Chronic Non Specific Lung Disease in the workforce:

occurrence, impact, and identification of CNSLD

Chronische Aspecifieke Respiratoire Aandoeningen in het beroep:
voorkomen, gevolgen en herkenning van CARA.

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1 Introduction

1.1 EPIDEMIOLOGICAL STUDIES ON RESPIRATORY DISEASE AND ITS OCCURRENCE AND IMPACT IN OCCUPATIONS

For many people the most important place of exposure to hazardous agents is the work environment; most hazardous agents are encountered in the work environment in considerably higher concentrations than in the general and domestic environment. Subjects occupationally exposed to dusts, gases, and fumes are at risk of developing respiratory diseases or aggravating existing respiratory conditions.

The relationship between occupational exposures and the occurrence of respiratory diseases has attracted much interest with regard to the aetiology of these disorders. For a long time, the attention was predominantly focused on respiratory diseases like silicosis and asbestosis. In the past decades, Chronic Non-Specific Respiratory Disease (CNSLD, see table 1 for definitions), increasingly has gained interest. Although the 'umbrella term' CNSLD, covering several diseases, mainly has been used in The Netherlands, this thesis continues to use this term in order to avoid the need of continuously discussing particular diagnoses and definitions in the studies referred to in this thesis.

Establishing a causal relationship between occupational exposures and CNSLD has not been straightforward. Dominance of other lung diseases, unsophisticated research techniques, the absence of longitudinal studies on occupationally exposed workers, omnipresent smoking habits, and the healthy worker effect obscured the relationship before the 1980s.[1-4] Nowadays, various airborne agents have been identified that may cause asthma,[5] chronic bronchitis,[6-7] and more specifically Chronic Obstructive Pulmonary Disease (COPD).[1] In various countries, a large number of studies have demonstrated the existence of a relationship among occupational exposure and CNSLD in specific occupational groups as well as in the general population.[8-15] In general population studies, relationships between occupational exposures and respiratory symptoms, decreased lung function and/or respiratory diseases were found, with strikingly similar odds ratios varying between 1.3 and 2.7 for

exposed workers as compared with unexposed workers.[9-12, 16, 17] The attributable risk of occupational exposure to dust and fumes to CNSLD in the general population is estimated to range between 11-19 percent[16] and 3-20 percent,[17] depending on the exposure distribution in the study population and the definition of CNSLD applied.

Table 1 Clarification of terminology

Chronic Non-Specific Lung Disease (CNSLD)
An umbrella-term for respiratory diseases, characterised by airflow obstruction with symptoms such as cough, phlegm production, shortness of breath, wheeze, and chest tightness. CNSLD comprises asthma and Chronic Obstructive Pulmonary Disease (COPD).

Asthma
A heterogeneous disorder characterised by cough, wheeze, and dyspnea, and variable degrees of reversible airflow obstruction, in which reversibility occurs either spontaneously or as a result of treatment.[18]

COPD
Airflow obstruction with prolonged cough, dyspnea, and wheeze as cardinal symptoms. Comprises of chronic obstructive bronchitis and emphysema.[18]

Surveillance (medical surveillance)

Definition:	The ascertainment of information for the purpose of detecting changes in trend or distribution in order to initiate intervention, control, or other investigation.[19]
Focus:	Population. Collection of information about individuals in order to examine patterns within a population (distribution and trends of incidence).
Purpose:	Primary prevention: identification and elimination of causes of disease

Screening

Definition:	The application of diagnostic procedures to asymptomatic people in order to classify them as likely, or unlikely, to have the disease that is the object of screening. People who appear likely to have the disease are investigated further to arrive at a final diagnosis.[20]
Focus:	Individuals in a population, often persons at high risk of a disease.
Purpose:	Secondary prevention: the early diagnosis and treatment of disease.

In contrast with the large number of studies on the role of occupational exposures in the aetiology of CNSLD, only occasionally the course of CNSLD in workers and the impact of CNSLD on their performance at work have been studied. Information about the impact of CNSLD on the performance of the workforce is limited. The impact of CNSLD can for instance be assessed by disability measures, such as sickness absence. In the past decade, in The Netherlands about 4 percent of the subjects with a permanent work disability were diagnosed as having a respiratory disease as primary cause of their disability. About 90 percent of these cases was caused by CNSLD. Based on observations in a Dutch population study, it has been estimated that 75 percent of sickness absence due to respiratory disorders has CNSLD as direct or indirect cause, and 15 to 20 percent of all sickness absence is assumed to be caused by CNSLD.[21] These figures are rough estimates as national registers of sickness absence in The Netherlands only cover about half of the working population. Moreover, in about three-quarters of all cases of sickness absence the diagnosis is unknown. National figures of sickness absence and (industrial) disability insurance are, therefore, insufficient to study the impact of CNSLD on the performance of the workforce. An alternative is the comparison of sickness absence among workers with and without respiratory symptoms.[22-24] The results of these studies indicate that sickness absence is indeed higher in workers with respiratory symptoms.

An important cause of the limited information about the impact of CNSLD is the selection process that forces workers with respiratory disease out of the workforce. The result of this selection process is known as the healthy worker effect.[25-29] The healthy worker effect indicates that, in general, a working population is healthier than the general population. The existence of the healthy worker effect has been known for a long time. Only few morbidity studies on CNSLD have addressed the healthy worker effect explicitly in the analysis.[12,30-34] The studies available show that, with the same age and similar smoking habits, the health status of those leaving the industry before retirement is worse than of those staying in the industry. Studies among coal workers have shown a positive association between respiratory symptoms and early retirement because of disability due to respiratory disease.[30] In another study, workers who left the industry early and who had respiratory symptoms during the following years demonstrated a stronger relationship between dust exposure and lung function decline than those workers who stayed in the industry.[31] Studies among grain workers show that workers who had left the grain industry had more respiratory symptoms during the initial survey[32] or had reduced methacholine thresholds[33] compared with those who remained in the grain industry.

In a general population study, workers exposed to dusts, gases, and fumes tended to change job more often than those without these occupational exposures.[12] Workers who changed jobs changed towards jobs with lower exposure levels or to physically less demanding jobs.

1.2 CURRENT PRACTICES IN OCCUPATIONAL HEALTH CARE

Acknowledging the physical and economic impact of CNSLD on the workforce, the need for health surveillance and screening programmes on CNSLD in occupational health have to be investigated (see table 1 for definitions).

Most emphasis so far in occupational health care has been on screening. Screening is the application of diagnostic procedures to asymptomatic people in order to classify them as likely, or unlikely, to have the disease that is the object of screening. People who appear likely to have the disease are investigated further to arrive at a final diagnosis.[20] Screening is essentially a tool for secondary prevention; detecting disease not yet under medical care and identifying those subjects needing further individual attention. Examples in occupational health care of possible screening instruments are the pre-placement medical examination and the periodic health examination. In these examinations, the occupational physician looks for risk factors that will identify the worker at high risk of developing disease. In the case of CNSLD, a number of risk factors have been identified which may predispose to the development of CNSLD. A first note to these examinations on CNSLD is that information on the interrelationship of individual traits and work-related risk factors is scarce. The role of risk factors in screening, and in particular in the pre-placement examination, for CNSLD is thus as yet undetermined.[35,36] Obviously, this is of primary importance in the discussion about the usefulness of screening during pre-placement medical examinations or periodic health examinations.

A second note on current practices in occupational health care is that surveillance is hardly practiced; the collected information about individuals obtained by (periodical) medical examination is not aggregated in order to examine patterns and trends in the population. These analyses would result in information on group-level and could lead to primary prevention: the identification and elimination of causes of the disease.

Since there is no gold standard available that distinguishes clearly between subjects with and those without CNSLD, one might argue that, at this stage, a sound basis for secondary (and primary) prevention of CNSLD in occupational health care is lacking.

Indeed, occupational physicians acknowledge the need for guidelines on diagnosis and treatment of CNSLD. This is rather surprising since each year large numbers of workers undergo pre-placement or periodic medical health examinations, answering questions about respiratory symptoms and performing lung function tests. This brings up the question whether these investigations are to any avail and whether the time and money invested in these surveillance programmes could be put to better use. Or, one might wonder, is it possible to improve the current procedures and practices in occupational health care in such a way that CNSLD will be detected at an early stage, and, subsequently, aggravation of the disease is prevented?

With these questions in mind this thesis deals with the two issues described in the previous sections: firstly, the impact of CNSLD on work performance and premature retirement and secondly, the possible contribution of surveillance and screening to occupational health care for workers with CNSLD.

1.3 OBJECTIVES OF THE THESIS

The objectives of this thesis are twofold:

1) To study the occurrence and impact of CNSLD in occupational groups. This objective addresses the following questions:
   * Are workers in a number of occupational conditions more prone to develop CNSLD?
   * How do workers with CNSLD cope in these work conditions with routine activities at work?
2) To support the identification of workers with CNSLD by evaluating the available diagnostic tests for CNSLD in an occupational setting. This objective addresses the following question:
   * Is it possible to improve the performance of health surveillance programmes for CNSLD with the use of currently available instrumentarium in occupational health care?

1.4 STRUCTURE OF THIS THESIS

Occurrence and impact of CNSLD

The first part of this thesis, chapters two to five, focuses on the questions on the occurrence and impact of CNSLD in a selected number of occupations. In search of the answers to these questions, four different health endpoints are described; the incidence of CNSLD, decline in lung function

over five years, development of laboratory animal allergy, and sickness absence. In chapter two a community-based approach has been used to compare the incidence of CNSLD in occupationally exposed versus non-exposed men. The most important aspect of the analysis is the relationship between various time-related exposure variables with CNSLD incidence, an approach common in cancer epidemiology, but not yet applied in respiratory occupational epidemiology. In chapter three, workers in the grain and animal feed industry have been selected to investigate the influence of particular exposures on CNSLD, characterised by decline in lung function over five years. The longitudinal design allows investigation into the prognosis of persons with CNSLD and the healthy worker effect, thereby, facilitating the standard setting for grain dust by the Dutch National Health Council. In chapter four a similar approach to investigate the influence of particular exposures on CNSLD, characterised by the development of laboratory animal allergy, has been adopted. In this study laboratory animal workers were followed from the start of their employment onwards. The analysis focuses on the role of risk and modifying factors, such as atopy and occupational exposure, on subsequent development of laboratory animal allergy. In chapter five the impact of CNSLD on workers' health is shown. This study describes determinants of sickness absence due to respiratory symptoms within a Dutch occupational setting.

Identification of workers with CNSLD

The second part of this thesis, chapters six and seven, addresses screening and surveillance of CNSLD at the workplace. In these chapters two possibilities for a better identification of workers with CNSLD are outlined. First, optimising the cut-off point between normal and abnormal test results. Second, combining several surveillance tests in the diagnostic decision. In chapter six, optimisation of spirometry is performed with techniques stemming from clinical decision analysis. Spirometry is one of the most used surveillance tests. This chapter studies the usefulness of clinical decision analysis for occupational health. In chapter seven determinants of CNSLD are used to estimate the probability of disease and compared to an estimate based on the prevalence of disease in the target group. Moreover, the usefulness of combining information from several tests is studied, using a stepwise design for health surveillance.

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Part 1

Occurrence and impact of CNSLD

2 Occupational exposures estimated by a population specific job exposure matrix and 25-year incidence rate of chronic nonspecific lung disease (CNSLD): the Zutphen Study[1]

ABSTRACT

The influence of occupational exposures on total mortality and respiratory mortality and morbidity was examined, employing a population specific Job Exposure Matrix (JEM). Moreover, the relationship between time-related variables of exposure to dust and chronic non specific lung disease (CNSLD) incidence was analysed, using time since first exposure and duration of exposure.

Occupational exposures in the Zutphen cohort were assessed by application of a JEM, arbitrarily considering jobs as exposed when at least 10% of men who had held the job of interest reported an exposure to one or more from a list of 27 chemical agents.

None of the exposures was related to mortality due to CNSLD, although results were influenced by the healthy worker effect and low mortality rates. Exposure to wood dust and a high probability of exposure to dust were associated with total mortality. Exposures to dust and solvents were statistically significantly related to CNSLD incidence. An exposure-response relationship was found for the probability of exposure to dust with CNSLD incidence. Time-related estimates of exposure to dust based on work history were negatively related to CNSLD incidence.

The results suggest the presence of a healthy worker effect, in a general population study, resulting in an underestimation of the relationship between occupational exposures and respiratory diseases based on the evidence published so far. The use of the full work history to determine exposure to dust lead to stronger relationships with CNSLD incidence, compared to conventional analyses using exposure at the start of follow-up.

1 Post WK, Heederik D, Kromhout H, Kromhout D. European Respiratory Journal 1994;7:1048-1055. Reproduced with permission from ERS Journals Ltd.

INTRODUCTION

In community-based and occupational group studies, the relationship between occupational exposures and total mortality and nonmalignant respiratory mortality and morbidity have been studied since the 1950s. Following the debate in the early 1960s on the aetiology of respiratory disorders, they were often considered as different expressions of one disease entity in The Netherlands. Therefore, it has been customary to gather all obstructive respiratory diseases under an umbrella term "chronic non specific lung diseases" (CNSLD). Recently, the use of this term has again been advocated.[1] In other European countries and in the United States of America a distinction is usually made between asthma and chronic obstructive pulmonary diseases (COPD).

Results concerning occupational risks for mortality have been conflicting. Some authors have stated that occupational exposures form a minor risk, as compared to the effect of smoking.[2,3] Others believe that an occupational exposure does augment the mortality risk.[4-8]

Morbidity due to CNSLD forms a major problem in populations occupationally exposed to dust, gases and fumes. It has been speculated that of all adult asthma cases 2-15% might be caused by occupational exposures, although the information underlying these figures has not been published explicitly.[9,10] Similar figures for COPD are lacking, but ample evidence for a causal relationship between occupational exposures and COPD exists.[11-13] Recently, the aetiological fraction of CNSLD attributable to occupational exposures has been estimated as 11-19% for males.[13,14] Several general population studies have shown a positive relationship between occupational exposures and symptom prevalence or incidence rate of CNSLD; in cross-sectional studies, odds ratios varied between 1.3-2.0 for exposed versus unexposed workers, and in longitudinal studies risks ratios were about 1.4.[15-25]

Information on occupational exposure to dust, gases and fumes was gathered mainly using questionnaires or by interviews. More recently, so-called Job Exposure Matrices (JEMs) have been introduced, to generate occupational exposures based on job titles.[14-17,25] The JEM provides the possibility of converting occupational titles into potential exposures in epidemiological studies.[26] In absence of detailed questionnaires or assessment by experts, exposure assessment using JEMs may provide useful information in large population studies.[25]

Information on the validity of exposure estimates generated by external JEMs has been reported on a limited scale only.[26-28] Kromhout et al.[28] compared exposure estimates generated with the Medical Research Council (MRC) JEM,[29] and with a population specific JEM based on self-reported data.

Their analysis suggests that the JEM based on self-reported data is superior in comparison with the MRC JEM. This could imply that the latter gives an underestimation of the true relationship between occupational exposures and CNSLD. Assuming more valid results when assessing exposure by a population specific JEM, we re-examined the influence of occupational exposures on total mortality and respiratory mortality and morbidity.

Most general population studies performed so far were cross-sectional. The longitudinal studies used information on occupational exposures at one point in time in relation to subsequent lung function changes, symptoms of CNSLD, or data on CNSLD incidence. In this study, information about time since first exposure and duration of exposure was used to facilitate an analysis between time-related exposure variables and CNSLD incidence.

SUBJECTS AND METHODS

Subjects

Since 1960 until 1985, risk factors for chronic diseases were investigated longitudinally in the Zutphen Study, the Dutch contribution to the Seven Countries Study.[30,31] Zutphen is an old industrial town in the eastern part of The Netherlands. In 1960, it had a population of 25,000 inhabitants.
A random sample of the male population, born between 1900 and 1919 and living in Zutphen for at least 5 years, was taken. Information on risk factors, such as smoking, was collected according to the Seven Countries Study protocol.[30] Information on cigarette smoking was used to compute the number of pack-years of cigarettes smoked. Pack-years were calculated as the product of the number of years smoked before 1960, and the number of packs of cigarettes smoked per day.

Medical examination

During the 25 years of follow-up, the morbidity of the 878 men was verified regularly. The vital status was checked at the end of the study. Each person underwent complete follow-up. One physician coded all information about morbidity and mortality during the follow-up, using strict criteria. The causes of death were coded according to the 8th revision of the International Classification of Diseases.[32] The mortality was considered due to CNSLD if ICD codes 490-496 were mentioned on the death certificate as primary, secondary or tertiary cause of death. For the diagnosis of CNSLD morbidity, the following criteria had to be met: 1) episodes of respiratory symptoms

(regular cough and phlegm for longer than three months, or episodes of wheezing) reported to the survey physician; or 2) a diagnosis of CNSLD by a clinical specialist. Incidence of CNSLD was defined as the first year in which CNSLD was diagnosed. More details about the medical examinations and coding of morbidity and mortality data have been reported elsewhere.[8,16]

Exposure assessment

In 1960, 1965, 1977/1978, and 1985, information about occupation was collected. The information about jobs was coded in 1989 according to the British Registrar General's classification of occupations.[33] Coding procedures have been described in detail elsewhere.[15] In 1977 and 1978, a complete work history of the surviving members of the 1960 cohort was obtained using a self-administered questionnaire.[28] The cohort members could also indicate to which of 27 (groups of) chemical agents they had been exposed in the jobs they had carried out during their working life.

A population specific JEM was generated for 10 specific exposures relevant for respiratory epidemiological purposes. To allow use of the total follow-up data, jobs held in 1960 were arbitrarily considered exposed when at least 10% of the men performing a job reported an exposure during the 1977/1978 interview, as described previously.[28] The JEM generated the following (groups of) exposures: welding materials and welding fumes; soldering fumes; pesticides; asbestos; oils (drilling oil, cooling oil and lubricants); wood dust (finishing and conservation products); solvents; paints (paint, varnish, lacquers and pigments); coal tar (asphalt, tar, pitch and bitumen). Also exposure to dust was generated comprising an exposure to asbestos, wood dust, cement, chalk or quartz. The cohort members with exposure to dust were subsequently divided into two groups with high and intermittent probability of exposure to dust, respectively. Jobs in which 10-50% of the men reported exposure to dust were considered to have an intermittent probability of exposure to dust. When over 50% of the men in a job reported exposure to dust, the job was considered to have a high probability of exposure to dust.

Based on the information of 1960, 1965, 1977/1978, and 1985, the occupational history of the cohort members was reconstructed. When available, self-reported information on exposure to dust and the period of exposure obtained during 1977/1978 interview was used.

For men exposed to dust, the duration of, and the time since the first exposure was computed. The exposure period ended in the year CNSLD was diagnosed, the year of death or the end of study. To calculate duration of exposure, information on the year of the first exposure and the year of cessation of exposure was used.

This information was obtained by using self-reported data concerning the period on which exposure to dust had occurred.

For members for whom this information was lacking (i.e. because they died before the 1977/1978 survey), the job held in 1960 was used to generate exposure to dust, using the population specific JEM. Average duration and time since first exposure were assigned, distinguishing two birth cohorts (born between 1900-1910; or between 1911-1920) broken down to 11 job categories according to the British Registrar General's 1966 classification of occupations (farmers; furnace workers; engineering and metal workers; wood and paper workers; textile workers and tailors; food processing workers; other production workers; construction workers and painters; transport workers; warehouse workers; and white collar workers).

Statistical analysis

Relationships between occupational exposures and total mortality, CNSLD mortality and CNSLD incidence were analysed using proportional hazard analysis, allowing for smoking habits (number of years smoked, or pack-years until 1960) and age.[34] The survival-analyses were performed using the PHREG procedure of SAS on a VAX computer.[35] The discrete algorithm was used, since the time-scale (person-years) was discrete. All exposures were first analysed separately, allowing for age and smoking habits. Two-sided p-values <0.05 were considered as statistically significant. The relationship between occupational exposures and CNSLD incidence was also analysed simultaneously. Using the stepwise option of PHREG, and allowing for age and smoking habits, specific exposures were included and excluded until the following conditions were met: the significance of the residual Chi-square was less than 0.25, and the significance of the relative risk was less than 0.10.

Relative risks were estimated from regression coefficients by taking the antilogarithm of the regression coefficients. Using the standard error of the regression coefficient, the 95% confidence intervals were estimated. For further details, reference is made to a previous paper.[8]

RESULTS

Of the group of 1088 men invited, 878 took part in the medical examination of 1960. For 11 men, information about occupation was incomplete. For 11 men, the number of cigarettes smoked and numbers of years smoked before 1960 was lacking; and for three men the duration was known, but no information about the quantity of tobacco consumption was available.

From the men at risk for CNSLD mortality and total mortality, a complete set of data from the baseline survey was available for 856 and 853 men, respectively. Fifty-seven subjects had experienced CNSLD before 1960 and were excluded from the analyses with CNSLD incidence, leaving a group of 796 men. A summary of confounding factors and outcome measures is given in table 1.

Approximately 50% of the 1960 cohort died during the follow-up period. However, only 53 deaths were due to CNSLD. When incident cases of CNSLD before 1960 were excluded, 33 of the 799 men at risk died of CNSLD. Given these numbers, a relative risk of 1.5 (β=0.80) can be detected with $p<0.05$. Almost 30% of the 796 subjects at risk developed CNSLD between 1960-1985. For every hundred person years of observation, 1.5 incident cases were observed, during 25 years of follow-up.

Table 1 Age, smoking habit, total mortality, CNSLD mortality, and CNSLD incidence of 867 men aged 40-59 years in 1960 in Zutphen

Confounding factors	**mean**		**SD**
Age (yrs)	50	±	6
Number of years (smoked yrs)*	28.7	±	11.2
Packyears cigarettes (pack/day.yrs)**	13.9	±	11.2
Outcome measures	**n**		**%**
Total mortality	425		49
CNSLD mortality (all subjects)	53		6
CNSLD mortality (without CNSLD cases)†	33		4
CNSLD Incidence†	233		29

*: N=856, for 11 subjects unknown; **: N=853, for 14 subjects unknown; †: N=796, 57 incident CNSLD cases before 1960 excluded.

