

# The cohort of young Danish farmers – A longitudinal study of the health effects of farming exposure

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**Abstract:** Working in agriculture poses a serious risk for development of respiratory diseases, especially when working in animal housing. Animal workers are exposed to a mixture of organic and inorganic dust together with fumes and gases, including allergens and microbial-associated molecular patterns with a potentially major impact on respiratory health and the immune system. Exposure to microbial agents in animal housing is associated with an increased prevalence of respiratory symptoms, including bronchial hyperresponsiveness, accelerated lung function decline, and neutrophil-mediated inflammation. These clinical findings are often seen without IgE-mediated sensitization. In fact it has been found in recent studies that the prevalence of atopic sensitization and atopic asthma is low among farmers compared with other populations. The SUS study was designed to identify the type and occurrence of respiratory symptoms and disease, and to investigate risk factors for respiratory disorders and changes in lung function among young farming students. The cohort of young Danish farmers was established in 1992/1994 and followed up in 2007/2008 with a participation rate of 51.7%. The cohort consists of 1734 male farming students, 230 female farming students, and 407 army recruits as controls.

**Keywords:** respiratory health, atopy, asthma, rhinitis, lung function, farming environment, occupational exposure, cohort study

## Introduction

The farming industry is an important export industry in Denmark, as well as in many other Western countries. Investigation of the occupational health hazards of farming is therefore of considerable interest to both the farming industry and the Danish community. Despite major changes in farming during recent decades, and an increased awareness of the potential hazards from agricultural exposure, the risk of lung diseases and loss of lung function in farm workers is still considerable.<sup>1</sup>

Working in agriculture poses a serious risk for development of respiratory diseases, especially when working in animal housing. Animal housing workers are exposed to a mixture of organic and inorganic dust together with fumes and gases, including allergens and microbial-associated molecular patterns (MAMP) with a potentially major impact on respiratory health and the immune system.<sup>2,3</sup>

Respiratory health effects in farming, especially in swine-confinement workers are well described. Exposure to microbial agents in a swine-confinement environment is associated with an increased prevalence of respiratory symptoms, including bronchial hyperresponsiveness (BHR), accelerated lung function decline, and neutrophil-mediated inflammation,<sup>2,4</sup> without IgE-mediated sensitization against swine and food allergens. In fact, it has been found in recent studies that

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the prevalence of atopic sensitization and atopic asthma is low in farmers compared with other populations. A low prevalence of allergy and allergic asthma has been found in studies of children<sup>5</sup> and young adults<sup>6</sup> born and raised on a farm,<sup>6</sup> as well as in adult farmers exposed to the same environment.<sup>7,8</sup> The general respiratory health of any farmer is also dependent on individual genetic makeup. It has been found that toll-like receptor (TLR) gene polymorphisms are important determinants of susceptibility to asthma and allergy.<sup>9</sup> TLRs are an evolutionarily conserved group of molecules which are a part of the innate immune system. TLRs are expressed in antigen-presenting cells and epithelial cells, and have microbial molecules as ligands.<sup>10</sup>

The SUS study was designed to identify the type and occurrence of respiratory symptoms, measure lung function, and investigate risk factors for respiratory disorders and annual rates of change in lung function among young farming students. Data were analyzed both as a cross-sectional study at baseline and as part of a case-control follow-up study over five years.

Most of the research in this area has been in the form of cross-sectional studies. Few cohort studies have been reported thus far and, to our knowledge, no studies have addressed the respiratory health of people entering the farming industry at a young age. Although sensitization to storage mites and other airborne allergens has been described, reports on sensitization to hog antigens have been inconclusive concerning the extent to which allergies contribute to the increased prevalence of respiratory symptoms in farm workers.

In an attempt to clarify the contribution of farming exposure to respiratory disease and loss of lung function over time, the SUS study was followed up with the SUS12 study. During the SUS12 study, the initial SUS cohort was re-examined. The SUS12 follow-up study in combination with the original data from the SUS study now allows for longitudinal investigation of risk factors and occupational influence on the development of respiratory disease. Furthermore, it is possible to investigate potential gene-environment interactions related to farming exposure. The SUS project group is collaborating with the European research group GABRIEL, which is focusing on genes important for asthma and gene-environment interactions among children and working adult populations, using a whole genome analysis and candidate gene approach (<http://www.gabriel-fp6.org/>).

