small sample size (< 50) if there is a clear justification	Very small sample size (< 50)
Analysis	Appropriate statistics for study design. Appropriate analysis for the type of sample and sampling strategy	Adequate statistical methods but better methods available	Appropriate analytical method but flaws in implementation OR inadequate analysis performed	Inappropriate analysis for the study design and type of sample

Appendix C. Total bacteria and total fungi/mould concentrations

See Figs. C1 and C2.

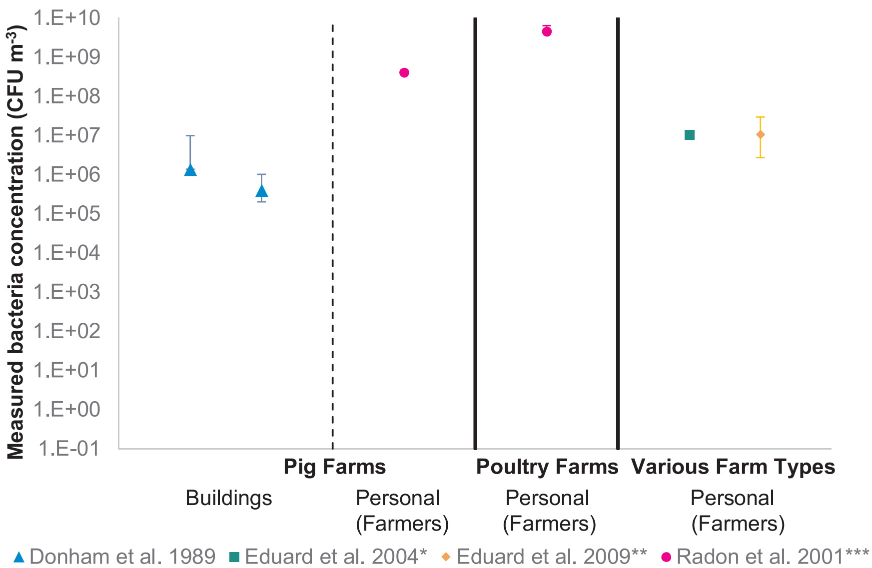

Fig. C1. Mean/median airborne total bacteria concentrations. The error bars represent the range of values presented in the studies, if provided.
*Units were provided as bacteria m^{-3} **Units were provided as cells m^{-3} ***Units were provided as ng m^{-3}.

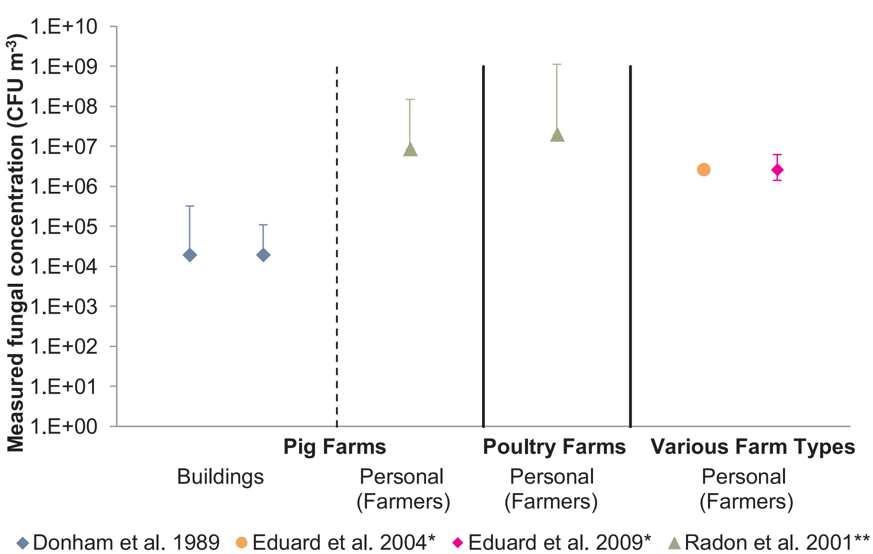

Fig. C2. Mean/median airborne total fungi/mould concentrations. The error bars represent the range of values presented in the studies, if provided.
*Units were provided as fungal spores m^{-3} **Units were provided as ng m^{-3}.

Appendix D. Explanations of the bias assessment scores

Table D1 presents the explanations of the bias assessment scores agreed for each study, using the risk of bias scoring tool (Appendix B).

Table D1
Bias assessment score explanations.

Author (year)	Risk of bias								
	Study design	Selection	Responder	Confounder	Exposure assessment	Outcome assessment	Sample size	Analytical	Total
Occupational studies measuring concentrations of bioaerosol components (n = 21)									
Bonlokke et al. (2012)	3	2	2	2	4	3	1	4	21
	Occupational pre-post shift Quasi-Experimental study	Excluded smokers, people with respiratory infections during previous week or lung disease. Full selection detail given in reference 20 - selected through personal contacts and visits, local telephone registers, registers of pork producers and preferentially within one hour's drive of Quebec. Authors note that subjects may be unrepresentative of farming population.	Full results available for 14 of 23 subjects. Response rate: 61%	Adjusted for height and weight. Only non-smokers participated.	Personal sampling for dust and endotoxin. Also continuous sampling of temperature, humidity, CO_2, NH_3 for at least 2hrs within swine building. Farms visited twice during winter.	Clinical examinations conducted on workers pre and post work exposure (first examination after unprotected work with swine, next after not handling pigs for 4 days). Standardised (ATS) questionnaire for respiratory disease. Standardised (ATS) lung function testing (FVC, FEV_1, PEF, FEF, MMEF). Also exhaled breath condensate (pH, CO2, IL-8). Pre and post work blood samples tested for inflammatory markers.	23 swine workers	Multivariate repeated measures analysis allowing for different measurement times. Sensitivity analyses excluding least exposed subjects. Wilcoxon signed rank, *t*-test, normality assumptions verified using Shapiro-Wilks test and Marida's test.	
Donham et al. (1989)	3	2	1	3	4	3	2	4	22
	Occupational pre-post shift (quasi-experimental)	Selected workers from selected Swedish swine farms – with original farm sampling frame being all those who were in a farming association (approximately 35% of total farms in area). Unclear how farm or worker selections were conducted of 57 swine farm workers and 55 matched controls (non-swine farmers) in same district of Sweden.	39 farms were invited to participate by letter, but 57 workers on 30 farms were tested. Unclear how many original invitees declined alongside those who just got involved on the da.	Adjusted for smoking (cigarette pack-years), age and baseline pulmonary function testing.	Gravimetric sampling of dust (total and respirable) using personal monitors and stationary sampling in 30 buildings on 28 farms at 1.2m high. Endoxtoxin analysis on dust. Microbial air sampling in same locations. Drager tubes used for ammonia, carbon dioxide and hydrogen sulfide concentrations. Also extracts from swine urine, swine blood, serum albumin, swine epithelium, dust from swine buildings, feed for swine for Dig-ELISA tests. Antigenic analysis on swine antigens and on dust collected from buildings.	Standardised (ATS) pulmonary function testing before and after day of work. (Respiratory measurements not done on control group.) Blood sample for serum antibodies to airborne allergens. Standardised (ATS) questionnaire before and after work shift (occupational history, health history, health symptoms).	57 swine workers, 55 controls.	Correlation/ regression and multiple regression analyses with multivariate model. Farms grouped into quartiles for air contamination. Chi-squared test, $p < 0.05$.	