Population-specific JEM based on 1960 job

Approximately 40% (327/853) of the cohort members had at least one specific exposure. Less then 10% of the cohort had been exposed to pesticides, asbestos, soldering fumes, wood dust, solvents, or coal tar. About 10% had been exposed to paints or welding fumes. Almost a quarter of the cohort had been exposed to dust. Sixteen percent had carried out jobs with an intermittent probability of exposure to dust, while 8% was classified as having a high probability of exposure to dust. For the exact numbers of exposed men and the number of deaths or subjects who developed CNSLD reference is made to tables 2 and 3 respectively. Specific exposures rarely occurred alone; soldering fumes, welding fumes, asbestos, wood dust, and tar coal always occurred in combination with another exposure. Nineteen percent of 114 men had only been exposed to dust. Unique exposures to pesticides, oils, solvents, and paints occurred on a very limited scale (less then 5%), not allowing separate analyses.

In all analyses, age and past smoking habits were included as confounders. An earlier analysis revealed that pack-years of cigarettes smoked was a better predictor of total mortality and CNSLD incidence than the number of years smoked.[15] The number of years smoked, however, was a better predictor of CNSLD mortality.[16] The relative risks per 25 pack-years smoked for total mortality and CNSLD incidence were 1.6 and 1.1, respectively, allowing for age. The relative risk per 10 years smoked for CNSLD mortality was 2.1. Age in 1960 was related to total mortality, CNSLD mortality and CNSLD incidence, with relative risks of 2.7, 2.0, and 1.4, respectively per 10 years increase of age, adjusted for smoking habits.

Results of the proportional hazard analysis applied to total mortality are given in table 2. Being occupationally exposed was not significantly related to total mortality. Only a high probability of exposure to dust was significantly related to total mortality. The relative risk of exposure to wood dust was borderline significantly elevated. Exposure to asbestos and to dust had not statistically significantly elevated relative risks for total mortality. Exposures to welding or soldering fumes, pesticides, oils, organic solvents, and coal tar were inversely related to total mortality, but statistically nonsignificant.

None of the specific exposures was significantly related to mortality due to CNSLD, even after exclusion of the prevalent CNSLD cases in 1960. Occupational exposure to at least one agent showed a statistically significant lower relative risk (RR) on mortality due to CNSLD for exposed men as compared to unexposed men (RR 0.49; confidence interval (CI) 0.26-0.92), but this association was no longer statistically significant after exclusion of the prevalent CNSLD cases (RR 0.73; CI 0.35-1.51).

Table 2 Relationships between different occupational exposures and 25 year total mortality, adjusted for age and smoking, in 853 men aged 40-59 years, at risk in 1960 in Zutphen

Exposure	Exposed men n	Exposed cases n	RR*	95% CI
Welding fumes	84	42	0.88	0.63 - 1.20
Soldering fumes	62	32	0.93	0.64 - 1.34
Pesticides	19	10	0.91	0.48 - 1.73
Asbestos	32	20	1.40	0.88 - 2.22
Oils	133	63	0.90	0.69 - 1.19
Wood dust	69	38	1.37	0.97 - 2.93
Solvents	80	41	0.95	0.69 - 1.32
Paints	84	42	1.02	0.74 - 1.41
Coal tar	49	22	0.71	0.46 - 1.10
Dust	198	101	1.03	0.82 - 1.29
Intermittent dust exposure**	136	63	0.87	0.66 - 1.14
High dust exposure**	62	38	1.47	1.04 - 2.08
At least one exposure	327	160	0.94	0.77 - 1.15

*: RR=Relative Risk; CI=Confidence Interval.
**: Simultaneously in one model

The proportional hazard ratios for specific occupational exposures on CNSLD incidence are presented in table 3. Being exposed to at least one agent resulted in an elevated relative risk of 1.5 compared to people without exposure. All survival analyses revealed positive relationships between CNSLD incidence and specific exposures. Exposure to asbestos showed a statistically non-significantly, elevated relative risk (RR 1.6; CI 0.90-2.93). The large confidence interval is in part due to the limited number of subjects occupationally exposed to asbestos (less than 5% of the cohort). Relationships with CNSLD incidence were statistically significant for exposure to dust and exposure to solvents (RR 1.4 and 1.7 respectively). Comparing 114 men with an exposure to dust only with 475 unexposed men resulted in a statistically significant elevated relative risk of 1.6 (CI 1.13-1.60). For other unique exposures, re-analysis in a similar fashion led to higher relative risks, but confidence intervals increased as well, because of the smaller numbers involved in analyses.

Table 3 Relationships between different occupational exposures with 25 year CNSLD incidence, adjusted for age and smoking, in 796 men aged 40-59 years, at risk in 1960 in Zutphen

Exposure	Exposed men	Exposed cases		
	n	n	RR*	95% CI
Welding fumes	77	26	1.12	0.74 - 1.69
Soldering fumes	56	18	1.02	0.63 - 1.65
Pesticides	18	7	1.38	0.64 - 2.95
Asbestos	31	12	1.63	0.90 - 2.93
Oils	124	41	1.13	0.80 - 1.58
Wood dust	66	23	1.31	0.85 - 2.02
Solvents	75	33	1.66	1.14 - 2.41
Paints	87	26	1.05	0.68 - 1.62
Coal tar	43	17	1.32	0.80 - 2.17
Dust	187	68	1.42	1.07 - 1.90
Intermittent dust exposure**	126	43	1.26	0.89 - 1.76
High dust exposure**	61	25	1.85	1.21 - 2.83
At least one exposure	321	112	1.46	1.12 - 1.89

*: RR=Relative Risk; CI=Confidence Interval

**: Simultaneously in one model

The results of the simultaneous analysis of exposure to dust and solvents are presented in table 4. The relationship between exposure and CNSLD incidence becomes slightly weaker than those compared to the risk ratios presented in table 3, but the findings are still consistent with the previous analyses. Although the criteria of significance were not met when exposure to solvents was analysed in combination with intermittent probability and high probability of exposure to dust, results of this model are also given in table 4. For an intermittent probability of exposure to dust, no relationship was found. For an exposure to solvents and high probability of exposure to dust, the results of the previous analysis were confirmed as well.

Time-related exposure to dust

In 1977/1978, information about work history of 633 men was obtained, comprising a total of 1610 observations. The number of men ever exposed to dust is smaller than obtained with the population specific JEM (151 (19%) versus 187 (23%)).

This difference is found because for 603 men the self-reported exposure to dust was used, which did not always correspond to the exposure data generated by the JEM, using the arbitrarily chosen 10% criterion for exposure.

Table 4 Relationship between occupational exposure to dust and solvents in one model and 25 year CNSLD incidence adjusted for age and smoking in 796 men, aged 40-59, at risk in 1960 in Zutphen

Exposure	RR*	95% CI
Model 1		
Solvents	1.48	1.00 - 2.20
Dust	1.31	0.96 - 1.77
Model 2		
Solvents	1.73	1.14 - 2.62
Intermittent dust exposure	1.04	0.72 - 1.52
High dust exposure	1.91	1.24 - 2.93

*: RR=Relative Risk; CI=Confidence Interval

Duration

The duration of exposure to dust varied between 5-54 years, with an average duration of 32.6 years (standard deviation 10.9). Figure 1 shows the relative risks and the 95% confidence interval for three subgroups by duration of exposure to dust, compared to a reference group without exposure to dust. The group exposed 1-20 years to dust had a statistically significant elevated risk for developing CNSLD, after allowing for smoking habits and age. Men exposed to dust for a longer duration, show a smaller risk for developing CNSLD than those with a shorter exposure time.

Time since first exposure

The time since initial exposure ranged between 9-72 years. The average time since first exposure was 44.6 years (standard deviation 13.1). Figure 2 presents the relative risks of three subgroups of time since first exposure, as compared with the groups of subjects without exposure.

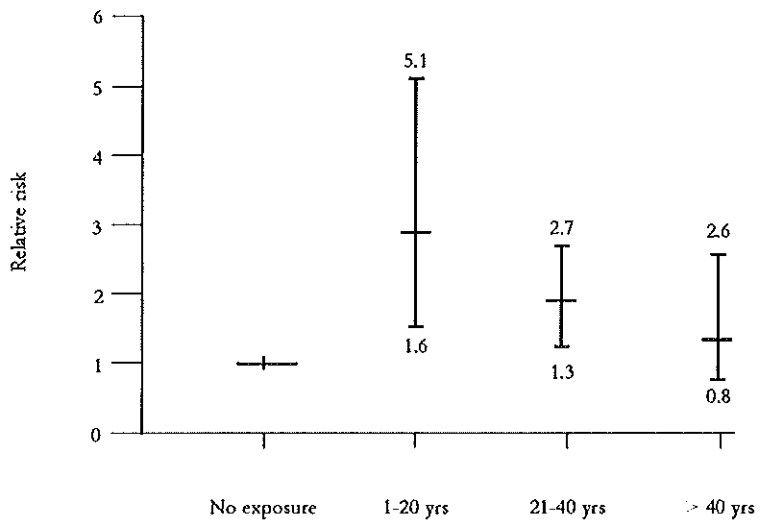

Figure 1 Relative Risk (RR) and 95% confidence interval (95% CI) for the relationship between duration of exposure to dust and 25 year CNSLD incidence corrected for age and smoking habits. Vertical bars indicate 95% CI. CNSLD: chronic non specific lung disease.

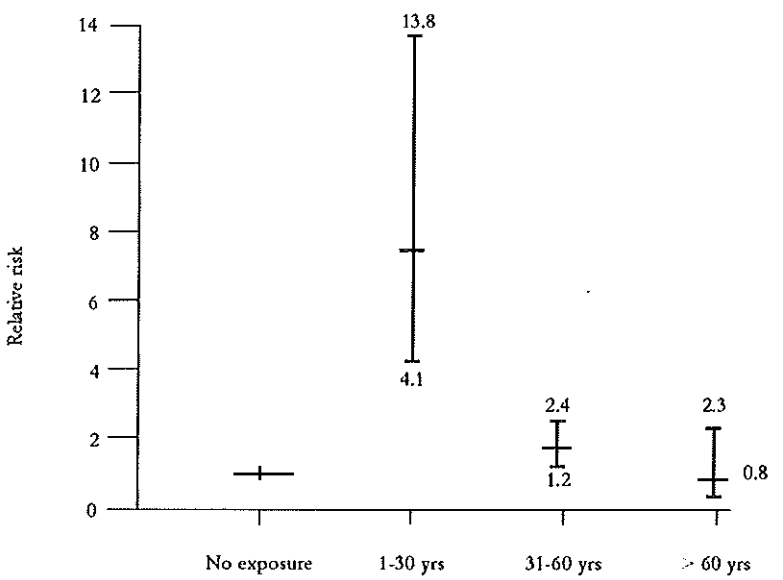

Figure 2 Relative Risk (RR) and 95% confidence interval (95% CI) for the relationship between time since first exposure to dust and 25 year CNSLD incidence corrected for age and smoking habits. Vertical bars indicate 95% CI. CNSLD: chronic non specific lung disease.

The results of analysing the relationship between the time since first exposure and the CNSLD incidence suggest that the risk on developing CNSLD is larger when exposure occurred more recently. For men who had been first exposed longest ago the relative risk was (statistically not significant) lower compared to men had never been exposed to dust.

The survival analysis for 7 years of follow-up, using the self-reported exposure data for 397 men obtained during the 1977/1978 survey, yielded similar results, though no longer statistically significant due to smaller numbers.

DISCUSSION

This study focused on occupational exposures, assessed with an internal JEM or self-reported exposure information, in relation to total mortality, cause specific mortality of CNSLD, and the development of CNSLD. A broad definition of CNSLD was used, comprising asthma, chronic bronchitis and emphysema. Considering the age of the population in 1960, the results of the study are probably biased towards more strongly age-related forms of CNSLD, such as chronic bronchitis and emphysema. COPD is expected to be predominant among most cases diagnosed as having CNSLD.[16]

The cumulative CNSLD incidence is high compared to prevalence figures, what might be explained by the definition of CNSLD used.[15,16] Although the diagnostic criteria used by clinical specialists could not be made explicit, the diagnosis of CNSLD did correlate well with symptoms of CNSLD (1960 questionnaire). This questionnaire comprised questions about cough, phlegm and shortness of breath. Analyses of the relationship between lung function in 1965 and 20 year CNSLD incidence also suggest that incidence data are valid. Lung function in 1965 was found to be a very strong predictor of subsequent CNSLD incidence.[8]

It is unlikely that the relationship between occupational exposures and health outcome is obscured by recall bias (overreporting of occupational exposures among the subjects with respiratory symptoms), because the study was not aimed at establishing the relationship between occupational exposures and respiratory symptoms or CNSLD. Selection bias towards higher occupationally exposed jobs was improbable because a random sample out of the population was taken. The results may still be influenced by a "healthy worker effect" though, because those with better health may be selected into the workforce.[36] This aspect will be discussed further on.

In all analyses, exposed men were compared to men not exposed to the exposure of interest.

However, members of the reference category could be exposed to exposures other than the specific exposure. On the other hand, exposed men could also be exposed to other exposures next to the specific exposure of interest. Consequently, true relative risks of a specific exposure can be obscured by interferences with other exposures. Since most exposures appeared in combination with others, separate analyses with unique exposures were hindered by restricted population size.

Mortality

An earlier study among the members of the Zutphen Study cohort still alive in 1965 showed a relationship between occupational groups and 20 year survival, after controlling for lung function, smoking habits and age.[8] In the present analyses, occupational exposure to at least one agent was not related to total mortality, and only exposure to wood dust and high probability of exposure to dust were significantly related to total mortality.

Men exposed to at least one agent according to the population specific JEM were found at lower risk for CNSLD mortality; though this relationship was no longer statistically significant after exclusion of the incident CNSLD cases who developed CNSLD before 1960. The results are influenced by low mortality rates from CNSLD and the limited number of persons exposed to specific exposures, leading to a considerable instability of the risk estimates, a reduced statistical power and large confidence intervals. Given the numbers in this study, a relative risk of 1.5 (β=0.80) could be detected with $p<0.05$. Furthermore, the healthy worker effect has influenced the results, since subjects suffering from CNSLD are likely to exchange exposed jobs for less exposed jobs.

A previous analysis showed a higher CNSLD mortality among blue collar workers than among white collar workers.[8] Since exposures generated with the population specific JEM were not related to CNSLD mortality, this could imply that the elevated relative risks found in the previous analyses were not related to occupational exposures, but to other factors related to socioeconomic status, such as housing, as suggested as an alternative explanation of the findings in the same paper. Since the mortality rate is very low, the results of the present analysis should not be generalized.

CNSLD incidence

The results of the analyses of the relationship between occupational exposures and CNSLD incidence confirm results from other community-based studies.

In cross-sectional studies, relationships between occupational exposures and respiratory symptoms, decreased lung function and/or respiratory disease were found, with odds ratios varying between 1.3-2.0.[14,15,19,21,24] In the few longitudinal community-based studies published, exposed workers had higher risks of respiratory dysfunction than unexposed workers, with risk ratios of about 1.4.[16,20]

The assumption that the internal JEM based on self-reported data gives more valid results could not be confirmed in this study. A comparison of the performance of both JEMs was made indirectly, by studying relationships with endpoints. A direct and more straight forward comparison of the performance of the population specific JEM and the MRC JEM is hindered by the differences in exposure attribution. Subjects with specific exposures to heavy metals, mineral dusts and adhesives, according to the MRC JEM, were previously found to be at significantly higher risk.[16] These exposures were not generated by the population specific JEM.

Using the population specific JEM, a strong relationship between exposure to solvents and CNSLD incidence was found. A cross-sectional analysis of the Zutphen Study,[15] also detected a statistically significant relative risk for exposure to solvents. This correlation was not present in the longitudinal analyses when the MRC JEM was used. Neither has any other general population study shown the existence of this relationship. The importance of the finding remains to be established, preferably by occupational population-based studies. It is possible that the 10% criterion in generating exposure is too lenient, leading to misclassification, especially false-positive. Such a bias can have a strong influence on the estimated relative risks.[28]

However, the consistency in the relationship between occupational exposure to at least one agend and to dust with CNSLD incidence for the cohort specific JEM and the external JEMs leads to the conclusion that the use of self-reported data gives at least similar information as the use of an external JEM.

Almost 30% of the Zutphen population was occupationally exposed to dust, gas or fumes, according to the MRC JEM, and had a relative risk on CNSLD of 1.40 (CI 1.07-1.85).[16] In the present study, exposure to dust comprises wood dust, asbestos, cement dust, talc, and quartz. Almost 40% of the men were occupationally exposed and had a risk ratio of 1.46 (CI 1.12-1.89) compared with unexposed men. The influence of exposure to dust on CNSLD incidence was of equal magnitude in previous and present analyses, with risk ratios of about 1.4. Analysing the subgroup of subjects only exposed to dust against subjects without any exposure revealed an even stronger relationship between exposure to dust and CNSLD incidence.

The most striking difference between the internal JEM and the MRC JEM was the exposure-response gradient for the probability of exposure to dust on CNSLD incidence. This association suggests the existence of an exposure response relationship and was not found with the external JEM.

An advantage of using self-reported data on exposure is the possibility to analyse time-related exposure estimates. In this particular study, the relationship between time-related exposure to dust and CNSLD incidence was analysed. A negative relationship between duration of exposure and CNSLD incidence was found. Subjects exposed for 1-20 years to dust has a clearly significant elevated risk for developing CNSLD (RR 2.9). Subjects exposed to dust for a longer duration, showed a lower risk for developing CNSLD (RRs 1.9 and 1.3). Subjects whose first exposure to dust occurred more recently were at higher risk for developing CNSLD, as compared to subjects with the longest time since the first exposure (RR 7.5 vs 0.9). It should be noted that subjects who had an exposure which began relatively recently, also have a limited duration of exposure. Because of the coherence between results with time since first exposure and duration of exposure, it is probable that these estimates do, to a certain degree, display the same effect. A further breakdown by both time since first exposure and duration of exposure was not feasible, because of the limited population size, resulting in unstable risk estimates, potential colinearity and missing observations.

Earlier analyses suggested that a selection effect influences relative risks found between occupational exposure and CNSLD incidence to a minor degree.[16] The more elaborate analyses with time-related estimates of exposure to dust did, however, suggest the existence of strong selecting processes, influencing the relationship between occupational exposures and CNSLD mortality. This finding is probably explained by subjects with initial exposures further back in the past, who transferred to other jobs or developed CNSLD before 1960 and were, therefore, excluded from analyses.

CONCLUSION

The consistency of the relationship between the occupational exposure to at least one agent and to dust and CNSLD incidence in the Zutphen cohort for the cohort specific JEM and external JEMs leads to the conclusion that the use of self-reported data gives at least similar information to the use of an external JEM. This supports the use of self-reported time-related exposure data in general population studies.

The gradient of response in relation to exposure to dust and the relationship found between time-related estimates of exposure to dust are important indications for a causal relationship between occupational exposure and CNSLD.[12]

Using the work history to determine exposure to dust lead to a stronger relationship with CNSLD incidence for specific subgroups compared to a conventional analysis using exposure at the start of follow-up. The existence of a healthy worker effect might have led to an underestimation of the risk estimates of occupation and occupational exposures on CNSLD in earlier studies. A similar approach, using time-related exposure variables as used in the present study, should be applied in other general population studies to confirm these findings.

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3 Decline in lung function related to exposure and selection processes among workers in the grain processing and animal feed industry[1]

ABSTRACT

Objectives

To follow up workers in the grain processing and animal feed industry five years after an initial survey, and to monitor exposures to organic dust and endotoxin and changes in prevalence of respiratory symptoms and lung function.

Methods

Outcome measures in the present survey were decline in lung function decline over five years, rapid annual decline in forced expiratory volume in one second (FEV_1) above 90 $ml.s^{-1}$, and loss to follow up.

Results

Among 140 workers included in the longitudinal analysis, annual decline in FEV_1 and maximal mod-expiratory flow (MMEF) was significantly related to occupational exposure to dust and endotoxin in the grain processing and animal feed industry. Assuming a cumulative exposure over a working life of 40 years with an exposure of 5 $mg.m^{-3}$, the estimated effect on the FEV_1 would be a decline of 157 $ml.s^{-1}$ (95% CI 13 to 300), that is, about 4% of the group mean FEV_1 and 473 $ml.s^{-1}$ (95% CI 127 to 800) of the MMEF (about 12%). Workers with a dust exposure >4 $mg.m^{-3}$ or endotoxin levels concentrations >20 $ng.m^{-3}$ at the 1986-88 survey had significantly higher risk of rapid decline in FEV_1 (odds ratio (OR) 3.3, CI 1.02 to 10.3). The relations between occupational exposure and decline in lung function in this study occurred, despite the selection through the healthy worker effect that occurred as well. Increasing working years was related to decreasing annual decline in FEV_1 and fewer people with rapid decline in FEV_1 (OR 0.04, 95% CI 0 to 0.61 for over 20 versus <5 working years in the grain processing and animal feed industry). The presence of respiratory symptoms at baseline was a strong predictor of subsequent loss to follow up. Baseline lung function was not found to be predictive of subsequent loss to follow up.

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However, among workers lost to follow up the number of working years was more strongly negatively related to baseline lung function than among the workers who were studied longitudinally.

Conclusions

The existence of the healthy worker effect implies that an exposure-response relation in the grain processing and animal feed industry may well be underestimated. This should be taken into account when health based recommended limit values are to be developed.

