THE ROLE OF OCCUPATIONAL EXPOSURE TO ANIMAL PRODUCTION IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE AMONG FARMERS IN IOWA AND NORTH CAROLINA

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ABSTRACT

Jessica L. Rinsky: The role of occupational exposure to animal production in chronic obstructive pulmonary disease among farmers in Iowa and North Carolina
(Under the direction of Steve Wing)

Individuals who work in animal production may be exposed to respiratory hazards including high concentrations of organic dust, gases, and chemicals. Long-term, chronic inhalation of these agents may contribute to risk of chronic obstructive pulmonary disease (COPD). I examined the association between work in animal production, including the use of insecticides, and the prevalence of COPD diagnosis and chronic bronchitis symptoms among 22,721 farmers who enrolled in the Agricultural Health Study (AHS) (1993-1997) and participated in the 2005-2010 interview. I also assessed the impact of restricting analysis to participants of the 2005-2010 interview.

To assess the impact of restriction, predictors of participation in the 2005-2010 interview were identified, example exposure-outcome associations estimated in the enrollment and 2005-2010 cohorts were compared, and the utility of inverse probability of selection weights (IPSW) to correct for selection bias was considered. Participation was related to age, state, race/ethnicity, education, marital status, smoking, and alcohol consumption. In example analyses, when case participation was differential with respect to exposure, estimates were biased; IPSW conditional on exposure and covariates failed to fully correct estimates. When participation was non-differential, estimates from 2005-2010 participants and the enrollment cohort were similar rendering IPSW unnecessary.

Using log binomial regression and inverse probability of exposure weights to address confounding, I estimated the association between animal production, insecticide use and COPD diagnosis and symptoms. Raising beef cattle, hogs, or poultry was associated with greater prevalence of chronic bronchitis symptoms. Farmers with medium/large animal operations had 1.51 (95% CI: 1.21, 1.89) times the prevalence of chronic bronchitis symptoms than those raising no animals. Applying insecticides to livestock and use of coumaphos, diazinon, dichlorvos, malathion, parathion, carbaryl, and permethrin were also associated with greater prevalence of chronic bronchitis. Personal use of diazinon and trichlorfon were associated with a greater prevalence of COPD diagnosis.

These results support an association between animal production, including use of insecticides, and chronic bronchitis, a component condition of COPD. Further investigation of animal production- and insecticide-related risk factors for COPD is necessary. There is also a need for continued monitoring of the respiratory health of farmers and workers involved in animal production.

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LIST OF ABBREVIATIONS

ACGIH	American Conference of Industrial Hygienists
AFO	Animal feeding operation
AHS	Agricultural Health Study
ATS	American Thoracic Society
CAFO	Confined animal feeding operation
CATI	Computer assisted telephone interview
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
DAG	Directed acyclic graph
EPA	Environmental Protection Agency
EU	Endotoxin unit
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
IPEW	Inverse probability of exposure weights
IPSW	Inverse probability of selection weights
IRB	Institutional Review Board
NHANES	National Health and Nutrition Examination Survey
NIOSH	National Institute of Occupational Safety and Health
OR	Odds ratio
OSHA	Occupational Safety and Health Association
PEL	Permissable exposure limit

PR	Prevalence ratio
RD	Risk difference
REL	Recommended exposure limit
RR	Risk ratio
RUP	Restricted use pesticide
SE	Standard error
TWA	Time weighted average

CHAPTER 1.
SPECIFIC AIMS

Food animal production has become increasingly industrialized during the past several decades [1]. Industrial animal production facilities rely on confinement and heavy inputs to produce large numbers of animals on limited land [2]. As a result, individuals working in or around animal production facilities may be exposed to high concentrations of particulates, gases, and chemicals [2-13]. Chronic inhalation of these agents has been linked with short-term decline in respiratory function [3, 5, 14-20], symptoms of respiratory irritation [4, 5, 8, 16, 19, 21-23], and increased risk of certain respiratory conditions [14, 19].

Chronic obstructive pulmonary disease (COPD) is a disease process caused by an inflammatory response to inhalation of noxious particles [24]. Globally and domestically, COPD (ICD-10 codes J40-J44) [25], is a major cause of morbidity and mortality [24, 26-29]. Although a large proportion of COPD is attributable to smoking [24], occupational exposures may play an important role in disease pathogenesis [9, 10, 12, 13, 24, 30-33]. Studies of agricultural workers have noted similar or increased prevalence of COPD-related conditions and symptoms (i.e. chronic bronchitis, chronic cough and phlegm) as compared to the general public [3, 4, 8-10, 12, 13, 15, 32, 34-36], despite lower rates of smoking [37, 38]. Among agricultural workers, those working in industrial animal production appear to experience some of the highest burdens of COPD-related symptoms [13, 21, 32, 39].

Despite this knowledge, few studies have examined the link between work in animal production and COPD specifically. Available work has mainly been conducted in Europe and may not represent the exposure and disease patterns in the United States [15, 40]. Previous work

from the United States has relied on large administrative databases lacking detailed exposure and covariate information, or small samples of farmers and farmworkers, which lack the ability to examine potentially important modifying factors [9, 13-15].

The Agricultural Health Study (AHS) [41, 42] provides a unique opportunity to examine the association between animal production work and the prevalence of COPD among a large population of farmers. Farmers enrolled in the AHS produce animals on small and large operations allowing for consideration of exposure to the full spectrum of animal production. Although the AHS provides this opportunity, approximately 54% of farmers did not participate in a follow-up interview conducted between 2005 and 2010, approximately 12-years after study enrollment. Only those who participated in the 2005-2010 interview were able to report information about the onset of COPD-related symptoms and diagnoses.

To examine the association between work in animal production and COPD among the farmers in the AHS, I addressed the following aims:

Aim 1: Evaluate the potential for attrition to bias effect estimates estimated from farmers participating in the 2005-2010 interview of the Agricultural Health Study.

- **1a:** Identify a set of enrollment characteristics predictive of and strongly associated with participation
- **1b:** Quantify the range of bias affecting effect estimates due to selective participation in a follow-up interview under conditions relevant to analysis of the association between work in animal production and COPD.
- **1c.** If evidence suggests bias due to selective participation, determine the utility of inverse probability of selection weights to correct for such bias.

Hypothesis: Demographic, behavioral, medical history, and agricultural characteristics reported at enrollment will be predictive of participation in the 2005-2010 interview. Some bias due to selective participation may be present in analyses restricted to farmers who participated in the 2005-2010 interview. However, because selective participation will be predicted by measured enrollment variables, inverse probability of selection weights will reduce the magnitude of bias.

Aim 2: Quantify the association between work in animal production and the prevalence of COPD among AHS farmers.

2a. Quantify the association between type and number of animals raised and COPD.

2b. Quantify the association between personal use of chemical classes of insecticides registered for use on or around animals and COPD.

Hypothesis: Farmers engaged in raising animals using industrial practices (e.g., use of inecticides on or around animals, confinement of animals) will exhibit a greater prevalence of COPD than farmers who are not engaged in industrialized animal production activities.

CHAPTER 2.
BACKGROUND

History of animal production

Traditionally, food animals were raised outdoors on diversified farms. Since the mid-20th century, methods of animal production have undergone substantial changes. The number of small farms with diverse production of many animal species has decreased while operations which specialize in the production of large numbers of one species of animal have increased [43]. The term industrial animal production (North American Industrial Classification System code: 112 [44]) is used to describe these large-scale operations that often rely on the confinement of animals in factory-like buildings and increased use of inputs including chemicals (e.g., pesticides and cleaning agents), antibiotics, food, and water to produce large numbers of animals on limited land [1, 2, 9, 39, 45-47]. In the United States, these industrial operations, referred to as animal feeding operations (AFOs), produce a large proportion of livestock and poultry used for meat, dairy products and eggs [45, 48]. There are currently an estimated 450,000 AFOs in the United States. Iowa and North Carolina are two of the top producing states for swine and poultry [49].

Occupational exposures in animal production

The change from raising animals outside on pasture to a model that concentrates large numbers of animals inside buildings has led to changes in the types and intensity of respiratory hazards present in the production environment [39, 46]. The main respiratory hazards are organic dusts, gases, and chemicals. Organic dust, defined as airborne and settled particulate matter of biologic origin [13] may include molds and spores, bacteria, mites and their excreta, as well as

particles of animal feed, dander, urine, and feces. One component of organic dust particularly important to respiratory disease is endotoxins, or lipopolysaccharide complexes from the cell walls of gram-negative bacteria [50]. Many gases are found in the animal production environment including ammonia, hydrogen sulfide, methane, carbon dioxide, and carbon monoxide along with other odorants and volatile organic compounds [51-57]. Chemicals present in the animal production environment include pesticides (mainly insecticides) and cleaning agents. Insecticides are used to control insects including cockroaches, flies, and external parasites on animals (e.g., mites, lice) [58, 59]. Historically, organophosphate, pyrethroid/pyrethrin, and carbamate insecticides [58, 60] have been the most common types used in animal production. **Table 1** provides a list of insecticides belonging to these chemical classes along with the year each was first registered for use in the United States. Recently use of pyrethroids/pyrethrins has increased to compensate for a decline in use of organophosphates, which are more acutely toxic to birds and mammals [60]. Insecticides used in animal production come in different forms including sprays, dusts, dips, granules, tags, and pours [61, 62]. Each of these formulations has different implications for human respiratory and skin exposure. In addition to insecticides, disinfectants containing chloramine-T or quaternary ammonium compounds alone or in combination with aldehydes [13, 52] are also used.

Organic dust, gases, and chemicals mix together in the animal production environment. The composition of the mixture can vary widely dependent on the type of facility, waste disposal system, type and age of animals being produced, type of feed and bedding used, activities being conducted, season, geographic location, and ventilation system [39, 51, 52, 63]. And, individual exposure will vary by work site (inside or outside) and use of personal protective equipment (e.g., gloves, masks, respirators).

Regulation of exposures relevant to human respiratory health

Some of the agents present in the animal production environment are regulated in workplaces by the Occupational Safety and Health Administration (OSHA), and agencies including the National Institute of Occupational Safety and Health (NIOSH), and the American Conference of Industrial Hygienists (ACGIH) have set recommendations on exposure limits (**Table 2**). However, OSHA enforcement does not apply to family farmers. In addition, animal production facilities often have a small number of employees, and employers with 10 employees or fewer during a calendar year are not typically required to keep OSHA injury or illness records [64]. Many of the insecticides used in industrial animal production are designated restricted use pesticides (RUP) and therefore their sale is regulated by the US Environmental Protection Agency [65]. This classification requires that the substance only be used by, or under the supervision of, a certified pesticide applicator.

Previous work has documented concentrations of dust, gases, and endotoxin in industrial swine [5, 16-18, 23, 57, 66-77], poultry [66, 69, 78, 79], and dairy operations [56, 69]. Concentrations vary widely and, at times, exceed recommended exposure levels.

Respiratory health effects from occupational exposure to animal production

Inhalation of the agents present in the animal production environment is known to result in an inflammatory response in the airways and lungs [39, 80, 81]. Personal exposure to insecticides outside of the animal production environment has also been linked with inflammation, impaired respiratory muscle function, and other effects on the respiratory system in both animal [82] and human studies [83, 84]. Individuals involved in animal production exhibit increased prevalence of many respiratory symptoms and conditions compared with the general public and other rural populations. These symptoms and conditions include cough,

phlegm, chronic bronchitis, asthma, wheeze, and organic dust toxic syndrome [10, 13, 85]. Long-term, chronic inhalation of the agents present in the animal production environment has the potential to result in a chronic inflammatory response in the airways and lungs manifesting as COPD. However, the association between work in animal production and COPD remains largely unexplored.

Chronic obstructive pulmonary disease

COPD is a broad term that refers to a collection of conditions responsible for irreversible airflow limitation [24, 86]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD as a disease state "characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases" [87, 88]. Chronic bronchitis and emphysema are two conditions included under the term COPD. Chronic bronchitis is defined on the basis of clinical presentation of the presence of cough and sputum production for at least three months in each of two consecutive years [88]. This clinical presentation is due to hypersecretion of mucus in the large airways [24]. Emphysema is defined morphologically as "an abnormal permanent enlargement of air spaces distal to terminal bronchioles, accompanied by destruction of their walls without obvious fibrosis" [89]. The term COPD may also be used to refer to other conditions such as constrictive bronchiolitis (a fibrotic disease of the small airways) [24, 90], and other causes of non-reversible airway obstruction.

As indicated in the disease definition, the inflammation of airways in COPD is initiated by inhalation of noxious particles or gases. The mass of the particles inhaled dictates where in the respiratory system they deposit and the biological response [81, 91]. Typically, the lungs' defense mechanisms respond to deposition of particles through coughing, mucociliary transport,

and the innate immune system [92]. However, when the defense system is overwhelmed or fails, a disease process may begin. Because of the strong defense mechanism of the respiratory system, long-term exposure to agents is usually required for the development of COPD [88, 93] although high peak exposures may play a role in hastening the onset of symptoms or exacerbating the condition [88].

The inflammatory response to the presence of inhaled particles causes direct destruction of lung tissues and impairment of the defense mechanisms, which usually repair damaged tissue, leading to inflammation and manifestation of COPD symptoms [94]. A range of inflammatory cells are involved with neutrophils, macrophages, and CD8+ T cells predominating [94]. Neutrophils and macrophages release proteases, disrupting the balance of proteases and antiproteases in the lung leading to increased proteolysis. Oxidative stress and inflammatory mediators also play a role in the pathogenesis of COPD [88]. This inflammatory response leads to destruction in the lung parenchyma, characteristic of emphysema, and mucus hypersecretion and cilliary disfunction, characteristic of chronic bronchitis. Destruction of air spaces and mucus hypersecretion lead to airflow limitation and air trapping, gas-exchange abnormalities, and changes in the pulmonary vasculature [88]. These occurrences in the lungs have both local and systemic manifestations [89]. Genetic or host factors must also play a role as not all individuals exposed to respiratory irritants develop disease [94].

Challenges in Diagnosing COPD for Research Purposes

Diagnosis of COPD is complicated and relies on several components – physical exam, documentation of symptoms, radiographic studies, and spirometry. Ideally, case ascertainment in epidemiologic research would rely on a gold-standard set of diagnostic criteria. However, this comprehensive diagnostic approach is often not feasible for research studies that involve large

populations, especially studies spread over a wide geographic area or reliant on mail or telephone contact with participants in order to reduce burden of participation [95]. Consequently, alternatives for identifying cases of COPD are necessary for research. Spirometry has been recommended to provide an objective, standardized and simplified approach to ascertaining cases of airway obstruction, and some studies have relied solely on this diagnostic approach [96, 97]. However, spirometry still requires in-person assessment of study participants by trained staff. Spirometric results also lead to wide variation in disease estimates depending on the population and how disease definitions are applied. For example, in a study of National Health and Nutrition Examination Survey (NHANES) participants (2007-2010), the prevalence of COPD ranged from 10-21% depending on the criteria applied to spirometric results [97].

Alternatively, studies have used self-report of a doctor diagnosis of COPD. Participant report of a doctor diagnosis relies on many pieces including receiving a valid diagnosis, patient understanding of the diagnosis, and accurate patient recall and reporting of the diagnosis. Little work has been done to validate the use of self-reported diagnoses. Studies that have conducted spirometry and collected self-report of doctor-diagnosed COPD, consistently show that self-report results in an under ascertainment of COPD compared with spirometry [27, 29]. This may be because self-reported diagnosis is more representative of clinically relevant disease that has driven someone to seek care, while spirometric results also represent those with subclinical obstruction. The Nurses' Health Study directly validated self-report of doctor-diagnosed COPD, including chronic bronchitis and emphysema [95]. Among this population, 89-92% of self-reported emphysema, 81-93% of COPD, and 79-84% of chronic bronchitis cases were confirmed to be accurate based on medical record review and uniform diagnostic criteria.

Ascertainment of COPD cases in epidemiologic studies is imperfect whether spirometric measures of obstruction or self-report of diagnoses are used. Self-reported doctor diagnosis may lead to some false-positive reports of diagnoses due to attribution of symptoms to a diagnosis by the participant themselves or misdiagnosis. However, when relying on self-report, under-reporting of COPD may be more likely [95, 98]. Incorporation of self-reported information on symptoms used to define chronic bronchitis in a physician's office (e.g., chronic cough and phlegm for more than 3 months over two consecutive years) may aid in reducing the number of false-negatives.

Epidemiology of COPD

The domestic and global burden of COPD is large and is continuing to grow [87, 88]. COPD is the third leading cause of death in the United States and is expected to be the third leading cause of death globally by 2030 [86, 88]. The impact of COPD-related morbidity is also large. In the United States during 2010, approximately 10.3 million physician office visits, 1.5 million emergency room visits, and 699,000 hospital discharges were attributed to COPD or its complications [26]. In 2008, the direct costs attributed to COPD were more than $50 billion [26]. In addition, disability and impaired quality of life resulting from COPD add to the high social costs of the condition [27].

The prevalence of COPD is difficult to determine as it varies greatly based on disease definition, method of measurement, and population under study. In the United States, estimates range between 5-7% of the general population reporting a physician diagnosis of COPD [26, 29, 99]. Estimates based on spirometry range between 10-20% [97].

Cigarette smoking is widely recognized as the most important exposure related to COPD [27, 86, 88, 99]. It is estimated that 80% of individuals who have COPD in the United States are

or were smokers [86]. Many of the other risk factors for COPD influence disease risk through smoking. Older age, male gender, white race, low education and socio-economic status, and poor diet and obesity are associated with increased risk of COPD [26, 28, 29, 86, 87, 97, 100, 101]. In addition, specific genetic mutations, asthma and other airway disease, and perinatal events and childhood respiratory illness are also positively associated with risk of COPD [86]. Recently, more attention has been paid to environmental pollution and occupational exposures as risk factors [24, 31, 86, 98, 102-113].

Occupational exposures have been identified as important in the etiology of many of the underlying conditions and symptoms of COPD since the 19th century [98, 112]. However, occupational exposures remain somewhat unexplored due to an emphasis on smoking as the most influential risk factor. In addition, the dominance of more traditional occupational respiratory diseases such as pneumoconiosis has also led to little focus of research on occupational risk factors for COPD [108, 111].

Occupational exposures and COPD

In 2003, the American Thoracic Society (ATS) released a statement and review of the literature on the association between occupational exposures and COPD [108, 109]. The statement and several studies published since indicate that among US adults the attributable fraction of COPD due to occupational exposures is 15-20% [31, 98, 106, 108, 109]. This estimate may also be as high as 30% for never smokers [31]. Agriculture is one of the industries that is recognized as having a high burden of COPD [31, 108, 109, 114]. And, within the agricultural sector, those working in animal production have been identified as a high-risk group [31, 114].

Occupational exposure to animal production and COPD

In 2004, Monso et al. reported the prevalence of COPD among a sample of 105 non-smoking animal confinement workers from Denmark, Germany, Switzerland, and Spain [14]. Using spirometry and the GOLD criteria, COPD was identified in 18 workers (17%). The prevalence of COPD was associated with increasing levels of dust exposure. This study was small and could not stratify results by the type of animal produced. To my knowledge, no other studies have explicitly examined the burden of COPD among animal production facility owner/operators or workers.

Previous work has examined the burden of COPD-related symptoms and chronic bronchitis among animal production facility owner/operators and workers. Most research has focused on work in industrial swine or poultry production and industrial and non-industrial dairies. The prevalence of chronic bronchitis reported in these studies ranges between 8 and 46% depending on the animal produced (swine, poultry, dairy) and whether study participants were farm owner/operators or workers. Prevalence of chronic cough (10-57%), chronic phlegm (5-58%), and shortness of breath (9-32%) varied similarly [5, 8, 19, 20, 23, 73, 115-127].

Research examining the respiratory effects of work in animal production has mainly focused on exposure to organic dusts and gases. However, insecticides are commonly used in animal production and a positive association between exposure to insecticides and COPD diagnoses or symptoms has been reported. In a recent study involving two cohorts from The Netherlands, de Jong et al. (2014) reported that exposure to pesticides was associated with lower pulmonary function measures and an indication of obstructive disease [128]. This study assigned exposure based on current or last held job title/description and included no information about type, intensity, or frequency of pesticide use by participants [129]. In India, Chakraborty et al.

observed increased prevalence of respiratory symptoms (cough, dyspnea), chronic bronchitis, and COPD among Indian farmers using organophosphate and carbamate insecticides as compared to controls [130]. Although the population was fairly young (median age: 40 years; range: 25-53), COPD was diagnosed (using GOLD criteria) in 18% of the agricultural workers compared with 7% of the comparison group.

Most of the research examining the association between use of specific insecticides and COPD-related symptoms and conditions among farming populations has been completed within the AHS [131-134]. Researchers have reported statistically significant associations between ever use of insecticides (carbaryl, carbofuran, DDT, heptachlor, diazinon, malathion, and permethrin for crops), lifetime days of use (carbaryl, DDT, dichlorvos, malathion, and permethrin used on crops), and increased odds of a self-reported doctor diagnosis of chronic bronchitis [133].

A limited number of studies have explicitly considered the effect of joint exposure to animals and insecticides. Using information from the Iowa Farm Family Health Study, Sprince et al. reported that persons who apply pesticides to livestock had significantly increased odds of phlegm (1.9; 95% CI: 1.02, 3.57) as compared to those who did not apply pesticides to livestock after adjusting for smoking [135]. In the AHS, Hoppin et al. (2007) found that pesticide applicators who reported applying pesticides to animals had increased odds of chronic bronchitis as compared with those who did not report applying pesticides to animals (OR: 1.39; 95% CI: 1.18, 1.64). Beyond this work, the effects of joint exposure to animals and insecticides remains largely unexplored.

Strengths and limitations of previous work

Previous work has provided firm evidence that work in animal production may contribute to the global burden of COPD. However, only one previous investigation has been focused on the association between work in animal production and COPD specifically. Research examining the prevalence of respiratory symptoms or airway obstruction has mainly been conducted in Europe and therefore may not reflect the methods of animal production used or the distribution of COPD in the United States. Most of these studies have been cross-sectional and consequently may not include farmers that have left work due to respiratory illness. Finally, previous work conducted in the United States has been conducted using either large, administrative databases with little information on personal exposures and covariates or small samples with detailed personal exposure or disease information. Both of these designs prohibit consideration of joint exposure effects and modification by smoking and other potentially important contributing factors.

The Agricultural Health Study: A Unique Opportunity

The AHS provides a unique opportunity to examine the role of work in animal production in the etiology of COPD among a large cohort of farmers followed over a median 12 years. AHS participants come from two major animal producing states and include small, traditional farms as well as large, industrial farms.

Selective participation: A methodological challenge

At enrollment, the AHS cohort included 52,394 farmers. However, the cohort has experienced attrition over time. Sixty-four percent of farmers participated in an interview occurring approximately five years after enrollment (1999-2003). An investigation of non-participation in this interview revealed that non-participants were younger, less educated, and

had poorer health behaviors but fewer diagnosed medical conditions than participants [136]. Non-participants also had lower reported pesticide use overall but some variation existed between farmers in North Carolina and Iowa. As part of this analysis, investigators estimated odds ratios using the full cohort and the cohort of farmers who participated in the 1999-2003 interview for 1) use of chlorpyrifos and depression reported at enrollment; 2) smoking and chronic lung disease reported at enrollment; and, 3) smoking and incident cancer [136]. Odds ratios estimated from interview participants for each exposure-outcome association were similar to those from the cohort present at enrollment.

The next interview (2005-2010) occurred roughly 12 years (range: 8-16 years) after study enrollment. This interview included questions about respiratory diagnoses and symptoms that were not included on questionnaires used at enrollment or during the previous interview. Approximately 46% of enrolled farmers participated in the 2005-2010 interview [137]. Farmers who did not participate are missing information about COPD.

Loss to follow-up has become a frequently discussed problem for large cohort studies, especially those following older populations over a lengthy period [138, 139]. The most common approach to handle loss is to restrict analyses to those with complete information. The effects of restriction on estimates of disease occurrence and exposure-disease associations has been examined using simulated examples [140-143], directed acyclic graph (DAG) theory [144, 145], and some real-world examples [146]. These investigations indicate that results of analyses restricted to participants are only valid under certain conditions. Depending on the magnitude and distribution of loss, varying levels of bias and loss of precision may be present in study results [141, 142, 147-149].

Characterizing attrition by identifying how study variables relate to participation can help conceptualize the extent of bias and precision loss that may result from restricting analysis to those who remain under study [144]. As previously demonstrated through simulation studies [140, 141, 149] and the application of DAG theory [144, 145, 150], bias can occur if attrition is related to the exposure and outcome under study, or to factors related to both the exposure and outcome. As approximately 54% of the original cohort of farmers was not able to report respiratory symptoms and diagnoses at follow-up, it is necessary to consider how selection bias may influence results of the proposed analysis.

Tables

Table 2.1. Organophosphate, pyrethroid, and carbamate insecticides and the year first registered for use in the United States [151-153]. Partially reproduced from Hoppin et al. (2012) [151].