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Table D1 (*continued*)

Author (year)	Risk of bias								
	Study design	Selection	Responder	Confounder	Exposure assessment	Outcome assessment	Sample size	Analytical	Total
Donham et al. (2000)	3	3	2	4	4	3	3	4	26
	Occupational pre-post shift (quasi-experimental)	Selected 257 poultry workers from Iowa state register and 120 blue collar comparisons from a small electrical firm.	Overall response rate not given. Response rates 60% for turkey producers and 42% egg producers.	Controlled for age, gender, years working in poultry industry, smoking status and education.	Personal sampling for dust (total and respirable), endotoxin (total and respirable), ammonia.	Pulmonary function test before and after work shift (ranging 2–4hrs) (FEV_1, FEF_{25-75}). Respiratory symptoms using standardised ATS questionnaire.	257 poultry workers. 150 controls (postal & electronics plant workers)	Univariate analysis. Log transformation if not normally distributed. Spearman correlation coefficients. Assessed cross shift decline in lung function of 3, 5, 10% or greater against quartiles of each exposure parameters. Multiple logistic regression.	
Dosman et al. (2006)	3	2	1	3	4	3	1	3	20
	Experimental	Twenty lifetime non-smoking male subjects 18–35 yr of age were recruited by placing advertisements in local newspapers and the University of Saskatchewan Campus newspaper and by placing postings in the Royal University Hospital and University of Saskatchewan. Details of selection given in reference Senthilselvan et al. (1997). Subjects were never-smokers, screened by questionnaire and allergens. Excluded if previous swine barn exposure, asthmatic, allergies or other adverse medical history.	Response rate not described.	Dealt with major confounders by exclusion of smokers, those with a history of swine barn exposure, atopics, asthmatics and atopics. Did not adjust for further confounders.	Two exposures per individual (low & high dust/endotoxin). Subjects spent 5hrs in swine barn riding a bike while wearing personal air sampler. Total dust and endotoxins in dust (converted to endotoxin conc in air) were measured. Also measured NH_3, CO_2, H_2S in the barns.	Standardised (ATS) lung function tests (FEV1, FVC, FEF_{25-75}). Nasal lavage and blood samples for inflammatory markers.	20 non-farming subjects.	t-tests, Mann-Whitney test	

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Table D1 (*continued*)

Author (year)	Risk of bias								
	Study design	Selection	Responder	Confounder	Exposure assessment	Outcome assessment	Sample size	Analytical	Total
Eduard et al. (2004)	2	3	3	4	4	3	4	4	27
	Cross-sectional	Farmers selected from government register of farmers in 3 regions (coastal, inland and mountainous). Reasons for choosing these regions not fully explained.	Participation rate 79%. Excluded those with incomplete data on smoking, farm work, exposure and those who had retired or changed work for health reasons.	Adjusted for age, gender, smoking, asthma in family, years of farm work, full/part time and type of farm (crop or single/multiple livestock types). Atopy was treated as a confounder in asthma model and also as an effect modifier.	Personal exposures to total dust (gravimetric), fungal spores (SEM), bacteria (FM), endotoxins (Limulus assay) and ammonia (Drager tubes) measured as farmers performed typical tasks (288 sampling sessions on 127 farms, 5 year exposure duration).	Spirometric testing, blood samples for IgE by RAST and questionnaire. Stratified sampling of 2253 subjects for atopy testing. Unclear if questionnaire used standardised questions	10792 subjects invited, 8482 farmers underwent medical exam, with subset for atopy testing.	Multiple logistic regression Correlations studied by Goodman-Krusal tau and Spearman's rank correlation coefficients. Hosmer-Lemeshow test to assess fit of asthma model.	
Eduard et al. (2009)	2	3	3	3	3	3	4	4	25
	Cross-sectional	Farmers selected from national register of farmers. A stratified sample taken from these for atopy assessment. 290 farms randomly selected for exposure measurements, but this included crop farms.	Participation rate for spirometry, blood sampling, & questionnaire: 79%. Exposure measurements taken on 127 of the 290 farms (rate: 44%)	Adjusted for age, gender and smoking status (pack years). Adjusted atopy results for stratified sampling of source population. Adjusted FEV/FVC results for height squared.	Measured total dust, actinomycete spores, endotoxins, bacteria, antigens, mites and silica by three dust samples taken during farm tasks, max sample duration 1 h. Personal monitoring for H2S. Ammonia by indicator tubes. 21% of measurements were taken on crop farms.	Self-administered questionnaire for respiratory symptoms (chronic bronchitis, cough, phlegm, asthma). Lung function (FEV, FCV, COPD). Atopy by blood serum for IgE by RAST.	8483 farmers in spirometry, blood sampling, & questionnaire. Subset of 1213 for atopy assessment.	Arithmetic mean used to calculate annual exposure. Pearson product moment correlation and Spearman rank correlation coefficients. Multiple logesitc regression for exposure and COPD/bronchitis. Multiple linear regression analysis for exposure and FEV_1/FVC.	
Hoffmann et al. (2005)	3	2	1	3	4	3	1	3	20
	Experimental	16 participants were selected from a study of farming apprentices (reference 38) who had not worked with swine for at least three months. 8 were symptomatic (cases), 8 were not (controls). It is unclear how the participants were selected from the larger study of farming apprentices	Response rate not described	Cases and controls were matched for smoking a status (and assumed sex) and were of similar age (26 and 27 respectively)	Direct personal sampling on all participants for respirable and inhalable dust and endotoxin	Blood samples were taken before exposures, three times during exposure, and four times post exposure (up to 21 h after). Spirometry was taken before and immediately after exposure, BAL was taken21 h after exposure. Clinician was not blinded to exposure	16 participants (8 cases, 8 controls)	Data were tested for normality and transformed in necessary. t-tests for normally distributed data, Wilcoxon and Mann-Whitney for non-normally distributed data. Correlations	