INTRODUCTION

Exposure to organic dusts may cause acute or chronic respiratory symptoms often accompanied by changes in lung function.[1] Grain dust has been most extensively studied.[2-4] Other organic dusts which have been studied include dusts associated with the manufacture of coffee, tea, spices, soy, fur, and animal food.[1]

In the mid-1980s a cross sectional study at 14 different sites in the grain processing and animal feed industry in The Netherlands was undertaken to explore relations between exposure to organic dust and respiratory symptoms and chronic changes in lung function.[5] The findings of this study suggested that both symptoms and lung function were clearly related to (present and historical) exposure to endotoxins. A considerably weaker relation was found for exposure to inspirable dust. This finding is in agreement with exposure studies that show that the airway response to grain dust represents an acute inflammatory response to inhaled toxins, such as endotoxin.[6] Several investigators have suggested a possible role of endotoxin in the aetiology of chronic bronchitis.[7,8] An exposure-response relation of exposure to endotoxins with prevalence of chronic bronchitis, forced expiratory volume in one second (FEV_1), and byssinosis has been reported in the cotton industry.[9]

Cumulative exposure to organic dust in the grain processing and animal feed industry seemed to affect lung function independently of the present exposure.[5] This led to the assumption that both present and previous exposure are important predictors of decline in lung function. The effect of exposure to organic dust in animal feed industry on lung function might at least be partially reversible.[5,10]

Finally, some observations suggested that exposure related selection was present. Lung function was generally lower in control subjects than in animal feed workers, chronic phlegm was less prevalent in the highest category of exposure to dust, and shortness of breath and chest tightness were inversely related to number of years worked in animal feed production.

Other studies in grain industry also found indications of the healthy worker effect.[1,3,4,11]

Among workers exposed to grain dusts several longitudinal studies have been conducted in which the effect of exposure on change in lung function has been studied.[2,4,10,12] These studies suggested that annual losses in lung function is greater among workers exposed to grain dust than in an unexposed population.[4] A cumulative effect of exposure has been found[12] as well as a dose-response relation with level[2,10] or duration of exposure.[4] Only in few epidemiological studies in grain workers has a reliable characterisation of exposure been included, which is necessary to explore exposure-response relations. In the period 1991-93, another cross sectional study was carried out among the workers still working at the fourteen animal feed mills, and who participated in the original cross sectional study of 1986-88. The goal of the this study was to analyse exposure response relations for exposure to organic dust in the grain processing and animal feed industry, with some emphasis on the role of exposure to endotoxin. Furthermore, this study considered the healthy worker effect by studying the correlation of respiratory symptoms and lung function during the first survey with loss to follow-up at the second survey.

SUBJECTS AND METHODS

Study population

In the study by Smid et al. among workers in the grain processing and animal feed industry in The Netherlands, data from 315 people were used in the analysis.[5] With new information on smoking history, gathered during the second survey, smoking status at the time of the first survey could be established for another 5 workers. Of those 320 subjects, 144 participated in the second survey and had a complete data set. Four workers had ever worked in maintenance and were therefore excluded from analyses. The 156 workers who participated in the first study, but not in the second, were classified as lost to follow up. Detailed reasons for lost to follow up are not available, as most of the workers had left the work site. However, some (estimated 5%-10%) were still employed, but were unable to participate during the second survey, because of illness, holidays or high workload.

METHODS

Exposure

In 1988-86, eight hour personal inspirable dust samples were taken from the production workers in eight facilities. Exposure measurements were repeated less intensively during the 1990-92 survey, and especially in those facilities with no previous exposure samples. Gravimetric dust and endotoxin concentrations were measured in the samples with the limulus amoebocyte lysate (LAL) test. Details of sampling methods and analyses are given elsewhere.[13] Several proxies of exposure were available:

* categories of exposures: high (>10 $mg.m^{-3}$) and intermediate (4-≤10 $mg.m^{-3}$) dust exposure at first survey vs. no or low exposure (≤4 $mg.m^{-3}$) or high (>40 $ng.m^{-3}$) and intermediate (20-≤40 $ng.m^{-3}$) exposure to endotoxins at first survey vs. no or low exposure (≤20 $ng.m^{-3}$);
* change in exposure category between the first and second surveys: low-high are workers with no or low exposure at the first survey, and intermediate or high exposure at the second or workers with intermediate exposure at first survey and high exposure at the second, high-low are workers with high exposure at the first survey and intermediate or no or low exposure at the second or workers with intermediate exposure at first survey and no or low exposure at second survey vs always low workers with no or low exposure who had an at both surveys, and always high workers who had an intermediate or high exposure level at both surveys;
* average level of exposure during first survey;
* number of working years in the grain processing and animal feed industry;
* number of working years with exposure in the grain processing and animal feed industry;
* cumulative exposure to dust or endotoxin, defined as the number of working days in a specific exposure category multiplied by the average daily level of exposure of each exposure category that the worker has worked in.

These exposure proxies measures were computed for the interval between the first and second surveys, and the period between the time of first employment in the grain processing and animal feed industry and the first survey. These periods add up to the duration of employment in the grain processing and animal feed industry, since first employment until the second survey.

Health examination

A short self-administered questionnaire, which has also been used during the first survey, was used to collect information on respiratory symptoms.[5] The questions included chronic cough and chronic phlegm, shortness of breath, ever and frequent wheezing, and chest tightness. Forced expiratory lung function measurements were conducted on Mondays, between 11.00 and 15.00, after at least 48 hours without exposure to organic dusts. Production workers underwent lung function tests shortly before or just after the start of the afternoon shift. Vicatest-V dry rolling seal spirometers (Mijnhardt, Bunnik, The Netherlands) were used. Measurements and procedures, including body temperature and pressure saturated adjustments, were carried out according the standards of the European Respiratory Society[14] and were similar to those applied during the first survey. Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), peak expiratory flow (PEF), maximum mid-expiratory flow (MMEF) and maximum expiratory flow rates, and 75%, 50% and 25% of the vital capacity (MEF75%, MEF50%, and MEF25% respectively) were recorded.

Statistical analyses

Exposure characterisation and grouping of mean exposure levels were evaluated by analysis of variance (ANOVA) of within and between group variance (PROC NESTED). The ratio between these two components of variance were used to evaluate different categorisations of job title groups. Relations between exposures and longitudinal change in lung function were analyzed with SAS software. The change in lung function was defined as the difference between lung function at the first survey minus the lung function level at the second survey and standardized for the time between the surveys. The effects of exposure on lung function, corrected for age, height, and smoking, were studied with linear regression models. Age and height at the time of the second survey and smoking status were included in the regression models as potential confounders. Smokers and former smokers were compared with never smokers. Subjects who smoked in the year preceding or during the first survey and who still smoked during the second survey, or who stopped smoking within a year before the second survey were defined as smokers. Former smokers were defined as people who stopped smoking more than a year before the first survey and had not smoked in the period between the two surveys or who had stopped smoking after the first survey, but more that a year before the second survey. Regression models did not improve with quantitative measures of smoking status, such as number of pack-years of cigarettes. These analyses are not included in this paper.

RESULTS

Exposure assessment

During the first survey 520 personal exposure samples were gathered. Another 179 personal samples were gathered during the second survey. Especially during the first survey, repeated measurements were taken. Therefore, mean exposure per person and function and period could be calculated. This resulted in 187 and 168 personal dust concentrations for several job titles. Except for a significantly lower level of exposure to organic dust for crane drivers (t-test, $p<0.05$), no differences in average dust concentrations per function category between the first and second surveys were found. Only the average endotoxin concentrations for crane drivers and production managers were significantly lower during the second survey (t-test, $p<0.05$). Combining results of both surveys seemed, therefore, to be justified. The mean concentration per person and function was computed, resulting in a total of 353 personal average exposure. Next, the average exposure level per function group was calculated.

A more refined categorisation than the one used in the first cross sectional study was considered essential, as the relatively large number of dust samples in the category 'other' allowed distinction of two highly exposed job titles (silo worker and miller). One of the facilities (facility X) was found to have a significantly higher average dust and endotoxin concentration for several job titles (unloader, facility operator, press operator, and production manager) than the other facilities. At five facilities with similar production procedures and techniques (referred to as facility Y), unloaders had a significantly lower level of exposure than at the other facilities. The level of exposures of press operators and bulk loaders working at these facilities was higher than the average level at the other facilities. In the present analyses, the optimal categorisation distinguishes 12 instead of the former 7 exposure groups and accounts for differences in average exposure between job categories and the different facilities already mentioned. The ratios of the within and between group variance compare favourably with the earlier categorisation into eight job groups and into high, intermediate, or low exposure used in the analyses of the first survey and show a clearer distinction in exposure between relatively homogeneous groups. Table 1 shows the mean concentration of dust and endotoxin for each job title and facility.

Table 1 Mean dust and endotoxin concentrations per job title and facility

	Dust ($mg.m^{-3}$)			Endotoxin ($ng.m^{-3}$)		
	12 facilities	Facility X	Facility Y	12 facilities	Facility X	Facility Y
Unloader	18.2	83.6	8.1	50.2	176.9	4.8
Crane driver	4.0			69.4		
Silo operator	14.1			30.3		
Miller	20.3			99.0		
Production workers:						
Facility operator	1.7	17.2		4.6	36.2	
Press operator	3.5	9.6	5.4	4.4	20.8	13.4
Bulk loader	5.0		6.1	6.9		53.5
Other	8.5			33.6		
Premixer	5.7			3.6		
Sacker	4.8			4.7		
Expedition	3.0			19.4		
Production manager	2.5	8.2		7.8	3.0	28.8

Population characteristics

The average time interval between the surveys was five years. Table 2 shows the mean age, as well as mean exposure concentration and working years in the period between the surveys (concurrent exposure) and in the period before the first survey (previous exposure) for the 140 workers who attended the two surveys and the 156 workers who participated in the first survey only.

Among the 140 workers who attended both surveys, many of the smokers had stopped smoking after the first survey, and no one had started smoking.

Respiratory symptoms and lung function

In general, the prevalence of respiratory symptoms is low among the 140 workers who attended both surveys. Less than 5% of the workers reported chronic respiratory symptoms. Twenty-five workers (18%) reported at least one of these respiratory symptoms. Ten workers (7%) reported one or more of the following chronic obstructive respiratory symptoms: chronic cough, chronic phlegm or shortness of breath and eight (6%) reported asthma like symptoms: frequent wheezing or chest tightness.

Table 2 Population characteristics

	Lost to follow up (n=156)		Included in longitudinal analysis (n=140)	
	Mean	SD	Mean	SD
- Age during 1986/88 survey (y)	41.8	12.0	37.7	9.3*
- Concurrent working (y)	-		5.0	0.4
- Concurrent average dust exposure ($mg.m^{-3}$)	-		7.9	9.3
- Concurrent average endotoxin exposure ($ng.m^{-3}$)	-		24.8	29.0
- Previous working years (y)	14.9	10.4	12.5	8.4*
- Previous average dust exposure ($mg.m^{-3}$)	6.4	8.0	7.6	10.8
- Previous average endotoxin exposure ($ng.m^{-3}$)	20.3	23.1	23.0	28.7
- Non smokers (n (%))	26 (17)	37 (26)**		
- Smokers (n (%))	94 (60)	74 (53)		
- Former smokers (n (%))	36 (23)	29 (20)		

* $p<0.05$; *t* test; ** $p<0.05$; χ^2 test

Among those lost to follow up, significantly more workers reported chronic cough, chronic phlegm, and frequent wheezing (table 3), and lung function was also significantly lower, than among workers who attended both surveys (see table 3). Among those lost to follow up, eight (5%) of the workers had an FEV_1 below 70% predicted (based on age and standing height) and three (2%) had an FEV_1 below 50% predicted, compared with three (2%) and zero (0%), respectively, among those who attended both surveys. These differences, however, were not significant. On average, lung function decreased between the two surveys. Table 3 shows the range in annual change in lung function. Nineteen workers (14%) had an annual decrease in FEV_1 of more than 90 $ml.s^{-1}$.

Table 3 Respiratory symptoms and lung function among workers lost-to-follow up and workers included in longitudinal analysis

	Lost to follow up (n=156) n (%)	Included in longitudinal analysis (n=140) n (%)
chronic cough	20 (13)	6 (4) *
chronic phlegm	12 (8)	2 (1) *
shortness of breath	12 (8)	5 (4)
ever wheezing	30 (13)	18 (13)
frequent wheezing (>1 week)	12 (8)	3 (2) *
chest tightness	8 (5)	6 (4)
>1 respiratory symptom	42 (27)	25 (18) **
>1 chronic obstructive respiratory symptom (cough, phlegm and/or shortness of breath)	30 (19)	10 (7) *
>1 asthma like symptom (frequent wheeze and/or chest tightness)	17 (11)	8 (6)

	1986-88 Lung function mean	SD	1986-88 Lung function mean	SD	Annual change in lung function range
FVC (l)	5.22	0.93	5.44	0.85***	-0.165 to 0.094
FEV_1 ($l.s^{-1}$)	3.96	0.95	4.24	0.78***	-0.159 to 0.103
MMEF ($l.s^{-1}$)	3.51	1.60	3.97	1.43***	-0.272 to 0.327

* $p<0.05$; ** $p<0.10$; χ^2 test; ***$p<0.05$, t test

Measures of exposure and decline in lung function

Exposure levels

Table 4 gives the predicted average decline in lung function expressed as an average decline for a forty year old non-smoker according to exposure category during the 1986-88 survey and the change in exposure category between the two surveys. All three lung function variables showed an increased decline with increasing exposure. For FEV_1 and MMEF this relation was significantly higher for high exposure to dust (>10 $mg.m^{-3}$) as compared with low exposure to dust (<4 $mg.m^{-3}$) and was of borderline significance for the high exposure to endotoxin compared with no or low exposure to endotoxin.

Assuming a cumulative exposure over a working life of 40 years in the grain processing and animal feed industry the estimated effect on FEV_1 would be 896 $ml.s^{-1}$ with an exposure to dust exceeding 10 $mg.m^{-3}$ (95%-CI 65 to 1727).

Table 4 Results of a regression analysis of decline in lung function on exposure category, corrected for age, standing height, and smoking, in 140 grain processing workers and animal feed workers: annual decline for a 40 year old non-smoker according to exposure category

	FVC(ml)		$FEV_1(ml.s^{-1})$		MMEF($ml.s^{-1}$)	
Exposure	dust	endotoxin	dust	endotoxin	dust	endotoxin
low	-40.7	-45.0	-35.8	-36.8	-28.2	-28.9
intermediate	-57.6	-52.6	-48.6	-48.5	-45.0	-51.6
high	-52.1	-51.7	-58.2*	-59.0**	-86.7*	-83.6**

* p<0.05; ** p<0.10; Δlung function=Interval + $ß_1$ age + $ß_2$ height + $ß_3$ smoking + $ß_4$ (intermediate) + $ß_5$ (high)

Subjects who either remained in the highest category of exposure to dust or changed to another dust exposure category had a significantly larger decline in FVC (table 5). For exposure to endotoxins a similar, non-significant, trend was found. For FEV_1 and MMEF the largest decline was found among workers who remained highly exposed or went from jobs with high or intermediate exposure to jobs with lower exposure.

With the derived linear regression equation; a 40 year old non-smoker, with no exposure at the 1986-88 survey would show an annual decline in FVC, FEV_1 and MMEF of 45 $ml.s^{-1}$, 36 $ml.s^{-1}$ and 25 $ml.s^{-1}$, respectively. For a worker with an average exposure at the 1986-88 survey the annual decline would be 48 $ml.s^{-1}$, 43 $ml.s^{-1}$ and 42 $ml.s^{-1}$. The differences were significant for FEV_1 and MMEF. Table 6 shows the differences in annual lung function related to concentrations of dust and exposure to endotoxins, after adjustment for age and smoking status by linear regression. These analyses show that when a cumulative exposure was assumed over a working life of 40 years with an exposure of 5 $mg.m^{-3}$, the estimated effect on the FEV_1 would be a decline of 157 $ml.s^{-1}$ (about 4% of the group mean FEV_1; 95% CI 13 to 300) and 473 $ml.s^{-1}$ on the MMEF (about 12%; 95% CI 127 to 820).

Table 5 Results of a regression analysis of decline in lung function on change in exposure category, corrected for age, standing height, and smoking, in 140 grain processing workers and animal feed workers: annual decline for a 40 year old non-smoker according to exposure category

	FVC(ml)		FEV_1(ml.s^{-1})		MMEF(ml.s^{-1})	
Exposure	dust	endotoxin	dust	endotoxin	dust	endotoxin
always low	-29.8	-40.5	-29.5	-34.6	-31.9	-29.4
always high	-55.4*	-54.9	-47.6**	-56.9*	-45.6	-73.8**
high-low	-55.2*	-51.5	-63.7*	-54.6**	-103.0*	-70.9
low-high	-59.5*	-50.8	-48.2	-39.4	-27.9	-25.1

* $p<0.05$; ** $p<0.10$; Δlung function=interval + β_1 age + β_2 height + β_3 smoking + β_4 (always high) + β_5 (high-low) + β_6 (low-high)

Table 6 Regression of annual decline in lung function on exposure levels at 1986-1988 survey, corrected for age, standing height, and smoking, in 140 grain processing workers and animal feed workers

	FVC (ml)			FEV_1 (ml.s^{-1})			MMEF (ml.s^{-1})		
	β_4	SE	R^2	β_4	SE	R^2	β_4	SE	R^2
Dust exposure at 1986-1988 survey	-.219	.418	4.0	-.784*	.368	11.6	-2.366*	.884	7.0
Endotoxin exposure at 1986-1988 survey	-.122	.158	4.2	-.326*	.139	12.2	-.740*	.338	5.4

* $p<0.05$; ** $p<0.10$; Δlung function=interval + β_1 age + β_2 height + β_3 smoking + β_4 (exposure level)

Duration of exposure

A strong inverse relation between the number of working years in the grain processing and animal feed industry and decline in lung function was found, which was even stronger when the regression analysis was restricted to the period before the first survey. Table 7 gives the decline in predicted lung function for a 40 year old non-smoker according to the number of years worked in the industry before the 1986-88 survey.

Table 7 Results of a regression analysis of decline in lung function on numbers of years in animal feed industry, corrected for age, standing height, and smoking, in 140 grain processing workers and animal feed workers: annual decline for a 40 year old non-smoker according to number of years in the industry

Number of working years at baseline	FVC (ml)	FEV_1 ($ml.s^{-1}$)	MMEF ($ml.s^{-1}$)
0 - <5 years	-72.3	-74.7	-99.1
5 - <10 years	-59.3	-51.4**	-50.1
10 - <20 years	-34.7*	-35.3*	-23.6*
>20 years	-21.4*	-17.8*	-32.9

* $p<0.05$; ** $p<0.10$; Δlung function=interval + β_1 age + β_2 height + β_3 smoking + β_4 (always high) + β_5 (high-low) + β_6 (low-high)

The annual decline in lung function showed an inverse relation with the number of working years before the first survey; the decline decreased with increasing number of years in the industry. The strongest relation was found for FEV_1. For a 40 year old, lifetime non-smoker the annual decline in FEV_1 would be about 75 $ml.s^{-1}.yr^{-1}$ for less than 5 working years; 51 $ml.s^{-1}.yr^{-1}$ for 5-10 working years; 35 $ml.s^{-1}.yr^{-1}$ for 10-20 working years; and 18 $ml.s^{-1}.yr^{-1}$ for more than 20 working years in the grain processing and animal feed industry. When the analyses were repeated with the number of years exposed, the largest decline was in the workers who had been exposed for 5-10 years, significantly larger than the decline among workers exposed for less than 5 years. Workers with longer exposure showed an increased annual decline compared with workers with no exposure or less than 5 years of exposure, but the differences did not reach the significance. Stratification into age groups did not improve the models, either in terms of significance or explained variance.

Measures of exposure and decline in FEV_1 larger than 90 $ml.s^{-1}.yr^{-1}$

Nineteen workers (14%) had rapid annual decrease in FEV_1 of 90 $ml.s^{-1}$ or more. With logistic regression analysis relations between several exposure measures and a rapid decline in FEV_1 were found, that is, workers with exposure to a concentration of dust of more than 4 $mg.m^{-3}$ at the 1986-88 survey had an odds ratio (OR) of 3.3 (95% CI 1.02 to 10.3) for having a rapid decline in FEV_1. For workers with an exposure to concentration of endotoxins exceeding 20 $ng.m^{-3}$ the OR was 3.2 (95% CI 1.1 to 9.2).

Respiratory symptoms, lung function and loss to follow up

Age and respiratory symptoms were found to be the strongest predictors of loss to follow up. No significant relation between lung function and loss to follow up have been found with lung function as the sole explanatory variable or in combination with other explanatory variables.

Exposure to dust or endotoxin showed no statistically significant association with subsequent los to follow up. Simultaneous comparison of workers with high and intermediate exposure at time of the 1986-88 survey with workers with no or low exposure resulted in an OR of 0.78 (p=0.49) for high dust exposure and 1.68 (p=0.06) for intermediate dust exposure and ORs of 0.76 (p=0.47), and 1.12 (p=0.14) for high and intermediate exposure to endotoxins, respectively.

The effect of confounders, exposure proxies, and respiratory symptoms on the FEV_1 at the 1986-88 survey were compared with linear regression analysis between the 140 workers studied longitudinally and the 156 workers lost to follow up. Between those groups the strength of the relation between exposure to dust or presence of respiratory symptoms and of FEV_1 was different. Among those lost to follow up, lung function was more affected by the presence of respiratory symptoms whereas among the workers in the longitudinal analysis exposure to dust had a stronger effect on the FEV_1. The effect of exposure to endotoxins of more than 20 $ng.m^{-3}$ was similar in both groups.

In both groups there was a positive correlation between the decrement in FEV_1 at the 1986-88 survey and the number of working years; the lung function of workers with more than 20 years experience in the grain processing and animal feed industry showed the largest decrements compared with workers who worked less than 5 years in the industry. Workers with 5 to 10 years experience and 10 to 30 years showed intermediate decrements, but were not significantly different from workers who had worked less than 5 years in this industry (see figure 1).