Organophosphates	Registration
Chlorpyrifos	1965
Coumaphos	1958
Diazinon	1948
Dichlorvos	1948
Fonofos	1967
Malathion	1955
Parathion	1954
Phorate	1959
Terbufos	1974

Carbamates	Registration
Carbaryl	1947

Pyrethroids	Registration
Allethrin	1981
Bifenthrin	1985
Cyfluthrin	1987
Cyhalothrin	1988
Cypermethrin	1984
Deltamethrin	1994
Esfenvalerate	1973
Fenpropathrin	1989
Fluvalinate	1988
Permethrin	1977
Resmethrin	1967
Tefluthrin	1989
Tetramethrin	1968
Tralomethrin	1993

Table 2.2. Regulatory limits and recommendations for workplace exposure to dust, endotoxin, and gases.

	Dust		Endotoxin	Gases	
	Total[a] (mg/m^3)	**Respirable[b] (mg/m^3)**	**Total[d] (EU/m^3)**	**Ammonia (PPM)**	**H_2S (PPM)**
OSHA PEL[c]	15	5	Not Listed	50	20[e]
NIOSH REL	Not Listed	Not Listed	Not Listed	25	10
ACGIH TLV	10	3	Not Listed	25	10

OSHA = Occupational Safety and Health Administration
PEL = permissible exposure limit
NIOSH = National Institute for Occupational Safety and Health
REL = recommended exposure limit
ACGIH = American Conference of Industrial Hygienists
TLV = threshold limit value

[a] Total dust includes all airborne particles, regardless of their size or composition [154].

[b] Respirable dust refers to dust particles that are small enough to penetrate the nose and upper respiratory system and deep into the lungs (< 10 μm) [154].

[c] Based on an 8-hour time weighted average (TWA) exposure

[d] Although no OSHA PEL or NIOSH REL is listed, other countries have suggested limits. The Netherlands recommends a health-based exposure limit of 50 Endotoxin units (EU)/m^3. Researchers in the United States have recommended a human-health based limit of 100 EU/m^3 [155].

[e] Exposures shall not exceed 20 ppm (ceiling) with the following exception: if no other measurable exposure occurs during the 8-hour work shift, exposures may exceed 20 ppm, but not more than 50 ppm (peak), for a single time period up to 10 minutes [156].

CHAPTER 3.
NON-PARTICIPATION IN A STUDY FOLLOW-UP INTERVIEW AND SELECTION BIAS: AN EXAMPLE FROM THE AGRICULTURAL HEALTH STUDY

Introduction

Prospective cohort studies are important tools for identifying preventable causes of disease [157-159]. However, studies that follow participants over time are susceptible to attrition, including loss to follow-up and death [140, 141, 159-161]. If analyses are limited to participants who remain under study, attrition may result in biased measures of disease occurrence or exposure-disease associations [140, 150, 159]. As previously demonstrated through simulation studies [140, 141, 149] and the application of DAG theory [144, 145, 150], bias can occur if attrition is related to both the exposure and outcome under study, or to factors related to both the exposure and outcome. Therefore, identification of factors related to attrition can help evaluate the potential for bias in studies using data collected only through study visits or interviews.

Identifying factors associated with attrition can be useful in determining whether selection bias may affect study results. In addition, with attrition-related factors identified, investigators can determine the utility of analytical methods (e.g., inverse probability weighting, multiple imputation of missing data, sensitivity analyses) to illustrate or mitigate the effects of attrition. As these analytical methods have become easier to implement, analyses of cohort studies have begun to include formal evaluation of the potential impacts of attrition on results and the use of analytical methods to mitigate those impacts [143, 162, 163].

The AHS is a longitudinal cohort study that enrolled 52,394 private pesticide applicators, hereafter "farmers," who applied for restricted use pesticide licenses in Iowa and North Carolina between 1993 and 1997 [41, 42]. The AHS was designed to evaluate the potential health effects of farming-related exposures among pesticide applicators and their spouses [41]. Cancer incidence, mortality, and end-stage renal disease are obtained through linkage with state and federal sources [41, 164] and, therefore, analyses of exposures measured at enrollment and these outcomes are unaffected by attrition. Since enrollment, information on specific farming activities and other health outcomes is collected at interviews occurring approximately every five years. In the second interview, occurring between 2005 and 2010, information about lifestyle, specific farming activities, and incident disease was collected. Approximately 46% of farmers enrolled in the AHS responded to this interview (60% of those contacted) presenting a potential challenge for evaluating exposures or incident disease self-reported at this interview. Here, I identify characteristics associated with participation in the 2005-2010 interview, evaluate the extent to which attrition may influence results from analyses restricted to interview participants, and consider the utility of inverse probability of selection weights to correct for selection bias in studies of incident outcomes reported by participants during follow-up interviews.

Methods

To enroll in the AHS, farmers completed a questionnaire, which requested information on demographics and lifestyle, medical history, and farming activities. Between 1999 and 2003, farmers were re-contacted to respond to a Computer Assisted Telephone Interview (CATI) to update information on farming activities. Investigators have previously examined factors associated with non-participation during this interview [136].

Another interview was conducted between 2005 and 2010. At this time, farmers were asked to provide updated information on lifestyle and farming activities, and to report a range of incident medical conditions. Reasons for non-participation in this interview have been described previously [137]. Briefly, three groups of farmers were not contacted for this interview: 1) farmers who refused further contact prior to the interview; 2) farmers who died prior to interview identified through linkage with state mortality records and the National Death Index [41]; and, 3) farmers who were administratively excluded because of non-participation in study activities since enrollment, pilot testing of materials, and other reasons explained previously [137]. Farmers contacted for the 2005-2010 interview either completed the CATI or a reason for non-response was noted. Reasons for non-response included: 1) refusal; 2) inability to reach the person by phone; and, 3) illness prohibiting participation. For the present analysis, farmers who were not contacted or who did not respond to the 2005-2010 interview are referred to as non-participants, whereas, those who completed the interview are referred to as participants.

The AHS was approved by the Institutional Review Boards (IRBs) of the National Institutes of Health and its contractors. The current analysis was also approved by the IRB of the University of North Carolina at Chapel Hill. Participants indicated initial informed consent by completing the enrollment questionnaire. Copies of all questionnaires are available on the study Web site (http://www.aghealth.nih.gov/collaboration/questionnaires.html).

Basline predictors of participation

I considered exposures and covariates reported on the enrollment questionnaire, and commonly used in other AHS analyses as predictors of participation in the 2005-2010 interview. These variables included demographic and lifestyle factors (age, state, gender, race/ethnicity, education, marital status, smoking status, and alcohol consumption), medical conditions (heart

disease, asthma, other chronic lung disease, kidney disease, diabetes, Parkinson's disease, depression, tuberculosis, and pneumonia), personal use of pesticides (ever use, percent of time using, lifetime years of use, days per year of use, and ever use of functional groups and chemical classes), and other farm work/farm characteristics (farm size, work in hog or poultry confinement, number of livestock and poultry, and major income producing animals). I examined the distribution of each variable by participation status (participants vs. non-participants) and by reason for non-participation (death vs. refusal/exclusion). I estimated crude associations between variables and participation and categorized variables to preserve the shape of the association between each factor and participation.

I removed variables with more than 10% missing data from consideration. I then used logistic regression models and a backward elimination approach to identify a set of variables that described the relationship between covariates reported on the enrollment questionnaire and participation in the 2005-2010 interview. I began by removing variables with a non-significant χ^2 statistic (two-sided test, $\alpha=0.05$), ending with demographic and lifestyle variables which were hypothesized to be the most strongly predictive of participation. I then removed variables that although predictive of participation based on the χ^2 statistic, were not strongly associated with participation ($-0.40<\beta<0.40$). I report regression coefficients (β) and standard errors (SE) to show the direction, magnitude and precision of the association between each variable and participation. Wald χ^2 values are also reported to indicate the contribution of the variable to the prediction of participation. The presented results indicate the set of enrollment variables that are predictive of and strongly associated with participation. Estimates for other variables adjusted for the set of predictors are provided.

Assessing selection bias

Cancer incidence for members of the AHS was ascertained by linkage of the enrollment cohort with state (Iowa, North Carolina) cancer registries through December 31, 2010. Consequently, the association between enrollment information and cancer incidence over the period from enrollment through 2010 is not affected by attrition (except for the small proportion of farmers who leave the state) and can be estimated for the full cohort. In contrast, most other health outcomes are self-reported by participants during follow-up interviews and therefore case status is unavailable for non-participants. The present analysis is meant to serve as an example of the potential impact of attrition on analyses of associations between agricultural exposures and self-reported health outcomes when estimated using information ascertained from farmers participating in the 2005-2010 interview. Because complete-case ascertainment for cancer is available, I used cancer outcomes to illustrate conditions under which restricting analyses to 2005-2010 participants may result in biased effect estimates.

For this example, I defined two cohorts within the AHS. The full cohort includes all farmers who enrolled in the AHS (N = 52,394). The second cohort, a subset of the full cohort (referred to as the sub-cohort) includes farmers who participated in the 2005-2010 interview (N = 24,171). Within the full and sub-cohorts, I examined three exposure-outcome associations: 1) a strong, well-established association – ever smoking and incident lung cancer [165]; 2) a weaker, well-established association – ever smoking and incident bladder cancer [166]; and, 3) an association usually observed to be null – ever smoking and incident prostate cancer [167, 168]. These outcomes differ in mortality and disability rates that may impact participation in study activities. I assigned farmers as ever or never smokers based on information reported at enrollment while cancer incidence was obtained from cancer registry information. **Figure 3.1**

illustrates the relationships between ever smoking (E), each incident cancer outcome (D), a vector of covariates (Z) and selection (S) for each association.

I estimated the association between ever smoking and each incident cancer outcome in the full cohort and in the sub-cohort. For each smoking-cancer association, I used inverse probability of exposure weights (IPEW) to address confounding. The application of IPEW is a form of direct standardization that creates a "pseudo-population" in which the distributions of confounding variables are similar across exposure groups [169-171]. Confounders and risk factors for each cancer outcome were identified by previous literature [172], and included age at censoring, state, gender, education, race/ethnicity, and marital status. Alcohol consumption was also included in the model to estimate weights for the ever smoking-bladder cancer association. The association for ever smoking and prostate cancer was restricted to male farmers. First, I used logistic regression models to estimate the predicted probability of ever smoking (i.e., propensity scores for smoking for each individual), conditional on confounders or non-confounding risk factors for each cancer outcome. Next, I assigned each individual a weight equal to the inverse of the predicted probability that the individual had his/her observed smoking status. To stabilize each individual's weight, I multiplied each weight by the marginal probability of their observed smoking status.

I applied IPEW to log-binomial and linear-binomial models to estimate standardized cumulative incidence, risk differences (RDs), and risk ratios (RRs) for the three ever smoking-cancer associations. Models included one explanatory term for ever smoking. The application of weights induces within-subject correlation by weighting individuals to represent themselves as well as others with similar covariate patterns. To account for this within-subject correlation, I used robust variance estimates to calculate standard errors and 95% confidence intervals [170].

These robust estimates are equivalent to generalized estimating equation estimates using an independent working covariance matrix [173]. I considered the estimated association for the full cohort as the target parameter of interest.

In this example, I examine incidence proportions so results will apply to the outcomes reported as part of the 2005-2010 interview with limited information on timing of onset and diagnosis (e.g., COPD). Because timing of cancer diagnosis is available, I repeated analyses using a time-to-event approach and conclusions remained the same (results not shown).

Inverse probability weighting for selection bias

A second set of weights – stabilized inverse probability of selection weights (IPSW) – were estimated to address non-participation in the 2005-2010 interview. I estimated stabilized IPSW using logistic regression models. The numerator for each individual's stabilized IPSW was the marginal probability of their observed participation status in the overall study population; the denominators were calculated in two ways. First, the denominator for each individual's stabilized IPSW was equal to their predicted probability of their observed participation status conditional on smoking (E), the vector of variables identified as predictors of participation (Z), and disease status (D). These weights, referred to as IPSW|E,Z,D are necessary to remove selection bias when attrition is related to exposure, covariates, and the outcome. In practice, non-participants are missing disease status, and simpler weights, conditional on E and Z are often used. Simpler weights may suffice in some but not all settings. Therefore, I estimated a second set of weights with denominators for each individual equal to their predicted probability of their observed participation status conditional only on E and Z. I refer to this set of weights as IPSW|E,Z.

Among the sub-cohort, using log-binomial and linear-binomial models I estimated cumulative incidence, RRs, RDs for the three ever smoking-cancer associations after applying IPSW|E,Z,D and IPSW|E,Z.

For each analysis, adjustment for confounding and selection was achieved by applying a product of the IPEW and IPSW [169, 171, 174]. The distribution of all weights used in these analyses are provided in **Table 3.1**. Weights were well-behaved with means close to one and no extreme values (<0.05 or >20). All analyses were performed using SAS, version 9.3 (SAS Institute, Inc., Cary, North Carolina).

Results

A total of 28,223 farmers did not participate in the 2005-2010 interview (**Figure 3.2**). Thirteen percent of non-participants died prior to interview. Other reasons for non-participation included refusal at the current interview or a previous point, exclusion, an inability to be contacted, and illness.

Baseline predictors of participation

The set of enrollment variables that were identified as predictive of and strongly associated with participation included age, state, race/ethnicity, education, marital status, smoking status, and alcohol consumption (**Table 3.2**). Age less than 40 or older than 70 years was associated with a decrease in log odds of participation compared to 40-49 year olds. As age at enrollment increased death explained an increasing portion of non-participation. Enrollment in North Carolina, race/ethnicity other than non-Hispanic white, having less than a high school degree, not being married or living as married, and heavy drinking were associated with a decrease in log-odds of participation. Current smoking at enrollment, regardless of the number of

pack-years, was associated with a decrease in log-odds of participation compared to never smokers. As the number of pack years increased for former and current smokers, death explained a greater proportion of non-participation. Males also had a lower log-odds of participation than females.

Medical conditions, pesticide use, and farm characteristics reported at enrollment were not included in the set of variables predictive of and associated with participation (**Tables 3.3-3.5**). Self-report of a doctor diagnosis of heart disease, diabetes, and Parkinson's disease at enrollment was associated with a decrease in log-odds of participation. Generally, variables indicating personal pesticide use or raising animals were associated with small increases in log-odds of participation. Several of these variables were significant predictors but were not strongly associated with participation or the characteristic was rare. Size of farm was predictive of participation but was missing for 11% of the cohort.

Assessing selection bias

Ever smoking was weakly associated with participation – a greater proportion of ever smokers were non-participants compared with never smokers (**Table 3.6**). Overall, incident lung cancer had a strong, inverse association with participation, incident bladder cancer was not associated with participation, and incident prostate cancer had a weak, positive association with participation. The proportion of non-participation due to mortality was greatest for lung cancer, followed by bladder cancer, and then prostate cancer.

The number and proportion of participants by smoking and cancer outcome is shown in **Table 3.7**. Because of lower participation among never and ever smoking lung cancer cases compared with non-cases, the cumulative incidence estimates of lung cancer from the sub-cohort were underestimates compared to those from the full cohort. Participation among lung cancer

cases was also differential with respect to smoking – a smaller proportion of ever-smoking lung cancer cases participated than never-smoking lung cancer cases. Similar proportions of bladder cancer cases and non-cases participated in the 2005-2010 interview leading to similar cumulative incidence estimates from the full and sub-cohorts. A greater proportion of prostate cancer cases participated compared with non-cases. This led to an overestimate of the cumulative incidence of prostate cancer in the sub-cohort compared to the full cohort. Participation for bladder and prostate cancer cases and non-cases was non-differential with respect to smoking.

Standardized estimates of the RR (95% CI) and RD (95% CI) for smoking in the full and sub-cohorts are shown in **Figures 3.3 and 3.4**. Because of differential participation of lung cancer cases with respect to smoking, the sub-cohort RR and RD were underestimates of the effect of ever smoking on lung cancer estimated in the full cohort. Precision was reduced for the sub-cohort RR and its 95% CI contained the full-cohort estimate. Non-differential participation of bladder and prostate cancer cases by smoking status led to sub-cohort RR estimates similar to full cohort estimates. The sub-cohort RD for ever smoking and bladder cancer was also similar to the full cohort RD. For ever smoking and prostate cancer, the sub-cohort RD was on the opposite side of the null and less precise but was not significantly different than the full cohort RD.

Illustrating bias reduction through IPSW

Differential participation of lung cancer cases by smoking status indicated the need for IPSW|E,Z,D to fully correct for selection bias. Application of IPSW|E,Z,D produced RR and RD estimates similar to, but less precise than, full-cohort estimates (**Figures 3.3 and 3.4**). Under these conditions, simpler IPSW|E,Z were unable to fully correct sub-cohort estimates. The sub-cohort RR and RD estimates for ever smoking and bladder cancer were already similar to full-cohort estimates. Although RR and RD estimates for ever smoking and prostate cancer were

similar to full-cohort estimates, application of IPSW|E,Z shifted estimates to the same side of the null as full-cohort estimates.

Discussion

Forty-six percent of farmers enrolled in the AHS participated in the 2005-2010 interview occurring a median 12 years after enrollment. Both loss (through non-response or exclusion) and mortality contributed to attrition within the cohort. The enrollment variables age, state, education, race/ethnicity, marital status, smoking, and alcohol consumption were predictors of participation in the 2005-2010 interview; prevalent disease, personal use of pesticides and raising animals, variables often considered as exposures in AHS analyses, generally were not strongly associated with participation. Using outcomes with complete-case ascertainment (incident cancers) as examples, I identified conditions under which restricting analyses to participants of the 2005-2010 interview may introduce bias. In the absence of the exposure and outcome being strongly predictive of participation, sub-cohort results were similar to full-cohort estimates. Further, when the exposure and outcome were weakly associated with participation but were not associated with each other, little bias was observed. The identification of predictors of participation from enrollment data and conditions under which analyses that must be restricted to sub-cohort participants may produce results similar to those from the full cohort can be used to inform analyses of associations involving incident disease reported only as part of the 2005-2010 interview.

Loss due to non-response or exclusion was the main reason for non-participation in the 2005-2010 interview. However, mortality accounted for greater proportions of non-participants among farmers 60 years and older at enrollment compared with those younger than 60. Mortality was also greater for smokers compared with never smokers and those reporting a diagnosis of

one of several chronic medical conditions at enrollment; although residual confounding by age may partially explain these associations. A greater proportion of deaths also occurred among farmers with less than a high school education, reporting more than 20 years of pesticide use, or living or working on smaller properties. Although death accounted for greater proportions of non-participants within specific sub-groups, a majority of non-participants were either excluded (28%), could not be reached (35%), or refused to participate (23%).

Observed associations between enrollment factors and non-participation were similar to those found within other cohort studies. Other researchers have observed non-participation in study follow-up activities associated with younger and older age [175-179], male gender [177, 178, 180], minority race/ethnicity [178], lower levels of education [161, 175, 178, 179], and marital status other than married [175, 179-181]. Although mortality was a major contributor to non-participation among older farmers, younger farmers may have less time to participate in study activities or be unwilling to participate for other reasons. Smoking [175, 178, 179, 181, 182] and heavy alcohol consumption [179, 182] have also been consistently associated with attrition in previous work; as has abstention from alcohol [179], which was not observed here. Finally, as observed here for farmers reporting a diagnosis of heart disease, diabetes or Parkinson's disease, other researchers have observed that persons reporting general poor health [176] or chronic illness [182] participate less in study activities. I hypothesize that other chronic conditions (e.g., asthma, other chronic lung disease, kidney disease, depression) were not associated with participation in the AHS partly because these conditions may not lead to mortality or the onset of severe disability as rapidly as some of the previously mentioned conditions. The proportion of farmers who died prior to the 2005-2010 interview was larger for

diagnoses that were associated with participation compared with the ones that were not, consistent with this hypothesis.

Relationships between enrollment characteristics and participation were consistent with factors associated with participation in the 1999-2003 interview with a few notable exceptions [136]. In the previous investigation, odds of participation increased with increasing age; however, that investigation excluded those who died prior to interview. This exclusion, coupled with the aging of the cohort since the previous interview may partially account for the difference. Individuals reporting illness at enrollment were more likely to participate in the 1999-2003 interview, which the authors suggested could be explained by the "worried ill" phenomenon [136]. I did not observe this phenomenon in the present investigation. It is possible that with more time, the "worried ill" phenomenon has faded. Farmers reporting a diagnosed medical condition at enrollment have had more time to experience complications that may lead to non-participation. Elevated mortality rates for farmers reporting a diagnosed medical condition compared with those who did not, provides evidence supporting this explanation. Although the "worried ill" phenomenon was not observed for medical conditions reported at enrollment, a greater proportion of incident prostate cancer cases than non-cases participated in the 2005-2010 interview. This could indicate that disease-related interest in participation may be operating along with disease-related reasons for non-participation.

Although specific farm activities were not strongly associated with participation, similar to the previous investigation [136], I observed that the proportion of participation among farmers reporting no personal pesticide use and no animal production at enrollment, was lower than farmers actively engaged in these activities at enrollment. This observation may indicate that farmers who were actively engaged in using pesticides or other farming activities may have had

a stronger interest in participating in a study of the health effects of such exposures. Alternatively, it is possible that farmers who reported infrequent pesticide use at enrollment or who were not involved in other activities, were less healthy than other farmers and therefore were unable to participate in study interviews.

Researchers have previously used simulation studies and DAG theory to investigate the potential impacts of attrition in cohort studies [140-142, 145, 183]. However, few studies include investigations of potential impacts of attrition in a real-world setting [143]. Using three examples, I identified conditions under which analyses that must be restricted to interview participants produced similar effect estimates to those from the full cohort. I illustrated that effect estimates estimated from those who remain under study may be biased when exposure and outcome are associated and, participation is associated with the exposure and outcome under study leading to differential participation of cases or non-cases by exposure status. This could occur when the outcome under study is associated with rapid mortality or disability rates precluding participation soon after diagnosis. Under the conditions examined here, the RR estimated from 2005-2010 interview participants was much less precise than the full-cohort RR, leading it to contain the full cohort estimate within its bounds. This was not the case for the RD. Alternatively, when the outcome under study was not strongly associated with participation resulting in non-differential participation of cases and non-cases by exposure, sub-cohort RD and RR estimates were similar to, although less precise than, estimates from the full cohort.

When both the exposure and outcome were predictive of participation, I demonstrated that IPSW|E,Z,D improved sub-cohort estimates. Simpler weights estimated using only exposure and covariates were unable to fully correct estimates in this scenario. When the outcome was weakly associated with participation, and the true association was null IPSW|E,Z returned

estimates to the same side of the null but did not substantially alter conclusions. Finally, when the outcome was not associated with participation, IPSW were unnecessary. Collectively, these observations align with findings from simulation studies and theoretical examples [141, 142, 144, 145].

The examples considered here do not pertain to analyses of the association between exposures measured at enrollment and outcomes obtained through registries (e.g., cancer, mortality). Alternatively, these results have implications for the design of future analyses of associations between agricultural exposures and outcomes reported only by participants of the 2005-2010 interview. For example, several respiratory outcomes, including COPD and asthma, are reported only by participants of the 2005-2010 interview. Applying pesticides and raising animals at enrollment do not appear to be strongly associated with participation in the 2005-2010 interview. In addition, many of the outcomes reported during the 2005-2010 interview (e.g., allergy, chronic obstructive pulmonary disease, diabetes, arthritis) do not have high rates of rapid mortality or disability precluding participation soon after diagnosis and, therefore, would not be expected to be strongly predictive of participation in study activities after enrollment. Although these results and previous observations within the AHS [184] indicate that IPSW may not be necessary to correct effect estimates under these conditions, IPSW may be useful when the exposure of interest is a stronger predictor of participation, as has been demonstrated previously using simulations [142] and in other cohorts, some with similar attrition to the AHS [178, 181, 185, 186]. Further, weights may be useful for confirming that there are no substantial differences in results when weights are applied. To that end, the predictors of participation reported here can inform the construction of weights for future AHS analyses.

Although I was able to evaluate associations between many enrollment characteristics and participation, it is possible that other unmeasured characteristics were important predictors of participation. Specifically, I was not able to examine associations between many of the incident diseases reported as part of the 2005-2010 interview and participation because they were unavailable for non-particpants. It is possible that enrollment information and incident cancer do not adequately represent the participation experience of farmers who develop other medical conditions during follow-up. I was also unable to evaluate associations between updated agricultural work and participation for the full cohort. Engagement in farming activities after enrollment may be an important predictor of participation in later interviews. In addition, it is possible that different criteria for identifying variables important in predicting participation would produce an alternative set of predictor variables. Although this is true, I demonstrated that using the identified set of variables, I was able to estimate weights that produced RR and RD estimates from the sub-cohort of participants that were similar to the full-cohort estimates. This supports the idea that weight models were well-specified. Further, I found that results estimated using IPSW were robust to the inclusion of several additional variables in weight-generation models. However, weight models were sensitive to the inclusion of variables with large amounts of missing data and to the exclusion of variables identified here as strongly associated with participation. This illustrates the importance of meeting the assumptions implicit in the use of inverse probability weighting including no model misspecification [169]. Finally, it must be noted that the three examples used to examine the potential for selection bias represent a small set of assumptions. Many other sets of conditions could be explored, which may result in alternative conclusions.

Specific to the AHS, understanding the make-up of the cohort participating in the 2005-2010 interview can help focus efforts on ensuring participation in future interviews and guide analyses aimed at evaluating associations between agricultural work and incident disease self-reported by participants. Beyond the AHS, this investigation serves as an applied example supporting previous theoretical work regarding the effects of attrition on the estimation of effect estimates from long-term cohort studies. This work also demonstrates that statistical tools are available for evaluating the impact of attrition on results, particularly if detailed information on predictors of attrition is collected at study enrollment.