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Table D1 (*continued*)

Author (year)	Risk of bias								
	Study design	Selection	Responder	Confounder	Exposure assessment	Outcome assessment	Sample size	Analytical	Total
Hoffmann et al. (2005)	3	2	1	1	4	3	1	3	18
	Experimental	16 subjects who had previously worked in pig farming but were not currently exposed. The original sampling frame was a study where all students in second stay at farming school in Denmark in 1992-4 were invited to participate with 79% response rate, from which those < 26 years were selected. Selection criteria given in reference 11 (and reference 38 of reference 11) but do not state clearly how the final 16 were selected, in particular whether they were those previously with or without symptoms after exposure	Response rate not described.	Included 8 smokers. Did not adjust for confounders.	Single exposure (3hrs exercising) in a swine confinement building. Personal sampling for total and respirable dust, and lipopolysaccharides LPS (endotoxin).	Clinical examination one week before, during and one day after exposure, followed up to two weeks after exposure. Bronchoscopy one week before and one day after with inflammatory score assigned by un-blinded physician and BAL taken for IL-6 & TNF-alpha; peripheral blood taken for serum IL-6 and TNF-alpha at baseline and one day after exposure.	16 non-naïve subjects.	Personal exposures log transformed if not normally distributed. Non-normal distributed data evaluated with Wilcoxon test, normally distributed data with paired *t*-tests.	
Larsson et al. (1992)	2	2	2	2	4	3	1	2	18
	Cross-sectional	Not much detail given about selection criteria. Random sample of male, non-smoking swine farmers from a national register in Sweden near Stockholm. Data for several reference groups used for comparison (lung function: 20 male, non-smoking office workers of comparable age; bronchial provocation: 11 female non-farmers; BAL fluid: 25 (12females) never smoking, never farming, mean age 25). Unclear how these comparison groups were selected	32 selected, 7 refused, 2 excluded (asthma), 3 not contactable. 20 farmers from 18 farms took part in the study. Participation rate: 62.5%	Subjects were all selected to be non-smoking males with no cardiac disease and normal chest roentgenograms. No other confounders discussed, especially re reference groups.	Exposure measured in buildings during 1 h of work with pigs. Total dust (with estimates of respirable fraction) and endotoxin by personal sampling.	'Standardised' questionnaire (no further detail) for airway symptoms of cough, phlegm, nasal obstruction, throat irritation. Standardised peak expiratory flow diurnal variability using published method. Standardised (ATS) lung function testing, bronchial metacholine challenge, skin prick test, blood samples for antibody detection by DIG-ELISA, with BAL performed one week later.	20 Farmers	Student's *t*-test or Mann-Whitney *U* test and Spearman's rank correlation, with $p < 0.05$.	

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Table D1 (*continued*)

Author (year)	Risk of bias								
	Study design	Selection	Responder	Confounder	Exposure assessment	Outcome assessment	Sample size	Analytical	Total
Palmberg et al. (2002a-,b)	3	1	1	2	4	3	1	4	19
	Experimental	Eight swine farmers and nine non-farmers. Recruitment and selection criteria not given, but participants were non-smokers, healthy with no previous allergies.	Response rate not described.	Gender: 8 farmers all male, 9 non-farmers mixed gender. Age distribution different between the two groups. All non-smokers, no allergies but did not make adjustments or otherwise consider further confounders.	Personal sampler worn to measure total dust and endotoxins (one per pair of study subjects) while subject weighed pigs for 3 h.	Standardised (ATS) lung function testing (VC, FEV_1, PEF), methacholine challenge test, nasal lavage, blood samples for leukocyte analysis & interleukin6. Questionnaire for symptoms of headache, chills, mental fatigue, muscle pain, malaise (graded 1–5). Oral temperature..	8 swine farmers, 9 controls	Results as median values (25th-75th%iles). Student's *t*-test to compare lung function. Wilcoxon's signed rank test, Mann-Whitney *U* test. Spearman rank correlation test. $P < 0.05$.	
Palmberg et al. (2004)	3	1	1	1	4	3	1	2	16
	Quasi-experimental, pre and post exposure in a swine house	Healthy non-smokers, 7 male and 15 female previously unexposed or only occasionally exposed to farming. Selection criteria unclear.	Participation rate not provided.	Not adjusted. All subjects were non-smoking.	Personal sampling (intra-nasal device) used for endotoxin collection whilst working in swine building for 3 h with 10 mins exposure time per hour. Also measured inhalable and respirable dust with samplers in the breathing zone on 1–2 subjects per exposure occasion. Also measured ammonia and H2S at 1.5m height.	Standardised (ATS) lung function (PEF, FEV_1), bronchial methacholine provocation test, and nasal lavage and blood sampling for antibodies (1 week prior to exposure and after 7hrs from start of exposure). Self-reporting of symptoms before & after exposure.	22 subjects (11 with a respirator)	Wilcoxon's signed rank test. Mann-Whitney *U* test. Student's *t*-test. Spearman rank correlation test with correction for multiple comparisons.	
Portengen et al. (2005)	2	3	3	3	3	3	2	4	23
	Case-control study taking data from study also reported in Preller et al. 1995	194 farmers selected from a group of 1133 male pig farm owners working > 5hrs/day on pig farm where chronic respiratory symptoms were reported in questionnaire. 100 control subjects selected randomly from symptom-free farmers. Original study selection described in references	Full data for 81/94 farmers and 81/100 controls. Response rates: 86% and 81% respectively.	Adjusted for age, smoking habits and case-control status. Also considered familial history of atopy, history of allergic symptoms, in childhood, disinfectant use and number of years working with pigs but found no effect. Complete data (endotoxin exposure, personal characteristics, serology) only available for 81 subjects and 81 controls.	Personal inhalable dust samples taken twice (summer and winter), but sampling duration unclear. Endotoxin extraction and testing using Lymulus amebocyte. Long-term, time-weighted average exposure was estimated by log-transformed exposure levels and modelled to include outdoor temperature, farm characteristics and 8 farming activities.	Blood samples for IgE, standardised (European Community for Steel and Coal) lung function testing, airway hyperresponsiveness by histamine provocation.	94 farmers, 100 controls.	Generalised additive modelling using log transformed exposure and (where needed) outcomes. Multiple logistic regression model with smoothed curves.	