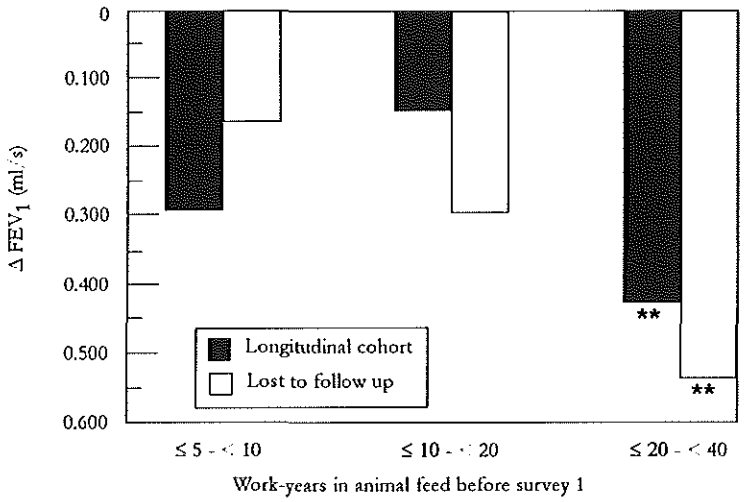

Figure 1 Differences in baseline FEV_1 for number of working years for 140 workers remaining in the grain processing and animal feed industry and 156 workers lost to follow up, corrected for age, standing height, and smoking (baseline $FEV_1 = \beta_1 age + \beta_2 height + \beta_3 smoking + \beta_5$ (5-10 working years) + β_6 (10-20 working years) + β_7 (>20 working years))

DISCUSSION

Relation between exposure and decline in lung function

In this study, exposure in the grain processing and animal feed industry is related to change in FEV_1 and MMEF. Higher exposure to dust and endotoxin resulted in higher declines in FEV_1 and MMEF, which were significantly different from the decline in lung function in workers with no or low exposure. Assuming a lifelong exposure of 40 years, the effect of exposure to concentrations of dust exceeding 10 $mg.m^{-3}$ on the FEV_1 would be almost 900 $ml.s^{-1}$ (95% CI 65 to 1727).

A significant relation between decline in FEV_1 and MMEF and cumulative exposure proxies was also found. Assuming a cumulative exposure over a working life of 40 years with an exposure at the first survey of 5 $mg.m^{-3}$, the estimated effect on the FEV_1 would be about 4% of the group mean FEV_1. The effect on the MMEF would be about 12% of the group mean MMEF. These figures are lower than using categorical exposure proxies, but are in agreement with the earlier cross sectional analysis of Smid et al.[5]

Comparison of FEV_1 measurements in grain handlers with data of a general population study indicates that workers exposed to grain dust have yearly losses in lung function greater than would be expected in an unexposed population.

A cumulative effect of exposure has been suggested by Tabona et al.[12] who found that decrement in lung function was greater in older grain handlers. Later research by Enarson et al. showed that the higher the dust concentration, the higher the likelihood of a rapid decline in lung function.[10] Workers with the worst trend in spirometry over a six year period showed an average rate of decline in FEV_1 of 100 $ml.s^{-1}.yr^{-1}$. The study of Pahwa et al. suggested a positive relation between annual loss of lung function and number of years in the grain industry, leveling off during the later years of employment.[4] Mean annual loss of FEV_1 and (FVC) was 9.2 $ml.s^{-1}.yr^{-1}$ and 21 $ml.s^{-1}.yr^{-1}$ for workers in the industry less than 5 yr., and increased to 52.6 $ml.s^{-1}.yr^{-1}$ and 60.8 $ml.s^{-1}.yr^{-1}$ for workers in the industry for more than 20 yr. The FEF25-75 showed a similar trend.

Other recent studies on grain dust have indicated that impairment of lung function is related to cumulative grain dust exposure as well as to the duration of exposure.[2,5] Huy et al. found an apparent dose-response trend among the workers exposed to grain for annual change in FEV_1 and MMEF.[2] They also found that the control group showed annual changes in FVC, FEV_1 and MMEF comparable with those found in the group exposed to intermediate grain concentrations. Smid et al. found decreased lung function values with increasing exposure to both dust and endotoxin in a cross-sectional study. The number of years employed in the animal feed industry and estimated cumulative exposure were clearly related to lung function.

Another finding of the previous analyses is that both symptoms and lung function were more clearly related to exposure to endotoxins than to dust. In the current analyses, dust and endotoxin have, in general, effects of similar magnitude on lung function. In longitudinal studies of lung function, test variability usually exceeds annual variability, which might reduce the power of the study and make it more difficult to detect differences in effect of dust and exposure to endotoxins on decline in lung function.

Buist and Vollmer concluded that to develop clinically notable airflow obstruction the average yearly rate of decline in FEV_1 over an adult live probably needs to be greater than 90 $ml.s^{-1}.yr^{-1}$ or about three times that found in non-smokers.[18] In the present study, despite the limited number of subjects with rapid decline in FEV_1, defined as an annual decline of 90 $ml.s^{-1}$ or more, rapid decline in FEV_1 was significantly related to exposure to dust and endotoxin, with ORs around 3.2 at exposure to concentrations of dust of 4 $mg.m^{-3}$ or more. The analyses show that being exposed at either survey or both resulted in an excessive decline, compared with the workers with low exposure on both surveys. It is likely that acute and chronic effects intermingle. This is in agreement with the earlier observation that both present and previous exposures are important predictors of decline in lung function.[5]

Healthy worker effect

In the earlier study in the grain processing and animal feed industry by Smid et al. some results were indicative of selection processes interacting with obvious exposure effects.[5] In other studies the healthy worker effect has also been found.[1,3,4,11] In the analyses of five cross sectional studies among grain elevator workers, grain workers as well as civic workers who took part in all five surveys over a period of 12 years were found to be a selected 'healthier' group.[3] The mean lung function of this subgroup was higher than the lung function of workers in cross sectional surveys. Furthermore, the mean lung function of workers participating in all studies increased over the observation period.

In the present analysis the healthy worker effect has also been found. There was a negative association between decline in lung function and number of years in the grain processing and animal feed industry; the decline in lung function decreases with increasing working years (table 7). The ORs of rapid decline also decreased with the number of working years. Compared with the workers with less than 5 years in the grain processing and animal feed industry, workers with more than 20 years had a significantly decreased OR of 0.04 (95% CI 0 to 0.61).

Loss to follow up

The healthy worker effect can be studied by comparing workers remaining in the industry with workers who have left the industry. Therefore, workers who participated in both surveys were compared with workers who participated in the first survey only. These consisted mainly of workers who were no longer working in the industry, but also of workers who unable to attend, due to holidays, work load or illness.

Age and respiratory symptoms were found to be the strongest predictors of loss to follow up. Although workers who were studied longitudinally had a significantly higher lung function at the first study than those workers who were who were lost to follow up (table 3), no significant effect of lung function at the first survey on subsequent loss to follow up could be found when age was included in the model as well. This discrepancy between symptoms and lung function was also found in the earlier study.[5] The present analyses confirm the possible explanation for this discrepancy put forward by Smid et al. that the healthy worker effect might be more pronounced for people with perceived symptoms than for people with minor changes in lung function.

No significant relations between exposure to dust and endotoxin and subsequent loss to follow up could be found. However, changing the cut off between high and low exposure suggested that in subjects with the highest levels of exposure selection might have taken place, resulting in healthier workers, although in workers with intermediate exposures the selection processes are still occurring.

The influence of age, smoking status, respiratory symptoms, and exposure on FEV_1 at the first survey was compared between workers who were studied longitudinally and the workers who were lost to follow up. Smid et al found a significant decrease in lung function with an increase in production years. For the FEV_1 a difference of 0.14 $l.s^{-1}$ (SE 0.04) was found for 10 years of production work.[5] The current analyses show that this relation is stronger in workers who were lost to follow up than in workers who were studied longitudinally. In the workers who were studied longitudinally a difference of 0.15 $l.s^{-1}$ (SE 0.07) was found for 10 years in the industry. In workers who were lost to follow up the difference was 0.17 $l.s^{-1}$ (SE 0.11).

In conclusion, the current analysis shows a relation between occupational exposure in the grain processing and animal feed industry and decline in lung function over a five year period. Decline is related to concentrations of dust and endotoxin and the decline in lung function between the two surveys is also affected by exposure before the first survey. This was shown with proxies for cumulative exposure. The results of this study should be interpreted by considering the influence of the healthy worker effect. Obviously, the selection processes weaken the relations we found between exposure and decline in lung function, probably diminish the power to detect respiratory disorders, and may lead to an underestimation of exposure-effect relations, and consequently of the health risks for workers in the grain processing and animal feed industry.

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4 Respiratory allergy in laboratory animal workers: a retrospective cohort study using pre-employment screening data[1]

ABSTRACT

Objectives

To study the role of exposure, atopy, and smoking in the development of laboratory animal allergy (LAA) in a retrospective cohort study.

Methods

Between 1977 and 1993, 225 people received a pre-employment screening when they started a job at a Dutch research institute where they were going to work with laboratory animals. After active follow up 136 of them (60.4%) could be traced and were sent a questionnaire with extensive questions on allergic symptoms, smoking habits, and job history. 122 people (89.7%) sent back a completed questionnaire. Those who were accepted for a job at the institute and did not have allergic symptoms at the start of the job were selected as cohort members. After selecting people with complete data on start and end date of jobs, exposure intensity, atopy, and smoking, the cohort consisted of 99 people with an average time of follow up of 9.7 years. LAA was defined as a positive response to a set of questions in the questionnaire. The mean number of hours a week a person was exposed to laboratory animals at entry of the cohort was used as a surrogate for exposure, and was divided into four categories.

Results

19 cohort members (19.2%) reported LAA. More people with asthmatic symptoms were found in the high exposure categories. More atopic than non-atopic people reported asthmatic symptoms (13% v 6%). The mean time until development of symptoms of LAA was about 109 months in non-atopic people (n=9), and 45 months in atopic people (n=10) (t test; $p<0.05$). Time until development of symptoms of LAA was shorter at a higher intensity of exposure, except for those exposed for less than two hours a week. A proportional hazard regression analysis showed that exposure and atopy were significant determinants of LAA. An increased relative risk (RR) was found for non-atopic people exposed to laboratory animal allergens for more than two hours a week.

1 Kruize H, Post WK, Heederik D, Martens B, Hollander A, Beek E van der. Occupational and Environmental Medicine 1997;54:830-835. Reproduced with permission from the BMJ Publishing Group.

Atopic people had an even higher risk when exposed to laboratory animals for more than two hours a week (RR above 7.3). Sex, smoking, and age were not risk factors. More atopic than non-atopic people were absent from work or transferred because of allergies.

Conclusions

This study showed that exposure and atopy are significant predictors of LAA and that the risk of developing LAA remained present for a much longer period (> 3 year) than considered before.

INTRODUCTION

People who work with laboratory animals are at risk of developing an allergy to the animals they work with. Prevalence rates of 10%-30% have been found, and give an impression of the magnitude of the health risks.[1,2] Urinary proteins of laboratory animals are the cause of laboratory animal allergy (LAA).[1,2] Mild symptoms of LAA are rhinitis, and skin and eye reactions.[1,3,4] Asthma is a more severe form that develops in about 17%-71% of cases of LAA.[1] There are some suggestions that most cases develop LAA two to three years from initial exposure to the allergen.[1,2] However, the evidence for this is limited and is mainly based on clinical data. No unbiased estimates of time till sensitisation are available from well designed epidemiological studies.

Allergen concentrations are known to vary considerably, and depend on stock density, tasks performed, ventilation rates,[5] cage design, bedding type, air filtration, and humidity.[2] Despite these findings, few studies focused on the relation between exposure intensity and duration and development of LAA. Recent findings from a cross sectional study performed suggest that work related symptoms are related to exposure intensity (expressed either in terms of dust or aeroallergen concentrations) at the time of onset of symptoms of LAA.[6] Generally, crude proxies have been used to characterise exposure to allergens. In one cross sectional study the degree of exposure to animals had a positive and significant association with the presence of LAA, but duration of employment was not related to LAA.[7] Renström et al.[8] examined the differences for several response variables in an exposed and a matched non-exposed group (36 pairs) which were sampled out of a large group of laboratory animal workers. After two years of follow up no clear differences were found between the two groups in incidence of LAA, specific IgE, and atopy. Work related allergic symptoms were reported more often at follow up. Several studies have shown that atopic people are at higher risk of developing LAA.[1,6,7,9] One study showed that people with atopy develop LAA earlier than those without.[3] Furthermore it has been mentioned that atopic people are more likely to develop the allergy in a more severe form.[1,4,6]

Smoking is also suggested to be related to LAA, possibly by increasing mucosal transport of allergens, but evidence is not conclusive.[1] Age and sex are said to be effect modifiers in the development of occupational asthma as well, but have hardly been studied in relation to LAA.

Most studies published have cross-sectional designs and potentially have several forms of bias. A recently conducted cross-sectional study in laboratory animal workers showed that a clear exposure-response relation between exposure to urinary proteins and allergic sensitisation could only be found in workers employed for less than four years, probably because of the healthy worker effect.[10] Quantitative unbiased estimates of these factors are therefore not available. Moreover, in cohort studies of laboratory animal workers there was a shorter period of follow up than the time until sensitisation.[3,7,8]

This cohort was followed up for longer than most other cohorts of laboratory animal workers and all participants were free of symptoms at the start of follow up. The time after which symptoms of LAA developed was known and this allowed calculation of incidence density ratios (IDRs). The primary aim of this study was to determine the effect of exposure intensity on the development of LAA and the role of other variables, such as atopy, smoking, calendar period, sex and age.

METHODS

Between 1977 and 1993, 225 people underwent pre-employment screening for a job with laboratory animals at three parts of a Dutch research institute. Pre-employment screening was done by the Allergy Centre of Utrecht and consisted of a full respiratory and allergy anamnesis. Skin prick tests to house dust mite, pollen, and several animals, were performed at the Allergy Centre. All participants were tested for cats, dogs, or animals to which they had been exposed. In 1993 and 1994, home addresses of these people were traced. Personnel records of the Dutch Research Institute were used, as well as registries of the pension fund. For the remaining cases, a CD-ROM telephone guide was consulted within 30 km of the laboratories. For 136 people (60.4%) addresses were found and they were sent a questionnaire with extensive questions on work related allergic symptoms, smoking habits, and job history. One hundred and twenty two people (89.7%) returned the questionnaire. People with allergic symptoms before getting the job, and those who finally did not get a job at the institute, were excluded from the cohort. Traced people with incomplete data on their job history (date starting or ending jobs), exposure, atopy, or smoking were excluded from further analyses. Therefore the cohort used in the analyses included 99 symptom free participants (72.8%). The date a person started a job at the institute was defined as cohort entry date.

Allergic symptoms

The self-administered questionnaire contained questions about personal history of allergic symptoms to common allergens, history of allergic symptoms to laboratory animals, and intensity of contact with laboratory animals, and has been used earlier in a study on LAA.[10,11] Allergic symptoms due to working with laboratory animals were defined as the presence of allergy during working hours, or after contact with laboratory animals (Do you have any of the following symptoms during work, after contact with laboratory animals (please specify animal species)?). Self-reported allergic symptoms were divided into four groups: nasal symptoms, defined as sneezing and runny nose (production of nasal secretions); skin symptoms defined as itching or red skin; eye symptoms, defined as itching or smarting eyes; and asthma, defined as presence of shortness of breath and wheezing. The questionnaire used came from another study in laboratory animal workers.[10,11] The sensitisation period was defined as the period between the first exposure to laboratory animals and the first occurrence of symptoms of LAA.

Exposure

As a surrogate for exposure intensity the mean number of hours a week a person was exposed to laboratory animals at baseline was used. Exposure intensity was divided into four categories in most analyses with roughly similar numbers of participants. The exposure intensity categories were: < 2 hours a week, 2 - < 15 hours a week, 15 - < 38 hours a week and ≥38 hours a week on average. Potential exposure before cohort entry was omitted. Some participants had been exposed during training, but the average exposure duration during training was less than three months.

Other variables

People were atopic if they had a positive skin prick test at baseline to house dust mite, pollen, or an animal (cat, dog, or other animal they had been exposed to outside the workplace). A recently published paper showed that atopy defined on the basis of atopic sensitisation to other animals was the best predictor of LAA.[11] Smoking at baseline was used in the analyses. No distinction was made between smoking cigarettes, cigars, or a pipe.

Three calendar periods for those entering the cohort were distinguished with baseline date: 1973-80, 1981-6, and 1987-94.

Analyses

Statistical analyses were performed with Statistical Analyses Software (SAS). Mean and median sensitisation periods were calculated with Proc Univariate. Incidence density rates were calculated by dividing the number of cases of LAA by the sum of person-years for each person from the entry date to the cohort until the end of the follow up (1993-4), or until the first symptoms of LAA were reported. Survival analyses were performed with proportional hazard techniques.

RESULTS

Of the 225 people who underwent a pre-employment medical, 89 (39.6%) could not be traced and 136 were sent a questionnaire. Eleven (8.1%) reported personal reasons for refusing participation and three (2.2%) had died. Of the 122 people who completed the questionnaire, 13 were excluded from the cohort because they reported symptoms of LAA at the pre-employment medical[9] or finally did not start working at the institute.[4] Nine people with incomplete data on when starting or ending jobs, exposure intensity, atopy, or smoking were also excluded from further analyses. This resulted in a cohort of 99 people (72.8%). Since baseline data were available for all 225, the prevalence of atopy could be studied in cohort members and those who were not included in the cohort. Prevalence of atopy did not differ significantly between the two groups (31.2% (31/99) versus 40.2 (49/122) respectively, Fisher's exact test, $p>0.15$). Similar inclusion criteria were applied in this comparison.

Allergic symptoms

Table 1 shows general characteristics of the cohort. Nineteen people reported LAA, resulting in an incidence of LAA of 19.2%. The incidence in the first year of employment was 4.0%, that is, four of the LAA cases. Seventeen of the LAA cases (89.5%) reported an allergy to rats, seven (36.8%) to mice, four (21.1%) to guinea pigs, and three (15.8%) to rabbits (table 1). Most cases reported nose or skin symptoms. Asthmatic symptoms were reported by 42.1% of the LAA cases. Asthmatic symptoms were always, except for one subject, accompanied by other symptoms.

People with asthmatic symptoms were only found among people who worked with laboratory animals for more than two hours a week on average. More atopic than non-atopic people developed asthmatic symptoms (13% versus 6%).

Table 1 General descriptive information on 99 laboratory animal workers

	n	%
Participants	99	100
Female workers	44	44.4
Atopic workers	31	31.3
Smokers at cohort entry	47	47.5
LAA	19	19.2
Rat allergy	17	17.3
Mouse allergy*	7	7.1
Guinea pig allergy*	4	4.1
Rabbit allergy*	3	3.1
Work related allergy symptoms*		
Rhinitis*	14	14.3
Asthma*	8	8.2
Eye*	11	11.2
Skin*	15	15.3
Age at cohort entry (mean (range))	25	16-44

*n = 98 due to missing information in one of the questionnaires

Sensitisation period

The mean sensitisation period for non-atopic people with LAA (n=9) was about 109 months and differed significantly from the mean sensitisation period of atopic people with LAA (n=10), which was about 45 months (Kruskal Wallis, $p<0.05$). The mean sensitisation period decreased with increasing exposure intensity, except for the lowest exposure category (table 2). The two highest exposed categories (exposure intensity >15 hours a week) had a significantly shorter mean sensitisation period than the two categories with the lowest exposure (exposure intensity < 15 hours a week; Kruskal Wallis test, $p<0.05$). Thirteen of the 23 cases of LAA were referred to the Allergy Centre of Utrecht by the Occupational Health Service because these workers developed symptoms of LAA. For these cases, the difference between the onset of symptoms of LAA reported by questionnaire and clinically confirmed LAA reported in the medical files was two years maximum, with a Pearson correlation of >0.90 ($p<0.05$).

Table 2 Mean and median time until development of LAA symptoms (in month) for 19 laboratory animal workers with self reported LAA

	LAA cases			
	(n)	Mean	Median	Range
All cases	19	76	63	<1-270
Non-atopic cases	9	109	98	7-270
Atopic cases	10	45	27	<1-117
Exposure < 2 h/week	2	83	83	30-36
2 ≤ Exposure < 15 h/week	6	133	113	83-270
15 ≤ Exposure < 38 h/week	7	58	56	1-192
Exposure ≥ 38 h/week	4	16	14	<1-36

Incidence Density Rates

The overall IDR was 1.97 cases per 100 person-years (table 3). The IDR increased with increasing exposure intensity. The IDR for atopic people was more than three times higher than for non-atopic people.

Smokers had a higher IDR than non-smokers. Men seemed to have a higher IDR than women. The risk of developing LAA seemed to increase with time, as indicated by the IDR by calendar period.

Survival analysis

Table 4 shows the characteristics of the exposure intensity categories. An analysis with exposure intensity, atopy, smoking at baseline, calendar period, sex and age in one model, showed that sex and age were not significantly related to LAA, with relative risks (RR) of 0.8 ($p=0.71$) and 1.0 ($p=0.49$) respectively. Therefore, age and sex were excluded from subsequent models.

A weak period effect seemed present. The risk of developing LAA was, however, non-significantly increased in people who started their job at the institute at a later calendar date.