Despite the wealth of research on sensitisation, lung disease, and lung function done in farm workers in the last three decades, important questions remain unanswered. There is no unequivocal documentation of which dust components in

the exposure have adverse health effects. Incidence studies of health outcomes which include reliable, representative, and valid exposure assessments have yet to be published. Incidence studies with asthma and COPD as outcomes still need to be performed. The question of phenotypes and genotypes of asthma and the association with exposure is yet to be fully answered. There is currently no knowledge of any time window for the “protective effect” of being raised on a farm regarding sensitisation, inflammation, and lung disease. Does childhood exposure to rural allergens confer an overall protection, or does the individual experience an increase in sensitization with time in a dose-dependent manner? Does the protective effect of farming exposure on allergic sensitization continue over time? Additionally, how can a supposed high allergen exposure convey loss of sensitization? What is the association between changes in sensitization and the risk of respiratory disorders? What influence does occupational activation of MAMPs have on the diseases encountered in farming?

## Trial design

This research included both a cohort study which was a cross-sectional comparison of type and occurrence of respiratory symptoms in farming students and nonfarming rural controls and a longitudinal study which investigated new cases of respiratory disease over time in relation to farming exposure.

## Study population

The cross-sectional study consisted of 2478 farming students identified during their second stay at the farming schools in Denmark during the period February 1992 to February 1994. Of 2004 students (81%) who indicated that they wished to participate, 40 (2%) did not attend for their baseline clinical assessment. The final group consisted of 1734 male and 230 female farming students. Army recruits were invited to participate as controls, provided that they came from rural areas but were not planning on becoming farmers. There were 967 eligible army recruits of whom 592 (61%) agreed to participate. A random sample of 407 of these recruits were chosen and used in the study. The demographics of the cohort are presented in Table 1 and their lung function and respiratory symptoms are summarized in Table 2.

## Follow-up

The subjects were investigated at baseline and then followed up with annual questionnaires and phone interviews for five years. All new respiratory symptoms were recorded. All subjects reporting new asthma symptoms and a matched

**Table 1** Demographic and exposure characteristics of the cohort (n = 2,371)

	Female students (n = 232)	Male students (n = 1734)	Male controls (n = 405)
<b>Demographics</b>			
Age (yrs) <sup>§</sup>	19.1 (17–47)	18.5 (17–49)	19.0 (18–23)
Height (cm) <sup>§</sup>	169 (149–192)	183 (161–198)	181 (166–197)
Smokers*	73 (32)	554 (32)	136 (34)
<b>Exposures</b>			
Hours farm work/week <sup>§</sup>	37 (0–72)	40 (0–100)	0 (0–65)
Work with swine*	67 (29)	433 (25)	10 (3)
Work with cattle*	66 (28)	575 (34)	18 (4)
Work with swine and cattle*	22 (10)	231 (13)	13 (3)
Field work*	89 (39)	1125 (66)	64 (16)

Notes: <sup>§</sup>Median (min – max), \*n (%).

control group without symptoms were offered a clinical assessment to establish a diagnosis. In 2007 a comprehensive follow-up of the cohort was done using the Danish Civil Registration System to track new addresses, deaths, and emigration in the cohort. Of the 2371 participants, 2262 were identified to have a new Danish address, while 26 had died, and 51 had emigrated or did not have a permanent address. Thirty-two subjects could not be identified, most often because of incorrect registration of their unique personal identity number during the baseline study.

## Measurements

### Health outcome

At baseline the original SUS questionnaire was used, and in SUS12 this was extended to include further questions from the European Community Respiratory Health Survey (<http://www.ecrhs.org>). Lung function was measured with a dry bellow spirometer and with a spirometer (MicroMedical<sup>®</sup>; Lyngby Denmark). For the SUS12 study the

software was transferred for use on portable computers using the Windows 2000 platform. BHR was recorded according to the Yan method<sup>11</sup> with a calibrated DeVilbiss No 40 nebulizer (DeVilbiss Healthcare, LLC, Johnstown, PA, USA) connected to an “artificial hand” which uses compressed air to produce a pressure pulse similar to that created by a hand.<sup>12</sup> For skin prick tests (SPT), a panel of nine common inhalant allergens (grass, mugwort, horse, dog, cat, house dust mites, moulds [*Alternaria alternata* and *Claudosporium herbarum*], extended with three storage mites [*Tyrophagus putrescentiae*, *Lepidoglyphus destructor*, and *Acarus siro*], and swine and cow dander were used (Soluprick<sup>®</sup>, ALK-Abello, Copenhagen, Denmark).