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Table D1 (*continued*)

Author (year)	Risk of bias								
	Study design	Selection	Responder	Confounder	Exposure assessment	Outcome assessment	Sample size	Analytical	Total
Preller et al. (1995)	2	3	3	2	4	3	2	4	23
	Cross-sectional	Selected 194 farmers from a group of 1133 male pig farm owners who had at least two respiratory symptoms (or no symptoms for control) and working > 5hrs/day with pigs.	Data for long term average dust and endotoxin exposure available for 161 (83.0%) farmers. Interviewed 150 farmers (out of 164 using disinfectants, 91.5%).	Adjusted for age and smoking. Adjusted for standing height for lung function only.	Personal inhalable dust, endotoxins and personal ammonia samples taken during one shift in summer and one in winter over average 8.3 h. Modelling for long term average exposure. Also considered use of disinfectant as potential cause of respiratory symptoms.	Standardised lung function tests (as in Portengen et al. (2005)): FVC, FEV_1, MMEF, PEF. Self-reported respiratory symptoms using standardised (MRC) questions: chronic cough, chronic phlegm, ever wheezing, shortness of breath, chest tightness (asthma).	94 farmers, 100 controls.	Multiple linear regression analysis lung function and multiple logistic regression analysis for chronic respiratory symptoms. Used geometric mean of both time-weighted exposure concentrations.	
Radon et al. (2000)	3	4	4	2	4	3	2	4	26
	Occupational pre-post shift (quasi-experimental) and cross-sectional	All 100 pig farmers claiming compensation for suspected occupational health disease in region of Germany. 86M, 14F, mean age 47, reported to be representative of commercial pig farms, study participants were on farms with median of 360 pigs.	Questionnaire response rate 100%. Response rate for RAST:99%.	Adjusted for smoking and, duration of employment, but other details of confounders put in multivariate models were not given.	Personal sampling for respirable dust, endotoxin measured in dust. Ammonia and carbon monoxide monitored in confinement house at 1.5m above floor.0g of settled dust collected from 5 locations/farm from walls/floor/grain milltransit area/ mattress. Vacuum used to collect dust from home mattresses. Dusts analysed for allergens.	Structured interview with standardised questions (MRC). Standardised (ATS) lung function testing. IgE antibody measurements with RAST on blood sera.	100 farmers. Sample size calculation provided but did not clearly relate to the analysis results presented and was not interpreted in relation to the study.	Multiple logistic regression. Mann-Whitney *U* test. Chi-squared values with 3 or 4° of freedom. Square roots of mite/ allergen concentrations were used. Spearman rank correlation.	
Radon et al. (2001)	3	4	3	3	4	4	2	4	26
	Occupational pre-post shift (quasi-experimental) and cross-sectional	A subset of a large European questionnaire study of farmers were followed up and assessed over a working day. A randomly selected subset of 40 pig farmers in Denmark (of 2002 farmers in original questionnaire, response rate 80.6%) and 36 poultry farmers in Switzerland (of 1542 farmers with 81.6% response rate) were chosen for respiratory measurements.	Questionnaire response rates 80.6% and 81.6%. Response rate for lung function testing was not given.	Adjusted for smoking (park years). Lung function results adjusted for age and height.	Questionnaire: farm characteristics (numbers/type of animal, heating/ ventilation systems, floor type, cleaning frequency, air exhaust location), respiratory symptoms.	Standardised questionnaire (based on ECHRS) on respiratory symptoms within previous year (phlegm, shortness of breath, wheezing, cough, chronic bronchitis, asthma).	76 farmers.	t-test, Fisher's exact test, Mann-Whitney *U* test, multiple linear regression.	
					Personal monitors collected samples over	Lung function: FVC, FEV_1, MMEF. Standardised			

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Table D1 (*continued*)

Author (year)	Risk of bias								
	Study design	Selection	Responder	Confounder	Exposure assessment	Outcome assessment	Sample size	Analytical	Total
					mean 118 min; analysed for total dust and concentration of endotoxins and microbes (total bacteria and fungi). Point measurement of ammonia, CO_2, temperature, humidity and air velocity in each animal house.	spirometry (ATS, trained technician) before and after feeding animals in morning. Results analysed blindly.			
Sahlander et al. (2010)	3	1	1	1	3	3	1	3	16
	Experimental	36 subjects - 12 non-smoker pig farmers, 12 smoker pig farmers, 12 non-smoker non-farmers. Excluded one subject (pregnant) and another due to technical problems. Recruitment process and selection criteria not described	Response rate not described	Did not adjust for confounders	Exposure comprised 3 h in a pig barn, weighing pigs. Air sampling in breathing zone on 1–2 subjects for inhalable and respirable dust (not all subjects or each time).	Blood samples (neutrophils, moncytes, Toll-like receptor CD14, IL2, IL4, IL13, IFN-gamma). LPS challenge for IL-6 and IL-8	36 subjects	Simple regression and ANOVA with Fisher's PLSD and paired *t*-tests. For IL6 data, Freidman and Wilcoxon signed rank, Kruskal-Wallis and Mann-Whitney.	
Schiffman et al. (2005)	3	2	4	4	3	3	1	1	24
	Experimental	48 healthy volunteers recruited by advertisement in workplaces and screened by phone for eligibility against inclusion criteria – needed to be healthy adults, excluded if asthma, smoking, allergies, medication use, heart/lung disease, occupational exposure, pregnancy. Unclear if representative of exposed population.	All selected subjects completed the study.	Confounders excluded by study inclusion criteria.	Healthy volunteers placed in an exposure chamber for 2 x 1-h sessions; control session breathing clean air, then exposure session using emissions from a swine house diluted to levels likely to be found downwind. Exposures at least 10 days apart. Measured H_2S, ammonia, endotoxin, total suspended particles, VOCs and odour.	Standardised examination using questionnaire (mood), standardised (digit span) tests for memory, attention, clinical examination (blood pressure, heart rate, respiratory rate), nasal lavage with inflammatory markers measured, salivary IgA. Unclear if standard published protocols used for lung function testing (FVC, FEV_1, FEF_{25-75}).	48 subjects (24 male, 24 female)	48 subjects (24 male, 24 female)	