Figures and Tables

Figure 3.1. Directed acyclic graphs illustrating the associations between ever smoking (E), the cancer outcome of interest (D), a vector of covariates (Z), and selection (S) among 24,171 farmers who participated in the 2005-2010 interview. The three associations depicted are ever smoking and A) incident lung cancer; B) incident bladder cancer; and, C) incident prostate cancer. Dotted lines indicated associations induced by conditioning on selection (a collider). + signs indicate the strength of the association between E, D, and Z.

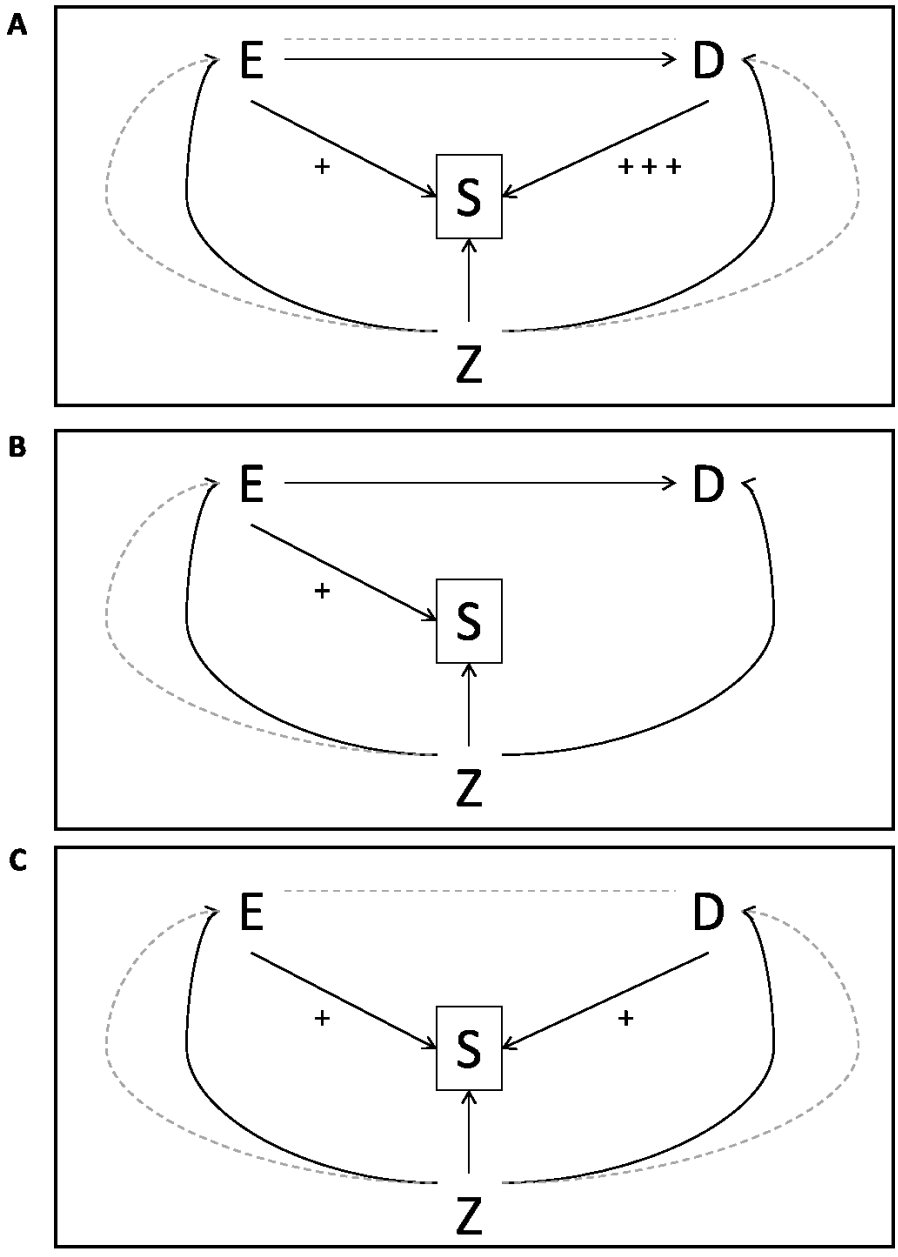


Figure 3.2. Description of participation and non-participation in the 2005-2010 interview, Agricultural Health Study.

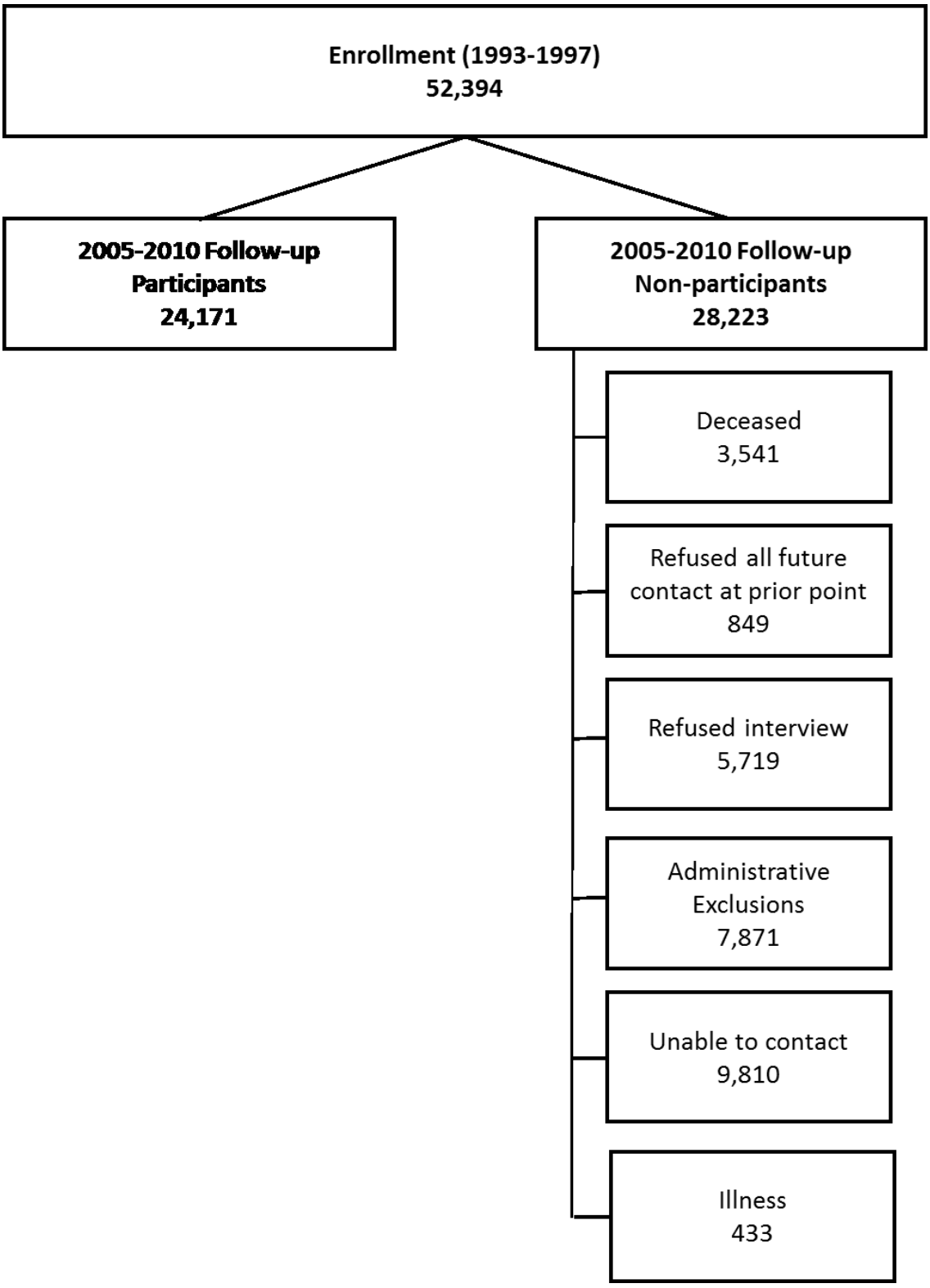


Figure 3.3. Standardized risk ratios (95% CI) indicating associations between ever smoking and A) incident lung cancer; B) incident bladder cancer; and, C) incident prostate cancer among 52,394 farmers present at enrollment and the sub-cohort of 24,171 farmers participating in the 2005-2010 interview.

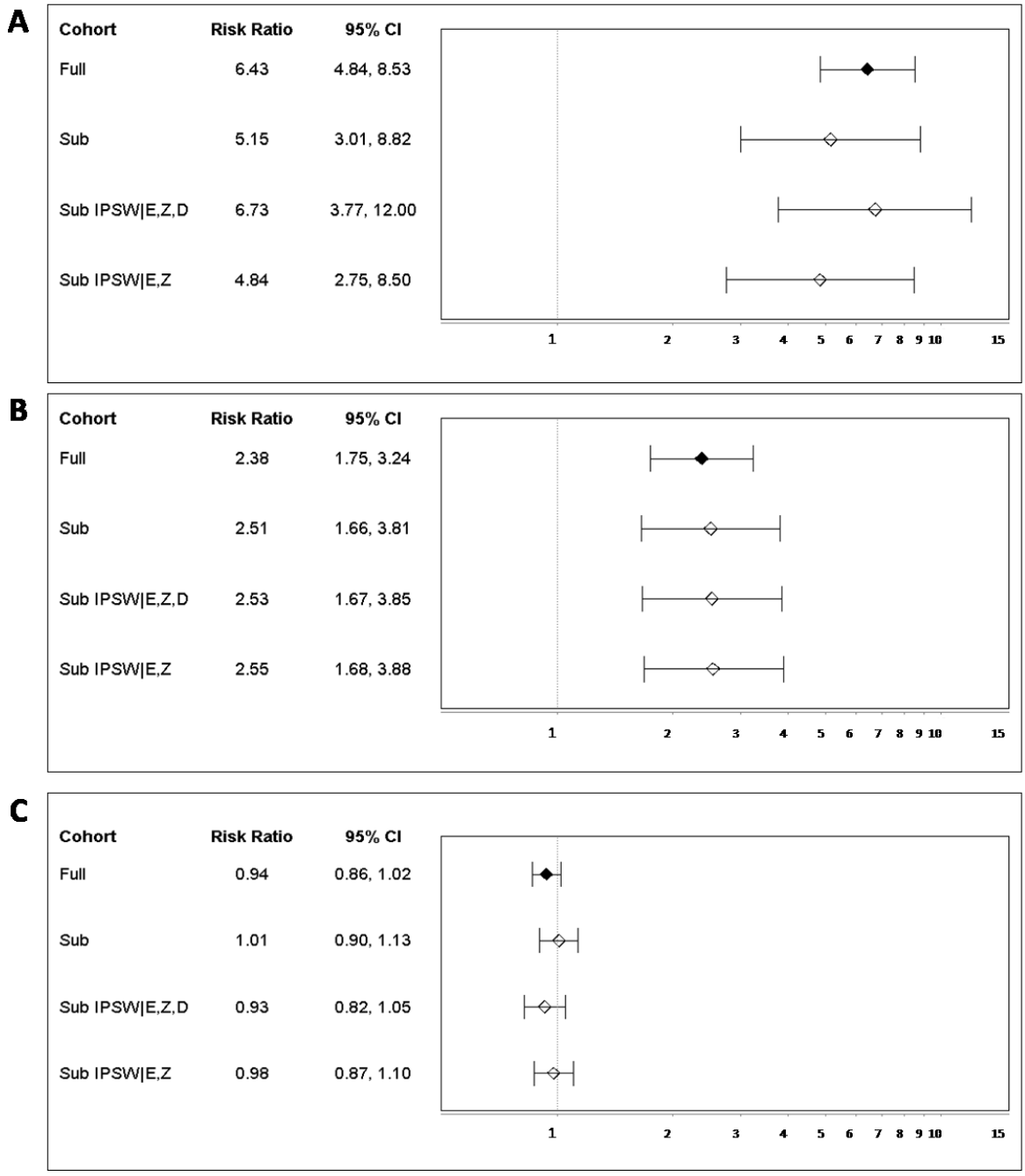


Figure 3.4. Standardized risk differences/1,000 persons (95% CI) indicating associations between ever smoking and A) incident lung cancer; B) incident bladder cancer; and, C) incident prostate cancer among 52,394 farmers present at enrollment and among the sub-cohort of 24,171 farmers participating in the 2005-2010 interview.

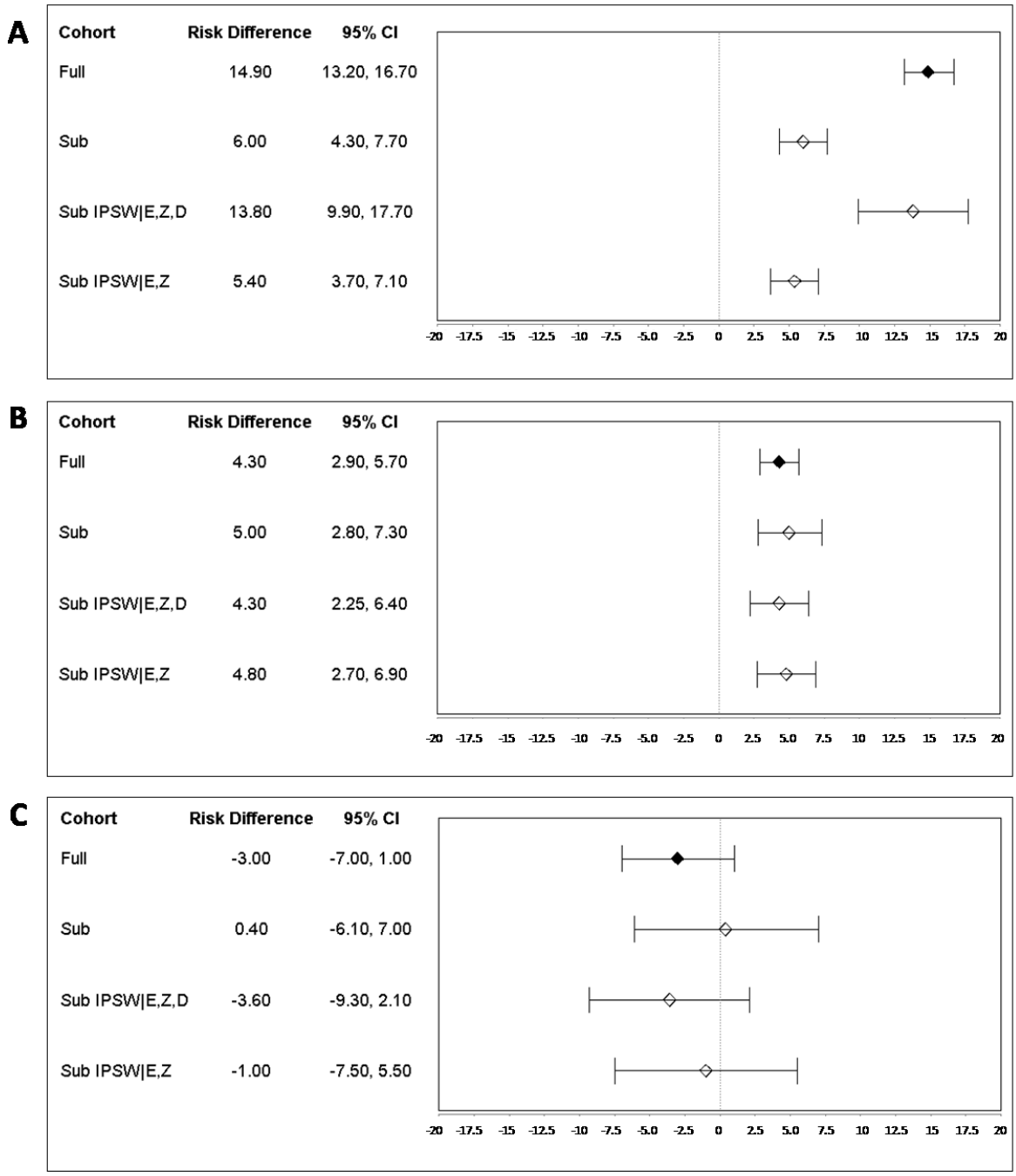


Table 3.1. Distribution of stabilized inverse probability of exposure and selection weights applied to analyses of the association between ever smoking and 1) incident lung cancer; 2) incident bladder cancer; and, 3) incident prostate cancer.

	Mean	SD	Min	5th	25th	50th	75th	95th	Max	Sum
IPSW|E,Z,D										
Lung cancer	0.9999	0.2361	0.5529	0.7206	0.8332	0.9710	1.1248	1.4088	6.6040	48208
Bladder cancer	0.9999	0.2227	0.5875	0.7313	0.8438	0.9735	1.1265	1.4053	5.5454	48205
Prostate cancer	0.9999	0.2251	0.5849	0.7282	0.8354	0.9662	1.1204	1.4041	5.8415	47004
IPSW|E,Z	0.9999	0.2226	0.5879	0.7314	0.8433	0.9735	1.1275	1.4046	5.5121	48205
IPEW Full cohort[a]										
Lung cancer[a]	1.0000	0.3370	0.5603	0.6533	0.7816	0.9251	1.0780	1.7023	6.7487	49198
Bladder cancer	1.0002	0.4056	0.4965	0.6148	0.7386	0.8691	1.1521	1.7444	7.2308	47016
Prostate cancer	0.9995	0.3337	0.5667	0.6500	0.7888	0.9312	1.0717	1.7291	4.2260	47929
IPEW Sub-cohort[a]										
Lung cancer	1.0005	0.3850	0.5260	0.6415	0.7612	0.8907	1.1112	1.7506	10.5890	23109
Bladder cancer	1.0010	0.4613	0.4744	0.5948	0.7278	0.8383	1.1745	1.8154	9.9001	22235
Prostate cancer	0.9995	0.3731	0.5219	0.6425	0.7668	0.8974	1.1046	1.7538	4.6703	22457
IPEW*IPSW|E,Z,D										
Lung cancer	0.9774	0.5065	0.4426	0.5788	0.7188	0.8276	1.0175	1.8181	13.3305	21713
Bladder cancer	0.9772	0.5598	0.4046	0.5413	0.6746	0.8283	1.0473	2.0028	12.5342	21708
Prostate cancer	0.9794	0.4993	0.4312	0.5783	0.7220	0.8412	1.0263	1.8173	8.6708	21186
IPEW*IPSW|E,Z										
Lung cancer	0.9786	0.5052	0.4432	0.5799	0.7206	0.8336	1.0133	1.8253	13.4019	21739
Bladder cancer	0.9772	0.5595	0.4045	0.5453	0.6807	0.8277	1.0485	2.0133	12.5300	21707
Prostate cancer	0.9776	0.4972	0.4648	0.5811	0.7167	0.8380	1.0207	1.8167	8.1685	21147

SD = Standard deviation

IPSW|E,Z = inverse probably of selection weights conditional on ever smoking (E) and (Z) which includes age, state, race/ethnicity, education, marital status, and alcohol consumption.

IPSW|E,Z,D = inverse probably of selection weights conditional on ever smoking (E), (Z), and the specified cancer outcome (D).

[a] Estimated using indicator variables for age at censoring, state, gender, race/ethnicity, education, and marital status. Alcohol consumption was included for the ever smoking-bladder cancer association. The ever smoking-prostate cancer analysis was restricted to male farmers.

Table 3.2. Associations between demographic and lifestyle variables reported at enrollment (1993-1997) and participation in the 2005-2010 interview among 52,394 farmers, Agricultural Health Study.

Enrollment characteristics	Enrolled	Participants		Non-participants						
				Refusals/Exclusions		Deaths				Wald
	N =52394	N = 24171	%[a]	N = 24682	%[a]	N = 3541	%[a]	β[b]	SE	χ^2
Age										
<30 years	4493	1443	32	3019	67	31	1	-0.65	0.04	221.61
30-39 years	12141	5205	43	6788	56	148	1	-0.23	0.03	67.66
40-49 years	14108	7012	50	6749	48	347	2	Ref		
50-59 years	11155	5913	53	4491	40	751	7	0.21	0.03	51.84
60-69 years	7768	3781	49	2723	35	1264	16	0.11	0.03	10.72
70-79 years	2487	784	32	836	34	867	35	-0.54	0.06	84.98
80 + years	242	33	14	76	31	133	55	-1.84	0.29	40.73
State										
Iowa	31876	15760	49	14572	46	1544	5	Ref		
North Carolina	20518	8411	41	10110	49	1997	10	-0.23	0.02	93.91
Gender										
Female	1362	674	49	616	45	72	5	0.23	0.07	10.36
Male	51031	23496	46	24066	47	3469	7	Ref		
Race/Ethnicity										
White	49345	23202	47	22891	46	3252	7	Ref		
Black	1172	336	29	705	60	131	11	-0.55	0.10	32.29
Hispanic	523	206	39	285	54	32	6	-0.48	0.19	6.69
Other	288	93	32	153	53	42	15	-0.25	0.11	5.55
Missing	1066									
Education										
< High school degree	5224	1840	35	2580	49	804	15	-0.32	0.04	57.56
High school grad/GED	24061	10739	45	11720	49	1602	7	Ref		
Some college	12119	5988	49	5608	46	523	4	0.23	0.02	83.31
≥ College grad	8589	4740	55	3490	41	359	4	0.44	0.03	239.30

Enrollment characteristics	Enrolled	Participants		Non-participants						
				Refusals/Exclusions		Deaths				Wald
	N =52394	N = 24171	%[a]	N = 24682	%[a]	N = 3541	%[a]	β[b]	SE	χ^2
Missing	2401									
Marital Status										
Married/Living as	43692	21114	48	19468	45	3110	7	Ref		
Divorced/Separated	2299	756	33	1437	63	106	5	-0.57	0.05	116.81
Widowed/Never married	6143	2228	36	3617	59	298	5	-0.24	0.03	48.51
Missing	260	260								
Smoking status (pack years)										
Never	26690	13031	49	12476	47	1183	4	Ref		
Former, <5	5635	2907	52	2448	43	280	5	0.07	0.03	4.54
Former, 5-29	6168	2974	48	2654	43	540	9	-0.06	0.03	3.63
Former, ≥ 30	2831	1275	45	1060	37	496	18	-0.12	0.05	6.80
Current, <15	2980	1027	34	1825	61	128	4	-0.35	0.05	57.49
Current, 15-44	3618	1405	39	1912	53	301	8	-0.37	0.04	79.66
Current, ≥45	1263	503	40	550	44	210	17	-0.36	0.07	26.94
Missing	3209									
Alcohol consumption[c]										
None	16837	7936	47	7255	43	1646	10	Ref		
Light drinker	30521	14481	47	14603	48	1437	5	-0.10	0.02	17.95
Heavy drinker	1113	375	34	708	64	30	3	-0.42	0.07	32.80
Missing	3923	3923								

[a] The % shown is the proportion of participation, or non-participation (by death and refusals/exclusions), by the specified level of each enrollment characteristic.

[b] β coefficient is the change in log odds of participation comparing the specified level of each characteristic to the referent.

[c] Heavy drinkers reported consuming five or more drinks on the same occasion on each of five or more days in the past 30 days, light drinkers reported consuming at least one drink on at least one day during the past 12 months but did not qualify as a heavy drinker [187].

Table 3.3. Associations between diagnosed medical conditions measured at enrollment (1993-1997) and participation in the 2005-2010 interview among 52,394 farmers, Agricultural Health Study.

	Enrolled	Participants		Non-participants						
Medical diagnoses[a] reported at enrollment				**Refusals/Exclusions**		**Deaths**				
	N =52394	**N = 24171**	**%[b]**	**N = 24682**	**%[b]**	**N = 3541**	**%[b]**	**B[c]**	**SE**	**Wald χ^2**
Heart disease	2637	1122	43	933	35	582	22	-0.22	0.04	26.26
Asthma	2599	1245	48	1169	45	185	7	0.03	0.04	0.60
Other chronic lung disease	1808	850	47	707	39	251	14	0.03	0.05	0.33
Kidney disease	481	226	47	164	34	91	19	0.02	0.10	0.03
Diabetes	1471	578	39	586	40	307	21	-0.36	0.06	41.48
Parkinson's	75	25	33	27	36	23	31	-0.59	0.26	5.00
Depression	1828	886	48	772	42	170	9	0.03	0.05	0.36
Tuberculosis	113	52	46	51	45	10	9	0.01	0.20	<0.01
Pneumonia	7137	3550	50	2992	42	595	8	0.07	0.03	7.70

[a] Data were missing for 1-8% of medical diagnoses.

[b] The % shown is the proportion of participation, or non-participation (by death and refusals/exclusions), by the specified level of each enrollment characteristic.

[c] β coefficient is the change in log odds of participation comparing the specified level of each characteristic to the referent adjusted for age, state, race/ethnicity, education, smoking, and alcohol consumption.

Table 3.4. Associations between pesticide use variables reported at enrollment (1993-1997) and participation in the 2005-2010 interview among 52,394 farmers, Agricultural Health Study.