Table 3 Number of LAA cases, sum of person-years of follow up, and incidence density ratios (IDRs); overall, by atopic status, sex, exposure, and smoking at cohort entry

	LAA cases (n)	Sum of person-years	IDR cases/100 person-years
All cases	19	964.6	1.97
Non-atopic cases	9	722.6	1.25
Atopic cases	10	242.0	4.13
Exposure < 2h/week	2	232.2	0.86
2 ≤ Exposure <15 h/week	6	210.3	2.85
15 ≤ Exposure <38 h/week	7	309.8	2.26
Exposure ≥ 38 h/week	4	212.3	1.88
Non-smokers	10	542.8	1.84
Smokers	9	421.8	2.13
Men	10	496.0	2.02
Women	9	469.0	1.92
1973-80	7	461.6	1.52
1981-6	9	411.8	2.19
1987-94	3	91.3	3.29

Table 4 Risk factors of LAA and LAA related end points by exposure intensity categories for 99 laboratory animal workers

	Exposure < 2 h/week	2≤Exposure <15 h/week	15≤Exposure <38 h/week	Exposure ≥38 h/week
Total in category	25	25	25	24
LAA cases	2 (8)	6 (24)	7 (28)	4 (17)
Asthma	0 (0)	2 (8)	3 (12)	3 (13)
Atopy	11 (44)	6 (24)	7 (28)	7 (29)
Women	6 (24)	11 (44)	12 (48)	15 (63)
Smoking at baseline	9 (36)	12 (48)	13 (52)	13 (54)
Absent from work due to symptoms*	0 (0)	0 (0)	3 (13)	3 (13)
Transferred to another job*	0 (0)	1 (4)	3 (13)	4 (17)
Age (mean (range))	27 (17-24)	30 (20-44)	23 (17-42)	20 (16-32)

*n = 98 due to missing information in one of the questionnaires

Table 5 shows the results of the remaining model. The RRs for the four exposure categories were 1.0, 5.3, 5.1, and 3.6 respectively. The relative risk for the category with an exposure intensity between two and 15 hours a week was significant, and the RR for the category with an exposure intensity between 15 and 38 hours a week was of borderline significance. When these four exposure intensity categories were rearranged into two categories, a non-exposed category (exposure intensity < 15 hours a week), and an exposed category (exposure intensity >15 hours a week) a corrected RR of 1.5 was found ($p=0.47$).

Although most atopic people were in the non-exposed category, the RR was still higher in the exposed category.

Survival analysis assumes proportionality of survival curves for all exposure categories. This implies that the curves of the four exposure categories should not cross. In most cases these assumptions were not violated although after about 100 months of follow-up curves crossed in some analyses for some exposure categories. An analysis limited to 100 months of follow up did not result in different risk estimates.

People with atopy were at greater risk of developing LAA. A relative risk of 4.2 ($p<0.05$, 95% confidence interval (95% CI) 1.5 to 11.3) was found for atopy, corrected for exposure intensity, calendar period, and smoking (table 5).

Table 5 Results from simple univariate proportional hazard regression analyses of symptoms of LAA by exposure and potential confounders in 99 laboratory animal workers

	LAA/n	RR	(95% CI)
Exposure<2	2/25	1.0	-
2 ≤ Exposure < 15 h/week	6/6	5.3*	(1.0 - 27.6)
15 ≤ Exposure < 38 h/week	7/25	5.1†	(0.9 - 28.0)
Exposure ≥ 38 h/week	4/24	3.6	(0.6 - 21.5)
Non-atopic cases	9/68	1.0	-
Atopic cases	10/31	4.2*	(1.5 - 11.3)
Non-smokers	10/52	1.0	-
Smokers	9/47	0.8	(0.3 - 2.1)
1973-80	7/35	1.0	-
1981-86	9/38	1.6	(0.5 - 4.6)
1987-94	3/26	1.8	(0.4 - 8.3)

*p<0.05, †p<0.10

Table 6 shows a separate analysis for atopic and non-atopic people. Atopic people seemed to have an increased risk of developing LAA when exposed. The RRs for the three exposure intensities were 8.0, 7.3, and 8.3 respectively. For non-atopic people, the pattern was about the same as for atopic people; but RRs were lower.

When participants with an exposure intensity of less than 15 hours a week were compared with participants with a higher exposure intensity, a difference was found in the number of people who reported absence from work because of allergic symptoms (0% versus 13%). The proportion of people who were transferred to another task or job because of allergic symptoms also differed among these two categories (respectively 2% versus 15%).

A significant difference in the number of people who were transferred to another task or job because of their symptoms of LAA was also found between atopic and non-atopic people (16% versus 5% respectively, $p<0.10$). The difference between atopic and non-atopic people in absenteeism was small: 10% versus 5% respectively.

Table 6 Multiple proportional hazard regression of LAA on exposure corrected for atopy (only first model) and smoking, for the whole population and stratified by atopy in 99 laboratory animal workers

	All workers		Non-atopic cases		Atopics cases	
	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)
Reference category	1.0	-	1.0	-	1.0	-
2 ≤ Exposure < 15 h/week	5.3†	(1.0 - 25.9)	2.5	(0.3 - 24.5)	8.0†	(0.8 - 79.5)
15 ≤ Exposure < 38 h/week	5.1†	(0.9 - 22.6)	2.5	(0.2 - 24.8)	7.3†	(0.7 - 72.5)
Exposure ≥ 38 h/week	3.6	(0.5 - 17.6)	1.1	(0.1 - 18.5)	8.3†	(0.8 - 85.7)
Smokers	0.8	(0.3 - 2.2)	1.6	(0.4 - 6.9)	0.6	(0.2 - 2.1)
Atopic cases	3.8*	-	-	-	-	-

*p<0.05, †p<0.10

DISCUSSION

This study shows that both non-atopic and atopic people seemed to have an increased risk related to exposure intensity when exposed to laboratory animal allergens. Atopic people developed LAA significantly earlier and in more severe forms (asthma) than non-atopic people. The time until development of the first symptoms of LAA was longer than reported in previous studies.[1,2] In this study the mean time until development of the first symptoms was 76 months, with a maximum of 270 months. The risk of developing LAA remained present, even after three years of exposure to laboratory animals.

This study had possible selection bias because of loss to follow up, which could could be related to LAA or the allergen exposure. Of 225 people who were eligible to participate in this study, 122 completed the questionnaire. Most of the non-response (86.4%) occurred because the address was unknown, despite active follow up. Other causes of non-response were a change in name because some women married, and some women were not expected to pay a pension contribution and were therefore not registered by the pension fund. A few people had emigrated, particularly researchers. People were also not recorded in the CD-ROM telephone guide. Despite high rates of loss to follow up, selection bias seems unlikely, since a similar prevalence rate of atopy was found in non-participants and participants. Also, the distribution of men and women was similar in non-participants and participants. Participants and non-participants were evenly distributed over the three cohort entry periods. Although non-response was considerable, the final cohort still consisted of 99 people (72.8% of the people who were sent a questionnaire), many participants in comparison with other cohort studies.[4,8]

People at risk were followed up until the development of LAA. The presence of the first symptoms of LAA was determined by questionnaire. This could have been vulnerable to responder bias. However, a comparison of the value of the self reported information on the time a participant developed the first symptoms of LAA with medical information present at the Allergy Clinic showed that of all 23 cases of LAA, 13 were again seen by the medical specialist (BM) during the follow up period. For all these cases LAA was confirmed clinically by SPT or by serological testing. For these 13 cases, the difference between the time of onset of symptoms reported by questionnaire and reported in the medical files was two years at most and the correlation between the two sources of information was high (Pearson correlation > 0.90). These results for a subgroup of cases of LAA suggest that the self reported information was valid for presence and onset of LAA.

For 10 cases, no additional information could be found in the records of the Allergy Centre, probably because they were not referred to this clinic by the occupational health service. No cohort members who did not report symptoms in the questionnaire during the follow up were seen at the Allergy Centre after the initial evaluation. Although this cannot be seen as a complete evaluation of the validity of the questionnaire used, it does suggest that recall of symptoms agreed with the clinical evaluation of symptoms made during the follow up and that no over or underreporting occurred. It also suggests that those who developed symptoms during the follow up attributed those correctly to working with laboratory animals. This also implies that the relations reported can most probably not be explained by the presence of recall bias. This also seems unlikely as the relation with atopy in this study is comparable with what is commonly found in the scientific literature.[10,11,13]

The incidence of LAA (19.2%) was comparable with figures given in other studies.[1,2,6]

The incidence in the first year was already 4.0%. Botham et al.[3] reported a decrease in incidence after two and three years of follow up. However, they did not allow for a reduction of the population at risk after the first year of follow up due to development of LAA in some workers. Those who developed LAA during the first year of follow up are not at risk any more during subsequent years and should be removed from the calculations of risk in the second and third year. Recalculation from their tables shows a slight increase in incidence in the second and third year of follow up compared with the first year. In our study laboratory animal workers were still at risk after having worked for three years with animals at the institute, although the risk decreased after this period.

In this study an increased risk was found for people exposed to laboratory animals for more than two hours a week. The risk decreased for people exposed for more hours a week. This could probably be explained by a healthy worker effect. The number of people who were transferred to another task or job because of allergic symptoms increased with increasing exposure intensity (0%, 4%, 13%, and 17% respectively). Kibby et al.[7] also reported a positive association between exposure intensity and the presence of LAA in their prevalence study (prevalence ratio (PR) 1.75; 95% CI 1.06 to 2.39; χ^2=4.97; p=0.03). In their study exposure intensity was the self reported number of hours a day, days a week, and weeks in six months of contact with laboratory animals.

In our study time until onset of the first symptoms of LAA was shorter at higher intensities of exposure, except for the category with lowest exposure.

The exception could be explained by the highest number of atopic people in this category and the few cases of LAA in this category. People exposed more intensely developed asthmatic symptoms faster. Exposure intensity was a surrogate for the exposure level. It was self reported in the questionnaire and could therefore be biased. This surrogate of exposure has been used in other studies as well. Results from the study by Hollander et al.[10] suggest that this surrogate is strongly correlated with the exposure proxy that performed best in the analysis; the number of hours that a person worked with rats multiplied by the antigen level. Exposure before the first job was not considered extensively because all participants were symptom free at the start of this job.

Atopy seemed to be strongly related to the development of LAA. A significant RR of 4.2 was found for atopy in a multiple regression model with exposure intensity, smoking, and calendar period. In other studies comparable RRs were reported.[7,8] In the prospective study of Botham et al.,[3] LAA was defined with questionnaires annually. Their data were confirmed clinically only in a few cases. In that study more non-atopic people developed LAA after two and three years. During the first year 19%-43% of atopic people developed LAA compared with 3%-6% of the non-atopic people, but rates became similar during later years. There were some indications that atopy was an effect modifier. In our study atopic people developed symptoms of LAA earlier than non-atopic people. Atopic people also developed LAA more often than non-atopic people. Atopic people had a higher overall increased risk than non-atopic people after being exposed to laboratory animal allergens. A higher percentage of people with asthmatic symptoms was found among atopic people than non-atopic people. This has been confirmed by a few other studies.[2,4,6,12] Also more atopic people were absent from work or transferred to another job because of symptoms of LAA. Most atopic people were found in the non-exposed category (exposure intensity < 2 h/week). This might be indicative of self selection among the participants. It is also possible that advice of the Allergy Centre, where the pre-employment medicals were performed, was responsible for this result. Unfortunately, a detailed comparison of the results of this study with other studies is not possible, because the definition of atopy differs considerably between studies.

Most follow-up studies were based on an assumed sensitisation period of about three years.[3,7,8] However, our study results showed on average a longer sensitisation period. This could be the result of survivor bias, due to using a cohort selected by means of a pre-employment screening, and excluding people with symptoms of LAA. Also some other studies reported a longer time until development of first symptoms of LAA than is generally assumed.[14-16]

Few studies gave proper estimates of the mean time to sensitisation, because the duration of follow up was too short or the series was of more severely affected patients, which could lead to serious bias. Therefore, these studies were not able to estimate correct or unbiased RRs. Furthermore, it seems justified to suggest that in follow up studies a longer follow up should be considered. More research on determinants of the duration of the sensitisation period would be of interest.

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5 Relations between respiratory symptoms and sickness absence among workers in the animal feed industry[1]

ABSTRACT

Objective

The survey aimed at studying the associations between prevalent respiratory symptoms in an occupational population and sickness absence due to respiratory disorders.

Methods

A cross-sectional survey among male workers in an animal feed mill was conducted. A total of 303 production workers and 102 office clerks completed a questionnaire on respiratory complaints, smoking habits, and occupational history. The questionnaire was used to identify workers with respiratory symptoms in the past 12 months. During this period all spells of sickness absence were recorded. Causes of sickness were classified in broad categories encompassing respiratory symptoms, influenza, musculoskeletal disorders, and others.

Results

Logistic regression analysis showed that workers with respiratory complaints experienced a higher sickness absence than those without respiratory complaints. Adjusted for age, and smoking the odds ratio (OR) for sickness prevalence was 1.9 among office clerks and 2.6 among blue-collar workers. Smoking increased the risk on sickness absence with 2.4 and 1.6, respectively. When restricting the analysis to sickness due to respiratory complaints, subjects with respiratory complaints had significantly higher risks for absence prevalence and absence rate than those without respiratory complaints. There were no differences in sickness absence between workers with asthma like complaints and those with chronic bronchitis like complaints.

Conclusion

The clear associations between respiratory complaints and prevalence and rate of respiratory sickness absence indicate that workers with respiratory complaints are at risk of temporary disability and, thus, may experience a reduced ability to cope with routine activities at work.

1 Post WK, Burdorf A, Bruggeling TG. Occupational and Environmental Medicine 1994;51:440-446. Reproduced with permission from the BMJ Publishing Group.

INTRODUCTION

Asthma, chronic bronchitis, and emphysema are significant causes of morbidity and mortality in most affluent societies.[1-4] Although the precise definitions of the particular diseases have been vigorously debated for many years, these chronic non-specific lung diseases (CNSLD) share common features such as shortness of breath, wheezing, chronic cough, and chronic phlegm production.[5] Several surveys in occupational populations have shown that various agents in the working environment play a part in the aetiological mechanisms underlying these respiratory symptoms.[4,6,7]

Given the abundant number of publications on occupational asthma and chronic obstructive pulmonary disease it is surprising that the ability of workers with respiratory symptoms to cope with routine activities at work has been studied only occasionally. Sickness absence is an important measure of ill health and often a prominent source of information to act on in occupational health care. Consequently, it may be an interesting measure of morbidity to evaluate the influence of respiratory symptoms on work capacity. Sickness absence is influenced by social and psychological factors as well as illness state and work requirements.[8] These factors intermingle in determining the subject's possibility to maintain a normal performance at work.

A few studies have documented that sickness absence is increased among workers with respiratory symptoms. An early survey among electrical workers showed that chronic cough, diminished forced expiratory volume, and chronic phlegm production were predictive of days of sickness absence due to respiratory illness.[9] This finding was confirmed in a study among workers of a fertilizer factory, which showed that subjects with persistent chronic cough and phlegm production were absent because of chest diseases more often and longer than workers without these symptoms.[10] One study added to the list of possible predictors of days of respiratory sickness absence, pronounced shortness of breath, and chronic wheeze.[11]

These studies have presented evidence that sickness absence may be a useful measure to evaluate the consequences of having respiratory symptoms at work. Moreover, knowledge of the causes of sickness absence could possibly contribute to secondary prevention by identifying subjects with respiratory symptoms and subsequent illness at a sufficiently early stage to prevent permanent disability.[12]

The primary aim of this survey was to study determinants of sickness absence due to respiratory symptoms. Factors under study included the presence of respiratory symptoms, smoking, age, amount of exposure, and other job characteristics.

A secondary goal was to evaluate the usefulness of routinely collected data on sickness absence in establishing prevention programmes for workers with respiratory symptoms.

SUBJECTS AND METHODS

A respiratory health survey was conducted among male workers in an animal feed mill in The Netherlands. Subjects employed in their present job for at least 12 months were invited to participate in the study. Female workers were excluded because of too small numbers, especially in the blue collar jobs. Workers who had taken early retirement as well as workers who became permanently disabled during the study period were also excluded. None of second group became disabled due to respiratory diseases. The population consisted of the entire workforce of the animal feed mill, comprising blue collar workers at different production departments, maintenance personnel, and office clerks. Production workers and maintenance personnel were regularly exposed to organic dusts, such as various grains and cassava, which may cause respiratory symptoms.[13] Maintenance workers were also exposed to other hazardous agents like soldering and welding fumes, oils, and solvents.[6] The office clerks were used as controls as occupational exposure to inhalable agents was almost zero in this group.

Information on respiratory symptoms, smoking habits, and work history was gathered from a self administered questionnaire. The questions on respiratory symptoms resembled those from a standardised European questionnaire.[14,15] Questions asked about complaints of chronic cough, chronic sputum secretion, wheezing, shortness of breath, and attacks of chest tightness (asthma). Subjects who reported at least one of these symptoms were classified as prevalent case of respiratory symptoms. Asthma like symptoms were derived from questions on wheezing for at least one week in the past two years, shortness of breath at any time in the past two years, or chest tightness in the morning at any time in the past two years. Chronic bronchitis like symptoms were defined as chronic cough or chronic phlegm for at least three months a year in the previous two consecutive years. The remaining workers with other respiratory complaints or a combination of asthma like and bronchitis like complaints were classified as miscellaneous. For subjects with one or more respiratory symptoms, additional information on medical consumption, and frequency and duration of their symptoms in the six months before presenting the questionnaire was required. Workers with respiratory complaints who consulted their general practitioner or a specialist, took medication to alleviate their symptoms, or reported to have had symptoms almost daily during the past six months were considered to be cases with severe respiratory complaints.

The questionnaire also categorised workers into non-smokers (never smoked), current smokers (currently smoking cigarettes, cigars or pipes), and former smokers (formerly smoked regularly but stopped smoking for at least one year before the study). Those who stopped smoking less than one year before the study were classified as current smoker. The section covering occupational history collected information on job titles and duration of employment in the current and previous companies. Employment in the current job was used as a proxy of duration of exposure to organic dusts. Previous jobs were assigned the presence or absence of exposure to allergens.

The company register of sickness absence was used to retrieve sickness absence records covering the year before giving the questionnaire. Due to changes in the register a longer period for collecting retrospectively valid data was not feasible. This register is part of the company's insurance system. If a worker falls ill, he is obliged to report his absence to the administration office. Subsequently, these workers are visited by a trained layman who reports on complaints and causes of the sickness to the register. Although the company policy is that absent workers should be visited on the first day of absence, in practice absences of two days or less usually go without a diagnosis of the cause. Every week the trained layman and the occupational physician discuss the medical background of absent workers. Workers who have been absent for four weeks or those with severe problems are invited to the medical service on site. The occupational physician examines these workers and documents his diagnoses in medical files. The company register of sickness absence comprises frequency and duration of sickness absences and diagnoses according to the International Classification of Diseases. It provides the following outcomes of sickness absence for each worker:

1 Absence rate; the total number of calendar days of sickness absence in the past 12 months, expressed as a percentage of 365 days.
2 Absence frequency; the total number of periods of sickness absence in the past 12 months.
3 Absence duration; the mean number of calendar days of periods of sickness absence in the past 12 months.
4 Absence prevalence; the percentage of workers with at least one period of sickness absence in the past 12 months.

The layman's reports and the physician's diagnoses were used to categorise the cause of sickness absence into six groups (by one of the authors, TB). The categories distinguished were respiratory symptoms, influenza, back pain, other musculoskeletal disorders, other diseases, and reasons unknown.

The group of respiratory symptoms included the respiratory symptoms mentioned in the questionnaire, cold, pneumonia, and sore throat.

Categorical data were analysed by Mantel-Haenszel χ^2-tests. The hypothesis that the means of normally distributed variables differ significantly was tested with two-tailed t-tests. Continuous variables not normally distributed are presented as medians and ranges and were analysed by the Mann-Whitney U test. The measure of association between risk factors and respiratory symptoms was the odds ratio (OR). Unconditional logistic regression analysis was performed to determine the influence of age, smoking habits and work history on respiratory complaints. Similar analyses were employed to study the effect of age, smoking habits, work history and respiratory complaints on total sickness absence and sickness absence due to respiratory symptoms. These analyses were restricted to absence prevalence and absence rate as these variables were most stable in the population under study. Thus the absence rate as an overall measure of absence was preferred to separate analyses of frequency and duration. Because the distributions of rates of sickness absence were highly skewed, the absence rates of all causes and of respiratory symptoms were dichotomised at 2.4% and 1.4% among office workers and at 7.6% and 3.1% among blue collar workers. By this procedure subjects with a high absence rate (the highest quartile) could be compared with subjects with a low absence rate.

RESULTS

Four hundred and thirteen (80%) workers completed the questionnaire. Data on smoking habits were incomplete for six production workers and two office clerks, resulting in a useful response of 303 (76%) blue-collar workers and 102 (86%) office clerks. Of the workers who failed to return the questionnaire sickness absence records were traced to employ a non-response analysis. In both groups responders and non-responders had a similar prevalence of absence. Among the office clerks the non-responders showed a slightly higher frequency (1.9 versus 1.5) and higher mean duration (4.4 versus 3.0) of absence and thus a higher absence rate (2.9 versus 1.8) than the responders. Non-responding blue-collar workers were sick more often (2.5 versus 2.0) and consequently had a higher absence rate (7.3 versus 6.2). The best part of their increased absence rate could be explained by differences in sickness absence due to influenza.

Table 1 gives some characteristics of both occupational groups, stratified by the presence of at least one respiratory symptom (defined as the presence of CNSLD).