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Table D1 (*continued*)

Author (year)	Risk of bias								
	Study design	Selection	Responder	Confounder	Exposure assessment	Outcome assessment	Sample size	Analytical	Total
Vogelzang et al. (1997)	2	4	2	3	4	3	3	4	25
	Cross-sectional	Study group comprised 200 randomly selected from these responders to a questionnaire to 2433 male pig farm owners re respiratory symptoms. Recruited to study group if one or more chronic respiratory symptoms (cough/phlegm/ shortness of breath/ever or frequent wheezing/ asthma/chest tightness). Also selected 199 responders with no respiratory symptoms. 98 (symptomatic) and 100 (asymptomatic) selected for environmental & personal measurements.	Response rate to initial questionnaire: 62%. Unclear on response rate for study group.	Adjusted for age, smoking behaviour, farm characteristics. Stratified by symptoms	Personal exposure to dust, endotoxin, ammonia during a working day (average 8.4hrs) in summer & winter. Also examined use of disinfectant, wood shaving as bedding, automated dry feeding, feed pellets and location of air exhaust.	Standardised (ERS) lung function testing and bronchial responsiveness to histamine challenge.	196 pig farmers. 199 controls.	Multivariable logistic regression. Log transformed exposures. Chi-squared and *t*-tests.	
Vogelzang et al. (1998)	4	4	3	2	4	3	2	4	26
	Prospective cohort study	171 farmers followed over a 3-yr period. Selected from survey of 1504 pig farmers. 200 (symptomatic) and 199 (asymptomatic) pig farmers working > 5hrs/ day with pigs were interviewed & medically examined. Cohort comprised 98 & 100 of those deemed consistently symptomatic & asymptomatic, with 171 farmers participating on both occasions.	Complete data available for 146 of 171 cohort members from 198 selected. Response: 74%	Adjusted for age, smoking (pack years), baseline FEV_1. Excluded results for one participant who contracted severe pulmonary disease during follow-up.	Personal exposure to dust on farms during 8.3hr working shift on two days (one in summer, one in winter). Endotoxins in dust by limulus assay. Long term average exposure to dust was calculated by mathematical modelling considering farm characteristics with validation study conducted.	Standardised (ERS) lung function testing (FEV_1, FVC) in 1992 and 1995. Different spirometers used in later period for some individuals but the impact of this was investigated	Total of 171 farmers.	Multiple linear regression analysis with log transformed exposures	

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Table D1 (*continued*)

Author (year)	Risk of bias								
	Study design	Selection	Responder	Confounder	Exposure assessment	Outcome assessment	Sample size	Analytical	Total
Vogelzang et al. (2000)	4	4	3	2	4	3	2	4	26
	Prospective cohort study, same study as Vogelzang 1998 for different outcome	171 farmers followed over a 3-yr period. Selected from survey of 1504 pig farmers. 200 (symptomatic) and 199 (asymptomatic) pig farmers working > 5hrs/day with pigs were interviewed & medically examined. Cohort comprised 98 & 100 of those deemed consistently symptomatic & asymptomatic, with 171 farmers participating on both occasions.	Complete exposure data available for 146 (dust &endotoxin exposure) and 140 (ammonia exposure) from 198 selected. Response rate: 71–74%	Adjusted for age, smoking (pack years) and baseline FEV1. Considered small caliber airways and farm characteristics.	Personal exposure to inhalable dust measured on farms during 8.3hr working shift on two days (one in summer, one in winter). Endotoxins in dust by limulus assay. Long term average exposure to dust was calculated by mathematical modelling considering farm characteristics. Personal exposure to ammonia.	Standardized (ERS) lung function testing and standardised protocol (referenced to Hargreave et al) bronchial responsiveness to histamine challenge. Histamine provocation protocol was checked in a validation study.	171 farmers of which 125–135 had dust, endotoxin or ammonia measurements	Multiple linear regression. Used trimmed means to eliminate distortion from those farmers who experienced very high exposures on one of the days.	
Zejda et al. (1994)	2	3	1	3	3	3	2	4	21
	Cross-sectional study	Selected from register of pork producers. Swine farmer defined as working > 2hrs/day in building with > 200 pigs. Selection was not totally random as participants could only be included if employer agreed access to barns for measurements.	Response rate not given.	Work pattern, smoking, age, height.	Environmental measurements in 50 swine buildings: CO2, ammonia, total dust, respirable dust, airborne endotoxin. Performed once in summer, once in winter in all rooms of barns.	Lung function (FEV_1, FCV, MMEF) with questionnaire for respiratory symptoms (chronic bronchitis, chronic cough, chronic phlegm, chest wheezing, chest tightness)	54 swine producers.	Multivariate analyses and general linear models. Arithmetic mean to calculate average exposure. Shaprio-Wilk W test, $p < 0.05$. Chi-squared test with Yates' correction or Fisher's Exact test. Spearman correlation analysis. Exploration of attenuation of exposure response in relation to seasonal variation in environmental measures. Interaction with work duration.	

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Table D1 (*continued*)