	Enrolled	Participants		Non-participants						
				Refusals/Exclusions		Deaths				
Pesticide use at enrollment	**N =52394**	**N = 24171**	**%[a]**	**N = 24682**	**%[a]**	**N = 3541**	**%[a]**	**β[b]**	**SE**	**Wald χ^2**
Ever mixed/applied pesticides										
Never	450	120	27	305	68	25	6	Ref		
Ever	50620	23643	47	23613	47	3364	7	0.58	0.12	23.8
Missing	1324									
Personally apply pesticides										
Never	2253	855	38	1227	54	171	8	Ref		
< half the time	11330	4962	44	5575	49	793	7	0.18	0.04	24.81
≥ half the time	34728	16951	49	15641	45	2136	6	0.35	0.03	111.09
Missing	4083									
Lifetime years of mixing/applying										
None	498	143	29	326	65	29	6	Ref		
≤ 1 year	1116	409	37	644	58	63	6	0.11	0.08	2.05
2-5 years	5571	2247	40	3060	55	264	5	0.23	0.05	20.48
6-10 years	7469	3175	43	3892	52	402	5	0.22	0.05	20.63
11-20 years	15987	7644	48	7611	48	732	5	0.32	0.05	48.05
21-30 years	11672	5978	51	4888	42	806	7	0.34	0.05	52.76
>30 years	6494	3339	51	2298	35	857	13	0.41	0.05	64.80
Missing	3587									
Days/year mixing/applying										
None	498	143	29	326	65	29	6	Ref		
< 5 days	8691	4132	48	3811	44	748	9	0.39	0.05	72.75
5-9 days	11330	5498	49	5028	44	804	7	0.36	0.05	65.50
10-19 days	14349	7156	50	6388	45	805	6	0.42	0.04	89.58
20-39 days	9240	4206	46	4541	49	493	5	0.28	0.05	37.37

Pesticide use at enrollment	Enrolled	Participants		Non-participants						
				Refusals/Exclusions		Deaths				
	N =52394	N = 24171	%[a]	N = 24682	%[a]	N = 3541	%[a]	β[b]	SE	Wald χ^2
40-59 days	2408	984	41	1300	54	124	5	0.18	0.06	9.60
60-150 days	1572	589	37	893	57	90	6	0.11	0.07	2.66
> 150 days	349	120	34	205	59	24	7	-0.01	0.13	<0.01
Missing	3957									
Ever use[c]										
Fungicides	19094	8944	47	8735	46	1415	7	0.15	0.02	47.34
Fumigants	12168	5890	48	5241	43	1037	9	0.21	0.02	72.35
Herbicides	49678	23327	47	23068	46	3283	7	0.28	0.06	24.97
Insecticides	47312	22487	48	21692	46	3133	7	0.29	0.04	52.66
Organochlorines	25465	13190	52	10016	39	2259	9	0.26	0.02	150.40
Organophosphates	44796	21443	48	20476	46	2877	6	0.19	0.03	38.01
Carbamates	33222	16260	49	14563	44	2399	7	0.25	0.02	137.94
Pyrethroids	11006	5604	51	4947	45	455	4	0.14	0.02	34.82
Triazines	39260	18834	48	17967	46	2459	6	0.04	0.02	3.42
Phenoxy	38852	18855	49	17452	45	2545	7	0.12	0.02	27.79
Use of chemically resistant gloves										
No	16021	6697	42	8412	53	1710	11	Ref		
Yes	34112	16618	49	16264	48	1830	5	0.10	0.02	20.48
Missing	8									

[a] The % shown is the proportion of participation, or non-participation (by death and refusals/exclusions), by the specified level of each enrollment characteristic.

[b] β coefficient is the change in log odds of participation comparing the specified level of each characteristic to the referent adjusted for age, state, race/ethnicity, education, smoking, and alcohol consumption.

[c] Derived from reported use of individual pesticides. Fungicides include benomyl, captan, chlorothalonil, maneb/mancozeb, metalaxyl, and ziram. Fumigants include aluminum phosphide, carbontetrachloride/carbon disulfide (80/20 mix), ethylene dibromide, and methyl bromide. Herbicides include alachlor, butylate, chlorimuron-ethyl, dicamba, EPTC, glyphosate, imazethepyr, metolachlor, paraquat, pendimethalin, petroleum oil, trifluralin, phenoxy (2,4-D, 2,4,5-T, 2,4,5-TP), triazines (atrazine, cyanazine, metribuzin). Insecticides include carbamates (aldicarb, carbaryl, carbofuran), organochlorines (aldrin, chlordane, DDT, dieldrin, heptachlor, lindane, toxaphene), organophosphates (chlorpyrifos, coumaphos, diazinon, dichlorvos, fonofos, malathion, parathion, phorate, terbufos, trichlorfon, and pyrethroids (permethrin for animals, permethrin for crops). Data were missing for 1-12% of pesticide use variables.

Table 3.5. Associations between farming characteristics measured at enrollment (1993-1997) and participation in the 2005-2010 interview among 52,394 farmers, Agricultural Health Study.

Farm characteristics at enrollment	Enrolled	Participants		Non-participants						
				Refusals/Exclusions		Deaths				
	N =52394	N = 24171	%[a]	N = 24682	%[a]	N = 3541	%[a]	β[b]	SE	Wald χ^2
Size of farm (acres)										
Didn't work on a farm	1875	780	42	869	46	226	12	-0.10	0.05	3.71
< 5	1787	877	49	707	40	203	11	0.27	0.05	24.72
5-49	4557	2235	49	1839	40	483	11	0.23	0.04	37.01
50-199	8311	4063	49	3536	43	712	9	Ref		
200-499	13076	6326	48	6036	46	714	5	-0.13	0.03	22.51
500-999	10339	4871	47	5058	49	410	4	-0.22	0.03	52.58
>1,000	6849	2886	42	3771	55	192	3	-0.34	0.03	103.54
Missing	5600									
Work in swine confinement										
No	38440	17282	45	18173	47	2985	8	Ref		
Yes	13954	6889	49	6509	47	556	4	0.06	0.02	7.74
Work in poultry confinement										
No	50445	23309	46	23718	47	3418	7	Ref		
Yes	1949	862	44	964	49	123	6	0.04	0.05	0.81
No. of poultry										
Didn't work on a farm/None	41042	19316	47	19178	47	2548	6	Ref		
< 50	2128	1119	53	894	42	115	5	0.30	0.05	40.88
50-99	527	269	51	232	44	26	5	0.17	0.09	3.33
100-999	607	286	47	277	46	44	7	0.04	0.08	0.20
1,000-10,000	127	61	48	60	47	6	5	0.22	0.19	1.36
> 10,000	990	406	41	524	53	60	6	-0.10	0.07	2.04
Missing	6973									

Farm characteristics at enrollment	Enrolled	Participants		Non-participants						
				Refusals/Exclusions		Deaths				
	N =52394	N = 24171	%[a]	N = 24682	%[a]	N = 3541	%[a]	β[b]	SE	Wald χ^2
No. of livestock										
Didn't work on a farm/None	15477	6706	43	7491	48	1280	8	Ref		
< 50	6349	2972	47	2866	45	511	8	0.17	0.03	30.19
50-99	3824	1874	49	1694	44	256	7	0.18	0.04	24.53
100-499	8851	4508	51	3918	44	425	5	0.19	0.03	46.17
500-999	5209	2570	49	2455	47	184	4	0.17	0.03	23.86
1,000+	6359	3017	47	3142	49	200	3	0.04	0.03	1.63
Missing	6325									
Major income producing animals										
Beef cattle	19398	9540	49	8753	45	1105	6	0.09	0.02	21.18
Dairy cattle	2884	1503	52	1257	44	124	4	0.21	0.04	27.44
Hogs/swine	16492	8085	49	7693	47	714	4	0.04	0.02	2.81
Poultry	1948	892	46	922	47	134	7	0.06	0.05	1.28
Sheep	1670	883	53	699	42	88	5	0.11	0.05	4.31
Eggs	643	289	45	300	47	54	8	0.03	0.08	0.16
Other farm animals	951	429	45	463	49	59	6	-0.04	0.07	0.32

[a] The % shown is the proportion of participation, or non-participation (by death and refusals/exclusions), by the specified level of each enrollment characteristic.

[b] β coefficient is the change in log odds of participation comparing the specified level of each characteristic to the referent adjusted for age, state, race/ethnicity, education, smoking, and alcohol consumption.

Table 3.6. Associations between ever smoking (E) reported at enrollment (1993-1997); incident lung, bladder, and prostate cancer (D) obtained from state cancer registries and participation (S) in the 2005-2010 interview among 52,394 farmers, Agricultural Health Study.

	Enrolled	Participants		Non-participants				β^a	SE	Wald χ^2
				Refusals/Exclusions		Deaths				
	N = 52394[b]	N = 24171	%[c]	N = 24682[b]	%[c]	N = 3541[b]	%[c]			
Ever smoker										
No	25175	13031	49	12476	47	1183	4	Ref		
Yes	21845	10622	45	11107	47	2122	9	-0.18	0.02	88.79
Lung cancer										
No	48635	22985	47	22769	47	2881	6	Ref		
Yes	555	111	20	155	28	289	52	-1.17	0.10	125.17
Bladder cancer										
No	45552	21622	47	21180	46	2750	6	Ref		
Yes	240	125	52	69	29	46	19	0.19	0.12	2.48
Prostate cancer										
No	42360	19913	47	19989	47	2458	6	Ref		
Yes	1973	1124	57	662	34	187	9	0.36	0.05	62.91

[a] β coefficient is the change in log odds of participation comparing the specified level of each characteristic to the referent adjusted for age, state, race/ethnicity, education, marital status, and alcohol consumption.
[b] Numbers do not sum to totals because of exclusions for prevalent cancer cases (lung cancer: N = 28; bladder cancer: N = 67; prostate cancer: N = 418) and farmers missing data on predictors of participation (lung cancer: N = 5370; bladder cancer: N = 5359; prostate cancer: N = 5107).
[c] The % shown is the proportion of participation, or non-participation (by death and refusals/exclusions) by the specified level of each enrollment characteristic.

Table 3.7. Joint distribution of ever smoking and 1) incident lung cancer; 2) incident bladder cancer; and, 3) incident prostate cancer among the full cohort (N = 52,394) and the sub-cohort of farmers participating in the 2005-2010 interview (N = 24,171).

	Case Participation N (%[a])	Non-case Participation N (%[a])	Cumulative Incidence[b] /1000 persons (95% CI)	
Lung cancer				
Full cohort				
Never Smoker	59 (100)	26039 (100)	2.8	(2.1, 3.6)
Ever Smoker	496 (100)	22596 (100)	17.7	(16.2, 19.4)
Phase 3 cohort				
Never Smoker	17 (29)	12772 (49)	1.4	(0.9, 2.4)
Ever Smoker	94 (19)	10213 (45)	7.4	(6.0, 9.1)
Bladder cancer				
Full Cohort				
Never Smoker	67 (100)	25093 (100)	3.1	(2.4, 4.0)
Ever Smoker	173 (100)	20432 (100)	7.4	(6.3, 8.6)
Phase 3 Cohort				
Never Smoker	37 (55)	12354 (51)	3.3	(2.4, 4.7)
Ever Smoker	88 (51)	9268 (50)	8.3	(6.6, 10.5)
Prostate cancer				
Full cohort				
Never Smoker	995 (100)	23263 (100)	48.3	(45.5, 51.4)
Ever Smoker	977 (100)	19091 (100)	45.3	(42.7, 48.1)
Phase 3 cohort				
Never Smoker	578 (58)	11344 (48)	56.6	(52.2, 61.4)
Ever Smoker	545 (56)	8567 (44)	57.1	(52.6, 61.9)

CI = confidence interval

[a] The % shown is the proportion of farmers participating in the respective exposure-disease category.

[b] Cumulative incidence is estimated from log binomial models with inverse probability of exposure weights. It is presented per 1,000 persons.

CHAPTER 4.
ANIMAL PRODUCTION AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE AMONG PRIVATE PESTICIDE APPLICATORS

Introduction

High levels of organic dust, gases and chemicals are present in the animal production environment [13, 57, 188, 189]. Inhalation of these agents can result in an inflammatory response in the airways [11]. Chronic obstructive pulmonary disease (COPD), an important cause of morbidity and mortality in the United States, arises from an enhanced chronic inflammatory response in the airways to noxious particles or gases [24]. The term COPD includes chronic bronchitis, emphysema, and other causes of irreversible airway obstruction. Although smoking is the most important risk factor for COPD, research has demonstrated that the fraction of COPD in the United States related to occupational exposures may be between 15-20% and as high as 30% for never smokers [31, 98, 109]. This research has generated a call to identify work-related risk factors for COPD.

Large studies of surveillance data from the United States have indicated an increased risk of COPD for workers employed in the agriculture industry [31, 85, 114], and specifically for persons involved in animal production [85]. Using small, cross-sectional studies researchers have shown associations between levels of organic dust and endotoxin in animal production facilities and increased prevalence of conditions considered under the term COPD, including chronic cough and phlegm, chronic bronchitis, and airway obstruction [13, 189]. A small but growing body of literature also supports the potential for a link between exposure to pesticides and COPD [128-130, 133, 135, 190], including the insecticides commonly used to control pests in the

animal production environment [130, 133]. Finally, studies of other occupational groups have demonstrated associations between occupational exposure to cleaning agents used in the animal production environment (e.g., chloramine-T, quaternary ammonia) and related respiratory conditions such as asthma [191-193]

Despite recognition of a link between specific exposures present in the animal production environment and symptoms indicative of COPD, only one previously published study focuses on the association between work in animal production and COPD explicitly. In the previous study, the prevalence of COPD among never-smoking animal farmers working in confinement buildings in Europe was 17% [14]. In addition, limited research into COPD-related symptoms has been conducted in the United States among large cohorts of farmers or farm workers with detailed information about smoking and other relevant confounding or modifying factors. Finally, few studies have had the ability to consider the contribution of exposure to insecticides as part of the animal production environment.

The aim of the present analysis is to estimate associations between exposure to animals and use of insecticides and COPD among farmers in the AHS. The AHS provides a unique opportunity to examine these associations in a large cohort of farmers from two major animal producing areas in the United States.

Methods

Study Population

Between 1993 and 1997, pesticide applicators applying for or renewing their pesticide-use license in Iowa and North Carolina were invited to enroll in the AHS [41]. A total of 52,394 private pesticide applicators, hereafter "farmers," enrolled in the study by completing an

enrollment questionnaire in which information about demographics and lifestyle, medical history, farm characteristics, and farming activities was requested. Farmers were sent home with a take-home questionnaire requesting additional information about medical history, farm characteristics, and farming activities, which 22,916 (44%) returned. Farmers who did not return the take-home questionnaire were older but did not substantially differ in other ways from those who returned the questionnaire [194]. During a median 12 years, two computer assisted telephone interviews (CATIs) were conducted. 33,457 farmers (64%) responded to the first interview (1999-2003) and 24,171 farmers (46%) responded to the second interview (2005-2010). A total of 21,142 farmers responded to both interviews. Information on work with animals and use of insecticides was collected as part of all three interviews while detailed information on respiratory symptoms and diagnoses was collected only during the 2005-2010 interview.

Investigators have previously compared enrollment characteristics of farmers participating in the 1999-2003 interview to those who did not participate [136]. **Chapter 3** provides an in-depth investigation and discussion of participation in the 2005-2010 interview. Demographic and lifestyle characteristics were predictive of participation at each interview. Examples used to evaluate the extent of bias that may impact studies restricted to interview participants indicate that substantial bias should be of concern when it is hypothesized that the exposure and outcome under study were strongly predictive of participation leading to differential participation of cases or non-cases with respect to exposure. The exposures of interest here, use of insecticides and raising animals, when measured at enrollment, were not strongly predictive of participation in the 2005-2010 interview. Chronic lung disease reported at enrollment was also not associated with participation in the 2005-2010 interview. The outcome

of interest, COPD, although a major cause of morbidity and mortality, is a chronic condition that is typically not associated with rapid death or severe disability upon onset of symptoms or diagnosis [195]. For these reasons, I assume that effect estimates estimated from farmers participating in the 2005-2010 interview would likely be similar to those obtained from the full cohort had COPD information been available for all farmers in the AHS. Consequently, the analyses presented here are restricted to the 24,171 farmers participating in the 2005-2010 interview of the AHS. I excluded an additional 453 farmers because of missing information on COPD diagnoses and symptoms. Finally, I excluded 997 farmers with missing information on important covariates. After all exclusions, the study population consisted of 22,721 farmers.

The AHS was approved by the Institutional Review Boards (IRBs) of the National Institutes of Health and its contractors. The current analysis was also approved by the IRB of the University of North Carolina at Chapel Hill. Farmers indicated informed consent by completing the enrollment questionnaire. Copies of all questionnaires are available on the study Web site (http://www.aghealth.nih.gov/collaboration/questionnaires.html).

Exposure assessment

Raising animals and personal use of insecticides registered for use on or around animals were used as proxies for exposure to the animal production environment. Questions about exposures at each interview differed slightly. See **Figure 4.1** for a detailed description of the information collected at each interview**.**

Raising animals

Lifetime history of raising animals was not available; information about raising animals was only available during specific periods while each farmer was under study. Farmers reported

the presence of beef cattle, dairy cattle, hogs, poultry (including broilers and layers), and sheep/goats present on the property where each farmer lived or worked at the time of interview (enrollment), in the year prior to interview (1999-2003), and since the time of last interview (2005-2010). Binary indicator variables were created to indicate the presence of each type of animal at each interview.

The number of each type of animal on the property was reported at the two follow-up interviews. Although information about confinement and waste management would be necessary to distinguish between industrial vs. pasture-raised operations, I used the number of animals as an approximate indicator of the presence of industrial animal production on a farmer's property. This approximation was made by applying the US Environmental Protection Agency (US EPA) regulatory definitions for confined animal feeding operations (CAFOs) [196] to the reported number of each type of animal. I categorized farmers as working on an operation with no animals or on an operation that met the definition of a small or medium/large animal feeding operation. These assignments were made assuming that all reported animals were of mature weight. Small operations included both operations with a small number of animals raised on pasture without confinement and operations that may be raising animals in confinement. These operations would be regulated as a CAFO if the permitting authority deemed the operation to be a significant contributor of pollutants. Medium and large operations are likely to be raising animals in confinement, and, therefore, these operations were considered as one category. Variables indicating the type of animal operation based on each animal type were combined into a summary variable indicating the type of animal operation based on all animal types produced on the property. Only results for the summary variable are presented here as this variable

accounts for the production of several animal types on one property and preserved adequate sample size.

Insecticide use

Lifetime use of insecticides belonging to major classes of insecticides formerly or currently registered to control pests on animals or in and around animal production facilities was available from each interview. **Table 4.1** provides a list of these insecticides and the animals they are used on or around. I examined ever use, current use, and lifetime days of use of ten organophosphates (chlorpyrifos, coumaphos, diazinon, dichlorvos, fonofos, malathion, parathion, phorate, trichlorfon, terbufos), one carbamate (carbaryl), and one pyrethroid insecticide (permethrin) reported at all three interviews. At enrollment, lifetime days of use was reported only on the take-home questionnaire for four insecticides (diazinon, malathion, parathion, and carbaryl). Ever use, current use, and lifetime days of use of six additional pyrethroids/pyrethrins (pyrethrins, pyrethrum, cyfluthrin, lambda cyhalothrin, esfenvalerate, tefluthrin) were reported as part of the two follow-up interviews but not at enrollment.

Binary indicator variables for each insecticide indicated lifetime ever or never use at each interview. Lifetime days of use for each insecticide were calculated as the product of frequency of application (days/year) and duration of application (years) reported at each interview. I examined the distribution of lifetime days of use of each insecticide. I categorized lifetime days to preserve the shape of the association with COPD and to ensure adequate sample size of cases and non-cases within each exposure level. After exploration of multiple cut points a three-level variable categorized as never users, users with less than or equal to median days of use, and users with greater than median days of use was used.

Outcome assessment

As part of the 2005-2010 interview, farmers reported ever receiving a diagnosis of chronic bronchitis, emphysema, or COPD. Farmers also reported cough and bringing up phlegm and the number of years they experienced these symptoms. For this analysis, I define COPD in two ways: 1) report of at least one relevant diagnosis (chronic bronchitis, emphysema, COPD); and, 2) report of symptoms that meet the clinical definition of chronic bronchitis (productive cough for three months or more during two consecutive years) [87]. Both definitions are considered here as the term COPD encompasses a range of conditions – some resulting in airflow limitation (chronic obstructive bronchiolitis and emphysema), and chronic bronchitis which is not necessarily associated with airflow limitation [197]. Consequently, considering both diagnoses and relevant symptoms allows for the identification of potential exposure effects on the range of conditions included under the term COPD [197].

Because COPD diagnoses and symptoms were not reported at enrollment, it was not possible to confidently exclude prevalent cases. Further, because of the questions used to collect exposure information at each interview it was not possible to establish clear temporality of changes in exposure during study follow-up and onset of symptoms or diagnosis. Consequently, this analysis will examine the prevalence of COPD reported at the 2005-2010 interview.

Statistical Analysis

I examined the distribution of demographic and lifestyle characteristics reported at enrollment for all participants and by COPD status to describe the study population. I then examined the distribution of animal and insecticide use variables reported at each interview to identify temporal variation in production of animals or use of insecticides for the study population. I also examined temporal variation in animal production and insecticide use by

COPD status as differences between cases and non-cases over time could indicate a healthy-worker survivor effect.

Using previous literature and directed acyclic graphs (DAG) [198], I identified age, state, gender, education, and smoking as confounders of associations between animal production, insecticide use and COPD. For this analysis I used stabilized inverse probability of exposure weights (IPEW) to create a "pseudo-population" where the distributions of confounding variables are similar across exposure groups. This is a form of direct standardization that results in no association between the exposure and confounders in the analysis population [169-171]. Linear, logistic, or polytomous/ordinal logistic regression models were used to estimate the predicted probability of exposure (i.e., propensity scores), conditional on the identified confounders for continuous, binary, and multi-level exposures, respectively. For these models, I included age, state, gender, education and smoking categorized as shown in **Table 4.2**. Next, I assigned each individual a weight equal to the inverse of the predicted probability that the person had his/her observed exposure. Finally, to stabilize each individual's weight, I multiplied each one by the marginal probability of their observed exposure level.

Stabilized weights were applied to log-binomial models that included the exposure as the only explanatory variable. From these models, I estimated prevalence ratios (PRs) quantifying the associations between each exposure variable and prevalent COPD reported as part of the 2005-2010 interview. The application of weights induces within-subject correlation by weighting individuals to represent themselves as well as others with similar covariate patterns. To account for this within-subject correlation, I used robust variance estimates to calculate standard errors and 95% confidence intervals (CIs) [170]. These robust estimates are equivalent to generalized estimating equation estimates using an independent working covariance matrix [173].

I used four criteria to evaluate the appropriateness of calculated weights: 1) nearness of the mean to one; 2) the size and number of extreme weights (<0.05 or >20); 3) positivity; and, 4) an informal validity-precision tradeoff [169]. To informally assess the validity-precision tradeoff, I truncated the stabilized weights by resetting weights less (or greater) than a designated percentile to the value of that percentile. Treating the PR derived from the untruncated weights as most "valid," I examined how the weights, the corresponding PRs, and their 95% CIs changed with increasing truncation. Because the untruncated weights demonstrated means close to one with few extreme values, I present results generated using the untruncated weights only. The distribution of the weights used in these analyses are presented in **Supplementary Table S4.1**.

Based on previous literature, I evaluated smoking [27, 31] and early life exposure to farm animals [199, 200] as potential effect measure modifiers. I also evaluated state as an effect measure modifier because animal production practices [43, 151] and smoking rates vary by state [201]. I examined interactions between type of animal raised and ever/never use of the insecticides examined. To assess the presence of modification, I estimated two sets of IPEW [202]. First, I estimated stabilized weights for the modifying factors. Second, including a term for the modifying factor in the exposure prediction model, I estimated stabilized weights for the main exposure. I then multiplied the two sets of weights and applied the product of the two exposure weights to log-binomial models including a term for the main exposure, the modifier, and an interaction term between the two. Modification on the multiplicative scale was considered to be present if stratum-specific PRs differed (90% CIs did not contain the other point estimate) or if the p-value for the Wald chi-square statistic for the interaction term was less than 0.1. Departures from additive effects were also considered by calculating the risk for those who

are jointly unexposed, exposed only to one of the two exposures, and the jointly exposed. These risks were then used to calculate the absolute excess risk due to interaction [202].

I considered exposures to be associated with COPD if the confidence interval did not include 1.00 or if 0.87>PR>1.15 with a confidence limit ratio <2. These criteria were used to capture statistically significant associations and associations of the same order of magnitude often observed in studies of environmental and occupational exposures that do not reach statistical significance because of limited sample size.

Sensitivity analyses

I conducted several sensitivity analyses to consider the robustness of results to alterations in the study population and to control for confounding and selection effects. First, I reanalyzed the data excluding farmers <40 years old at enrollment because these individuals may require longer follow-up to observe COPD. I also reanalyzed the data excluding farmers reporting a doctor diagnosis of asthma, as asthma symptoms may be easily confused with symptoms of chronic bronchitis [203, 204] and have also been found to be related to use of pesticides, exposure to cleaning agents [191-193], and work with animals [15, 32, 39, 131, 132, 205, 206]. Results of these sensitivity analyses did not alter conclusions and are not presented here.