### Exposure data

At baseline and annually for five consecutive years, questionnaire information about the number and type of housed animals and amount of work done in these settings was recorded for all subjects in the cohort. In the case-control

**Table 2** Lung function and respiratory symptoms in the cohort

	Female students		Male students		Male rural controls	
	Smokers (n = 73)	Non-smokers (n = 159)	Smokers (n = 554)	Non-smokers (n = 1180)	Smokers (n = 136)	Nonsmokers (n = 269)
<b>Lung function mean (SD)</b>						
FEV <sub>1</sub>	3.49 (±0.47)	3.61 (±0.55)	4.57 (±0.58)	4.64 (±0.61)	4.75 (±0.59)	4.70 (±0.65)
FVC	4.04 (±0.55)	4.14 (±0.67)	5.48 (±0.68)	5.42 (±0.72)	5.57 (±0.69)	5.50 (±0.78)
<b>Respiratory symptoms N (%)</b>						
Asthma	5 (6.8)	10 (6.3)	35 (6.3)	46 (3.9)	4 (2.9)	11 (4.1)
BHR	6 (8.5)	15 (9.8)	66 (12.2)	94 (8.2)	9 (7.2)	22 (8.5)
Hayfever	14 (19.2)	20 (12.6)	48 (8.7)	109 (9.3)	18 (13.2)	42 (15.6)

<sup>§</sup>Median (min – max), \*(n) may vary due to missing values (%).

Abbreviation: BHR, bronchial hyperresponsiveness.

study, detailed hygienic information was recorded on, eg, type of feeding systems, type of litter, use of respirators, and cleaning procedures.

In SUS12, a more comprehensive exposure assessment including personal measurements and exposure modeling has been applied. One hundred farms were randomly selected and stratified by type and size in a defined geographical area among the remaining active farming population of the initial SUS cohort. Approximately 250 farmers employed in the selected farms have been monitored during the summer and winter of 2008–2009. Full-shift personal inhalable dust samples (one in each season) are being collected on 37 mm glass fiber filters using GSP sampling heads at a flow rate of 3.5 L/min from every farmer. Concurrently, farmers are asked to fill in a detailed diary regarding their working activities for one week in each period (14 days in total). Walk-through surveys and personal interviews are performed to collect information on technical parameters and farm characteristics with known or suspected influence on the levels of exposure. Models on associations between technical parameters, farm characteristics, working tasks and exposure (dust and MAMPs) including within- and between-worker variability will be developed using regression analysis based on linear mixed-effect models. The derived equations will be used along with questionnaire data on historical exposure

and exposure information from two previous studies<sup>13,14</sup> to estimate current and retrospective exposure in the follow-up study.

## Completeness of follow-up

The cohort consists of 2371 participants; for the SUS12 study, only 2262 of these could be identified with an address in Denmark, because some of the participants had immigrated, died, or were simply lost to follow-up. Of the identifiable participants, only 1170 were available to be re-examined, representing an overall attrition rate of 51.7%, which was attributable to several reasons, including subjects choosing not to participate in the follow-up study, failure to attend for their follow-up appointment, and/or not responding to letters or phone calls.

## Ongoing release of data

The SUS study has so far lead to the publication of 13 peer-reviewed articles,<sup>6,15–26</sup> one thesis,<sup>27</sup> and several presentations at international conferences. An overview of the 13 articles and the main findings is summarised in Table 3.

The study showed that sensitisation to mites, animal dander, and pollen was higher in controls than in farming school students.<sup>16</sup> Analyses published in 2002 demonstrated a lower prevalence of allergic symptoms, BHR, and sensitisation measured with skin prick test, and specific

**Table 3** Published articles originating from the SUS study

References	Main findings
15	The resistance of the mini-Wright flow meter causes less variation in recordings but reduce peak expiratory flow.
16	Skin prick tests to house dust and storage mites were more prevalent among controls compared with male and female farming students; size of house dust mite weal and number of positive skin prick reactions were associated with BHR.
17	No relation between asthma and farming exposure was seen, but lung function was slightly reduced in the male farming students compared with male controls. Prevalence of asthma was related to smoking, female sex, and family history of asthma and allergy.
18	The shape of the maximum expiratory flow-volume curve reflects exposure in farming.
19	S and Z $\alpha_1$ -antitrypsin alleles are risk factors for BHR in young farmers indicating a gene/environment interaction.
20	LDS using FEV <sub>1</sub> is the best spirometric index to measure short time repeatability of histamine bronchial testing.
6	Farming students born and raised on a farm had lower prevalence of allergic symptoms, BHR, positive SPT, and specific IgE than students raised on a farm.
21	Selenium measured both in serum and urine is associated with mild asthma and atopy.
22	For asthmatics the time domain index $\alpha_{1.75}$ was found to discriminate better among the flow indices applied whereas for BHR the LDS using FEV <sub>1</sub> was superior to other measures of BHR.
23	CD3 levels in young farmers correlate with respirable dust exposure levels during work in swine-confinement housing.
24	Exposure to work-related levels of swine dust upregulates CD106 in human alveolar macrophages.
25	A single exposure to organic dust in non-naïve nonexposed volunteers induces long lasting symptoms of endotoxin tolerance.
26	CD14/-260 and CD14/-651 promoter polymorphisms associated with atopy prevalence in young adults with farm exposure.