Author (year)	Risk of bias								
	Study design	Selection	Responder	Confounder	Exposure assessment	Outcome assessment	Sample size	Analytical	Total
Community-based studies measuring concentrations of bioaerosol components (n = 1)									
Schinasi et al. (2011)	3	2	1	2	3	2	2	4	19
	Panel study (quasi-experimental)	Non-smoking residents, > 18yrs, < 1.5 miles of hog operation recruited via community organisations (Concerned Citizens of Tillery & Alliance for a Responsible Swine Industry). Not random sample and unclear if representative of population.	Response rate not reported	Adjusted for morning versus evening sampling, but found no significance and did not include in model. Similarly considered but did not need to include adjustment for community. All participants were non-smokers. Personal confounders controlled by design as each individual acts as their own control. Did not account for temperature, viral activity (e.g. flu) etc.	Ambient monitoring of H_2S, endotoxin, PM_{10}, $PM_{2.5}$, $PM_{2.5-10}$ measured continuously for 2 week periods in communities nr CAFOs.	Symptom questions developed from community semi-structured interviews and residents trained to conduct lung function testing with machine reporting of quality of blows. Self-reported physical symptoms (respiratory: cough, irritation of skin/eyes/nose/throat; gastrointestinal, neurologic and other symptoms over 12 h) and self-measured lung function (FEV_1 & PEF) of residents while sitting outside homes for 10 min, twice/day for the same 2 weeks as exposure sampling. Also recorded participant perception of hog odour during 10 min indoor and outdoor morning and evening and also hourly reports relating to previous 12 h.	101 participants in 16 communities.	Conditional fixed-effects logistic and linear regression models. Each participant served as own control.	
Community-based studies using proxy measures for exposure (n = 16)									
Borlee et al. (2015)	2	4	2	3	2	3	4	4	24
	Cross-sectional	GP selection criteria explained (in an earlier reference by the authors), 24 practices identified; 21 agreed to participate with patients invited to participate if specified criteria met. One per eligible household.	28163 subjects received questionnaire; 14822 responded (53.4%).	Adjusted for age, sex and smoking (never/ex/current). Potential self-selection bias was studied (using multiple logistic regression with "response" as dependent variable for association with exposure estimates, morbidity data (based on electronic patient records)) but found to be not significant.	Individual exposure assessment based on distance from home to farm addresses (bands 0–500m and 500–1000m) and licence data for each nearby farm (including no & type of animal and annual estimated fine dust emissions). Authors study relationships between each of the exposure variables.	Questionnaire sent by post to gather details to estimate exposure. Health effect data gathered from pre-existing electronic medical records of normal clinical examinations. Medical information was also available for non-responders, so comparisons could be made.	Questionnaire was sent to all those eligible - no sample calculation was carried out. Analysis performed on 12117 responders (after excluding farmers and if responder had lived at address < 1yr).	Methods appear appropriate – OR an CI presented	

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Table D1 (*continued*)

Author (year)	Risk of bias								
	Study design	Selection	Responder	Confounder	Exposure assessment	Outcome assessment	Sample size	Analytical	Total
Bullers (2005)	2	2	4	3	1	3	1	4	20
	Cross-sectional	Snowball sample of residents in rural area of North Carolina near industrial hog farms identified (by local activists) as distressed about potential effects of living near hog farms. Control group recruited using flyers to local businesses, selected if no previous hog farm exposure. Had also intended to interview employees of hog farms, but unable to do so.	All selected subjects completed the study	Age, education, household income, gender. Ethnicity was predominantly white	No modelling. Very limited detail on exposure. Exposed residents were "living near" hog farms, but no radius specified. No detail on size of hog farms.	Standardised questionnaire to assess "perceived control" (Pearlin's mastery scale), psychological distress (CES-D depression scale), frequency of physical health symptoms (headache, hearing/ear problems, burning/ watery eyes, runny nose, scratchy throat, sputum/ phlegm, cough, fever, asthma, bronchitis, nausea/vomiting, weakness, dizziness/ fainting, shortness of breath, wheezing, muscle aches/pains, skin rash/ hives, chest tightness, fatigue, diarrhoea).	48 residents, 34 control	Correlation between psychological distress/control and health symptoms. Differences between groups for physical health symptoms using *t*-test then multiple regression models also investigating impact of psychological distress and perceived control.	
Hooiveld et al. (2016)	2	2	1	2	2	2	4	4	19
	Cross-sectional	Selected GP practices in rural postcodes with high/low density of farms. 28(57%) vs 22(unknown%) of practices included, based on defined criteria. However, practices applied to participate and 57% of those who applied were included. EMR data for 119,036 people (19% of region) in high density farming area. EMR data for 78,060 (unknown%) in low density area.	Electronic medical record data from GPs were used. GPs were asked to participate, of which 49 applied. It is not stated how many GP practices were asked to participate in the first instance.	Only limited info on confounders was available from electronic records. Results were adjusted for registry duration, age, gender, number of inhabitants at postcode level and surface area. Also adjusted for socioeconomic status, but this had no effect. Recall bias ruled out by using GP records. Discussed selection bias - possibility that susceptible individuals may have moved from high exposure areas. Unable to adjust for air pollution from industry / traffic.	Number and type of farms (> 250 dairy cows, > 2500 veal calves, > 7500 pigs, > 1200 sows, > 120,000 laying hens, > 220,000 broilers or > 1500 goats) in postcode area. Also examined effects of farms in adjacent postcode areas.	Use of electronic medical records of patients registered with GPs in areas of high density of farms (and control area low density of farms.)	Electronic Medical Record data for 119,036 persons in high exposed group. EMR data for 78,060 in low exposed group.	Multilevel logistic regression analysis - OR and CI presented.	

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Table D1 (*continued*)