I also re-analyzed data excluding farmers who were suspected to have COPD at enrollment based on reported age at diagnosis or onset of symptoms at the 2005-2010 interview compared with their date of enrollment. This resulted in the exclusion of 539 cases (46%) who reported a diagnosis of COPD and 371 cases (31%) who reported chronic bronchitis symptoms. Although this was a substantial number of cases, besides reducing precision, conclusions did not differ substantially and, therefore, results are not presented here. After establishing that results were fairly robust to alterations in the study population and definitions of disease status, I

considered alternative specification of variables in the models used to generate weights. Adding additional variables to the weight-estimation models and alternative coding of variables did not substantially alter weights or results.

Finally, I conducted the main analysis using inverse probability of selection weights (IPSW) to account for the 28,223 farmers who enrolled in the AHS but did not participate in the 2005-2010 interview. Application of IPSW conditional on enrollment characteristics identified in **Chapter 3** did not alter conclusions and, therefore, results are not presented here.

All statistical analyses were conducted in SAS v9.3 (Cary, NC).

Results

Of the 22,721 farmers included here, 1,176 (5%) reported a COPD diagnosis while 1,216 (5%) reported symptoms meeting the clinical definition of chronic bronchitis (**Figure 4.2**). Little overlap was observed between these two groups. The 254 (1%) farmers reporting both a COPD diagnosis and symptoms meeting the clinical definition of chronic bronchitis are included in analyses of both outcomes.

The prevalence of COPD diagnoses and chronic bronchitis symptoms increased with increasing age and was greater among former and current smokers compared with never smokers and heavy drinkers compared with never drinkers (**Table 4.2**). Prevalence of COPD diagnoses and symptoms decreased with increasing education. Prevalence of COPD diagnoses was greater among farmers who enrolled in North Carolina compared to those from Iowa and among females compared to males. However, chronic bronchitis symptoms were more prevalent among farmers from Iowa than from North Carolina and among males than females.

Changes in exposures over time

Declines in the proportion of farmers raising each type of animal and actively using insecticides were observed during the study period. However, these declines did not differ by COPD status, or by other demographics. Changes also closely aligned with temporal trends in animal production and insecticide use documented in the general US population [2, 49, 207]. Estimates of associations with COPD diagnoses and chronic bronchitis symptoms were similar for exposure variables defined at each interview. Consequently, I present associations between exposures reported at the 2005-2010 interview and COPD diagnoses and chronic bronchitis symptoms wherever possible. Exposure variables from 2005-2010 interview were chosen because this allowed for consideration of lifetime use of insecticides, detailed information about raising animals, and consistency between exposure information presented.

Animal exposures

I observed no evidence of an association between raising animals and COPD diagnosis (**Table 4.3**). Raising beef cattle, hogs, or poultry was associated with an elevated prevalence of chronic bronchitis symptoms. Farmers working on small operations had an 18% greater prevalence of chronic bronchitis symptoms compared to those raising no animals (95% CI: 1.04, 1.34). Farmers working on medium or large operations, likely to be raising animals in confinement, had 51% higher prevalence of chronic bronchitis symptoms compared to those raising no animals (95% CI: 1.21, 1.89).

Insecticide Use

Applying insecticides to farm animals or animal shelters in the year prior to enrollment was not associated with a COPD diagnosis; however, this activity was associated with a 22% increase in prevalence of chronic bronchitis symptoms (95% CI: 1.08, 1.38) (**Table 4.4**). Ever

use of the organophosphates diazinon or trichlorfon, both registered for use on or around animals, and ever use of permethrin for crops was associated with increased prevalence of COPD diagnosis. Ever use of the following insecticides registered for use on or around animals was associated with increased prevalence of chronic bronchitis symptoms: coumaphos, diazinon, dichlorvos, malathion, carbaryl, and permethrin. Ever use of parathion, an organophosphate not registered for use on or around animals, was also associated with increased prevalence of chronic bronchitis symptoms.

When lifetime days of use were considered (**Table 4.5**), both categories of use of diazinon were associated with increased prevalence of COPD diagnosis compared with never users as were lifetime days of malathion use. Lifetime days of carbaryl was also associated with elevated prevalence of COPD diagnosis, but these associations were not statistically significant. Farmers reporting the highest category of lifetime days of use of coumaphos and malathion had increased prevalence of chronic bronchitis symptoms compared with never users. Both use categories of permethrin on animals were associated with greater prevalence of chronic bronchitis symptoms compared to never users. Users of parathion also had increased prevalence of chronic bronchitis symptoms, with the largest PR observed for farmers reporting less than or equal to the median number of days of use compared to never users.

Discussion

Occupational exposure to animal production has been previously linked with short-term decline in respiratory function [3, 5, 14-20], symptoms of respiratory irritation [4, 5, 8, 16, 19, 21-23], and increased risk of chronic bronchitis [3, 5, 15, 19, 39, 118, 120-122, 127, 208]. However, few researchers have investigated the role of occupational exposure to animal production in the etiology of COPD including diagnosed disease and symptoms or had the ability

to consider insecticide use as a component of work in animal production. In this analysis of a large cohort of US farmers, using type and number of animals produced and personal use of insecticides registered for use on or around animals, I present further evidence to support a link between animal production and chronic bronchitis symptoms. Further, I observed some evidence that personal use of specific insecticides may be associated with increased prevalence of diagnosed COPD. These findings support concerns about the respiratory health effects of exposure to animal production and provide further evidence that personal insecticide use may either play a role in the etiology or exacerbation of COPD or serves as a marker of other exposures related to these outcomes among farming populations.

Raising beef cattle, hogs, or poultry and raising animals on small, medium or large operations was associated with chronic bronchitis symptoms, but not with diagnosed COPD. Researchers have previously reported greater prevalence of chronic bronchitis [3, 5, 19, 20, 34, 118, 120-124, 127, 208] and cough and phlegm [5, 19, 20, 23, 73, 115-117, 120-123, 125, 126] among farmers and farm workers involved in production of cattle (mostly dairy), hogs, and poultry, mainly in industrial settings. Few researchers have considered the human respiratory health effects of occupational exposure to beef cattle production specifically, but similar levels of organic dust and endotoxin to those found in hog confinement facilities have been observed in cattle feedlots [209, 210].

Although these associations were observed here, simply raising animals is a crude proxy for exposure to animal production. Application of US EPA regulatory definitions [211] to identify operations as small, medium, or large animal feeding operations improved specificity of exposure to industrial animal production. Based on these definitions, medium and large operations are likely to be industrial simply due to the large number of animals produced.

However, it remains that owning or working on a medium or large operation does not indicate personal exposure to production. Further, I did not have information about age or size of animals, animal confinement practices, or waste management systems, all of which are required to conclusively determine type of operation. Use of these crude proxies for exposure to animal production likely resulted in some misclassification of exposure, which could have led to an exaggeration or attenuation of effects.

Associations were not observed between raising animals and COPD diagnoses independently of symptoms. There may be several explanations for these discrepant results. It is possible that these results indicate that the biological response to work in animal production may manifest as chronic bronchitis symptoms that do not drive farmers to seek or receive a COPD-related diagnosis. This hypothesis aligns with what has been reported with respect to occupational exposure to other dusty trades [111, 212]. It is also possible that limitations of the information available on animal production may partially explain the discrepancy. In addition to the limitations mentioned above, no information was available on personal exposure to animal production, including lifetime duration or intensity of work with animals. It is possible that this unmeasured information resulted in exposure misclassification that could operate differently in analyses of COPD diagnoses and chronic bronchitis symptoms. For example, if farmers with a COPD diagnosis removed themselves from work in animal production but those with symptoms remained, a healthy-worker survivor effect may be operating when considering COPD diagnoses as the outcome but not as strongly when considering chronic bronchitis symptoms. Researchers have previously documented that a healthy-worker survivor effect may influence results of studies of agricultural exposures and respiratory health outcomes [213-217]. Lacking lifetime information about work with animals, I could not directly examine the potential for the healthy-

worker survivor effect to influence effect estimates. Finally, it is also possible that chronic bronchitis symptoms reported here reflect chronic bronchitis and asthma, a cause of reversible airway obstruction. Occupational exposures have been accepted as important in the etiology of asthma [111]. COPD can be difficult to distinguish without a detailed clinical assessment and because some overlap exists [203]. Further, evidence suggests that asthma may be an important risk factor for COPD [203, 204, 218-220]. In the present study, a doctor diagnosis of asthma was more common among those with a COPD diagnosis (29%) or chronic bronchitis symptoms (16%) compared with farmers who did not report a COPD diagnosis or symptoms (6%) demonstrating some overlap between COPD and asthma in this population.

The observed associations between personal use of insecticides and COPD support mounting evidence that occupational use of insecticides may also contribute to disease burden or may be a marker for other relevant exposures. General use of pesticides has been linked with chronic bronchitis in a case-control study in Lebanon [221] as well as reduced pulmonary function and higher prevalence of mild and moderate or severe airway obstruction among two population-based cohorts in The Netherlands [128]. Among rural residents of Beijing, China, use of insecticides was associated with twice the odds of cough and phlegm [222]. Similar to what I report here, farmers in the Iowa Farm Family Health and Hazard Surveillance Project who applied insecticides to livestock had twice the odds of phlegm than farmers who did not [135]. However, these studies lacked information on type, frequency, and duration of pesticides used [129]. In the present analysis, the insecticides associated with chronic bronchitis symptoms included the organophosphates coumaphos, diazinon, dichlorvos, malathion, and parathion; the carbamate carbaryl; and, the pyrethoid permethrin (for animals). Use of diazinon, malathion, carbaryl, and permethrin (for crops) was also associated with increased prevalence of having a

COPD diagnosis. In a previous investigation in the AHS among farmers responding to the take-home questionnaire after enrollment associations between self-reported doctor diagnosis of chronic bronchitis and personal use of coumaphos, diazinon, dichlorvos, malathion, parathion, carbaryl and permethrin along with several other pesticides were also observed [133].

Results from a small number of human and animal studies have indicated mechanisms by which exposure to insecticides may affect pulmonary function [82, 83]. However, it is also possible that insecticide use may serve as a proxy for exposure to other agents such as dusts, gases, and other chemicals (e.g., disinfectants) in the farm environment. All of the insecticides observed to be associated with COPD or related symptoms in the present study, except parathion, were or are used on or around animals. However, many of these insecticides are also used on crops or for other purposes [223] and, therefore, the effects seen here cannot be ascribed solely to use in animal production. With the exception of permethrin, pyrethroids/pyrethrins were not consistently associated with an increased prevalence of COPD or related symptoms. Use of pyrethroids/pyrethrins has been increasing over the past decade as use of organophosphates, which are more acutely toxic, has declined [60]. The carbamate carbaryl was also widely used in poultry production until 2009 when this use was terminated [224]. Because use of pyrethroids/pyrethrins in animal production is relatively new, farmers have not been exposed to these pesticides for the same duration as organophosphates. Because pyrethroid/pyrethrin use is increasing, associations between personal use and respiratory disease may change and, therefore, should continue to be monitored.

Additional research is needed to better understand whether exposure to insecticides themselves or other agents in the environment where insecticides are used is most relevant for COPD, including the symptoms of chronic bronchitis. Future research focused on this question

should consider the relevance of using different pesticide formulations (e.g., sprays, dips, tags, and dusts), application methods, and use of personal protective equipment when working with insecticides to the risk of COPD. And, future research should consider and collect detailed information on the environment where application is occurring. These characteristics could influence personal exposure to insecticides, dust, gases, and other chemicals. Finally, the present study was limited to insecticides belonging to chemical classes registered for use in animal production. However, other classes of pesticides are associated with adverse respiratory health effects and, therefore, their association with COPD should also be considered [131, 132, 205, 206, 225].

Five percent of the present study population reported a qualifying doctor diagnosis of COPD (Iowa: 4%; NC: 8%) which is similar to the age-adjusted prevalence in the general population (6%) (Iowa: 5%; North Carolina: 7%) [99] despite a lower prevalence of smoking and a greater potential for a healthy-worker effect in the AHS. The 5% prevalence of chronic bronchitis symptoms observed in the AHS is lower than estimates of chronic bronchitis symptoms from other US studies of animal confinement workers (7-25%) [3, 15, 20, 116, 122, 127, 226]. Prevalence of both COPD diagnosis and chronic bronchitis symptoms are lower than the estimates of COPD based on spirometry among individuals involved in animal production (17%) [14] and the general public (10-20%) [97]. This is not surprising, as reliance on self-report is known to result in an underestimate of COPD compared with spirometry [27, 29, 95, 98]. Spirometry or clinical confirmation of case status could have improved ascertainment of COPD cases in the present study. Although the lack of clinical measures is a limitation, self-reported diagnosis may be more representative of clinically relevant disease that has driven someone to seek care while spirometric results also represent those with subclinical obstruction. Reliance on

self-report may have resulted in misclassification of COPD status. There is no evidence to indicate that misclassification would be differential with respect to the exposure and, therefore, most likely would result in bias toward the null [95].

In addition to limitations previously mentioned, several others should be considered when interpreting the results presented here. This analysis was restricted to farmers who participated in the 2005-2010 AHS interview. Restriction was necessary because COPD-related diagnoses and symptoms were not collected from all participants at previous interviews. Although it is possible that restriction could have induced bias, the magnitude of such bias should be negligible based on the results presented in **Chapter 3**. As presented in the previous chapter, substantial bias would be expected when both the exposure and outcome were predictive of participation. Raising animals and use of insecticides reported at enrollment were not strongly associated with participation in the 2005-2010 interview. Report of asthma or "other chronic lung disease" on the enrollment questionnaire was also not associated with participation in the interview. In addition, COPD is typically a slowly developing, chronic condition that does not result in rapid mortality or extreme disability immediately after onset of symptoms or diagnosis [195], thus making it less likely to interfere with participation in study activities than more acute or severe disease processes. Based on this information, it is unlikely that substantial bias of effect estimates would occur because of restriction to follow-up interview participants. Assuming negligible bias, IPSW would not be necessary to correct for selection effects. In sensitivity analyses, I observed that application of IPSW conditional on enrollment exposures and covariates strongly associated with participation in the 2005-2010 interview, resulted in no substantial change in results or conclusions.

In this analysis, I was unable to establish the temporal ordering of exposure and disease. COPD symptoms and diagnoses were only reported by most of the study population during the 2005-2010 interview. Although farmers reported age at diagnosis and number of years of symptoms, these reports were made a median 12 years after enrollment and for some many years after the receipt of diagnosis or onset of symptoms. In addition, exposure information was collected every five years with questions referring to different reference periods (e.g., year prior to interview, since last interview). Consequently, even using timing of diagnosis or symptoms provided by farmers, I was unable to construct temporal ordering of exposure and disease. For these reasons, I was unable to confidently conduct a time-to-event analysis. However, when I excluded cases suspected to be prevalent at enrollment based on timing of diagnoses and symptoms (COPD diagnosis: N = 539; chronic bronchitis symptoms N = 371), conclusions remained the same although precision of estimates was greatly reduced.

Another important characteristic of the AHS is that participants are recruited on the basis of being private pesticide applicators. Because of this design, few participants are truly unexposed to all pesticides. Consequently, farmers who use one pesticide must be compared to others who use different pesticide(s). If multiple pesticides are associated with disease risk, having no clear unexposed group would limit the ability to observe associations [227]. In addition, the AHS includes mainly farm owner/operators. Consequently, the AHS population may not represent farm workers who may receive greater exposure to the animal production environment than farm owner/operators. Therefore, the findings reported here are not directly generalizable to the farm worker population.

The large sample size and prospective nature of the AHS were important strengths of the present analysis. The sample size and extensive information about demographics and lifestyle

factors allowed for control of confounders and exploration of modification and interactions between exposures. Although I did not observe evidence of interactions between exposures or modification of the animal production-COPD associations examined, the ability to consider modification by smoking revealed that the observed associations were present among never, former, and current smokers alike. Because the AHS continues to follow farmers who change farming activities or even cease farm work, concerns common to cross-sectional studies regarding the exclusion of farmers who have left work are reduced. In addition, although there are many limitations of the exposure information, the AHS provides one of the most detailed assessments of personal insecticide use currently available.

The results of this investigation continue to add evidence that work in animal production and personal use of insecticides is correlated with COPD-related symptoms or diagnoses. The results support the call for further research into the role of occupational exposures, and specifically animal production-related exposures, in the etiology of COPD. It also demonstrates the need for prospective studies of farmers and farm workers in the United States to be conducted with improved information on animal production exposures. Only by addressing these limitations will the scientific and farming communities be able to identify animal production and insecticide use-related risk factors for COPD and methods for protecting at risk populations.

Figures and Tables

Figure 4.1. Illustration of the collection of exposure data and the timing of exposure information recorded at each interview. Lifetime ever use of all organophosphate insecticides, carbaryl, and permethrin was assessed on the enrollment questionnaire. Years and days of use of the following insecticides were assessed on the enrollment questionnaire: chlorpyrifos, coumaphos, dichlorvos, phorate, fonofos, terbufos, trichlorfon, and permethrin; and, on the take-home questionnaire: diazinon, malathion, parathion, and carbaryl. Ever use and years and days of use for all insecticides were reported as part of the 1999-2003 and 2005-2010 interviews.

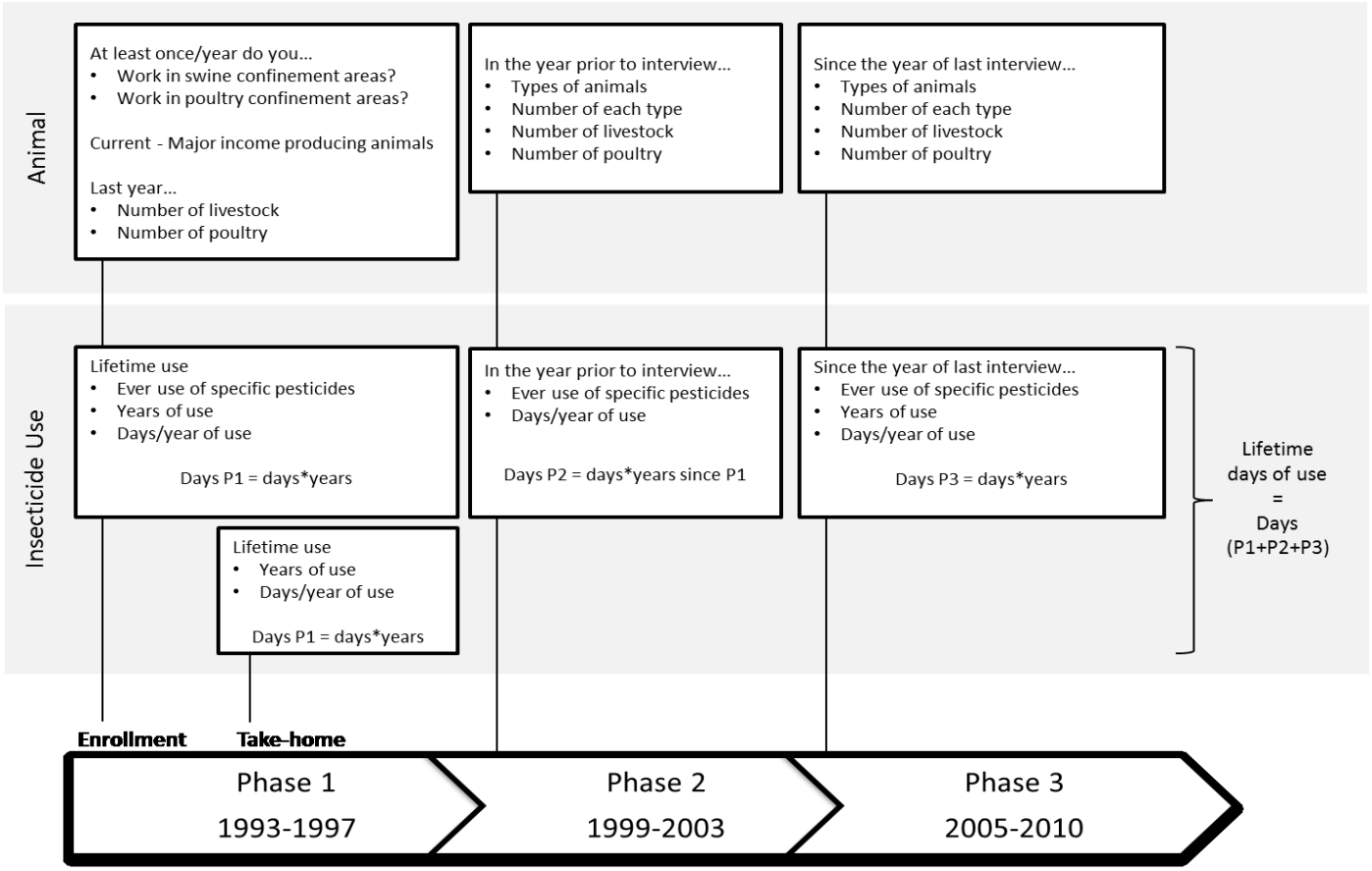
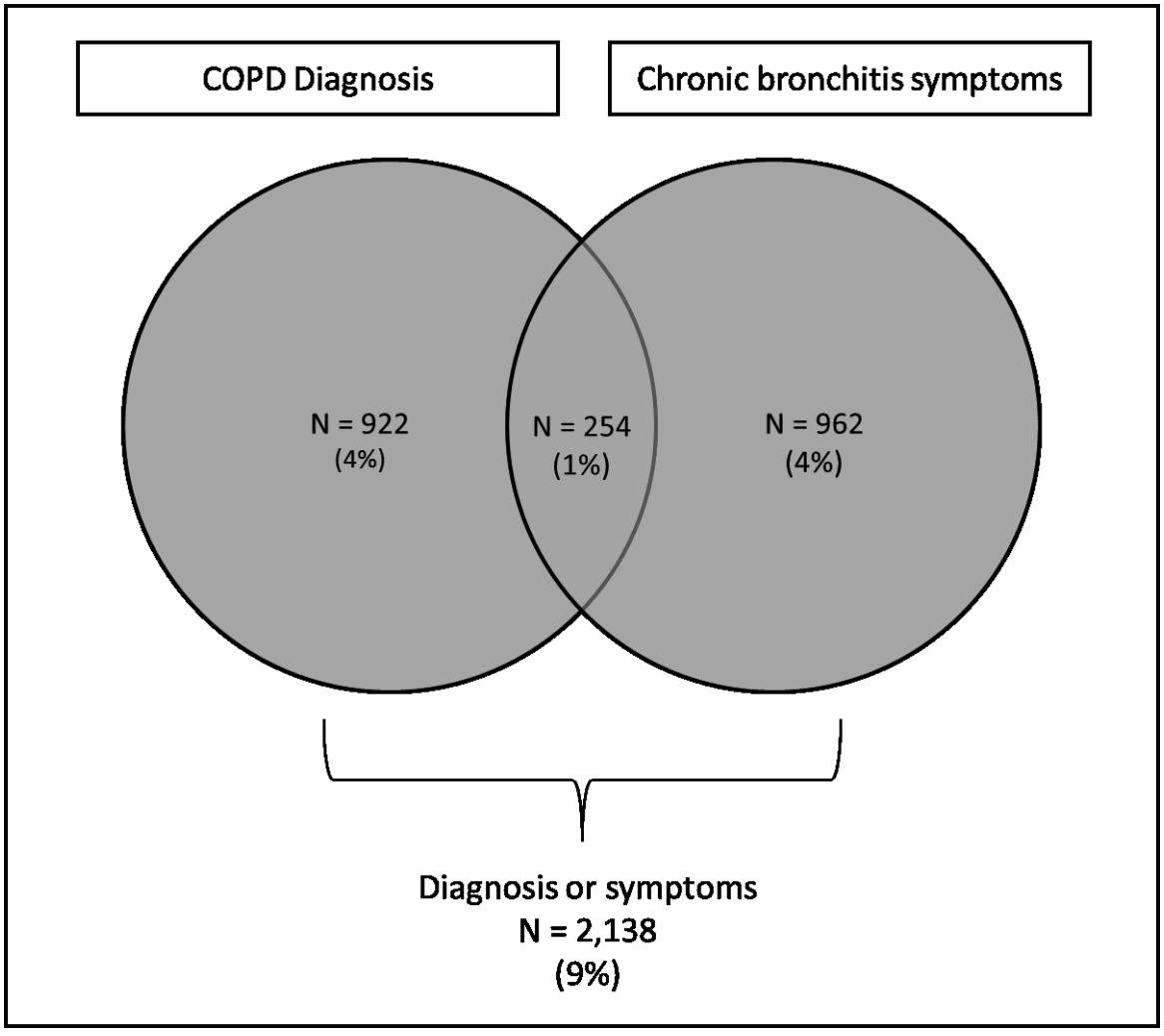


Figure 4.2. Distribution of diagnosis of COPD (including chronic bronchitis, emphysema, and COPD) and report of symptoms meeting the clinical definition of chronic bronchitis (cough and phlegm for at least three month over two consecutive years) among 22,721 farmers participating in the 2005-2010 interview, Agricultural Health Study.



Tables

Table 4.1. Insecticides of chemical classes registered for use on or around animals.