Table 1 Characteristics of office clerks and blue collar workers in an animal feed company, stratified by the presence of at least one respiratory symptom

	Office clercks			Blue collar workers		
	Total	No symptoms	≥ 1 symptom	Total	No symptoms	≥ 1 symptom
No	102	82	20	303	242	61
Age (y) (mean (SD))*[1,2]	38.3 (9-2)	38.9 (9-3)	36.1 (8-7)	42.3 (9-6)	41.5 (9-7)	45.1 (8-3)
Non-smokers (No (%))†[1,2]	46 (45)	38 (46)	8 (40)	56 (18)	52 (21)	4 (7)
Ex-smokers (No (%))†[1,2]	26 (26)	23 (28)	3 (15)	109 (36)	94 (39)	15 (25)
Smokers (No (%))†[1,2]	30 (29)	21 (25)	9 (45)	138 (46)	96 (40)	42 (69)
Years smoked (mean (SD))*[1,2]	23.7 (11-3)	24.1 (11-4)	22.7 (12-0)	22.1 (11-3)	20.0 (11-3)	27.0 (9-9)
Pack-years (mean (SD))*[2]	19.8 (13-3)	19.6 (13-3)	20.5 (13-9)	16.7 (13-7)	13.6 (10-9)	23.8 (16-7)
Working years (mean (SD))*[1]	13.2 (9-4)	13.7 (9-5)	11.2 (9-2)	16.8 (9-2)	16.6 (9-4)	17.4 (8.2)

*$p < 0.05$ (*t* test); †$p < 0.05$ (χ^2 test)

[1] Significant difference between office clercks and blue collar workers

[2] Significant difference between blue collar workers with and without respiratory symptoms

The blue-collar workers were, on average, older and had been employed longer at the animal feed mill than the office clerks. Also the smoking habits between the two groups differed significantly; the blue-collar workers were more often current smokers or former smokers.

On average, ex-smokers stopped smoking almost 12 years before the study. In both groups stratification by the occurrence of respiratory symptoms showed a positive association with current smoking. Blue-collar workers with respiratory symptoms also showed a considerable increase in the number of years of smoking and the total amount of cigarettes smoked (expressed as pack-years = number of packs of 20 cigarettes a day multiplied by the number of years smoked) when compared with blue-collar workers without these complaints. Among office clerks, these differences were not found between subjects with and without respiratory symptoms.

The prevalence of respiratory symptoms was 20% in both occupational groups. Table 2 presents the nature of the respiratory symptoms reported by the workers. For most respiratory complaints no significant difference was found between the office clerks and the blue-collar workers.

Table 2 Respiratory symptoms among office clercks and blue collar workers with chronic non-specific lung disease

	Office clercks (n=20) n (%)	Blue collar workers (n=61) n (%)
Chronic cough	9 (45)	28 (45)
Chronic sputum secretion	7 (35)	23 (37)
Shortness of breath	2 (10)	17 (27)
Ever wheezing	9 (45)	34 (55)
Wheezing for more than 1 week	2 (10)	21 (34)
Chest tightness (asthma)	5 (25)	15 (24)
Asthma like symptoms	4 (20)	19 (31)
Chronic bronchitis like symptoms	7 (35)	18 (30)
Miscellaneous	9 (45)	24 (39)
Symptoms before first job*	9 (45)	8 (13)

*$p<0.05$ (χ^2 test)

The prevalence of wheezing for at least one week in the past two years was higher among the blue-collar workers than the office clerks; this difference approached significance (34% versus 10%; p=0.09).

Classifying the respiratory symptoms into asthma like symptoms and chronic bronchitis like symptoms showed similar prevalences in both occupational groups. Among office clerks and blue-collar workers 15% and 30%, respectively, reported a combination of respiratory complaints associated with either asthma or chronic bronchitis. Among the office clerks 9 (45%) had experienced respiratory symptoms before their first employment ever, against only 8 (13%) blue-collar workers (χ^2 test, $p<0.05$). For 14 of 17 subjects the symptoms described fitted the presence of asthma at an early age. About half of the subjects with respiratory symptoms reported a gradually worsening of their symptoms in the past few years.

The natural history and severity of respiratory complaints in the past six months showed no pronounced differences between office clerks and blue-collar workers. About 78% (63) of the subjects had experienced respiratory symptoms in the past six months; of those 27% had experienced one spell, 30% had experienced 2 to 10 spells and the remaining 43% had experienced at least 10 spells.

The total duration of respiratory symptoms within the past six months indicated that 51% had symptoms for 7 days or less, 5% had symptoms lasting 8 to 14 days, and 44% reported more than 14 days to almost daily respiratory symptoms. In the past six months, the number of workers taking medicine was high; 37% had visited their general practitioner or lung specialist, and 30% reported taking medications for their respiratory symptoms.

Table 3 shows the information retrieved from the register of sickness absence. Both among the office clerks and the blue-collar workers the percentage of workers without any sickness absence was small, 26% and 18%, respectively. During the 12 months of study, the office clerks recorded 158 periods of absence covering 648 days. The corresponding figures for the blue-collar workers were 614 periods of absence covering 7093 days. About a quarter of the periods of sickness absence could not be attributed to a specific cause. This was predominantly due to short term sickness absence. Hence, the absence rate contained 5.7% days with sickness absence of unknown cause. The office workers had a significantly lower absence rate, primarily the result of shorter periods of absence. Respiratory symptoms and influenza accounted for 52% of the days lost among the office workers and for 21% among the blue-collar workers (χ^2-test, $p<0.05$). For the blue collar workers musculoskeletal disorders were the principal cause of sickness absence with a contribution of 30% to the total sickness absence.

Table 3 Total and cause specific sickness absence during 12 months among office clerks and blue collar workers in an animal feed company, stratified by the presence of at least one respiratory symptom

	Office clerks (n=102)		Blue collar workers (n=303)	
	No symptoms (n=82)	Respiratory symptoms (n=20)	No symptoms (n=242)	Respiratory symptoms (n=61)
Total sickness absence:				
Absence prevalence	58 (71)	17 (85)	193 (80)	56 (92)*
Absence frequency	1.3	2.5	1.9	2.5
Absence duration (days)	3.1	2.6	8.7	16.1
Absence rate (%)	1.7	2.0	5.3	10.1
Sickness absence due to respiratory disorders:				
Absence prevalence	11 (13)	7 (35)*	29 (12)	14 (23)*
Absence frequency	0.1	0.6	0.1	0.3
Absence duration (days)	0.6	1.3	0.2	4.4
Absence rate (%)	0.2	0.6	0.7	1.3
Sickness absence due to influenza:				
Absence prevalence	37 (45)	13 (65)	88 (36)	30 (49)
Absence frequency	0.6	1.2	0.5	0.7
Absence duration (days)	1.7	1.7	2.3	3.6
Absence rate (%)	0.6	0.8	0.8	1.6

*$p<0.05$ (χ^2 test). Numbers in parentheses are percentages.

When stratified by presence of respiratory symptoms the sickness absence showed a similar pattern in both groups. Among subjects with respiratory symptoms there were higher absence prevalences and absence rates caused by any sickness, by respiratory symptoms, and by influenza.

In the blue-collar groups, among those with respiratory symptoms a twofold absence rate was found, independent of the cause of sickness, as well as a much higher absence duration, most pronounced for respiratory sickness.

The logistic regression analysis of risk factors for the presence of respiratory complaints showed opposite trends for age in both groups. Among blue-collar workers the risk increased with age, whereas the youngest office clerks had the highest risk.

When including duration of employment instead of age in the logistic models, similar trends as those for age were found. Occupational history was not associated with the prevalence of respiratory symptoms. Respiratory symptoms were more prevalent among current smokers with ORs of 3.0 (95% CI 0.9-10.4) for office clerks and 5.2 (95% CI 1.8-15.7) for blue collar workers. Ex-smoking was not of statistically significant importance.

Tables 4 and 5 describe the influence of risk factors on absence prevalence and absence rates among office clerks and blue-collar workers. In the analyses presented, age showed no clear relation with various indices of sickness absence. The oldest office clerks were absent significantly less than the younger office clerks. This result is based on a small number of subjects, however. In both groups, smokers had a higher absence prevalence than non-smokers, but the differences were not statistically significant. Among blue-collar workers smoking habits did not influence the absence prevalence and absence rate due to respiratory sickness. By contrast, office clerks who smoked showed decreased risks for absenteeism due to respiratory symptoms (prevalence and rate), but these findings were not statistically significant.

Respiratory complaints were significantly associated with sickness absence due to all causes and due to respiratory symptoms. Office clerks and blue-collar workers with at least one respiratory complaint had ORs for absence prevalences and absence rates of 1.9 and 2.6, and 3.4 and 1.8, respectively. In general, when regarding absence due to respiratory symptoms, these associations were greatly increased. The corresponding ORs were 4.4 and 2.4, and 5.2 and 7.1, respectively. A consideration of only subjects taking medicine because of respiratory complaints, gave even stronger relations with sickness absence among blue-collar workers. Among blue-collar workers, the OR was 9.3 (95% CI 1.9-44.6) for subjects taking medicine because of their respiratory problems. In the subgroup of office clerks who sought medical care because of respiratory complaints the risk fell to 1.9 (95% CI 0.2-22.6).

Similar analyses with asthma like and chronic bronchitis like complaints showed no differences in absence prevalences and absence rates. One has to bear in mind that the number of subjects with asthma like or bronchitis like complaints was small.

Table 4 Influence of age, smoking habit, and respiratory complaints on absence prevalence, absence prevalence due to respiratory symptoms, absence rate, and absence rate due to respiratory symptoms among office clerks

Risk factor	No of workers	Absence prevalence OR (95% CI)	Absence prevalence due to respiratory symptoms OR (95%-CI)	Absence rate† OR (95%-CI)	Absence rate‡ due to respiratory symptoms OR (95%-CI)
Age (y):					
21-35	46	1.00	1.00	1.00	1.00
36-50	43	0.99 (0.32-3.11)	0.71 (0.19-2.64)	0.48 (0.15-1.54)	1.58 (0.19-13.40)
51-65	13	0.21* (0.05-0.94)	0.99 (0.15-6.44)	0.89 (0.19-4.20)	4.55 (0.39-53.73)
Smoking habit:					
Non-smoker	46	1.00	1.00	1.00	1.00
Ex-smoker	26	0.74 (0.22-2.48)	1.01 (0.24-4.20)	0.96 (0.22-4.09)	(2.26 (0.26-19.69)
Smoker	30	2.36 (0.62-8.97)	0.32 (0.07-1.53)	2.59 (0.81-8.30)	0.77 (0.07-8.11)
Respiratory complaints:					
No symptoms	82	1.00	1.00	1.00	1.00
³ 1 symptom	20	1.85 (0.47-7.28)	4.40* (1.31-14.93)	3.41*(1.18-10.14)	5.16 (0.86-30.75)

*p<0.05

† Dichotomised in office clerks with an absence rate ≤ 2.4% and office clerks with an absence rate > 2.4%

‡ Dichotomised in office clerks with an absence rate due to respiratory symptoms ≤ 1.4% and office clerks with an absence rate due to respiratory symptoms > 1.4%.

Table 5 Influence of age, smoking habit, and respiratory complaints on absence prevalence, absence prevalence due to respiratory symptoms, absence rate, and absence rate due to respiratory symptoms among blue collar workers

Risk factor	No of workers	Absence prevalence OR (95% CI)	Absence prevalence due to respiratory symptoms OR (95% CI)	Absence rate† OR (95% CI)	Absence rate‡ due to respiratory symptoms OR (95% CI)
Age (y):					
21-35	87	1.00	1.00	1.00	1.00
36-50	134	0.81 (0.38-1.69)	0.69 (0.31-1.51)	1.25 (0.66-2.36)	0.64 (0.10-4.18)
51-65	82	0.70 (0.31-1.59)	0.68 (0.28-1.65)	1.04 (0.51-2.13)	1.89 (0.34-10.64)
Smoking habit:					
Non-smoker	56	1.00	1.00	1.00	1.00
Ex-smoker	109	1.22 (0.55-2.70)	1.22 (0.46-3.24)	0.76 (0.36-1.62)	1.62 (0.17-15.79)
Smoker	138	1.64 (0.73-3.67)	0.97 (0.37-2.55)	0.99 (0.48-2.04)	0.96 (0.10-9.47)
Respiratory complaints:					
No symptoms	241	1.00	1.00	1.00	1.00
³ 1 symptom	61	2.64 (0.98-7.13)	2.42* (1.14-5.15)	1.82 (0.97-3.40)	7.10* (1.76-29.01)

*p<0.05

† Dichotomised in blue collar workers with an absence rate ≤ 7.6% and blue collar workers with an absence rate > 7.6%

‡ Dichotomised in blue collar workers with an absence rate due to respiratory symptoms ≤ 3.1% and blue collar workers with an absence rate due to respiratory symptoms > 3.1%.

DISCUSSION

This cross-sectional study was directed towards the occurrence of respiratory symptoms (chronic non-specific lung disease) and associated sickness absence among office clerks and blue-collar workers of a large animal feed mill in the Netherlands.

In both groups the prevalence of respiratory symptoms was about 20 percent. Another Dutch study in the animal feed industry, using the same questionnaire, found comparable prevalences for respiratory symptoms among blue-collar workers, office clerks and external controls.[13] A higher prevalence of respiratory symptoms among the blue-collar workers was anticipated as they were exposed daily to organic dusts such as various grains. Organic dusts have been associated with different respiratory symptoms, including asthma[13,16] and chronic bronchitis.[13,17,18] The cross-sectional approach in this study hampers any explanation for the modest prevalence among exposed workers, but evidence of a healthy worker effect among animal food workers and among grain elevator workers have been documented.[13,19] The non-response may also have contributed to the moderate prevalence of respiratory complaints because the analysis of non-response showed that in both groups sickness absence was higher in non-responders than in the subjects participating in this study.

The well-known role of smoking in the occurrence of respiratory complaints[20,21] was confirmed in the survey. Current smoking was strongly associated with respiratory complaints in both groups. Former smokers resembled life-time non-smokers, which could be explained by the finding that former smokers, on average, had stopped smoking for almost 12 years. The relation between age and respiratory complaints was ambiguous. Among the office workers there was a declining trend, whereas the blue-collar workers had an increased prevalence with age. Interpretation of these patterns is difficult. A possible cause could be that the respiratory symptoms included asthma and chronic obstructive pulmonary disease, which have different associations with age. Asthma expresses itself generally at an early age, whereas chronic bronchitis arises more often in older subjects. Separate analyses for asthma like complaints and for chronic bronchitis complaints, however, showed similar patterns in both groups. More likely, different mechanisms of a healthy worker selection play an important role. The proportion of office workers with respiratory complaints before entering the factory was substantially larger than the proportion among the blue-collar workers. Because age and duration of employment were strongly correlated, duration of employment had similar patterns of association with respiratory complaints.

The information collected on the severity of the respiratory complaints indicated that for the most subjects their complaints posed serious problems. Many had experienced several spells in the past six months, about 50% had symptoms for more than seven days, 37% sought medical care and 30% reported intake of medication. The seriousness of the respiratory complaints was also reflected in the figures of sickness absence. Workers with respiratory symptoms were absent significantly more often due to respiratory symptoms than those without. Table 3 shows that prevalence, frequency, duration and rate were increased among both the office clerks and the blue-collar workers. These findings are in agreement with the few publications on this matter.[9-11]

Respiratory complaints were strongly associated with sickness absence due to respiratory symptoms. Sickness absence was characterised by absence rate which was dichotomised to distinguish subjects with high and those with low absence rates. Several cut off points were used and the general pattern remained fairly constant. Office clerks with respiratory complaints showed an OR of 5.2 (95% CI 0.9-30.8) for absence due to respiratory symptoms compared with office clerks without these complaints. In the subgroup of office clerks who sought medical care because of respiratory complaints the risk fell to 1.9. Among the blue-collar workers, subjects with respiratory complaints had a sevenfold risk of absence due to respiratory symptoms, which was raised to 9.3 for subjects taking medicine because of their respiratory problems. This finding indicates that subjects with (more severe) respiratory complaints can more easily survive performing administrative tasks, whereas they are at higher risk performing tasks with exposure to organic dust. In general, subjects with respiratory complaints were absent more due to influenza. This result stresses the well known fact that subjects with respiratory complaints are at risk for contracting influenza.[22,23]

Viewing sickness absence due to any cause, subjects with respiratory complaints were also absent from their work more often and longer because of health problems than subjects without respiratory symptoms, the ORs were 3.4 (CI 1.2-10.1) and 1.8 (CI 1.0-3.4) on absence rate due to any cause for office clerks and blue-collar workers, respectively. Among the office workers this was partly due to the high contribution of respiratory symptoms and influenza in the total sickness absence. For blue-collar workers this contributed about 20%. A detailed analysis indicated that workers with respiratory symptoms and exposed to animal feed products experienced a higher absence prevalence and absence rate due to musculoskeletal symptoms than their colleagues without respiratory complaints. It may be postulated that subjects with respiratory complaints have a decreased stamina and endurance, and, hence, are at risk of becoming ill more easily than subjects without respiratory problems. This hypothesis remains speculative in a cross-sectional study.

Other risk factors for sickness absence studied were age and smoking habits. No apparent relation between age and absence due to respiratory symptoms was found. Current smoking did not affect absenteeism due to respiratory complaints. Former smokers, however, had a higher risk on sickness absence due to respiratory symptoms. This finding was not significant. Among office clerks current smoking was a risk factor for absence prevalence and absence rate due to any cause (OR 2.4 and OR 2.6, respectively), but these increased risks did not reach significance. In a large study among civil servants current smoking was found to be a risk factor for short time sickness absence (OR 1.5) and for long term sickness absence (OR 1.8).[8]

The current study has several limitations; most importantly its cross-sectional design, the limited size of the population under study, the lack of differentiation between short term and long term sickness absence, and the grouping of sickness causes into broad categories. A cross-sectional design is sensitive to selection processes in the workforce that are influenced by health state. These selection processes are likely to apply to a chronic disease such as respiratory disorders and, hence, the associations between respiratory symptoms and sickness absence may have been underestimated.[19,24] The limited size of the study population hampers detailed analyses and causes large 95% CIs, which prevents risk factors from reaching significance. This was particularly the case in the analysis of factors associated with respiratory absence. Therefore, it was not feasible to investigate the influence of important factors such as overall health, morbidity, and work requirements[8] on the sickness absence due to respiratory diseases.

The limitations of using sickness absence data were obvious in this study. In general, four variables can be studied. In the population under study frequency, duration, and rate of sickness absence were all highly skewed and prompted us to dichotomise the data in the analysis. The choice was made to focus on absence rate rather than frequency and duration, because rate was most stable in the statistical analysis. The disadvantage of this approach is that an absentee often sick is regarded similar to an absentee with a single spell of long sickness.

The sickness register introduced familiar problems, such as short absences without reported cause and broad categories of causes of sickness. For the current study it would have been of interest to retrieve specific diagnosis of sickness absence like asthma and chronic bronchitis. As most spells of absence were classified by the trained layman based upon the workers' complaints, retrieval of a specific diagnosis was not possible. The validity of the causes of absence was not studied.

It was anticipated, however, that the validity and consistency of the sickness absence data was sufficiently high as the experienced layman and the occupational physician discussed the diagnosis of absent workers each week.

The finding that office clerks and blue-collar workers with respiratory symptoms experienced a higher sickness absence due to this condition may offer additional opportunities to identify workers at risk for aggravation of their respiratory complaints. As sickness registers are instituted industrywide, sickness absence due to respiratory symptoms provides an instrument of continuous monitoring of an occupational population. Spells of respiratory sickness could be used to identify subjects at risk. The question whether these subjects will become permanently disabled cannot be answered with this study. In any case, secondary prevention is warranted in which respiratory complaints could be used as the focus, although the sensitivity and specificity are too limited to construct a particular screening programme.

CONCLUSION

The primary aim of this study was to determine risk factors for sickness absence due to respiratory symptoms. Workers with at least one respiratory complaint in the past 12 months showed a higher absence prevalence and absence rate for all causes of sickness than workers without respiratory complaints. These differences were more apparent when evaluating specifically sickness absence due to respiratory symptoms. Occupational exposure to animal feed products, such as grain dust, was of limited importance. Office clerks and blue-collar workers showed similar patterns between respiratory symptoms and sickness absence. These associations indicate that workers with respiratory symptoms are at risk for temporary disability.

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Part 2

Identification of workers with CNSLD

6 Choosing optimal values of FEV_1 and FEV_1/FVC for surveillance for respiratory disorders in occupational populations[1]

ABSTRACT

Pulmonary lung-function testing plays an important role in surveillance programs for occupational respiratory disorders. Spirometry is usually utilized by applying preset cut-off values to discriminate between healthy and unhealthy subjects.

This article demonstrates the usefulness of decision analysis techniques to arrive at an optimal diagnosis. The diagnostic performance of FEV_1 and FEV_1/FVC was evaluated by relative operating characteristics curves (ROCs), applied to data of a cohort gathered in 1965. Both parameters showed quite similar ROCs, with a maximal sensitivity of 40% at a specificity of 95% relative to the physician's diagnosis of respiratory disorder. The area under the curves was 0.75 for both FEV_1 and FEV_1/FVC, illustrating that misclassification of 25% of the subjects is likely to occur.

Regarding the consequences of a false-positive and a false-negative decision as of equal importance, the 5%-percentile (FEV_1 residual less than -1.2 l) would be the optimal cut-off. An FEV_1 residual below the lower 5%-percentile was six times more likely to appear in subjects with chronic non-specific lung disease (CNSLD) than in subjects without. The post-test probability of CNSLD was three to four times the pre-test probability. In occupational or public health practice, however, false-positive results need to be avoided, even at the expense of a higher false-negative rate. In those situations a more rigid cut-off between normal and abnormal values may be warranted.