Author (year)	Risk of bias								
	Study design	Selection	Responder	Confounder	Exposure assessment	Outcome assessment	Sample size	Analytical	Total
Hoopmann et al. (2006)	2	3	2	4	3	3	4	4	25
	Cross-sectional	A survey was conducted in intensively farmed areas in Lower Saxony (Local Authority of Cloppenburg, Emsland, Oldenburg and Vechtaas) as part of routine school entry examinations. Actual selection of schools not fully explained, but stated to be representative of the population. Parents were asked about symptoms of their 5–6 year old children	7943 questionnaires analysed (85% response rate) and 3867 could be used in association between endotoxin and asthmatic symptoms as excluded areas with no livestock facilities in immediate neighbourhood or no information available to model exposure. 5136 skin examination and 1552 atopy tests	Sex of the child, Older siblings, Perceived noise exposure as indicator of subjective environmental conditions, Smoking at home as indicator for second hand smoke, Breast feeding, minimum of three months, socio-economic status of parents, Dampness, mould in residence, Contact with cats in first year of life, Carpet in child's room. Atopic disease of parents treated as effect modifier. Sensitivity analyses.	Dispersion modelling of exposure to bioaerosols (endotoxin, fungi, bacteria, total dust) at place of residence	Standardised questionnaire using ISAAC study questions, clinical examination for atopic dermatitis plus IgE test on a subsample (pollen from British timothy, rye, birch, mugwort and Cladosporium herbarum, house dust mite, cat hair and dog hair)	3867 questionnaires used in exposure-response analyses	Multivariate logistic regression using log endotoxin as exposure variable	
Huijskens et al. (2016)	3	2	4	1	2	3	3	2	20
	Case-control	All patients > 18 years attending emergency wards of 2 hospitals with suspicion of community acquired pneumonia. Excluded if recent hospitalization, known bronchial	Study used all those attending A&E wards with CAP within timeframe. Algorithm was used to obtain control group with similar age range.	Confounders were not adjusted for. Authors discussed that licence data may overestimate numbers of animals (but not adjust for).	Presence and number of farms (swine, poultry, cattle, goats, sheep) within 1km of patients' homes, obtained by licence data.	Sampled patients by throat swab (408), blood (329) and urine (408) samples to perform microbial analysis for respiratory pathogens. Unclear re blinding of clinician.	408 patients and 1096 control subjects.	Chi-square test used to compare case and control groups, symptoms and presence / numbers of specific animals within 1km of home address. Multiple logistic regression but no adjustment for confounders or consideration of clustering or spatial autocorrelation.	
Mirabelli et al. (2006)	2	4	2	4	2	3	4	4	25
	Cross-sectional	Adolescents 12–14 years old from 265 schools in North Carolina.	21% of schools excluded. 79% of targeted schools answered questions about environmental conditions around the schools. 67% of eligible students responded.	Adjusted for age, race, Hispanic ethnicity, allergies, socioeconomic status, smoking, use of gas stove at home.	Estimated exposure based on school proximity to CAFOs (housing > 250 swine) and wind direction. Questionnaire of environmental conditions in school (mould, vermin, odour)	Self-reported symptoms of wheezing / asthma related by standardised questionnaire and supported by video. School survey of 245 schools	58,169 boys and girls	Random intercept binary regression taking account of school-level and student -level clustering. Associations estimated as probability ratios.	

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Table D1 (*continued*)

Author (year)	Risk of bias								
	Study design	Selection	Responder	Confounder	Exposure assessment	Outcome assessment	Sample size	Analytical	Total
Pavilonis et al. (2013)	2	4	1	4	2	4	3	4	24
	Cross-sectional	Subject data were obtained from a previous study – a population-based prospective cohort study. Children had been selected by stratified random sampling.	Response rate of the original cohort/loss to follow up by the second round actually used in the study was not reported.	Recognised risk factors controlled for (age, physician-diagnosed allergies, gender, parental history of asthma, premature birth, physician-diagnosed respiratory illness < 2yrs, smoking parent, working around livestock, cockroaches m^{-1}ould in home, dog/cat, household income, living/parents working on farm) using correlated logistic regression. Data obtained by questionnaire.	Sophisticated proxy for exposure but no measurements. Each child's exposure estimated using detailed metric including size of animal feeding operation, distance (inverse square) and prevailing wind direction. Data collected from tax records. Farms within 4.8km of home and factors included animal density, ventilation system, manure management, facility area.	Standardised questionnaire to determine self-reported prescription medication for wheeze and/or self-reported physician diagnosed asthma using trained interviewers and industrial hygienists. Blinded on study uses - data obtained for other purposes	565 children (aged 0–17 years) living in rural community in area of intensive agriculture.	Generalised estimated equations to allow for multiple children in some households. Logistic regression analysis.	
Radon et al. (2005)	2	4	2	3	2	3	4	4	24
	Cross-sectional	Postal survey of 10,864 German citizen aged 18–44 years who were residents of four municipalities with intensive animal production facilities, with 6416 individuals randomly selected for clinical investigation.	6937 participants (68%) responded to the questionnaire and 60% to the invitation for clinical examination.	Age, socio-economic status, passive smoking, number of siblings, parental allergy, education level. Analysis restricted to those born in West Germany (86%) as presumed similar childhood environment.	Number of animal facilities within 500m of residence, self-reported smell	Standardised (ECRHS and Short Form-12) questionnaire, standardised (ATS) lung function testing (FEV_1, FVC, FEV_1/FVC ratio), methacholine test for hyper-	6937 questionnaire answers and 2812 clinical examinations	Multiple linear logistic regression models and LOESS	
Radon et al. (2007)	2	4	2	3	2	3	4	4	24
	Cross-sectional	6937 Subjects aged 18–44 in 4 rural German towns with high density of animal feeding operations. Random sampling and total of 2571 had clinical examination.	Target population 10,252. Response rate 68% for questionnaire and 66% of those further randomised to clinical investigation	Adjusted for age, gender, passive/active smoking, level of education, family history of allergic disease, number of siblings. FEV1 also adjusted for passive smoking in childhood.	Odour annoyance and number of animal houses within 500 of home. Did not include details of numbers / types of animal or GIS house.	Self-reported asthma symptoms and nasal allergies, determined by postal questionnaire. Reporting bias was reduced by introducing	Questionnaire data for 6937 subjects - random sample for IgE, lung function, bronchial hyperresponsiveness.	Logistic and linear regression and adjusted Loess plots. Group differences analysed using chi-squared test for categorical variables. Continuous variables compared using Mann-Whitney *U* test or Kruskal-Wallis-ANOVA.	

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Table D1 (*continued*)