	Used in animal production	Type of animal
Organophosphates		
Chlorpyrifos	X	Swine, Poultry, Sheep/Goats
Coumaphos	X	Swine, Cattle
Diazinon	X	Swine, Cattle
Dichlorvos	X	Swine, Cattle, Poultry
Malathion	X	Swine, Poultry, Cattle, Sheep
Parathion		
Phorate		
Fonofos		
Terbufos		
Trichlorfon	X	Swine, Cattle
Carbamates		
Carbaryl	X[a]	Poultry
Pyrethroids/Pyrethrins		
Permethrin (crops)		
Permethrin (animals)	X	Swine, Cattle, Poultry, Sheep/Goats
Pyrethrins	X	Swine, Cattle, Poultry
Pyrethrum		
Cyfluthrin	X	Swine, Cattle, Poultry
Lambda Cyhalothrin	X	Swine, Cattle, Poultry
Esfenvalerate	X	Swine, Poultry
Tefluthrin		

[a] Carbaryl was used in poultry production until 2009.

Table 4.2. Associations between selected characteristics and COPD diagnosis and chronic bronchitis symptoms among 22,721 farmers participating in the 2005-2010 interview, Agricultural Health Study.

		COPD diagnosis				Chronic bronchitis symptoms			
	Total	Cases	Prev	PR[a]	95% CI	Cases	Prev	PR[a]	95% CI
Enrollment characteristics	**N = 22721**	**N = 1176**	**%**			**N = 1216**	**%**		
Age[b]									
<50 years	4862	82	2	Ref		208	4	Ref	
50-59 years	6874	226	3	1.93	1.52,2.47	344	5	1.16	0.99, 1.37
60-69 years	5718	358	6	3.66	2.91,4.60	296	5	1.18	1.00, 1.40
70-79 years	4213	394	9	5.45	4.34,6.84	285	7	1.58	1.33, 1.87
80 + years	1054	116	11	6.66	5.12,8.67	83	8	1.82	1.44, 2.32
State									
Iowa	15224	577	4	Ref		851	6	Ref	
North Carolina	7497	599	8	1.81	1.62,2.03	365	5	0.82	0.73, 0.93
Gender									
Female	622	40	6	1.20	0.89,1.63	23	4	0.67	0.45, 1.01
Male	22099	1136	5	Ref		1193	5	Ref	
Race/Ethnicity									
White, non-Hispanic	21712	1058	5	Ref		1137	5	Ref	
Other	533	37	7	1.24	0.91,1.70	22	4	0.76	0.50, 1.15
Missing	476								
Education									
< High school degree	1737	187	11	Ref		126	7	Ref	
High school graduate/GED	10480	577	6	0.80	0.68,0.94	587	6	0.81	0.67, 0.98
Some college	5853	256	4	0.76	0.63,0.92	314	5	0.80	0.65, 1.00
≥ College graduate	4651	156	3	0.55	0.44,0.68	189	4	0.61	0.49, 0.77
Marital Status									
Married/Living as married	19892	1066	5	Ref		1079	5	Ref	

		COPD diagnosis				Chronic bronchitis symptoms			
	Total	Cases	Prev	PR[a]	95% CI	Cases	Prev	PR[a]	95% CI
Enrollment characteristics	**N = 22721**	**N = 1176**	**%**			**N = 1216**	**%**		
Other	2802	106	4	0.94	0.78, 1.15	131	5	0.94	0.79, 1.13
Missing	27								
Smoking status									
Never	12605	329	3	Ref		489	4	Ref	
Former	7248	509	7	1.90	1.66, 2.18	401	6	1.37	1.20, 1.56
Current	2868	338	12	4.11	3.54, 4.78	326	11	3.33	2.90, 3.81
Alcohol consumption[c]									
None	7532	460	6	Ref		341	5	Ref	
Light drinker	13970	631	5	1.01	0.89, 1.15	789	6	1.18	1.03, 1.35
Heavy drinker	357	19	5	1.23	0.79, 1.91	34	10	1.69	1.20, 2.39
Missing	862								,
Size of farm (acres)									
Didn't work on farm/None	727	56	8	1.03	0.77, 1.38	47	6	1.21	0.88, 1.65
<5	820	64	8	1.11	0.84, 1.46	50	6	1.34	0.98, 1.82
5-49	2076	175	8	1.24	1.01, 1.52	106	5	1.07	0.85, 1.35
50-199	3886	227	6	1.12	0.94, 1.34	199	5	0.97	0.82, 1.15
200-499	6113	259	4	Ref		342	6	Ref	
500-999	4719	161	3	0.89	0.73, 1.07	245	5	0.95	0.81, 1.11
>1,000	2795	102	4	1.07	0.86, 1.33	146	5	0.98	0.81, 1.18
Missing	1585								

Prev = prevalence
PR = prevalence ratio
CI = confidence interval
[a] Estimates for state, gender, and race/ethnicity are adjusted for age. Estimates for education, marital status, and smoking are adjusted for age and state. Estimates for alcohol consumption and size of farm are adjusted for age, state, and smoking.
[b] Age reflects age at the 2005-2010 interview.
[c] Heavy drinkers reported consuming five or more drinks on the same occasion on each of five or more days in the past 30 days, light drinkers reported consuming at least one drink on at least one day during the past 12 months but did not qualify as a heavy drinker [187].

Table 4.3. Associations between raising animals and COPD diagnosis and chronic bronchitis symptoms among 22,721 farmers participating in the 2005-2010 interview, Agricultural Health Study.

		COPD diagnosis				Chronic bronchitis symptoms			
	Total	Cases	Prev	PR[a]	95% CI	Cases	Prev	PR[a]	95% CI
Exposure	**N = 22721**	**N = 1176**	**%**			**N = 1216**	**%**		
Type of Animal Raised									
Beef cattle	7689	321	4	0.96	0.85, 1.09	451	6	1.23	1.09, 1.38
Dairy cattle	888	30	3	1.08	0.69, 1.67	41	5	1.04	0.70, 1.54
Hogs	3514	86	2	0.85	0.61, 1.19	208	6	1.28	1.03, 1.59
Poultry/Eggs	1090	47	4	0.97	0.71, 1.33	63	6	1.22	0.93, 1.60
Sheep/Goats	777	34	4	1.09	0.76, 1.55	38	5	0.92	0.65, 1.30
Size of Animal Production[b]									
No animals	11963	761	6	Ref		613	5	Ref	
Small operation	7374	328	4	0.95	0.84, 1.09	411	6	1.18	1.04, 1.34
Medium/Large operation	3384	87	3	0.91	0.66, 1.25	192	6	1.51	1.21, 1.89

Prev = prevalence
PR = prevalence ratio
CI = confidence interval
[a] PRs were estimated using IPEW to address confounding. Weights were estimated using age at the 2005-2010 interview, state, gender, race, and education categorized as shown in Table 4.1.
[b] Size of animal production was determined using the number of animals produced on a farmer's property and categorized using the regulatory definitions of CAFOs [196]. Large and medium operations are likely to be raising animals in confinement.

Table 4.4. Associations between ever use of selected insecticides and COPD diagnosis and chronic bronchitis symptoms among 22,721 farmers participating in the 2005-2010 interview, Agricultural Health Study.

		COPD diagnosis				Chronic bronchitis symptoms			
	Total	Cases	Prev	PR[a]	95% CI	Cases	Prev	PR[a]	95% CI
Exposure	**N = 22721**	**N = 1176**	**%**			**N = 1216**	**%**		
Insecticide application to farm animals[b]	7254	300	4	1.08	0.94, 1.24	427	6	1.22	1.08, 1.38
Organophosphates									
Chlorpyrifos	10569	489	5	0.99	0.88, 1.11	589	6	1.11	0.99, 1.24
Coumaphos	2093	118	6	1.14	0.94, 1.38	140	7	1.26	1.06, 1.50
Diazinon	8108	506	6	1.20	1.06, 1.35	482	6	1.26	1.12, 1.42
Dichlorvos	2687	120	4	1.00	0.79, 1.28	178	7	1.34	1.08, 1.66
Malathion	16948	880	5	1.13	0.98, 1.29	956	6	1.30	1.13, 1.50
Parathion[c]	3727	262	7	1.11	0.95, 1.29	235	6	1.28	1.10, 1.49
Phorate[c]	8008	362	5	0.92	0.79, 1.07	487	6	1.06	0.94, 1.20
Fonofos[c]	4942	210	4	0.96	0.79, 1.18	311	6	1.08	0.91, 1.28
Terbufos[c]	8881	391	4	1.09	0.95, 1.25	499	6	1.04	0.92, 1.17
Trichlorfon	166	14	8	1.73	1.00, 2.99	6	4	0.67	0.27, 1.68
Carbamates									
Carbaryl	13700	814	6	1.08	0.94, 1.24	782	6	1.26	1.11, 1.43
Pyrethroids/Pyrethrins									
Permethrin (crops)[c]	3453	173	5	1.24	1.05, 1.46	169	5	1.02	0.86, 1.20
Permethrin (animals)	3970	143	4	1.01	0.81, 1.27	249	6	1.37	1.15, 1.64
Pyrethrins	353	16	5	1.18	0.69, 2.03	20	6	1.35	0.83, 2.22
Pyrethrum [c,d]	10	0	0			0	0		
Cyfluthrin	1789	44	2	0.77	0.49, 1.19	95	5	1.02	0.80, 1.29
Lambda Cyhalothrin	852	20	2	0.81	0.48, 1.37	34	4	0.83	0.52, 1.32
Esfenvalerate	381	15	4	0.97	0.50, 1.88	14	4	0.79	0.43, 1.48

		COPD diagnosis				Chronic bronchitis symptoms			
	Total	Cases	Prev	PR[a]	95% CI	Cases	Prev	PR[a]	95% CI
Exposure	**N = 22721**	**N = 1176**	**%**			**N = 1216**	**%**		
Tefluthrin[c]	770	24	3	0.84	0.46, 1.53	48	6	0.98	0.62, 1.57

Prev = prevalence
PR = prevalence ratio
CI = confidence interval

[a] PRs were estimated using IPEW to address confounding. Weights were estimated using age at the 2005-2010 interview, state, gender, race, and education categorized as shown in Table 4.1.

[b] Reported at enrollment.

[c] Not used on or around animals.

[d] PR (95% CI) not shown because no cases reported use of pyrethrum.

Table 4.5. Associations between categories of lifetime days of use of selected insecticides and COPD diagnosis and chronic bronchitis symptoms among 22,721 farmers participating in the 2005-2010 interview, Agricultural Health Study.

		COPD Diagnosis			Chronic bronchitis symptoms		
	Total	Cases	PR[a]	95% CI	Cases	PR[a]	95% CI
Lifetime days of use	**N = 23147**	**N = 1176**			**N = 1216**		
Organophosphates							
Coumaphos							
0	20472	1059	Ref		1070	Ref	
2-20	1138	64	1.10	0.85, 1.42	72	1.13	0.89, 1.44
21-3,550	882	46	1.09	0.80, 1.47	64	1.46	1.13, 1.88
Diazinon[b]							
0	9680	465	Ref		546	Ref	
1-19	1405	93	1.27	1.02, 1.60	85	1.10	0.87, 1.39
20-3,181	1482	110	1.35	1.07, 1.72	90	1.15	0.89, 1.48
Dichlorvos							
0	19903	1052	Ref		1038	Ref	
1-50	1298	55	0.80	0.52, 1.24	73	1.21	0.81, 1.83
50.75-8,530	1325	62	1.40	0.93, 2.12	98	1.32	0.90, 1.94
Malathion[b]							
0	4175	207	Ref		212	Ref	
1-20	4217	220	1.24	1.02, 1.50	239	1.14	0.95, 1.37
20.5-5,000	4176	240	1.25	1.04, 1.51	267	1.31	1.10, 1.57
Parathion[b,c]							
0	11524	580	Ref		645	Ref	
1-20.5	517	43	1.22	0.85, 1.75	43	1.55	1.09, 2.20
21-3,100	516	42	1.17	0.77, 1.78	33	1.23	0.80, 1.89
Carbamates							
Carbaryl[c]							
0	6957	290	Ref		759	Ref	
1-24	2716	155	1.15	0.94, 1.41	201	1.17	0.97, 1.40
24.5-3,100	3058	221	1.20	0.96, 1.48	185	1.13	0.91, 1.41
Pyrethroids							
Permethrin (crops)[c]							
0	19202	1003	Ref		1052	Ref	
1-18	1680	60	0.95	0.72, 1.26	73	0.80	0.62, 1.03
18.5-3,100	1643	104	1.53	1.24, 1.90	84	1.07	0.85, 1.36
Permethrin (animals)							
0	18623	1029	Ref		962	Ref	
1-24	1879	69	1.03	0.74, 1.44	115	1.40	1.06, 1.84

		COPD Diagnosis			Chronic bronchitis symptoms		
	Total	Cases	PR[a]	95% CI	Cases	PR[a]	95% CI
Lifetime days of use	**N = 23147**	**N = 1176**			**N = 1216**		
24.5-7,000	2040	71	1.05	0.76, 1.43	133	1.41	1.13, 1.77

PR = prevalence ratio
CI = confidence interval
[a] PRs were estimated using IPEW to address confounding. Weights were estimated using age at the 2005-2010 interview, state, gender, race, and education categorized as shown in Table 4.1.
[b] Limited to the 12,804 farmers who responded to the take-home questionnaire.
[c] Not used on or around animals.

Supplementary Table S4.1. Distribution of stabilized IPEW used to estimate associations between specific animal production activities and COPD diagnoses and chronic bronchitis symptoms.

						Percentiles					
Variable	**N**	**Mean**	**SE**	**Sum**	**Min**	**5th**	**25th**	**Median**	**75th**	**95th**	**Max**
Raising animals											
Beef cattle	20245	1.0001	0.1894	20247	0.6121	0.7561	0.8720	0.9751	1.0860	1.3134	2.8473
Dairy cattle	20245	1.0006	0.1534	20256	0.1879	0.9697	0.9805	0.9934	1.0115	1.0556	6.1099
Hogs	20245	1.0037	0.4896	20321	0.3117	0.5678	0.8810	0.9584	1.0679	1.2690	12.8483
Poultry	20245	0.9995	0.0944	20234	0.2880	0.9713	0.9826	0.9949	1.0106	1.0529	3.5647
Sheep/Goats	20245	0.9998	0.0763	20241	0.3485	0.9781	0.9892	0.9985	1.0092	1.0269	3.3748
Number of livestock	20245	1.0032	0.7118	20310	0.2809	0.5469	0.7294	0.8883	1.1129	1.6318	23.1662
Number of poultry	20245	0.9999	0.2301	20244	0.0985	0.9710	0.9827	0.9943	1.0097	1.0521	9.1044
Ever use of Insecticides											
Chlorpyrifos	20245	1.0000	0.1633	20245	0.6111	0.7951	0.8910	0.9799	1.0871	1.2375	3.2133
Coumaphos	20245	1.0000	0.0948	20245	0.5420	0.9357	0.9807	0.9996	1.0182	1.0523	3.3925
Diazinon	20245	1.0011	0.2841	20268	0.4850	0.6318	0.8402	0.9326	1.1119	1.5240	4.5153
Dichlorvos	20245	0.9997	0.3184	20238	0.3669	0.7076	0.9096	0.9969	1.0518	1.1467	8.8411
Malathion	20245	1.0005	0.2514	20256	0.3290	0.6329	0.8865	0.9494	1.0674	1.4683	3.2064
Parathion	20245	1.0001	0.2530	20247	0.3236	0.5753	0.9182	0.9535	1.0572	1.3761	7.7980
Phorate	20245	1.0075	0.5485	20397	0.5296	0.6464	0.7312	0.7963	1.1459	1.5913	13.5124
Fonofos	20245	1.0014	0.5559	20274	0.5450	0.6511	0.8118	0.8297	1.1183	1.2126	18.2986
Terbufos	20245	0.9983	0.3763	20211	0.6381	0.7245	0.7598	0.7885	1.2163	1.9226	8.8241
Trichlorfon	20245	1.0001	0.0483	20246	0.4223	0.9966	0.9975	0.9999	1.0017	1.0072	5.6431
Permethrin (crops)	20245	0.9997	0.1351	20238	0.4971	0.8097	0.9478	0.9910	1.0409	1.1470	2.4719
Permethrin (animals)	20245	0.9982	0.3556	20208	0.4225	0.6327	0.8672	0.9697	1.0838	1.2486	9.0062
Carbaryl	20245	0.9984	0.4317	20212	0.4496	0.6358	0.7234	0.8789	1.1249	1.6922	6.2234
Pyrethrins	20245	0.9991	0.0807	20226	0.2598	0.9859	0.9922	0.9975	1.0062	1.0205	6.4978
Pyrethrum	20245	0.9999	0.0116	20243	0.2834	0.9995	0.9997	0.9999	1.0001	1.0010	1.8654
Cyfluthrin	20245	0.9956	0.2063	20156	0.2833	0.8826	0.9495	0.9816	1.0364	1.1243	12.1045
Lambda Cyhalothrin	20245	0.9974	0.1571	20193	0.1908	0.9667	0.9755	0.9894	1.0139	1.0701	7.4623

						Percentiles					
Variable	**N**	**Mean**	**SE**	**Sum**	**Min**	**5th**	**25th**	**Median**	**75th**	**95th**	**Max**
Esfenvalerate	20245	0.9989	0.1091	20224	0.1215	0.9859	0.9895	0.9949	1.0031	1.0352	8.6006
Tefluthrin	20245	0.9986	0.7009	20217	0.2633	0.9656	0.9662	0.9960	1.0214	1.0579	81.9086
Lifetime days of use - categorized											
Coumaphos	20245	1.0002	0.1157	20248	0.5019	0.9330	0.9812	1.0001	1.0182	1.0505	4.2539
Diazinon	11118	1.0017	0.2935	11137	0.3114	0.5367	0.8868	0.9373	1.0530	1.5461	3.6864
Dichlorvos	11118	0.9997	0.3516	11115	0.3373	0.7031	0.8988	1.0048	1.0513	1.1382	9.8973
Malathion	11113	1.0002	0.2263	11115	0.4300	0.7013	0.8570	0.9537	1.1064	1.4177	2.7237
Parathion	11118	1.0000	0.2446	11118	0.2184	0.7450	0.9524	0.9615	1.0444	1.1928	5.6907
Permethrin (crops)	20243	1.0000	0.1833	20243	0.2953	0.7444	0.9460	0.9898	1.0416	1.1597	4.2622
Permethrin (animals)	20245	0.9972	0.3579	20189	0.3667	0.6272	0.8681	0.9707	1.0840	1.2497	10.7442
Carbaryl	11115	1.0024	0.6050	11142	0.3284	0.4027	0.7134	0.8313	1.0490	2.3129	7.9166

SE = standard error

CHAPTER 5.
DISCUSSION

Background

Over the past several decades, interest in identifying occupational risk factors for COPD has grown [13, 108, 228, 229]. Despite indication that farmers and farm workers engaged in animal production experience high prevalence of cough, phlegm, wheeze, and chronic bronchitis, little information is available about the burden of or occupational risk factors for COPD in this population [229]. Only in one previous study was COPD explicitely examined among persons working in animal production [14]. In addition, a growing body of evidence indicates that pesticide use, and specifically insecticides, may be associated with COPD. However, studies with detailed information about lifetime use history of specific types of pesticide are needed to further characterize this association [129].

The AHS provides a unique opportunity to examine the association between work in animal production and COPD while addressing some limitations of available work. The AHS is a large cohort of farmers, enrolled between 1993 and 1997 in two major animal producing states – Iowa and North Carolina. Investigators have collected information about animal production, lifetime use of insecticides, and covariates relevant to investigating COPD including smoking over approximately 12 years. One limitation of the AHS is that COPD diagnoses and symptoms were only collected from approximately 46% of the original cohort that responded to a follow-up interview occurring between 2005 and 2010. Although non-participation of 54% of the original cohort is a limitation, it presented an opportunity to investigate the potential effects of restricting

analyses of exposure-disease associations to individuals who participate and report incident disease during the 2005-2010 interview.

Therefore, this work had two main objectives: 1) to evaluate the potential for attrition in the AHS to bias results of analyses restricted to farmers participating in the 2005-2010 interview; and, 2) to quantify the association between work with animals and COPD among farmers in the AHS. This objective included considering the role of raising animals and use of insecticides in COPD.

Attrition in the AHS

The results presented in **Chapter 3** characterize participants of the 2005-2010 AHS interview, quantify the extent of bias that may be present in analyses limited to interview participants, and evaluate the utility of IPSW to reduce selection bias introduced by restriction of analyses to participants. Participation in the 2005-2010 interview was strongly associated with the enrollment variables age, state, race/ethnicity, education, marital status, smoking, and alcohol consumption; animal production and personal pesticide use reported at enrollment were not strongly associated with participation. Using this information, three example associations were evaluated within the full- and sub-cohorts to illustrate conditions under which selection bias may impact effect estimates generated from sub-cohort participants. When exposure and outcome status jointly affected the probability of participation, resulting in differential participation by cases or non-cases by exposure status, the RR and RD estimated from interview participants differed from full-cohort estimates. However, even with more than 50% attrition, when the exposure and outcome did not jointly affect participation, sub-cohort estimates were similar to full-cohort estimates. These examples serve as real-world demonstrations of theory regarding selective participation described previously [140, 144, 145].

IPSW has been proposed and applied in other cohort studies to correct effect estimates for non-participation [181, 186, 230]. The analysis presented in **Chapter 3** indicates that when exposure and outcome jointly affected participation, IPSW conditional on exposure and covariate information could not create an appropriate "pseudo-population" where a selection effect did not exist. When the outcome was not strongly predictive of participation, IPSW were unnecessary, as negligible bias was present in sub-cohort estimates. These observations support previous findings that application of IPSW to correct for non-participation in other AHS analyses did not substantially alter results [174, 184]. Further, these findings align with results of previous analyses examining the utility of IPSW using simulations and application within other cohort studies [142, 178, 181, 185, 186, 230].

Impact of findings

The results of this investigation directly informed the analysis of AHS data to estimate associations between animal production work and COPD. Raising animals and insecticide use reported at enrollment were not strongly associated with participation in the 2005-2010 interview. In addition, reporting a doctor diagnosis of asthma or "other chronic lung disease" at enrollment was not strongly associated with participation. Finally, despite being a major cause of morbidity and mortality, COPD is a chronic condition that individuals often live with for many years after the onset of symptoms or diagnosis [195]. Taken together, this evidence suggests that it is unlikely that work in animal production and COPD would be strongly predictive of participation in the 2005-2010 interview. Operating under this assumption, I estimated the effect of animal production and insecticide use on COPD among participants of the 2005-2010 interview assuming negligible selection bias.

These findings have broader implications for the AHS as well. The identification of enrollment factors associated with participation in study activities can inform efforts to improve participation in future AHS interviews. A majority of non-participants (87%) refused, were excluded, or could not be contacted for the 2005-2010 interview. Greater efforts to engage study participants in future interviews could reduce concerns about selection at subsequent interviews. These results can also provide a foundation for future investigations restricted to participants of the 2005-2010 interview to consider the potential for selection bias. Future analyses limited to 2005-2010 interview participants can use the results reported here to consider whether IPSW is useful to correct for potential selection effects and, if so, to guide variable selection for weight estimation models.

Beyond the AHS, this analysis provides a simple example of the importance of examining attrition in long-term cohort studies and considering impacts on analyses of exposure or outcomes only available for those that continue to participate in study activities. It has long been suggested that attrition >50% is of grave concern [141]. Although investigators should proceed with caution when dealing with large amounts of attrition, this report serves as a real-world example that substantial attrition may not always lead to substantial bias when analyses are restricted to participants remaining under study.

Researchers using these results to design future analyses should recognize the limitations of this work. This investigation was limited to considering the predictive ability and association of enrollment factors on participation in the 2005-2010 interview. There is potential that changes in lifestyle, work patterns, or health after enrollment may be associated with participation in later study activities. In addition, the three examples examined in this analysis represent a small set of

assumptions. There are many other sets of conditions that could be explored, which may result in alternative conclusions about the impacts of attrition and the utility of IPSW.

Animal production & COPD

The results presented in **Chapter 4**, support the hypothesis that animal production and insecticide use are associated with COPD-related morbidity, specifically symptoms of chronic bronchitis. Raising animals on a medium/large animal operation and specifically raising beef cattle, hogs, or poultry was associated with greater prevalence of chronic bronchitis symptoms. Applying insecticides to livestock and use of coumaphos, diazinon, dichlorvos, malathion, parathion, carbaryl, and permethrin were also associated with greater prevalence of chronic bronchitis. Little evidence was found to indicate an association between raising animals, insecticide use and COPD diagnosis. Personal use of diazinon and trichlorfon were associated with a greater prevalence of COPD diagnosis but other activities were not.