**Abbreviations:** BHR, bronchial hyperresponsiveness; LDS, log dose slope; SPT, skin prick test.

and total IgE in subjects raised on a farm, compared with upbringing elsewhere.<sup>6</sup> As opposed to a possible protective effect of being raised on a farm, low concentrations of alpha-1 antitrypsin and rare genotypes (ZZ, ZS, SS) were found to increase the risk of BHR, but only among the farming students, indicating a gene-environment interaction for the inflammatory asthma phenotype.<sup>19</sup> Preliminary analyses using available exposure data from other sources have found a dose-response relationship between estimated exposure to total dust and new onset of asthma.<sup>28</sup> Furthermore, the prevalence of chronic bronchitis, self-reported asthma with BHR, and BHR was low. The prevalence of self-reported asthma without BHR was high. Lung function was slightly lower in male farming students compared with controls. There was a weak or no association between smoking and respiratory symptoms as well as lung function. It was found that FEV<sub>1</sub> was the best index to measure basal lung function in response to bronchial provocation.

The SUS study has contributed significantly to our understanding of the inflammatory mechanisms involved in the immune response to organic dust exposure. This was investigated by exposing the participants for three hours to a swine-confinement environment containing dust and endotoxin levels at the lower end of the exposure range for Danish and European farms. It was found that dust exposure activated the complement system. Particularly for the farming students, C3d plasma levels correlated with respirable dust. Acute exposure was also seen to lead to other weak systemic inflammatory responses.<sup>23</sup> Further dust exposure studies suggest that there is a specific requirement for CD106 during inflammatory recruitment of monocytes in the human lung,<sup>24</sup> and this has previously been shown to be the case in the murine lung. Endotoxin tolerance has previously been described *in vitro* and in animal studies as a mechanism that modifies the threshold at which immune response occurs. It has also been found that long-lasting endotoxin tolerance and immune suppression may be induced by brief exposure to dust concentrations in the medium-low range of occupational levels.<sup>25</sup>

The SUS study has furthermore been used to investigate the correlation between selenium levels and asthma and atopy. It was found that selenium in serum and urine is associated with mild asthma and atopy.<sup>21</sup>

The longitudinal study provides data for investigating the incidence of respiratory disease in a farming environment. These data will also enable investigation of the interactions between genes and the environment and elucidation of the risk factors involved in the development of new asthma

cases. It will also be possible to investigate the effects of respiratory diseases on lung function, and identify the parameters that describe this change best. Finally it would be helpful to be able to estimate the effect of respiratory symptoms and disease on change of work environment for the individual.

## Strengths and weaknesses

The SUS cohort affords a unique opportunity for a longitudinal investigation of the effect of farming exposure on lung function and respiratory symptoms. To our knowledge, this cohort is unique. As already mentioned, lung function and respiratory symptoms have been assessed in all study participants in both at the SUS and the SUS12. It will also be possible using these data to assess respiratory health in relation to specific farming exposure for each subject. Additionally, important information on potential gene-environment interaction is emerging from this research through the GABRIEL collaboration. However, a potential weakness of this research is the relatively high attrition rate of approximately 50%, which might affect the significance of data generated by future statistical analyses.

## Access to data

A website has been created (<http://www.folkesundhed.au.dk/mil/forskning/sus12>), where the status of the SUS12 project is regularly updated. Specific questions regarding the cohort or the SUS12 project can be addressed to either Professor Torben Sigsgaard ([ts@mil.au.dk](mailto:ts@mil.au.dk)), Associate Professor Vivi Schlünssen ([vs@mil.au.dk](mailto:vs@mil.au.dk)), Associate Professor Øyvind Omland ([oo@rn.dk](mailto:oo@rn.dk)), or Senior Consultant Charlotte Hjort ([c.hjort@dadlnet.dk](mailto:c.hjort@dadlnet.dk)).

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## Disclosure

The author report no conflicts of interest in this work.

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