Author (year)	Risk of bias								
	Study design	Selection	Responder	Confounder	Exposure assessment	Outcome assessment	Sample size	Analytical	Total
						study as respiratory health in rural areas. Allergic sensitisation: IgE conc > 0.35kU/L in serum. FEV1 used to assess bronchial obstruction; hyperresponsiveness defined as > 20% drop in FEV1.			
Sigurdarson and Kline (2006)	2	2	2	3	2	3	2	4	20
	Cross-sectional	Two schools selected; 1/2 vs 10 miles from concentrated animal feeding operation in Iowa. Not sure if there were other schools that could have been included.	Response rate was 52.6% in study school; 54.4% in control school. Some participants (7%) declined.	Other causative factors included were: tobacco smoke exposure, living on a farm, rural residence, pet ownership.	Location of primary residence used as proxy for exposure to the single hog farm in study.	Questionnaire by post for self-reporting of physician-diagnosed asthma, wheezing (ever/past year), active inhaler use, asthma, emergency department visits in past year.	61 from study school, 248 from control.	Multiple logistic regression. Descriptive analyses used chi-squared test (dichotomous variables) or *t*-test (continuous variables).	
Smit et al. (2012)	2	4	1	2	2	3	4	4	22
	Cross-sectional	All patients of 27 GPs in area of high density farming were selected. Practices included only if pre-defined criteria were met.	Electronic medical record data from GPs were used. GPs were requested to participate. It is not stated how many GP practices were asked to participate in the first instance	Adjusted for age and gender only. Adjusting for socioeconomic status had no effect and was not included.	Distance from patients' homes to locations of farms within 1km radius; and 5km radii for goats. For all animal farms in study area the type and number of animals was obtained from licence data and included in exposure metric.	Q fever and pneumonia: Morbidity data from EMR and GP prescriptions. Multiple consultations for patient clustered into an episode using algorithm.	22,406 children and 70,142 adults.	Multiple logistic regression models using quartiles.	
Smit et al. (2014)	2	4	1	4	3	3	4	4	25
	Cross sectional with case-control subset	27 of 55 GP practices included in study based on pre-defined criteria. Also questionnaire sent to random sample of 758 patients with asthma and 1519 patients with low back pain (controls). Builds on Smit 2012.	Electronic medical record data from GPs were used. GPs were requested to participate, of which 55 responded and 27 were used. It is not stated how many GP practices were asked to participate in the first instance	Adjusted for age and gender only in cross-sectional dataset. Potential confounding was assessed in the case-control subset of 269 adult patients and 546 controls, gathering further data by questionnaire for home characteristics, presence of other farm animals, smoking, education, profession and farm childhood.	Distance from home address to farms within 500m and 1000m, including numbers and types of animals. Modelled PM10 emission from all farms within 500/1000m using licence database. Dust collectors placed in homes of subset group to measure PM. Endotoxin levels measured in 493 homes.	Assessment of standardised GP codes to describe asthma, COPD, hay fever/allergic rhinitis in the cross-sectional study. Standardised questions in questionnaire adapted from the European Community Respiratory Health Survey.	EMR records of 92,548 patients were assessed.	Multiple logistic regression. Sensitivity analyses with generalised estimating equations.	

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Table D1 (*continued*)

Author (year)	Risk of bias								
	Study design	Selection	Responder	Confounder	Exposure assessment	Outcome assessment	Sample size	Analytical	Total
			In the case-control study in a subset of participants, the response rate was 42% in the cases and 44% in the controls.				Potential confounding then assessed in subset of 815 cases and controls. Endotoxin levels measured in 493 homes.		
Thu et al. (1997)	2	2	1	1	1	2	1	1	11
	Cross-sectional	Residents living within 2 miles of swine production facility identified using 1992 Agricultural Census and telephone database – 10 households met selection criteria. Control group of rural residents not living near livestock.	Nine 'case' households of 27 contacted took part, involving 19 participants. Nine 'control' households of 188 households invited took part, involving 18 participants.	Confounders of gender, marital status, age, education are stated as not different in Table 1 but no formal testing was presented and these were not adjusted for in analyses.	Exposure defined as residence within 2 miles of a 4000 sow swine production facility. Unclear why this distance was chosen	Questionnaire (via interview) to assess health problems, psychological health and neighbourhood social issues. These were predominantly open-ended questions.	37 in total: 19 residents near swine farms and 18 participants from rural areas not near farms.	Interview data coded and entered into Paradox but no other details given on analysis for qualitative data. No details of quantitative analysis given in methods section. Wilcoxon test and one tailed *t*-test presented in results. Clustering by household not taken into account	
van Dijk et al. (2016a)	2	4	1	2	2	3	4	4	22
	Cross-sectional	Medical records for COPD and asthma patients from 15 GP practices in control area (low density of farms) and 15 in study area (high density of farms). GPs were included if met criteria for data quality.	Used electronic medical records from GPs in the study area. Only data from participating practices was used. It is unclear how many practices were originally asked to participate	Adjusted for age, gender, use of inhaler, diagnosis of depression, heart disease or heart failure. Did not adjust for smoking or socioeconomic status.	Individual exposure estimated for study group using distance from home address to farm (locations from licence data). Variables included distance, presence of one or more farms < 100m and < 500m from home, presence and number of specific farm animals < 500m. Individual exposure assessments unavailable for control group.	Exacerbations per patient year according to defined criteria. Additionally, 551 (30% of sample) COPD patients had FEV/FEC measurement data.	899 COPD patients and 2456 asthma patients in study area, 933 COPD and 2310 asthma patients in control area.	Multilevel Poisson regression analysis	
van Dijk et al. (2016b)	2	4	1	2	2	2	4	4	21
	Cross-sectional	Medical records from 16 (out of 55) rural GP practices if data met defined quality criteria. Questionnaire data on 531 patients with no missing data. Reanalysis of data collected in Smit et al. (2012) and Smit et al. (2014) papers	Same method as Smit et al. (2012) whereby records from selected GPs were used. GPs were asked to participate in the study. It is unclear how many practices were originally asked to participate	Adjusted for age, gender and number of chronic diseases in first model. In second model, also adjusted for distance from patient's home address to GP. Smoking and socio-economic status were not controlled for.	Distance from patients' home address and farms within 500m. Data on farm location, numbers and types of animals was used (from licence data). Also included inverse distance weighted modelled PM10 data.	Patient records of contact with their GP for respiratory symptoms. Association between self-reported symptoms and livestock exposure examined via case-control questionnaire for 1519 patient subset.	General practice contact data for 54,777 people.	Multilevel Poisson regression analysis with three levels and correction for over-dispersion.	

(*continued on next page*)

Table D1 (*continued*)

Author (year)	Risk of bias: Study design	Selection	Responder	Confounder	Exposure assessment	Outcome assessment	Sample size	Analytical	Total
Wing and Wolf (2000)	2	3	3	3	1	2	2	4	20
	Cross-sectional	Three communities with similar economic/ demographic characteristics: one near intensive hog farm, one near two intensive cattle farms and one 'control' in rural agricultural area with no livestock operations.	Response rate 86% with 155 interviews conducted. Excluded responders from households with farm workers.	Adjusted for age, gender, occupation, smoking habits of responder and household.	Comparison of responses from the three communities. No distance-based estimates or community or individual exposure measurements.	Questionnaire based on discussions with the community on frequency and occurrence of respiratory symptoms within previous 6 months, carried out face-to-face by trained interviewers.	155 interviews carried out.	Multiple linear regression, with sensitivity analyses using transformations accounting for skewness in dependent variables. Did not provide p-values as exposures were not randomised.	

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