The differences observed in associations between the exposures examined and COPD diagnoses and chronic bronchitis symptoms was surprising based on previous literature and the fact that chronic bronchitis is a component condition of COPD. However, in this population, there was little overlap between the farmers reporting a COPD diagnosis and chronic bronchitis symptoms, and there may be several explanations for these disparate findings. It is possible that these results indicate that the biological response to work in animal production may manifest as chronic bronchitis symptoms that do not drive farmers to seek or receive a COPD-related diagnosis. This hypothesis aligns with what has been reported with respect to occupational exposure to other dusty trades [111, 212]. It is also possible that limitations of the information available on animal production may partially explain the discrepancy. With the available exposure information, I was unable to determine if farmers who receive a COPD diagnosis

remove themselves from exposure while those with symptoms remain. This would indicate a healthy-worker bias [231] among those with a COPD diagnosis but not among those with chronic bronchitis symptoms. Researchers have previously documented that a healthy-worker survivor effect may bias results of studies of agricultural exposures and respiratory health outcomes [213-217]. It is also possible that chronic bronchitis symptoms reported here reflect chronic bronchitis and asthma, a cause of reversible airway obstruction. Occupational exposures have been accepted as important in the etiology of asthma [111] and COPD symptoms can be difficult to distinguish without a detailed clinical assessment and because some overlap exists [203]. Even if asthma partially explained the associations observed between work with animals and chronic bronchitis symptoms, the findings remain relevant because evidence suggests that asthma may be an important risk factor for COPD [203, 204, 218-220].

Results also provided evidence that use of specific insecticides was associated with prevalence of chronic bronchitis symptoms. In the present analysis, the insecticides associated with chronic bronchitis symptoms included the organophosphates coumaphos, diazinon, dichlorvos, malathion, and parathion; the carbamate carbaryl; and, the pyrethoid permethrin (for animals). Use of diazinon, trichlorfon, and permethrin (for crops) was also associated with increased prevalence of having a COPD diagnosis.

Organophosphate and carbamate insecticides have been associated with increased prevalence of COPD among nonsmoking agricultural workers in India [130]. These specific insecticides have also been associated with self-reported chronic bronchitis in the AHS among the sample of enrollment farmers returning the supplemental take-home questionnaire [133]. All of the insecticides found to be associated with increased prevalence of COPD in the present study except parathion were or are registered for use on or around animals. However, many of

these insecticides are also used on crops or for other purposes [223], and therefore the effects seen here cannot be ascribed solely to use on animals.

With the exception of permethrin, use of pyrethroids/pyrethrins were not found to be associated with COPD. Use of pyrethroids/pyrethrins in this cohort was rarer than organophosphates. However, use of pyrethroids/pyrethrins has been increasing over the past decade as use of organophosphates, which are more acutely toxic, has declined [60, 207]. Because use of pyrethroids/pyrethrins has begun to replace use of organophosphates, farmers may not have experienced long-term exposure to these insecticides. Consequently, personal exposure to pyrethroid/pyrethrin insecticides should continue to be monitored for adverse respiratory effects.

The observed associations between personal use of insecticides and COPD is especially relevant as interest in identifying pesticide-related risk factors for COPD has increased [129]. The associations observed here provide additional evidence that occupational use of insecticides may contribute to COPD directly, or may serve as a marker for other relevant exposures such as dust.

Impact of findings

The observations reported here provide further evidence that producing animals and using insecticides may contribute to the burden of COPD or its component conditions. These observations also support the call to consider the contribution of occupational risk factors for COPD among individuals involved in animal production. Continued work to identify specific risk factors for COPD and methods for reducing relevant exposures is necessary. Below I

describe some strengths and limitations of this work and offer suggestions to encourage future work.

Breadth vs. Depth: Limitations of large cohort studies

The AHS provided a unique opportunity to examine the association between animal production, insecticide use and COPD. However, the AHS is a large cohort study designed and administered by several federal agencies with a range of interests. These large studies are quite powerful – they follow large numbers of participants and collect data on a range of exposures and outcomes. The breadth of information available in the AHS allows researchers to explore a range of research questions. However, an important limitation of this approach is a lack of detailed information on all exposures and outcomes. This includes limited measurements of exposures or clinical outcomes. As the association between work in animal production and COPD has not been widely examined in other populations of farmers in the United States, the AHS provided an opportunity to characterize this association in a large cohort. However, because the AHS was not specifically designed to answer this question, there were many limitations encountered in this work and I describe some of the main challenges in the following paragraphs.

Limitations of exposure assessment

Available information about work in animal production was limited. In this analysis, type and number of animals produced were used as a proxy for exposure to animal exposure, and specifically to industrial animal production. This is problematic as presence of specific types of animals, or presence of large numbers of animals, does not indictate personal exposure to the animals or the production environment. Further, lifetime exposure information was not available as number and type of animals raised was only collected in reference to specific time points

during the study period. These limitations most certainly resulted in exposure misclassification. Misclassification could have been differential with respect to COPD diagnoses or symptoms, and there is potential that misclassification occurred differently in analyses examining COPD diagnoses and chronic bronchitis symptoms, contributing to the disparate findings. Misclassification of exposures could have biased results toward or away from the null depending on the magnitude and type. In future studies, direct measurement of personal exposure to dust, endotoxin, gases, and chemicals used in tandem with more detailed information about frequency and duration of work with animals could improve classification of exposure.

A major strength of this analysis was that lifetime information on use of specific insecticides was available. However, this information was self-reported and, therefore, is subject to recall and reporting bias. Researchers have previously considered concerns about the validity and reliability of self-reported pesticide information in the AHS. Self-reported use of pesticides compared reasonably well with pesticide registration information [152], and using enrollment data, 70–90% repeatability of self-reported pesticide use was found one-year after enrollment [232]. Future analyses could improve assessment of pesticide exposure by incorporating information about pesticide formulations (e.g., sprays, dips, tags, and dusts) used, application methods, and use of personal protective equipment when assigning exposure. With improved information about exposure to all of the agents in the animal production environment, a stronger evaluation of their role in COPD could be undertaken. Further, interactions between these exposures could be directly considered with more confidence allowing for a better understanding of the role of each agent individually and their joint contribution to disease risk.

Limitations of defining COPD

Farmers reported ever receiving a doctor diagnosis of COPD or experiencing the symptoms of chronic bronchitis as part of the 2005-2010 interview. Self-report of doctor diagnosis has been used in previous work including studies of the general US population [27, 29]. Supplementation of COPD diagnoses with symptom reports was a major strength of this study. Although self-report of a doctor diagnosis or symptoms is subject to recall and reporting error resulting in misclassification, there is no evidence to indicate that disease misclassification was differential with respect to exposure and probably resulted in attenuation of effects. Future work that complements self-report with spirometry or standardized clinical diagnosis, will be important in continuing to investigate the adverse respiratory health effects of exposure to the animal production environment. Because spirometry and medical exams can be time and resource intensive, alternative ways of validating a COPD diagnosis may be useful in future studies. For example, collection of information about use of COPD medication or other treatment may aid in identifying cases, and understanding overlap between symptoms and diagnoses.

Inability to establish a temporal relationship between exposure and COPD

Animal production and insecticide use information was collected in five-year intervals. Farming activities were assumed to be constant within each interval. COPD diagnoses along with the age of diagnosis were reported only at the 2005-2010 interview. Cough and phlegm was also reported at the 2005-2010 interview along with the number of years symptoms were present. This data collection approach prohibited establishing a clear temporal relationship between exposure and onset of symptoms and disease. It also made exclusion of prevalent cases challenging. Because of this, a time-to-event analysis of incident cases was not possible. Without a time-to-event analysis, I could not address questions about timing of onset of disease. Future

work following at-risk individuals over time with clear documentation of the timing of exposure and onset of COPD will be useful in evaluating the role of animal production in risk of COPD and determining whether these activities influence the timing of onset of disease.

Generalizability

AHS participants are mainly farm owner/operators. Consequently, the AHS population does not represent farm workers who may receive greater exposure to the animal production environment than farm owner/operators. Therefore, the findings reported here may not be generalizable to the farm-worker population. Future efforts to characterize the burden of and risk factors for COPD among farm-worker populations are necessary to understand the impact of occupational exposure to the agents present in the animal production environment.

Conclusions

This work continues to raise concerns about the respiratory health effects due to occupational exposures in animal production. It also supports the call to consider the role of insecticides in COPD among persons working in agriculture. In future work, researchers should examine the role of animal production and use of insecticides in COPD among farmers and farm workers with a focus on improving assessment of relevant exposures and COPD. Because there is substantial evidence that work in animal production and use of insecticides may be associated with respiratory symptoms, future research should also focus on the utility of establishing enforceable regulations and identifying potential improvements to protect workers from exposures with the potential to adversely impact respiratory health.

REFERENCES

1. Silbergeld, E.K., J. Graham, and L.B. Price, *Industrial food animal production, antimicrobial resistance, and human health.* Annu Rev Public Health, 2008. **29**: p. 151-69.

2. Pew Commission on Industrial Farm Animal Production, *Putting Meat on the Table: Industrial Farm Animal Production in America*, 2008, Pew Charitable Trusts and Johns Hopkins Bloomberg School of Public Health.

3. Cormier, Y., et al., *Respiratory health of workers exposed to swine confinement buildings only or to both swine confinement buildings and dairy barns.* Scand J Work Environ Health, 1991. **17**(4): p. 269-75.

4. Crook, B., et al., *Airborne dust, ammonia, microorganisms, and antigens in pig confinement houses and the respiratory health of exposed farm workers.* Am Ind Hyg Assoc J, 1991. **52**(7): p. 271-9.

5. Holness, D.L., et al., *Respiratory effects and dust exposures in hog confinement farming.* Am J Ind Med, 1987. **11**(5): p. 571-80.

6. Iversen, M. and R. Dahl, *Specific antigens in dust from swine confinement buildings.* Am J Ind Med, 1994. **25**(1): p. 49-51.

7. Jones, W., et al., *Environmental study of poultry confinement buildings.* Am Ind Hyg Assoc J, 1984. **45**(11): p. 760-6.

8. Andersen, C.I., et al., *Respiratory symptoms and airway obstruction in swine veterinarians: a persistent problem.* Am J Ind Med, 2004. **46**(4): p. 386-92.

9. Frank, A.L., et al., *Issues of agricultural safety and health.* Annu Rev Public Health, 2004. **25**: p. 225-45.

10. Langley, R.L., *Consequences of respiratory exposures in the farm environment.* N C Med J, 2011. **72**(6): p. 477-80.

11. Poole, J.A. and D.J. Romberger, *Immunological and inflammatory responses to organic dust in agriculture.* Curr Opin Allergy Clin Immunol, 2012. **12**(2): p. 126-32.

12. Popendorf, W., et al., *A synopsis of agricultural respiratory hazards.* Am Ind Hyg Assoc J, 1985. **46**(3): p. 154-61.

13. *Respiratory health hazards in agriculture.* Am J Respir Crit Care Med, 1998. **158**(5 Pt 2): p. S1-S76.

14. Monso, E., et al., *Chronic obstructive pulmonary disease in never-smoking animal farmers working inside confinement buildings.* Am J Ind Med, 2004. **46**(4): p. 357-62.

15. Omland, O., *Exposure and respiratory health in farming in temperate zones--a review of the literature.* Ann Agric Environ Med, 2002. **9**(2): p. 119-36.

16. Preller, L., et al., *Lung function and chronic respiratory symptoms of pig farmers: focus on exposure to endotoxins and ammonia and use of disinfectants.* Occup Environ Med, 1995. **52**(10): p. 654-60.

17. Schwartz, D.A., et al., *Determinants of longitudinal changes in spirometric function among swine confinement operators and farmers.* Am J Respir Crit Care Med, 1995. **151**(1): p. 47-53.

18. Zejda, J.E., et al., *Respiratory health status in swine producers relates to endotoxin exposure in the presence of low dust levels.* J Occup Med, 1994. **36**(1): p. 49-56.

19. Zejda, J.E., et al., *Respiratory health of swine producers. Focus on young workers.* Chest, 1993. **103**(3): p. 702-9.

20. Zuskin, E., et al., *Respiratory function in poultry workers and pharmacologic characterization of poultry dust extract.* Environ Res, 1995. **70**(1): p. 11-9.

21. Choudat, D., et al., *Respiratory symptoms and bronchial reactivity among pig and dairy farmers.* Scand J Work Environ Health, 1994. **20**(1): p. 48-54.

22. Donham, K.J., *Health effects from work in swine confinement buildings.* Am J Ind Med, 1990. **17**(1): p. 17-25.

23. Senthilselvan, A., et al., *Excess respiratory symptoms in full-time male and female workers in large-scale swine operations.* Chest, 2007. **131**(4): p. 1197-204.

24. *Chapter 12: Lung*, in *Robbins Basic Pathology*, J.C. Aster, et al., Editors. 2007, Elsevier/Saunders: Philadelphia, PA. p. 459-515.

25. National Institute for Occupational Safety and Health. *Rate File Information*. Life Table Analysis System 2010 December 6, 2012 [cited 2012 December 6]; Available from: http://www.cdc.gov/niosh/ltas/rates.html.

26. Ford, E.S., et al., *COPD surveillance--United States, 1999-2011.* Chest, 2013. **144**(1): p. 284-305.

27. Halbert, R.J., et al., *Global burden of COPD: systematic review and meta-analysis.* Eur Respir J, 2006. **28**(3): p. 523-32.

28. Mannino, D.M. and A.S. Buist, *Global burden of COPD: risk factors, prevalence, and future trends.* Lancet, 2007. **370**(9589): p. 765-73.

29. Mannino, D.M., et al., *Chronic obstructive pulmonary disease surveillance--United States, 1971-2000.* MMWR Surveill Summ, 2002. **51**(6): p. 1-16.

30. Bureau of Labor Statistics. *Agricultural Workers*. Occupational Outlook Handbook 2012 August 31, 2012 [cited 2012 November 4]; Available from: http://www.bls.gov/ooh/farming-fishing-and-forestry/agricultural-workers.htm.

31. Hnizdo, E., et al., *Association between chronic obstructive pulmonary disease and employment by industry and occupation in the US population: a study of data from the Third National Health and Nutrition Examination Survey.* Am J Epidemiol, 2002. **156**(8): p. 738-46.

32. Linaker, C. and J. Smedley, *Respiratory illness in agricultural workers.* Occup Med (Lond), 2002. **52**(8): p. 451-9.

33. Zejda, J.E. and J.A. Dosman, *Respiratory disorders in agriculture.* Tuber Lung Dis, 1993. **74**(2): p. 74-86.

34. Gainet, M., et al., *Twelve-year longitudinal study of respiratory status in dairy farmers.* Eur Respir J, 2007. **30**(1): p. 97-103.

35. Heederik, D. and T. Sigsgaard, *Respiratory allergy in agricultural workers: recent developments.* Curr Opin Allergy Clin Immunol, 2005. **5**(2): p. 129-34.

36. Pahwa, P., et al., *Prevalence of Chronic Bronchitis in Farm and Nonfarm Rural Residents in Saskatchewan.* J Occup Environ Med, 2012.

37. Stellman, S.D., P. Boffetta, and L. Garfinkel, *Smoking habits of 800,000 American men and women in relation to their occupations.* Am J Ind Med, 1988. **13**(1): p. 43-58.

38. Sterling, T.D. and J.J. Weinkam, *Smoking patterns by occupation, industry, sex, and race.* Arch Environ Health, 1978. **33**(6): p. 313-7.

39. Kirkhorn, S.R. and V.F. Garry, *Agricultural lung diseases.* Environ Health Perspect, 2000. **108 Suppl 4**: p. 705-12.

40. Monso, E., et al., *Region-related risk factors for respiratory symptoms in European and Californian farmers.* European Respiratory Journal, 2003. **21**(2): p. 323-331.

41. Alavanja, M.C., et al., *The Agricultural Health Study.* Environ Health Perspect, 1996. **104**(4): p. 362-9.

42. *Agricultural Health Study: Study & Cohort Descriptions*. [cited 2013 August 8]; Available from: http://aghealth.nih.gov/resources/orientation.html#desc.

43. Pew Commission on Industrial Farm Animal Production, *Economics of industrial farm animal production*.

44. United States Department of Labor. *Animal Production: NAICS 112*. Industries at a Glance 2013 [cited 2013 December 11]; Available from: http://www.bls.gov/iag/tgs/iag112.htm.

45. United States Deparment of Agriculture. *Animal Feeding Operations*. Livestock [cited 2013 March 10]; Available from: http://www.nrcs.usda.gov/wps/portal/nrcs/main/national/plantsanimals/livestock/afo/.

46. Weiss, S.T. and J.H. Ware, *Overview of issues in the longitudinal analysis of respiratory data.* Am J Respir Crit Care Med, 1996. **154**(6 Pt 2): p. S208-11.

47. *The CAFO Reader: The tragedy of industrial animal factories*, ed. D. Imhoff. 2010, Berkeley and Los Angeles, CA: University of California Press, Ltd.

48. Animal and Plant Health Inspection Service, *Overview of US livestock, poultry, and aquaculture production in 2011 and statistics on major commodities*, 2011, United States Department of Agriculture.

49. U.S. Environmental Protection Agency, *Profile of Agricultural Livestock Production Industry*, 2000: Washington DC.

50. Duquenne, P., G. Marchand, and C. Duchaine, *Measurement of endotoxins in bioaerosols at workplace: A critical review of literatureand a standardization issue.* Ann Occup Hyg, 2013. **57**(2): p. 137-172.

51. Cambra-Lopez, M., et al., *Airborne particulate matter from livestock production systems: a review of an air pollution problem.* Environ Pollut, 2010. **158**(1): p. 1-17.

52. Cole, D., L. Todd, and S. Wing, *Concentrated swine feeding operations and public health: a review of occupational and community health effects.* Environ Health Perspect, 2000. **108**(8): p. 685-99.

53. Donham, K.J., *Hazardous agents in agricultural dusts and methods of evaluation.* Am J Ind Med, 1986. **10**(3): p. 205-20.

54. Donham, K.J., et al., *Potential health hazards to agricultural workers in swine confinement buildings.* J Occup Med, 1977. **19**(6): p. 383-7.

55. Schiffman, S.S., J.L. Bennett, and J.H. Raymer, *Quantification of odors and odorants from swine operations in North Carolina.* Agricultural and Forest Microbiology, 2001. **108**: p. 213-240.

56. Kullman, G.J., et al., *Organic dust exposures from work in dairy barns.* Am Ind Hyg Assoc J, 1998. **59**(6): p. 403-13.

57. O'Shaughnessy, P., et al., *Assessment of swine worker exposures to dust and endotoxin during hog load-out and power washing.* Ann Occup Hyg, 2012. **56**(7): p. 843-51.

58. Wardhaugh, K.G., *Insecticidal activity of synthetic pyrethroids, organophosphates, insect growth regulators, and other livestock parasiticides: an Australian perspective.* Environ Toxicol Chem, 2005. **24**(4): p. 789-96.

59. Union of Concerned Scientists. *Industrial Agriculture*. Food & Agriculture 2012 August 3, 2012 [cited 2013 March 3]; Available from: http://www.ucsusa.org/food_and_agriculture/our-failing-food-system/industrial-agriculture/.

60. US Environmental Protection Agency. *Pyrethroids and Pyrethrins*. Reevaluation: Review of Registered Pesticides 2013 August 5, 2014 [cited 2015 January 28]; Available from: http://www.epa.gov/oppsrrd1/reevaluation/pyrethroids-pyrethrins.html.

61. *2014 North Carolina Agricultural Chemicals Manual*, N.S.U. College of Agriculture and Life Sciences, Editor 2014, North Carolina Cooperative Extension Service Raleigh, NC.

62. *Pesticide Formulations: Topic Fact Sheet*. 1999 [cited 2014 January 21]; Available from: http://npic.orst.edu/factsheets/formulations.html.

63. Kirkhorn, S.R. and M.B. Schenker, *Current health effects of agricultural work: respiratory disease, cancer, reproductive effects, musculoskeletal injuries, and pesticide-related illnesses.* J Agric Saf Health, 2002. **8**(2): p. 199-214.

64. *Partial exemption for employers with 10 or fewer employees, Recording and Reporting Occupational Injuries and Illness, 1904.1 Subpart B*, in *1904.1, Subpart B*, U.S.D.o.L. Occupational Safety & Health Administration, Editor 1994: United States.

65. US Environmental Protection Agency. *Restricted Use Products (RUP) Report*. 2013 [cited 2014 January 21]; Available from: http://www.epa.gov/opprd001/rup/.

66. Clark, S., R. Rylander, and L. Larsson, *Airborne bacteria, endotoxin and fungi in dust in poultry and swine confinement buildings.* Am Ind Hyg Assoc J, 1983. **44**(7): p. 537-41.

67. Donham, K., et al., *Environmental and health studies of farm workers in Swedish swine confinement buildings.* Br J Ind Med, 1989. **46**(1): p. 31-7.

68. Donham, K.J. and W.J. Popendorf, *Ambient levels of selected gases inside swine confinement buildings.* Am Ind Hyg Assoc J, 1985. **46**(11): p. 658-61.

69. Louhelainen, K., et al., *Total concentrations of dust in the air during farm work.* Eur J Respir Dis Suppl, 1987. **152**: p. 73-9.

70. Attwood, P., et al., *A study of the relationship between airborne contaminants and environmental factors in Dutch swine confinement buildings.* Am Ind Hyg Assoc J, 1987. **48**(8): p. 745-51.

71. Donham, K.J., *Association of environmental air contaminants with disease and productivity in swine.* Am J Vet Res, 1991. **52**(10): p. 1723-30.

72. Donham, K.J., et al., *Respiratory dysfunction in swine production facility workers: dose-response relationships of environmental exposures and pulmonary function.* Am J Ind Med, 1995. **27**(3): p. 405-18.

73. Heederik, D., et al., *Relationship of airborne endotoxin and bacteria levels in pig farms with the lung function and respiratory symptoms of farmers.* Int Arch Occup Environ Health, 1991. **62**(8): p. 595-601.

74. Jolie, R., L. Backstrom, and P. Gunderson, *Airborne contaminants and farmers health in swine farms with high and low prevalence of respiratory diseases in pigs.* Ann Agric Environ Med, 1998. **5**(1): p. 87-92.

75. Reynolds, S.J., et al., *Longitudinal evaluation of dose-response relationships for environmental exposures and pulmonary function in swine production workers.* Am J Ind Med, 1996. **29**(1): p. 33-40.

76. Cormier, Y., et al., *Farming practices and the respiratory health risks of swine confinement buildings.* Eur Respir J, 2000. **15**(3): p. 560-5.

77. Radon, K., et al., *Lung function and work-related exposure in pig farmers with respiratory symptoms.* J Occup Environ Med, 2000. **42**(8): p. 814-20.

78. Donham, K.J., et al., *Dose-response relationships between occupational aerosol exposures and cross-shift declines of lung function in poultry workers: recommendations for exposure limits.* J Occup Environ Med, 2000. **42**(3): p. 260-9.

79. Thelin, A., O. Tegler, and R. Rylander, *Lung reactions during poultry handling related to dust and bacterial endotoxin levels.* Eur J Respir Dis, 1984. **65**(4): p. 266-71.

80. Rylander, R., et al., *Effects of exposure to dust in swine confinement buildings--a working group report.* Scand J Work Environ Health, 1989. **15**(5): p. 309-12.

81. Schwarze, P.E., et al., *Particulate matter properties and health effects: consistency of epidemiological and toxicological studies.* Hum Exp Toxicol, 2006. **25**(10): p. 559-79.

82. Erdogan, S., et al., *Pulmonary effects of deltamethrin inhalation: an experimental study in rats.* Ecotoxicol Environ Saf, 2006. **63**(2): p. 318-23.

83. Konieczny, B., S. Kossmann, and M. Makuch, *Impaired respiratory muscle function in chemical plant workers producing chlorfenvinphos.* Ann Agric Environ Med, 1999. **6**(1): p. 21-5.

84. Ye, M., et al., *Occupational pesticide exposures and respiratory health.* Int J Environ Res Public Health, 2013. **10**(12): p. 6442-71.

85. National Institute for Occupational Safety and Health, *Respiratory disease in agricultural workers: Mortality and morbidity statistics*, 2007, Centers for Disease Control and Prevention.

86. Shapiro, S.D., J.J. Reilly, and S.I. Rennard, *Chapter 39: Chronic bronchitis and emphysema*, in *Mason: Murray and Nadel's Textbook of Respiratory Medicine*, Robert J. Mason, et al., Editors., Saunders Elsevier: Philadelphia, PA. p. 919-967.

87. American Thoracic Society, *Standards for the diagnosis and management of patients with COPD*, 2004.

88. Global Initiative for Chronic Obstructive Lung Disease, I., *Global strategy for the diagnosis, management, and prevention of Chronic Obstructive Pulmonary Disease (Revised 2011)*, 2011.

89. Hogg, J.C. and W. Timens, *The pathology of chronic obstructive pulmonary disease.* Annu Rev Pathol, 2009. **4**: p. 435-59.

90. Kreiss, K., *Occupational causes of constrictive bronchiolitis.* Curr Opin Allergy Clin Immuol, 2013. **13**: p. 167-172.

91. Valavanidis, A., K. Fiotakis, and T. Vlachogianni, *Airborne particulate matter and human health: toxicological assessment and importance of size and composition of particles for oxidative damage and carcinogenic mechanisms.* J Environ Sci Health C Environ Carcinog Ecotoxicol Rev, 2008. **26**(4): p. 339-62.

92. West, J.B., *Respiratory Physiology: The Essentials*. 8th ed. 2008, Baltimore, MD: Lippincott Williams & Wilkins.

93. National Heart Lung and Blood Institute. *What is COPD?* Health Topics: COPD 2012 June 8, 2012 [cited 2013 January 17]; Available from: http://www.nhlbi.nih.gov/health/health-topics/topics/copd/.