INTRODUCTION

Chronic obstructive pulmonary diseases (COPD) and asthma are important diseases in occupational health. Many agents in the work environment have been identified as inducing both respiratory diseases.[1-3]

1 Post WK, Steyerberg EW, Burdorf A, Heederik D, Kromhout D. Journal of Occupational and Environmental Medicine 1996;38:673-680. Reproduced with permission from the American College of Occupational and Environmental Medicine

There is evidence that patients with these airway diseases who cease exposure to the causal agent have a better long-term prognosis than those who do not.[4,5] With the rationale that secondary prevention is useful, prevention programs aimed at early detection of COPD and asthma among workers at risk have been suggested.[6] Regular surveillance has been advocated, in which case identification triggers further medical testing or intervention. In occupational health, such programmes often comprise a short questionnaire on respiratory symptoms because this is both economical and acceptable to workers. Nowadays, lung-function tests, especially forced-expiratory maneuvers, are often part of routine health examinations in occupational medicine since spirometry is a useful addition in establishing the diagnosis of COPD and, to a lesser extent, asthma.[4]

A surveillance procedure with spirometry requires the selection of an endpoint to define an abnormal level of FEV_1 or FEV_1/FVC. Traditionally, limits of normality were defined as a deviation by 20% of predicted values for healthy subjects. During the last decade, the lower boundary of the 95% confidence interval for a given pulmonary parameter has gained application as a decision criterion.[7] For a Gaussian distribution, a more precise estimate is the mean minus two standard deviations.[8] This has resulted in the American Thoracic Society's recommendation to use the lower 5% percentile of the reference distribution as a limit of normality.[9,10]

Though often assumed to be sensitive as well as specific, studies that estimate sensitivity and specificity of the FEV_1 and FEV_1/FVC ratio show the low sensitivity of the FEV_1 when applied to a general population. The FEV_1/FVC ratio is more sensitive, but less specific.[11-15]

The disadvantage of these traditional cut-offs is that they choose a rather arbitrary value for discriminating between normal and abnormal or fix the amount of persons with abnormal spirometry to about 5%. In the latter approach, in essence, these cut-offs represent the false-positive rate (type II error) that would be acceptable, but do not specify the desirable false-negative rate (type I error).[16] However, the cut-off between normal and abnormal depends on the relative costs of both errors and of the actual prevalence of the abnormal lung function. Different cut-offs can be chosen, depending on treatment decisions, health policy, and associated costs. At the optimal cut-off, the total cost, incurred by the imperfection of the test, is minimized.[17] An arbitrarily chosen cut-off seems inadequate to balance the benefits of early diagnosis (true-positive results) with the costs of overdiagnosis (false-positive results).[18] Moreover, the use of implicit unclear decision criteria will hamper the sound application of spirometry in surveillance programs.

An arbitrary chosen cut-off is not necessary, though, to evaluate or compare the performance of screening tests. Nor is an arbitrary chosen cut-off indispensable to determine the probability of disease in a subject with a particular lung-function test result, using clinical decision analysis techniques. Two clinical decision analysis techniques are particularly valuable in assessing the performance of spirometry in diagnosing respiratory disorders: the relative operating characteristic curves (ROCs) and the concept of pre- and post-test probability on disease.

ROCs allow a statistical examination of a test's ability to discriminate between subjects with and without the disease, over the full range of possible cut-off levels. Also, the performance of different tests can be compared by ROCs. Beck and Colice[19] showed the usefulness of ROCs in the evaluation of the classification of pulmonary-function tests in a clinical setting. The concept of pre- and post-test probabilities presents some quantitative but imprecise information about how much the probability has been changed by the test.[20] The test result is used to raise or lower the probability of COPD or asthma. It does not decide whether a subject does or does not have the disease of interest.

In this article, these techniques will be applied to study the relationship of spirometric parameters to the physician's diagnosis of chronic non-specific lung disorders (CNSLD) in the so-called Zutphen Study.[11,21,22] The rationale behind the choice of CNSLD, rather than the underlying diagnoses of COPD and asthma, was that among subjects, respiratory complaints such as chronic coughing and wheezing often intermingled and physicians cannot easily distinguish between COPD and asthma.[23] However, given the high age of the population and the high prevalence of smokers, COPD is most likely the underlying diagnosis in the vast majority of the CNSLD cases.[11] In this article, the implications of the outcomes of the ROC analysis for an "optimal" cut-off of spirometric parameters in occupational health surveillance will be discussed.

SUBJECTS AND METHODS

Population

The Zutphen Study is the Dutch contribution to the Seven Countries Study.[21,22] In 1960, a random sample of the male population of Zutphen was selected; all men were aged 40 to 59 years and had lived in Zutphen for at least five years. Participants who experienced CNSLD before 1960 were excluded from analyses. Follow-up data since 1965 were used because lung function tests were first performed in 1965.

The health status of the participants was regularly examined and verified. Each subject had a complete follow-up. Smoking habits were assessed according to the Seven Countries Study protocol.[21] The information available on current and past cigarette consumption (in 1965) was used.

The pack years of cigarettes smoked was computed as the product of the number of years smoked and the number of packs of cigarettes smoked per year. A pack of cigarettes is assumed to contain 25 cigarettes.

Medical examination

A detailed account on the medical examination has been reported elsewhere.[21,22] A questionnaire adapted from the British Medical Research Council questionnaire on respiratory symptoms[24] was administered by a physician who also did the medical examination. In those men who attended the 1965 survey, the vital capacity (VC) and the forced expiratory volume in one second (FEV_1) were measured with a water seal spirometer. Measured values were corrected for body temperature and pressure (BTPS). The VC was measured by three maximal inhalations and the highest VC was used for the calculations presented here. The FEV_1 was established by three attempts. The two highest values should not differ more than 50 ml. If the difference was more than 50 ml one additional attempt had to be produced. The mean of the two closest values was used for further calculations. The selected FEV_1 divided by the VC was calculated and used for further analysis. For each subject, reference values for FEV_1 and FEV_1/VC were calculated from the regression analyses of observed lung functions of all subjects in the study population, with age and height as predictors. Departures of the observed values from the predicted values were calculated and these residuals were used for further analysis.

In this study, all subjects were diagnosed as having CNSLD in the 1965 survey are considered. The diagnosis of CNSLD was based on respiratory complaints reported to the survey physician. The presence of CNSLD was coded according to the following criteria: (1) episodes of respiratory symptoms, such as regular cough and phlegm, for longer than three months in the past two years; or (2) episodes of wheezing and shortness of breath in the past two years. No attempt was made to distinguish COPD from asthma. The medical examination also included chest auscultation, but this information was not used in defining patients with CNSLD. The diagnosis of the survey physician was derived independently of any information on lung-function parameters. The spirometric tests were conducted by another physician after the medical examinations were completed.

Construction and analysis of ROCs

The distributions of FEV_1 and FEV_1/VC residuals were used to calculate the percentiles by steps of 2.5%. To construct the ROCs, the numbers of persons with test results beneath and above each percentile were compared with the numbers of persons with and without CNSLD, based on the physician's diagnosis. Based on 40 comparisons, the ROC curve was constructed, representing the true-positive rate (sensitivity) as a function of the false-positive rate (1-specificity) for all possible cut-off values of the diagnostic test. The curve is depicted in a square probability plot, bounded on the horizontal and vertical axes by 0 and 1. A test that engenders false-positive results at the same rate as true-positive results would produce a ROC curve on the 1:1 equation and does not supply any information. Any reasonable diagnostic test will display a curve in the upper left triangular region.

Associated with each ROC are the area under the curve (AUC) and the standard error of the estimate of AUC.[25] The AUC represents the proportion of subjects truly classified as either diseased or nondiseased: it is minimal when AUC is near 0.50, and it is optimal when AUC is 0.95 to 1.00. Because both curves have the exact number of normal and abnormal values, the correlation between the categorization of the normal values and that of the abnormal values has to be calculated. By taking this correlation into account, the area under different ROCs derived from the same data set can be compared.[26] Because the ROCs are constructed for the same population, a chi-square test with one degree of freedom was used to decide whether ROCs are significantly different at a given sensitivity (or specificity).[19]

Likelihood Ratio and Post-test Probability

The likelihood ratio (LR) is the ratio of the probability of a positive test result (x) in a diseased subject (D) and the probability of this result in a reference subject (R), $LR=P(x|D)/P(x|R)$. In case of dichotomized lung function measurements, $P(x|D)$, i.e., the probability of a positive test in a diseased subject, equals the sensitivity of the test. Similarly, the probability of a positive test in a reference subject, $P(x|R)$, equals 1-specificity. When the full range of test results is used, these probabilities become probability densities. The probability densities are estimated as relative frequencies from relative frequency polygons.[8] A frequency polygon is a nonparametric estimate of the unknown underlying probability density curve for the population.

The post-test or a posteriori probability, P(D|x), is the likelihood of disease, conditional on test result x.

Using the pre-test or a priori probability, P(D), and the probability on test result x in diseased or reference subjects, the post-test probability of, respectively, the presence or absence of disease can be calculated. The pre-test probability, the likelihood of disease before the test is performed, must be estimated, primarily on the basis of the prevalence of disease in the population under study. In case of a qualitative test or dichotomized test results, the outcome is either positive or negative. Using Bayes' Theorem, the post-test probability can be calculated from the sensitivity, the specificity, and the pre-test probability:[17]

$$P(D|x) = \frac{P(D) * sens}{P(D) * sens + (1 - P(D)\ (1 - spec))} \qquad (1)$$

Dealing with a quantitative test, the post-test probability is calculated from probability densities and the pre-test probability. Replacing the probabilities with odds (odds=p/(1-p)) and using the likelihood ratio function, the post-test odds can be calculated by:

$$odds(D|x) = odds(D) * LR(|D) \qquad (2)$$

Next, the post-test probability is obtained by

$$P(D|x) = \frac{odds(D|x)}{odds(D|x) + 1} \qquad (3)$$

Choice of optimal cut-off

To determine the cut-off for lung function parameters that is to be preferred in surveillance for CNSLD, the number of false-positive (FPR) and false-negative results (FNR) are considered with various cut-off points. The costs of these errors can be interpreted in economic terms, but also in relative values assigned to the importance of true and false diagnosis. Because true costs of overdiagnosing and underdiagnosing CNSLD are lacking, the effect on misclassification is evaluated for the following situations: false-positive results are more important, of equal importance, or less important than false-negative results.

This effect is demonstrated for a relative weight of costs of false-positive results five times larger than, equal to, and five times smaller than the costs of false-negative results, respectively. It is assumed that the optimal cut-off is the point at which the total costs of both errors are minimized.

RESULTS

Of the 878 men who participated in the physical examination in 1960, 40 had died before January 1, 1965. For 150 subjects, no lung-function data were available, and for another 11, the information on their occupation was insufficient to code. For nine persons, information about smoking habits was lacking. A group of 668 persons remained, of whom 94 subjects had experienced CNSLD in or before 1965. In table 1 the baseline information of the cohort is presented. Subjects with CNSLD are, on average, older, slightly shorter, and heavier smokers than subjects without CNSLD, but these differences were not statistically significant. The lung function of subjects with CNSLD was significantly lower compared with those without CNSLD.

The regression model with age (A in years) and height (H in centimeters) as predictor for the FEV_1 (in l) equals: 0.033H-0.04A-0.55.

The residual standard deviation of the predicted values was 0.618 l. For the FEV_1/VC ratio (in percent), the regression model is: -0.12H-0.41A+111.73, and the residual standard deviation 10.2%. One has to bear in mind that these

Table 1 Baseline characteristics of 668 men at the 1965 Zutphen Survey

	Subjects with CNSLD (n=94)		Subjects without CNSLD (n=574)	
	mean	SD	mean	SD
Age (years)	56.1	5.2	54.5	5.5
Height (cm)	173.3	6.5	174.0	6.5
Tobacco consumption (packyears)	441.2	328.7	408.9	301.7
FEV_1 (l.)*	1.91	0.40	2.94	0.46
FEV_1/FVC (%)*	57.9	14.4	71.3	8.3

* *t* test, $p<0.01$

regression models are based on a community-based population with a high proportion of smokers, of whom, based on job titles in 1960 and 1965, 30 to 40 % were occupationally exposed to dust, gas or fumes.[11,22,27]

The pre-test probability on CNSLD was arbitrarily set to 10%, based on the observation that for regular cough or phlegm for at least three months prevalences were observed in the range of 2 to 12%.

Figure 1 contains the ROCs for FEV_1 and FEV_1/VC residuals against the physician's diagnosis of CNSLD. A noninformative test is shown by the straight dotted line. The FEV_1 and the FEV_1/VC residuals showed quite similar ROCs. At the lower percentiles of the distribution of test results (lower left area of the plot), FEV_1/VC residuals had a slightly better performance than FEV_1 residuals, seeming more sensitive at the same specificity for the 2.5, 5, and 7.5% centiles. when the number of false results at these percentiles are compared, the differences were found to be not statistically significant (χ^2 test; $p>0.10$). The areas under the curve were 0.75 (standard error of the estimate (SEE) 0.03) and 0.76 (SEE 0.03), respectively, for the FEV_1 residuals and FEV_1/VC residuals. This implies that 25% and 24%, respectively, of the subjects are misclassified in the CNSLD or reference category. The difference between the AUCs was clearly not statistically significant.

The LR as a function of the FEV_1 residuals is a decreasing function. This implies that test values of diseased subjects tend to be smaller than those of the reference individuals. The LR equals 1 for an observed FEV_1 of 0.5 l

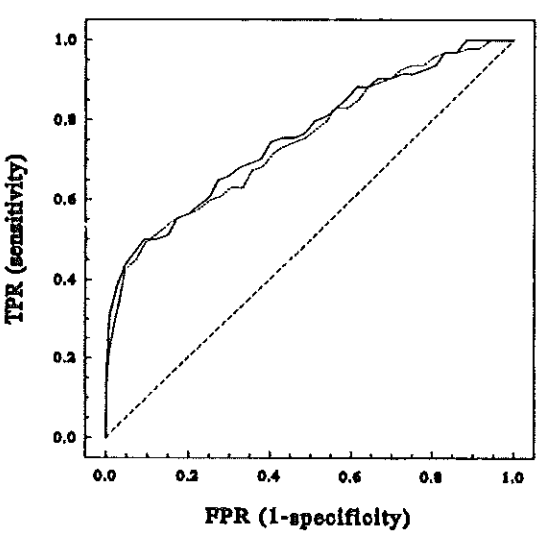

Figure 1 ROC Curve for the FEV_1 and FEV_1/VC residuals vs physician's diagnosis of CNSLD (.....: FEV_1; ——— ; ------: non-informative test)

below the predicted value (the lower 15% percentile). Thus, the likelihood of this result to appear in a subject with CNSLD is the same as in a subject without CNSLD.

Consequently, the post-test probability equals the pre-test probability, as is shown in figure 2. For FEV_1 residuals smaller than -0.5 l (thus below the lower 15% percentile), the LR is larger than 1. Therefore, the post-test probability on CNSLD is higher than the pre-test probability for a subject with an observed FEV_1 -0.5 l or more below the predicted value. For instance, an FEV_1 residual of -0.8 l (lower 10% percentile) is two times more likely, and a residual of -1.2 l (lower 5% percentile) six times more likely to appear in a subject with CNSLD. With a pre-test probability of 0.10, the post-test probability on CNSLD is about twice the pre-test probability for a FEV_1 residual of -0.8-0.9 l (lower 10% and 7.5% percentile). For a residual of -1.2 l (lower 5% percentile) the post-test probability is four times larger. When the difference between the observed and predicted value is larger than -0.5 l, the post-test probability on CNSLD is lower than the pre-test probability. In figure 2 the post-test probabilities are shown for the FEV_1 residuals. The post-test probability for residuals below -1.5 l are not shown.

These estimates are even higher, but imprecise because of the limited number of observations at these residuals. Given the similar ROCs for FEV_1

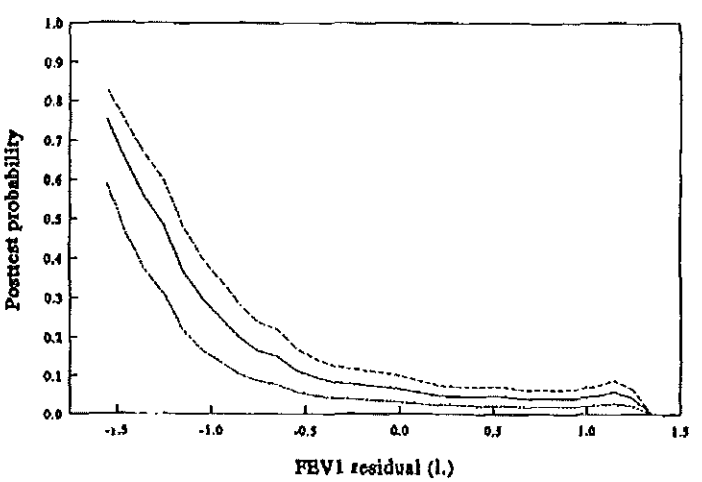

Figure 2 Post-test probabilities on CNSLD for FEV_1 residuals of -1.5 liters with pre-test probability on CNSLD estimated on 0.05, 0.10 and 0,15 (and 0,15 (.....: 0,05; ____ 0,10; -----0,15))

and FEV_1/VC, the analysis of pre-test and post-test probabilities for FEV_1/VC residuals was, not surprisingly, largely similar to the presented figures for FEV_1 residuals.

The sensitivity, the specificity, and the number of false-positive results and false-negative results at the lower percentiles are shown in table 2. The sensitivity and specificity of these residuals range between 16 and 53% and between 100 and 85%, respectively. A more rigid cut-off leads to a higher specificity, implying less false-positive results, but to a lower sensitivity, and thus more false-negative results. The last three columns present the total costs, using three different ratios of costs of false-positive results over false-negative results. The cut-off with minimum total costs is the 5% percentile, assuming equal costs for false-negative and false-positive results.

Table 2 Test characteristics for the lower 2.5 to 20% percentile of the distribution of FEV_1, Residuals.

Cut-off		Sensitivity %	Specificity %	False Positive Rate	False Negative Rate	Total Costs when $Cost_{FPR}$:$Cost_{FNR}$		
percentile	liters					1:5	1:1	5:1
≤ 2.5	≤ -1.60	16	100	1	79	396	80	84
≤ 5.0	≤ -1.20	27	98	9	69	354	78	114
≤ 7.5	≤ -0.90	34	97	18	62	328	80	152
≤10.0	≤ -0.80	43	95	26	54	296	80	184
≤12.5	≤ -0.70	45	93	42	52	302	94	264
≤15.0	≤ -0.55	49	91	54	48	294	102	318
≤17.5	≤ -0.50	51	88	68	46	298	114	386
≤20.0	≤ -0.42	53	85	83	44	303	127	459

* $Cost_{FPR}$ cost for false-positive results; $Cost_{FNR}$ cost for false-negative results.

With higher costs for false-positive results than false-negative results, a lower percentile would be chosen. A larger percentile would be more suitable when the false-negative results would cost more than the false-positive results.

DISCUSSION

This study aimed to evaluate spirometric lung-function tests. Expressing the quality of a pulmonary function test by single values of sensitivity and specificity may be insufficient, because continuous outcome parameters have to be dichotomized rather arbitrarily into normal (no disease) and abnormal (disease) values. One consequence of dichotomizing a continuous parameter is an overall reduced statistical power. Moreover, the magnitude of various measures of association (for instance, prevalence rate ratio) depends on the cut-off point used to dichotomize the parameter.[28] Instead of an arbitrarily chosen cut-off, ROC curves and LR functions were used to study the optimal criterion to distinguish between "diseased" and "reference" subjects and to evaluate its consequences for application in occupational health surveillance programs. The current analysis focussed on two spirometric parameters that are predominantly used in lung function tests; the FEV_1 and FEV_1/VC-ratio.

The data were gathered in a community-based survey in 1965 that was part of a longitudinal study with a still-ongoing follow-up. This choice was made to partly overcome the problem of arriving at a true "gold standard" for CNSLD, because any definition of CNSLD might raise questions. The long follow-up period could assure the relevance of the physician's diagnosis; the 1965 CNSLD diagnosis did correlate very well with subsequent respiratory morbidity and CNSLD mortality.[11] The prevalence of CNSLD was 14%. Selection bias towards diagnosing CNSLD was unlikely because the survey was not aimed specifically at studying respiratory symptoms. The reference diagnosis in this survey, based on a medical examination, most likely resembles the diagnosis setting in occupational health surveillance programmes. Although case definitions for clinical purposes have to be more precise, occupational physicians often use respiratory symptoms as primary diagnostic tools in broad monitoring programmes to identify subjects with chronic non-specific lung disease. Obviously, a precise clinical diagnosis will have to be made in subjects with a positive test outcome.

However, several limitations of the available data need to be addressed. The physician's diagnoses were based on CNSLD whereas nowadays a distinction in asthma and COPD is preferred. Because the diagnosis was based on a history of specific respiratory complaints, an appropriate distinction between asthma and COPD could not be made. It should be noted that in those days the use of the diagnosis CNSLD was heavily advocated.

Considering the age of the population in 1965 and the prevalence of 91% smokers in this cohort, the study is most likely biased toward more strongly age-related forms of CNSLD such as bronchitis and emphysema.

Moreover, the respiratory symptoms questionnaire applied in the survey emphasized irreversible obstructive pulmonary diseases.[29] During the 20-year follow-up of subjects who died from CNSLD, only one died of asthma.[11]

This particular cohort, however, was very useful in illustrating the importance of evaluating various cut-off values of lung-function parameters and their consequences for falsely diagnosing subjects as diseased or nondiseased. It clearly demonstrates the utility of the ROC technique and the concept of pre- and post-test probabilities. With application of these techniques in a community-based study, it has been demonstrated that ROC curves and LR have the ability to analyze various settings, and are not restricted to clinical decision analysis. It would be interesting to perform a similar analysis on contemporary data that enable separate decision analysis for asthma and for COPD, and to study differences in choosing the optimal cut-off values.

The constructed ROCs for the FEV_1 and FEV_1/VC ratio were quite similar, and the slight differences observed were not statistically significant. At the higher end of the distribution, some fluctuations between the two parameters were seen. Taking into account the low specificity, these cut-offs are not suitable for screening purposes in which false-positive results are to be avoided. Comparing the curves with other studies that reported sensitivity and specificity of these parameters, the current study yields better values. The "optimal" point of the curve is a sensitivity of 0.40-0.45 and a specificity of 0.95. Optimal means that the sensitivity and specificity are maximized and relative costs of false-positive and false-negative results are valued equally. Other studies in general populations[12,13] showed comparable values of specificity (0.90-0.95), but a poor sensitivity (0.20). Differences in the case definition and in prevalence of CNSLD may explain the low sensitivity.