94. Scanlon, P.D., *The pathogenesis and pathology of COPD: Identifying risk factors and improving morbidity and mortality.* Advanced Studies in Medicine, 2004. **4**(10A): p. S744-S749.

95. Barr, R.G., et al., *Validation of self-reported chronic obstructive pulmonary disease in a cohort study of nurses.* Am J Epidemiol, 2002. **155**(10): p. 965-71.

96. Lamprecht, B., et al., *COPD in never smokers: results from the population-based burden of obstructive lung disease study.* Chest, 2011. **139**(4): p. 752-63.

97. Tilert, T., et al., *Estimating the U.S. prevalence of chronic obstructive pulmonary disease using pre- and post-bronchodilator spirometry: the National Health and Nutrition Examination Survey (NHANES) 2007-2010.* Respir Res, 2013. **14**: p. 103.

98. Trupin, L., et al., *The occupational burden of chronic obstructive pulmonary disease.* Eur Respir J, 2003. **22**(3): p. 462-9.

99. Kosacz, N., et al., *Chronic Obstructive Pulmonary Disease among adults - United States, 2011.* Morbidity and Mortality Weekly Report, 2012. **61**(46): p. 938-943.

100. Mannino, D.M., et al., *Obstructive lung disease and low lung function in adults in the United States: data from the National Health and Nutrition Examination Survey, 1988-1994.* Arch Intern Med, 2000. **160**(11): p. 1683-9.

101. Guerra, S., et al., *The relation of body mass index to asthma, chronic bronchitis, and emphysema.* Chest, 2002. **122**(4): p. 1256-63.

102. Blanc, P.D., *Occupation and COPD: a brief review.* J Asthma, 2012. **49**(1): p. 2-4.

103. Blanc, P.D., et al., *Further exploration of the links between occupational exposure and chronic obstructive pulmonary disease.* J Occup Environ Med, 2009. **51**(7): p. 804-10.

104. Blanc, P.D., et al., *Occupational exposures and the risk of COPD: dusty trades revisited.* Thorax, 2009. **64**(1): p. 6-12.

105. Blanc, P.D., et al., *Occupational exposures and COPD: an ecological analysis of international data.* Eur Respir J, 2009. **33**(2): p. 298-304.

106. Blanc, P.D. and K. Toren, *Occupation in chronic obstructive pulmonary disease and chronic bronchitis: an update.* Int J Tuberc Lung Dis, 2007. **11**(3): p. 251-7.

107. Sunyer, J., et al., *Lung function decline, chronic bronchitis, and occupational exposures in young adults.* Am J Respir Crit Care Med, 2005. **172**(9): p. 1139-45.

108. Toren, K. and J. Balmes, *Chronic obstructive pulmonary disease: does occupation matter?* Am J Respir Crit Care Med, 2007. **176**(10): p. 951-2.

109. Balmes, J., et al., *American Thoracic Society Statement: Occupational contribution to the burden of airway disease.* Am J Respir Crit Care Med, 2003. **167**(5): p. 787-97.

110. Matheson, M.C., et al., *Biological dust exposure in the workplace is a risk factor for chronic obstructive pulmonary disease.* Thorax, 2005. **60**(8): p. 645-51.

111. Becklake, M.R., *Occupational exposures: evidence for a causal association with chronic obstructive pulmonary disease.* Am Rev Respir Dis, 1989. **140**(3 Pt 2): p. S85-91.

112. Greenhow, E., *Chronic bronchitis especially as connected with gout, emphysema, and diseases of the heart*. 1868, London: Longmans.

113. Harber, P., et al., *Effect of occupational exposures on decline of lung function in early chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2007. **176**(10): p. 994-1000.

114. Hnizdo, E., et al., *Airflow obstruction attributable to work in industry and occupation among U.S. race/ethnic groups: a study of NHANES III data.* Am J Ind Med, 2004. **46**(2): p. 126-35.

115. Donham, K.J., D.C. Zavala, and J.A. Merchant, *Respiratory symptoms and lung function among workers in swine confinement buildings: a cross-sectional epidemiological study.* Arch Environ Health, 1984. **39**(2): p. 96-101.

116. Donham, K.J., et al., *Environmental and health studies in swine confinement buildings.* Am J Ind Med, 1986. **10**(3): p. 289-93.

117. Bongers, P., et al., *Lung function and respiratory symptoms in pig farmers.* Br J Ind Med, 1987. **44**(12): p. 819-23.

118. Dosman, J.A., et al., *Respiratory symptoms and alterations in pulmonary function tests in swine producers in Saskatchewan: results of a survey of farmers.* J Occup Med, 1988. **30**(9): p. 715-20.

119. Iversen, M., et al., *Cross-sectional study of respiratory symptoms in 1,175 Danish farmers.* Am J Ind Med, 1990. **17**(1): p. 60-1.

120. Carvalheiro, M.F., et al., *Bronchial reactivity and work-related symptoms in farmers.* Am J Ind Med, 1995. **27**(1): p. 65-74.

121. Vogelzang, P.F., et al., *Respiratory morbidity in relationship to farm characteristics in swine confinement work: possible preventive measures.* Am J Ind Med, 1996. **30**(2): p. 212-8.

122. Zuskin, E., et al., *Respiratory symptoms and ventilatory capacity in swine confinement workers.* Br J Ind Med, 1992. **49**(6): p. 435-40.

123. Chaudemanche, H., et al., *Respiratory status in dairy farmers in France; cross sectional and longitudinal analyses.* Occup Environ Med, 2003. **60**(11): p. 858-63.

124. Mauny, F., et al., *Longitudinal study of respiratory health in dairy farmers: influence of artificial barn fodder drying.* European Respiratory Journal, 1997. **10**(11): p. 2522-2528.

125. Morris, P.D., S.W. Lenhart, and W.S. Service, *Respiratory symptoms and pulmonary function in chicken catchers in poultry confinement units.* Am J Ind Med, 1991. **19**(2): p. 195-204.

126. Reynolds, S.J., et al., *Cross-sectional epidemiological study of respiratory disease in turkey farmers.* Am J Ind Med, 1993. **24**(6): p. 713-22.

127. Dalphin, J.C., et al., *Prevalence of chronic bronchitis and respiratory function in a group of dairy farmers in the French Doubs province.* Chest, 1989. **95**(6): p. 1244-7.

128. de Jong, K., et al., *Pesticides and other occupational exposures are associated with airway obstruction: the LifeLines cohort study.* Occup Environ Med, 2014. **71**(2): p. 88-96.

129. Hoppin, J.A., *Pesticides and respiratory health: where do we go from here?* Occup Environ Med, 2014. **71**(2): p. 80.

130. Chakraborty, S., et al., *Chronic exposures to cholinesterase-inhibiting pesticides adversely affect respiratory health of agricultural workers in India.* J Occup Health, 2009. **51**(6): p. 488-97.

131. Hoppin, J.A., et al., *Animal production and wheeze in the Agricultural Health Study: interactions with atopy, asthma, and smoking.* Occup Environ Med, 2003. **60**(8): p. e3.

132. Hoppin, J.A., et al., *Pesticides and adult respiratory outcomes in the agricultural health study.* Ann N Y Acad Sci, 2006. **1076**: p. 343-54.

133. Hoppin, J.A., et al., *Pesticide use and chronic bronchitis among farmers in the Agricultural Health Study.* Am J Ind Med, 2007. **50**(12): p. 969-79.

134. Valcin, M., et al., *Chronic bronchitis among nonsmoking farm women in the agricultural health study.* J Occup Environ Med, 2007. **49**(5): p. 574-83.

135. Sprince, N.L., et al., *Respiratory symptoms: associations with pesticides, silos, and animal confinement in the Iowa Farm Family Health and Hazard Surveillance Project.* Am J Ind Med, 2000. **38**(4): p. 455-62.

136. Montgomery, M.P., et al., *Effects of self-reported health conditions and pesticide exposures on probability of follow-up in a prospective cohort study.* Am J Ind Med, 2010. **53**(5): p. 486-96.

137. Hoppin, J.A., et al., *Respiratory disease in US farmers.* Occup Environ Med, 2014. **71**: p. 484-491.

138. Fewtrell, M.S., et al., *How much loss to follow-up is acceptable in long-term randomised trials and prospective studies?* Arch Dis Child, 2008. **93**(6): p. 458-61.

139. Deeg, D., *Attrition in longitudinal population studies: Does it affect the generalizability of the findings? An introduction to the series.* J Clin Epi, 2002. **55**: p. 213-215.

140. Greenland, S., *Response and follow-up bias in cohort studies.* Am J Epidemiol, 1977. **106**(3): p. 184-187.

141. Kristman, V., M. Manno, and P. Cote, *Loss to follow-up in cohort studies: how much is too much?* Eur J Epidemiol, 2004. **19**(8): p. 751-60.

142. Kristman, V.L., M. Manno, and P. Cote, *Methods to account for attrition in longitudinal data: do they work? A simulation study.* Eur J Epidemiol, 2005. **20**(8): p. 657-62.

143. Twisk, J. and W. de Vente, *Attrition in longitudinal studies. How to deal with missing data.* J Clin Epidemiol, 2002. **55**(4): p. 329-37.

144. Daniel, R.M., et al., *Using causal diagrams to guide analysis in missing data problems.* Stat Methods Med Res, 2012. **21**(3): p. 243-56.

145. Westreich, D., *Berkson's bias, selection bias, and missing data.* Epidemiology, 2012. **23**(1): p. 159-64.

146. Kempen, G. and E. van Sonderen, *Psychological attributes and changes in disability among low-functioning older persons: Does attrition affect the outcomes?* J Clin Epi, 2002. **55**: p. 224-229.

147. Deeg, D.J., et al., *Attrition in the Longitudinal Aging Study Amsterdam. The effect of differential inclusion in side studies.* J Clin Epidemiol, 2002. **55**(4): p. 319-28.

148. Kempen, G.I.J.M. and E.v. Sonderen, *Psychological attributes and changes in disability among low-functioning older persons: Does attrition affect the outcomes?* Journal of Clinical Epidemiology, 2002. **55**: p. 224-229.

149. Soullier, N., E. de La Rochebrochard, and J. Bouyer, *Multiple imputation for estimation of an occurrence rate in cohorts with attrition and discrete follow-up time points: a simulation study.* BMC Med Res Methodol, 2010. **10**: p. 79.

150. Hernán, M.A., S. Hernandez-Diaz, and J.M. Robins, *A structural approach to selection bias.* Epidemiology, 2004. **15**(5): p. 615-25.

151. Hoppin, J.A., et al., *Lifetime organophosphorous insecticide use among private pesticide applicators in the Agricultural Health Study.* J Expo Sci Environ Epidemiol, 2012. **22**(6): p. 584-92.

152. Hoppin, J.A., et al., *Accuracy of self-reported pesticide use duration information from licensed pesticide applicators in the Agricultural Health Study.* J Expo Anal Environ Epidemiol, 2002. **12**(5): p. 313-8.

153. Office of Pesticide Programs. *Pesticide Chemical Search*. [cited 2013 December 10]; Available from: http://iaspub.epa.gov/apex/pesticides/f?p=CHEMICALSEARCH:1:0.

154. Occupational Safety & Health Administration. *Chapter 1: Dust and Its Control*. Dust Control Handbook for Minerals Processing [cited 2014 January 21]; Available from: https://www.osha.gov/dsg/topics/silicacrystalline/dust/chapter_1.html.

155. Donham, K.J., et al., *Chapter 8. Exposure limits related to air quality and risk assessment*, in *Iowa Concentrated Animal Feeding Operations Air Quality Study.*, I.U.S. Group, Editor. 2002, University of Iowa College of Public Health: Iowa City, IA. p. 164-183.

156. Occupational Safety & Health Administration. *Hydrogen Sulfide*. Chemical Sampling Information [cited 2014 January 21]; Available from: https://www.osha.gov/dts/chemicalsampling/data/CH_246800.html.

157. Nohr, E.A., et al., *Does low participation in cohort studies induce bias?* Epidemiology, 2006. **17**(4): p. 413-8.

158. Doll, R., *Cohort studies: history of the method. I. Prospective cohort studies.* Soz Praventivmed, 2001. **46**(2): p. 75-86.

159. Rothman, K.J., S. Greenland, and T.L. Lash, *Modern epidemiology*. 3rd ed. 2008, Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. x, 758 p.

160. Kleinbaum, D.G., H. Morgenstern, and L.L. Kupper, *Selection bias in epidemiologic studies.* Am J Epidemiol, 1981. **113**(4): p. 452-63.

161. Streib, G.F., *Participants and drop-outs in a longitudinal study.* J Gerontol, 1966. **21**(2): p. 200-9.

162. Van Beijsterveldt, C.E.M., et al., *Predictors of attrition in a longitudinal cognitive aging study: The Maastricht Aging Study (MAAS).* Journal of Clinical Epidemiology, 2002. **55**: p. 216-223.

163. Wolke, D., et al., *Selective drop-out in longitudinal studies and non-biased prediction of behaviour disorders.* Br J Psychiatry, 2009. **195**(3): p. 249-56.

164. Lebov, J.F., *Pesticide exposure and end-stage renal disease among pesticide applicators and their spouses in the Agricultural Health Study*, in *Department of Epidemiology*2014, University of North Carolina at Chapel Hill. p. 159.

165. Doll, R. and A.B. Hill, *Smoking and carcinoma of the lung; preliminary report.* Br Med J, 1950. **2**(4682): p. 739-48.

166. Brennan, P., et al., *Cigarette smoking and bladder cancer in men: a pooled analysis of 11 case-control studies.* Int J Cancer, 2000. **86**(2): p. 289-94.

167. Hickey, K., K.A. Do, and A. Green, *Smoking and prostate cancer.* Epidemiol Rev, 2001. **23**(1): p. 115-25.

168. Giovannucci, E., et al., *Smoking and risk of total and fatal prostate cancer in United States health professionals.* Cancer Epidemiol Biomarkers Prev, 1999. **8**(4 Pt 1): p. 277-82.

169. Cole, S.R. and M.A. Hernan, *Constructing inverse probability weights for marginal structural models.* Am J Epidemiol, 2008. **168**(6): p. 656-64.

170. Hernan, M.A., B. Brumback, and J.M. Robins, *Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men.* Epidemiology, 2000. **11**(5): p. 561-70.

171. Robins, J.M., M.A. Hernan, and B. Brumback, *Marginal structural models and causal inference in epidemiology.* Epidemiology, 2000. **11**(5): p. 550-60.

172. Brookhart, M.A., et al., *Variable selection for propensity score models.* Am J Epidemiol, 2006. **163**(12): p. 1149-56.

173. Cook, N.R., S.R. Cole, and C.H. Hennekens, *Use of a marginal structural model to determine the effect of aspirin on cardiovascular mortality in the Physicians' Health Study.* Am J Epidemiol, 2002. **155**(11): p. 1045-53.

174. Beard, J.D., et al., *Pesticide exposure and self-reported incident depression among wives in the Agricultural Health Study.* Environ Res, 2013. **126**: p. 31-42.

175. Benfante, R., et al., *Response bias in the Honolulu Heart Program.* Am J Epidemiol, 1989. **130**(6): p. 1088-100.

176. Boshuizen, H.C., et al., *Non-response in a survey of cardiovascular risk factors in the Dutch population: determinants and resulting biases.* Public Health, 2006. **120**(4): p. 297-308.

177. Langley, J.D., et al., *Factors associated with non-participation in one or two follow-up phases in a cohort study of injured adults.* Inj Prev, 2013. **19**(6): p. 428-33.

178. Littman, A.J., et al., *Assessing nonresponse bias at follow-up in a large prospective cohort of relatively young and mobile military service members.* BMC Med Res Methodol, 2010. **10**: p. 99.

179. Thomas, M.C., et al., *Non-attendance at re-examination 20 years after screening in the British Regional Heart Study.* J Public Health Med, 2002. **24**(4): p. 285-91.

180. Langhammer, A., et al., *The HUNT study: participation is associated with survival and depends on socioeconomic status, diseases and symptoms.* BMC Medical Research Methodology, 2012. **12**: p. 143.

181. Alonso, A., et al., *Predictors of follow-up and assessment of selection bias from dropouts using inverse probability weighting in a cohort of university graduates.* Eur J Epidemiol, 2006. **21**(5): p. 351-8.

182. Goldberg, M., et al., *Health problems were the strongest predictors of attrition during follow-up of the GAZEL cohort.* J Clin Epidemiol, 2006. **59**(11): p. 1213-21.

183. Greenland, S., *Quantifying biases in causal models: classical confounding vs collider-stratification bias.* Epidemiology, 2003. **14**(3): p. 300-6.

184. Beard, J.D., et al., *Pesticide Exposure and Depression among Male Private Pesticide Applicators in the Agricultural Health Study.* Environ Health Perspect, 2014.

185. Weuve, J., et al., *Accounting for bias due to selective attrition: the example of smoking and cognitive decline.* Epidemiology, 2012. **23**(1): p. 119-28.

186. Gottesman, R.F., et al., *Impact of differential attrition on the association of education with cognitive change over 20 years of follow-up: the ARIC neurocognitive study.* Am J Epidemiol, 2014. **179**(8): p. 956-66.

187. National Institute on Alcohol Abuse and Alcoholism. *Drinking levels defined* Overview of Alcohol Consumption [cited 2015 February 18]; Available from: http://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/moderate-binge-drinking.

188. Radon, K., et al., *Air contaminants in different European farming environments.* Ann Agric Environ Med, 2002. **9**(1): p. 41-8.

189. Senthilselvan, A., et al., *A prospective evaluation of air quality and workers' health in broiler and layer operations.* Occup Environ Med, 2011. **68**(2): p. 102-7.

190. Wilkins, J.R., 3rd, et al., *Prevalence of chronic respiratory symptoms among Ohio cash grain farmers.* Am J Ind Med, 1999. **35**(2): p. 150-63.

191. Arif, A.A. and G.L. Delclos, *Association between cleaning-related chemicals and work-related asthma and asthma symptoms among healthcare professionals.* Occup Environ Med, 2012. **69**(1): p. 35-40.

192. Preller, L., et al., *Disinfectant use as a risk factor for atopic sensitization and symptoms consistent with asthma: an epidemiological study.* Eur Respir J, 1996. **9**(7): p. 1407-13.

193. Purohit, A., et al., *Quaternary ammonium compounds and occupational asthma.* Int Arch Occup Environ Health, 2000. **73**(6): p. 423-7.

194. Tarone, R.E., et al., *The Agricultural Health Study: factors affecting completion and return of self-administered questionnaires in a large prospective cohort study of pesticide applicators.* Am J Ind Med, 1997. **31**(2): p. 233-42.

195. Shavelle, R.M., et al., *Life expectancy and years of life lost in chronic obstructive pulmonary disease: findings from the NHANES III Follow-up Study.* Int J Chron Obstruct Pulmon Dis, 2009. **4**: p. 137-48.

196. Agency, U.S.E.P., *Chapter 2. AFOs and CAFOs*, in *NPDES Permit Writer's Manual for Concentrated Animal Feeding Operations*2012. p. 2-1, 2-16.

197. Barnes, P.J., S.D. Shapiro, and R.A. Pauwels, *Chronic obstructive pulmonary disease: molecular and cellularmechanisms.* European Respiratory Journal, 2003. **22**(4): p. 672-688.

198. Greenland, S., J. Pearl, and J.M. Robins, *Causal diagrams for epidemiologic research.* Epidemiology, 1999. **10**(1): p. 37-48.

199. Radon, K., *The two sides of the "endotoxin coin".* Occup Environ Med, 2006. **63**(1): p. 73-8, 10.

200. Radon, K., *To live or not to live near a farm?* Occup Environ Med, 2014. **71**(2): p. 79.

201. Centers for Disease, C. and Prevention, *State-specific prevalence of cigarette smoking and smokeless tobacco use among adults --- United States, 2009.* MMWR Morb Mortal Wkly Rep, 2010. **59**(43): p. 1400-6.

202. Richardson, D.B., A. Kinlaw, and S.R. Cole, *Standardized binomial models for risk or prevalence ratios and differences*.

203. Gibson, P.G. and J.L. Simpson, *The overlap syndrome of asthma and COPD: what are its features and how important is it?* Thorax, 2009. **64**(8): p. 728-35.

204. Welte, T. and D.A. Groneberg, *Asthma and COPD.* Exp Toxicol Pathol, 2006. **57 Suppl 2**: p. 35-40.

205. Henneberger, P.K., et al., *Exacerbation of symptoms in agricultural pesticide applicators with asthma.* Int Arch Occup Environ Health, 2013.

206. Hoppin, J.A., et al., *Chemical predictors of wheeze among farmer pesticide applicators in the Agricultural Health Study.* Am J Respir Crit Care Med, 2002. **165**(5): p. 683-9.

207. Agency, U.E.P., *Pesticides industry sales and usage: 2006 and 2007 Market estimates*, 2011: Washington, D.C.

208. Melbostad, E., E. Wijnand, and P. Magnus, *Chronic bronchitis in farmers.* Scand J Work Environ Health, 1997. **23**(4): p. 271-280.

209. Von Essen, S., et al., *Respiratory issues in beef and pork production: recommendations from an expert panel.* J Agromedicine, 2010. **15**(3): p. 216-25.

210. McEachran, A., et al., *Antibiotics, bacteria, and antibiotic resistance genes: Aerial transport from cattle feed yards via particulate matter.* Environ Health Perspect, 2015.

211. U.S. Environmental Protection Agency Office of Water Office of Wastewater Management, *NPEDS permit writers' manual for concentrated animal feeding operations*, 2012.

212. Becklake, M.R., *Chronic airflow limitation: its relationship to work in dusty occupations.* Chest, 1985. **88**(4): p. 608-17.

213. Broder, I., et al., *Longitudinal study of grain elevator and control workers with demonstration of healthy worker effect.* J Occup Med, 1985. **27**(12): p. 873-80.

214. Chenard, L., et al., *Lung function and farm size predict healthy worker effect in swine farmers.* Chest, 2007. **131**(1): p. 245-54.

215. Radon, K., M. Goldberg, and M. Becklake, *Healthy worker effect in cohort studies on chronic bronchitis.* Scand J Work Environ Health, 2002. **28**(5): p. 328-32.

216. Thelin, A. and S. Hoglund, *Change of occupation and retirement among Swedish farmers and farm workers in relation to those in other occupations. A study of "elimination" from farming during the period 1970-1988.* Soc Sci Med, 1994. **38**(1): p. 147-51.

217. Zock, J.P., D. Heederik, and G. Doekes, *Evaluation of chronic respiratory effects in the potato processing industry: indications of a healthy worker effect?* Occup Environ Med, 1998. **55**(12): p. 823-7.

218. Burrows, B., *Airways obstructive diseases: pathogenetic mechanisms and natural histories of the disorders.* Med Clin North Am, 1990. **74**(3): p. 547-59.

219. Hogg, J., *Peripheral lung remodelling in asthma and chronic obstructive pulmonary disease.* Eur Respir J, 2004. **24**(6): p. 893-4.

220. Silva, G.E., et al., *Asthma as a risk factor for COPD in a longitudinal study.* Chest, 2004. **126**(1): p. 59-65.

221. Salameh, P.R., et al., *Chronic bronchitis and pesticide exposure: a case-control study in Lebanon.* Eur J Epidemiol, 2006. **21**(9): p. 681-8.

222. Zhang, L.X., et al., *Occupational and environmental risk factors for respiratory symptoms in rural Beijing, China.* Eur Respir J, 2002. **20**(6): p. 1525-31.

223. *North Carolina agricultural chemicals manual* 2014, North Carolina Cooperative, Extension Service, College of Agriculture and Life Sciences, North Carolina State University,: Raleigh, N.C. p. 67-180.

224. *Carbaryl: Amending product registrations to terminate uses and eliminate certain applicaiton methods*, US Environmental Protection Agency, Editor 2009. p. 11553-11557.

225. Schoenberger, C.I., et al., *Paraquat-induced pulmonary fibrosis. Role of the alveolitis in modulating the development of fibrosis.* Am Rev Respir Dis, 1984. **129**(1): p. 168-73.

226. Kimbell-Dunn, M.R., et al., *Work-related respiratory symptoms in New Zealand farmers.* Am J Ind Med, 2001. **39**(3): p. 292-300.

227. Rose, G., *Sick individuals and sick populations.* Int J Epidemiol, 1985. **14**(1): p. 32-8.

228. Bang, K.M., *Chronic obstructive pulmonary disease in nonsmokers by occupation and exposure: a brief review.* Curr Opin Pulm Med, 2015. **21**(2): p. 149-54.

229. Weinhold, B., *Agriculture-COPD link bolstered.* Environ Health Perspect, 2007. **115**(9): p. A444.

230. Shahar, E., A.R. Folsom, and R. Jackson, *The effect of nonresponse on prevalence estimates for a referent population: insights from a population-based cohort study.*

Atherosclerosis Risk in Communities (ARIC) Study Investigators. Ann Epidemiol, 1996. **6**(6): p. 498-506.

231. Arrighi, H.M. and I. Hertz-Picciotto, *The evolving concept of the healthy worker survivor effect.* Epidemiology, 1994. **5**(2): p. 189-96.

232. Blair, A., et al., *Reliability of reporting on life-style and agricultural factors by a sample of participants in the Agricultural Health Study from Iowa.* Epidemiology, 2002. **13**(1): p. 94-9.