The area under the curve (AUC) was about 0.75, illustrating that 25% of the subjects will be misclassified as to their disease status. This performance of the FEV_1 compares well with other widely used clinical tests. Most useful diagnostic tests have an area of 0.60 to 0.90. For instance, the assay for elastin-derived peptide as a test for COPD had an area of 0.87.[30] The AUC of the combination of clinically relevant predictors (including the FEV_1/VC ratio) in chronic bronchitis was 0.85.[31] Because the data of this survey were obtained in 1965, it is reasonable to assume that more recently performed tests, with substantially lower variation, will result in (even) higher areas under the ROC curves (assuming a similar prevalence of CNSLD, predominantly composed of subjects with COPD).

Some differences were found between our study and a similar analysis conducted by Beck and Colice.[19]

The study presented here showed no difference between the ROC curves for FEV_1 and FEV_1/VC. Beck and Colice reported an AUC of 0.52 for FEV_1, only slightly better than a noninformative test (with an area of 0.50). The FEV_1/VC was found to be a better discriminator, with an AUC of 0.86. However, these results were arrived at among subjects in a clinic. Patients with symptoms suggesting chronic airflow obstruction were compared with patients without these findings, but subjects with restrictive ventilatory defects were included in the reference group. In a restrictive disorder both lung volume and FEV_1 are reduced, but the FEV_1/VC ratio might be normal. In cases of obstruction, lung volume, FEV_1 and FEV_1/VC ratio are lower than expected.[4] Hence, the FEV_1 will be reduced in both groups and nondiscriminatory. In general, ROC curves derived from clinical populations (with a high prevalence of diseased subjects) cannot be generalized to populations with a low prevalence of respiratory diseases. When lung function tests are done as part of surveillance activities, a population at risk is tested, rather than individuals with respiratory symptoms or specific suggestion of CNSLD.[32]

The diagnostic performance of spirometry was also evaluated with pre-test and post-test probabilities. The pre-test probability on CNSLD was set to 10%, based on prevalence of respiratory symptoms in the survey population. This estimate is further supported by other Dutch community-based studies with a comparable prevalence of CNSLD symptoms.[33] The probability on CNSLD was doubled for a subject with an FEV_1 residual below the lower 10% percentile. For the lower 5% percentile post-test probability was three to four times the pre-test probability. These results support the recommendation of the American Thoracic Society to apply the lower 5% percentile as discriminatory limit between subjects with and without CNSLD,[9] that is, when the costs of false-positive and false-negative results are considered equal, as the more traditional analyses with sensitivity and specificity implicitly have assumed. For instance, in a clinical setting, where false-negative results should be avoided, even at the expense of the number of false-positive results, the optimal cut-off is around the 10% percentile. In an occupational health setting, however, false-positive results are considered to weigh more than false-negative results. Therefore, false-positive results should be avoided and a more rigid cut-off between normal and abnormal is warranted.

Several additional factors may determine the pre-test probability on CNSLD, such as age, smoking habits, atopic status, and past and family history of respiratory diseases. The pre-test probability should be based on the history and physical examination of an individual.

The concept of pre-test and post-test probabilities stresses the importance of knowledge about the subject. When interpreting test results, all available information has to be used.[20]

The pre-test probability on CNSLD is also important in establishing an appropriate cut-off. The optimal cut-off at which the costs of the test are minimized increases with the prevalence of the disease in the target group. As a consequence, in a clinical setting with a high pre-test probability, other cut-off values should be chosen than in occupational health care.

Because the data in this study stem from a community-based study, the results present a general feature of decision-making methods that is applicable to other public health or occupational health groups. In conclusion, a lower pre-test probability or a higher relative weight of false-positive results (as compared with false-negative results) demands a more rigid optimal cut-off. This implies that in preventive medicine, where tests are aimed at the (early) detection of disease in a group of apparently healthy subjects, and, consequently, the prevalence of disease is low, high specificity is preferred. This study shows that this type of analysis can be an important feature in evaluating spirometric test characteristics and, thus, in optimizing the performance of surveillance programmes. It would be interesting to perform similar analyses on data with cases of COPD and asthma defined with bronchial hyperresponsiveness tests and skin tests. This would enable physicians to study the relationship between case-definition in occupational health, based on spirometry and respiratory symptoms, and the diagnosis based on clinical criteria.

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7 Stepwise health surveillance for bronchial irritability syndrome in workers at risk of occupational respiratory disease[1]

ABSTRACT

Objectives

Questionnaires, lung function tests, and peak flow measurements are widely used in occupational health care to screen for subjects with respiratory disease. However, the diagnostic performance of these tests is often poor. Application of these tests in a stepwise manner would presumably result in a better characterisation of subjects with respiratory disease.

Methods

Cross-sectional data from workers exposed to acid anhydrides, to laboratory animals, and to flour dusts were used. Sensitivity and specificity were calculated from cross tables of different (combinations of) tests for bronchial hyperresponsiveness and bronchial irritability in the past four weeks (BIS). From sensitivity and specificity likelihood ratios were computed and change in probability of BIS was calculated.

Results

The prevalence of BIS was 7%, 7%, and 5%, respectively. In all groups questionnaire data provided excellent sensitivity but poor specificity, which was inherent on the broad definition of symptoms. Adding the forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) ratio yields almost perfect specificity, and peak expiratory flow (PEF) variability is intermediate in populations in which smoking induced or non-allergic respiratory diseases predominates. In occupational groups in which asthma is a problem, adding PEF measurements will optimise sensitivity and specificity in detection of BIS. The probability of BIS for subjects with a negative combined test outcome was lower than the probability before testing. Subjects with a positive combined test outcome had a probability of BIS after the tests at least three times the probability before.

Conclusions

Combined testing yields better sensitivity and specificity. An advantage of combined testing is an economy in the effort to screen for subjects with BIS. Combined testing resulted in more detailed estimation of the probability of BIS.

1 Post WK, Venables KM, Ross D, Cullinan P, Heederik D, Burdorf A. Occupational and Environmental Medicine 1998;55:119-125. Reproduced with permission from the BMJ Publishing Group.

INTRODUCTION

In occupational health care, a questionnaire on respiratory symptoms - such as chronic cough, production of phlegm, wheezing, chest tightness or breathlessness - and spirometry are the most widely used tests in surveillance programmes for obstructive lung diseases such as asthma and chronic obstructive pulmonary disease (COPD). For instance, in the United Kingdom, occupational physicians stated that the basis of the diagnosis in patients with occupational asthma reported to the surveillance of work related and occupational respiratory disease project (SWORD), included the history in 96% of the cases, lung function tests in 62%, serial peak flow in 56%, and serological measurement of IgE or IgG in 18%. In 6% of the cases bronchial challenge was carried out.[1] Because several tests are regularly used for detecting asthma a stepwise approach can be devised.[2,3] The stepwise combination of outcomes of tests may improve detection of subjects with disease. As there is no generally accepted definition of asthma or COPD, validation of a screening procedure comprising various tests should be evaluated by comparison with a selected standard.

Although measurement of non-specific bronchial hyperresponsiveness (NSBHR) has proved to be useful in the clinical assessment of patients with asthma or in occupational asthma, its usefulness in an epidemiological setting or occupational health care is still debatable.[4] Presence of NSBHR is usually regarded as the defining physiological characteristic of asthma,[5,6] but it is also associated with other respiratory diseases, such as COPD and bronchitis and with smoking.[7] The NSBHR is affected by reduction in airway calibre, which can be cause by several factors such as smoking or respiratory disease. Studies of NSBHR among smokers with and without chronic bronchitis suggest that smoking, chronic bronchitis, and NSBHR are related. In particular, smokers with chronic bronchitis often have levels of NSBHR greater than non-smokers, but less than asthmatic patients. It seems, therefore, of particular interest to the occupational physician to measure bronchial hyperresponsiveness to detect subjects with asthma or other respiratory disease - such as chronic bronchitis.

Disadvantages of using NSBHR as a gold standard is the demand on resources (apparatus, qualified personnel, and costs) and safety issues. Providing reasonable safety and stringent measures the test is not dangerous. A major disadvantage is that not all people with NSBHR report respiratory symptoms.[8,9] In epidemiological studies the combination of symptoms and NSBHR has therefore been recommended.[4,10,11]

In the current decision analysis study, we used the presence of NSBHR measured by histamine challenge testing in combination with questions on bronchial irritability in the past four weeks as the gold standard for the bronchial

irritability syndrome (BIS). We have previously developed a nine item questionnaire of bronchial irritability symptoms for asthma epidemiology.[12] Mortagy et al. used bronchial irritability symptoms in conjunction with a fall of 20% or more in FEV_1 at a provocative concentration of <0.5 g/l histamine to describe BIS. They found that the bronchial irritability syndrome was closely associated with asthma, but that BIS and asthma cannot be considered synonymous, as most subjects with BIS had not been diagnosed as asthmatic.[13]

We chose the most widely used tests in occupational health care, that is, presence of respiratory symptoms, spirometry, and serial peak flow measurements as screening instruments. Within occupational health care, a questionnaire survey, followed by spirometry seems the most logical approach for sequential testing. The performance of combined testing to identify subjects with respiratory disease was examined in three occupational groups with exposures incriminated as causing respiratory disease, especially asthma: workers exposed to acid anhydrides, laboratory workers exposed to rats or mice, and workers with occupational exposure to flour dusts.

METHODS

Study population

In the current study, data from studies among workers with exposure to acid anhydrides, laboratory animals, and flour dusts were analysed. These were the retrospective cohort study of 401 workers exposed to acid anhydrides; the baseline study of an ongoing follow-up study among 323 laboratory animal workers who handled a variety of animals including rats, and another 61 laboratory animal workers who handled exclusively mice; and the baseline study of an ongoing follow-up study 344 workers exposed to flour in bakeries and mills. Survey methods are described in detail elsewhere.[14,15]

Medical examination

All participants were asked to complete a questionnaire on age, sex, smoking history, occupational history, and respiratory symptoms.

Calibrated leak free Vitalograph spirometers were used to record FEV_1 and forced vital capacity (FVC). Up to six readings of FVC and FEV_1 were recorded, with a minimum of three readings until two reproducible curves were achieved (FEV_1 and FVC within 0.1 litres). The FEV_1/FVC ratio was derived from the largest FEV_1 and FVC. For each subject a predicted lung function variable was calculated with regression equations of the European Respiratory Society.[16]

The residual lung function (largest observed value - predicted value) was used in all analyses.

Among the laboratory workers and the flour workers, peak expiratory flow (PEF) records were made using mini-Wright peak flow meters. At each session, the highest value of three tests was recorded, with the best of two readings within 20 litres/minute of each other. Each subject was asked to make four readings a day, a total of 28 PEF readings over seven days. The PEF variability was calculated for each day with at least two blows, as amplitude%mean=100*(maximum-minimum)/mean (%). The mean value for all days was used in analyses. Subjects with < 21 readings over seven days were excluded from analyses.

Bronchial responsiveness was measured by a histamine inhalation test.[17] If the baseline FEV_1 was <1 l histamine challenge was not performed. The dose provoking a 20% fall in FEV_1 (PD_{20}) was estimated by linear interpolation of the last two log dose points, or by extrapolation up to 8 µmols.

Gold standard for BIS

In the current study the definition of BIS incorporates information on the histamine challenge test. Also, information was used about bronchial irritability in the past four weeks. The questions that were used were derived from a questionnaire of bronchial irritability symptoms.[12] Subjects with a PD_{20} less or equal to 8 µmols histamine, and reporting bronchial irritability in the past 4 weeks were classified as having BIS.

DEFINITIONS

Table 1 summarises the definitions used in this study. Subjects were classified as having symptoms if they reported at least one of the following: cough or phlegm on most days for three months a year, upper respiratory symptoms that occurred since the start of work at the site, or lower respiratory symptoms that occurred since the start of work at the site. As recommended by the American Thoracic Society,[18] the chosen cut off for the FEV_1/FVC ratio was the lower 5 percentile calculated with the formulas of the European Respiratory Society.[16] For the peak flow variability the cut off was an amplitude%mean peak flow greater or equal to 10%, which approximated the upper 95 percentile of the distribution of peak flow variability in these data stratified by occupational group and sex.

Table 1 Definitions

Variable	Criterion
NSBHR	$PD_{20} \leq 8 \mu mol$ histamine
BIS	bronchial irritability in last 4 weeks and NSBHR
Screening instruments	
Questionnaire	
History of asthma	Subjects who had asthma before first employment at current work site
History of bronchitis	Subjects who ever had bronchitis or had ever been told they had bronchitis
Chronic bronchitis symptoms	Cough and/or phlegm on most days for 3 months/year
Upper respiratory symptoms	Blocked, itchy, runny or sneezing nose and/or itchy or runny eyes since first employment at the site
Lower respiratory symptoms	Chest tightness, difficulty breathing and/or wheezing or whistling since first employment at the site
Spirometric lung function test	FEV_1/FVC residual ≤ predicted - 1.644*RSD (RSD: residual standard deviation (6.5% for women, 7.2% for men)
Serial peak flow recordings	Amplitude%Mean Peak flow ≥ 10%

ANALYSIS

The relation between the screening instruments and BIS was studied by cross tables, from which sensitivity and specificity were calculated; tests with continuous outcomes were therefore dichotomised into normal and abnormal results (Table 1). With the sensitivity and specificity of individual tests the likelihood ratios of positive and negative tests were computed. The likelihood ratio and probability before testing were used to calculate the probability of BIS after the tests.[19] Ideally, the probability before testing summarises all available information at time of testing. In the current study, the prevalence of BIS within each group was used as an estimate of the probability of disease before testing. After testing the probabilities are calculated for a positive and a negative test outcome. The resulting probability of BIS after one test is used as the probability before the next step.[19] The diagnostic performance of sequential testing in each group was evaluated by both change in probability of BIS and its sensitivity and specificity.

All analyses were performed using statistical analysis software.[20]

RESULTS

Number of subjects

For 263 acid anhydride workers, 327 laboratory workers, and 237 workers with exposure to flour dusts a complete data set was available comprising subject characteristics, atopic status, gold standard tests, and information on symptoms and lung function.

In the group of workers exposed to acid anhydrides no peak flow measurements were performed. Among the laboratory workers 65% performed at least 21 peak flow recordings over seven days, among the flour workers the response was lower, 49%. At the third step of the decision tree for stepwise surveillance, data of 256 laboratory workers and 166 flour workers were analysed.

BIS

The prevalence of BIS was 7% among acid anhydride workers, 7% among laboratory workers, and 5% among flour workers. Among the acid anhydride workers, and the laboratory workers another 29% of the workers and 39% of the flour workers reported bronchial irritability in the past four weeks but had a normal histamine challenge test. One per cent of the acid anhydride workers, 3% of the laboratory workers, and 2% of the flour workers had NSBHR, but did not complain of the bronchial irritability in the past four weeks.

Among the laboratory workers, significantly more subjects without peak flow measurements reported lower respiratory symptoms (41% vs. 27%), had a positive PD_{20} (17% vs. 7%), and had a borderline significantly higher prevalence of bronchitis symptoms (13% vs. 7%, $p=0.08$) and of bronchial irritability in the past four weeks (40% vs. 30%, $p=0.07$). Consequently, the prevalence of BIS was significantly higher among laboratory workers without peak flow measurements (12% vs. 4%). Among the flour workers, subjects without peak flow measurements had a higher prevalence of bronchial irritability in the past four weeks (47% vs. 36%), although this did not reach the level of significance ($p=0.09$).

Relationship between screening instruments and BIS

Table 2 gives the false positive rate (1-specificity) and true positive rate (sensitivity) of the screening instruments for detecting BIS. All three screening instruments, questionnaire, spirometric lung function test, and serial peak flow measurements, were related to the presence of BIS.

Table 2 Screening instruments by occupational group and BIS

	Acid anhydride Workers n=263; $PD_{20} \leq 8$ µmols=2 (8%) BIS 4 weeks=95 (36%)		Laboratory Workers n=327; $PD_{20} \leq 8$ µmols=33 (10%) BIS 4 weeks=118 (36%)		Flour Workers n=237; $PD_{20} \leq 8$ µmols=17 (36%) BIS 4 weeks=104 (44%)	
	no BIS 246 (93.5%)	BIS 17 (6.5%)	no BIS 304 (93.0%)	BIS 23 (7.0%)	no BIS 226 (95.4%)	BIS 11 (4.6%)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Questionnaire						
Chronic bronchitis symptoms	48 (20%)	9 (53%)	23 (8)	7 (30)*	41 (18)	5 (45)*
Upper respiratory symptoms	112 (46%)	10 (59%)	137 (45)	22 (96)*	103 (46)	9 (82)*
Lower respiratory symptoms	53 (22%)	14 (82%)*	82 (27)	22 (96)*	60 (27)	10 (91)*
≥ 1 symptom	131 (53%)	15 (88%)	169 (55)	23 (100)*	123 (54)	11 (100)*
Spirometric lung function test						
FVC residual ≤ 5th percentile	5 (2%)	1 (6%)	6 (2)	0 (0)	7 (3)	0 (0)
FEV_1 residual ≤ 5th percentile	7 (3%)	7 (41%)	6 (2)	0 (0)	14 (6)	2 (18)*
FEV_1/FVC residual ≤ 5th percentile	15 (6%)	11 (65%)*	10 (3)	3 (13)*	18 (8)	4 (36)*
Serial peak flow recordings†						
Amplitude % mean ≥ 10%	- -	- -	20 (10)	4 (44)*	22 (19)	2 (50)*

* value statistically significantly different from that for subjects without BIS (Continuous outcome t-test, discrete outcomes χ^2 or Fisher's Exact test; $p<0.05$);
† for 211 laboratory animal workers with 9 subjects with BIS and 117 flour workers with 4 subjects with BIS

If bronchial irritability in the past four weeks was not included in the definition of BIS, but NSBHR alone was used as a gold standard instead, the sensitivity as well as the specificity of symptoms versus NSBHR was smaller, but differences were trivial (sensitivity 78%, 90% and 80%, specificity 36%, 38% and 34% for acid anhydride workers, laboratory workers and flour workers respectively).

Sequential testing

Figures 1-3 show the decision trees for the different occupational groups. Beneath each tree, the sensitivity and specificity of the tree after each consecutive step is given.

The first step (questionnaire on respiratory symptoms) in sequential testing showed that in subjects without symptoms BIS was very unlikely. In the second step, additional spirometry in subjects with respiratory symptoms was very specific, but had low sensitivity. In terms of sensitivity and specificity, an abnormal FEV_1/FVC ratio was most accurate among the acid anhydride workers. Due to the low sensitivity of lung function testing among the laboratory workers and flour workers with respiratory symptoms, the probability of BIS in subjects with a negative spirometric lung function test dropped only marginally and was still higher than the initial probability before testing. In the third step of sequential testing, among workers with a normal spirometric lung function test, an abnormal peak flow variability augmented the probability of BIS, although the number of false positive results outnumbered the number of true positive results by far. The probability of BIS dropped to the initial probability of BIS for subjects with normal peak flow variability. In workers with an abnormal spirometric lung function test, the probability of BIS in laboratory animal workers and flour workers showed contradictory results.

DISCUSSION

The main goal of health surveillance programmes in occupational health care should be to detect workers with disabling disease early in its course, and ultimately, prevent progression to more severe disease with its associated morbidity and disability.[2] Ideally, surveillance tests must have good sensitivity to detect all people with the disease under study. To avoid many false positive results, high specificity is also of importance. As screening tests are performed on workers who have no clear symptoms or findings of disease, the probability of disease before testing is very low. Therefore, there will be many undiseased workers who are candidates for false positive results, and few diseased workers.

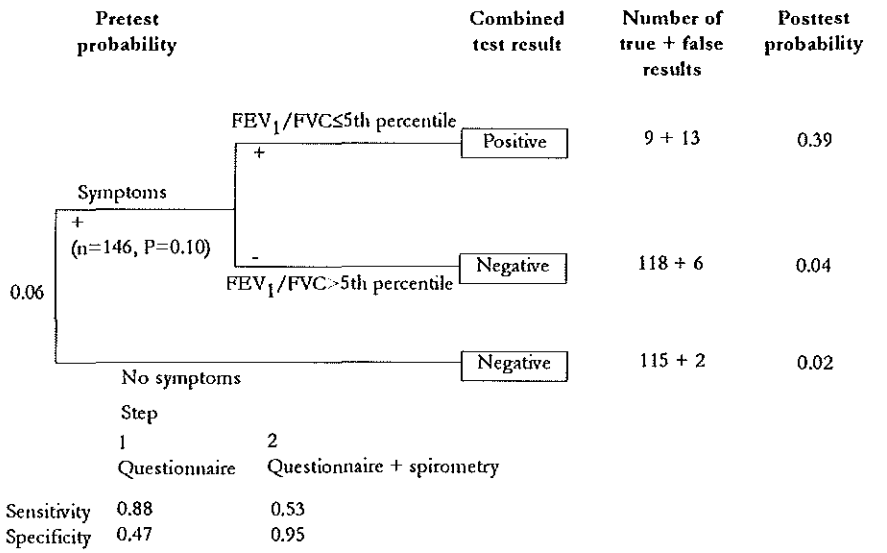

Figure 1 Stepwise health surveillance among workers with exposure to acid anhydrides. P=probability of BIS; n=number of subjects with test results; positive test outcome=combined testing suggesting BIS; negative test outcome=combined testing suggesting absence of BIS; true results=number of true positive results if combined test outcome is positive and number of true negative results if combined test outcome is negative; false results=number of false positive results if combined test outcome is positive and number of false negative results if combined test outcome is negative.

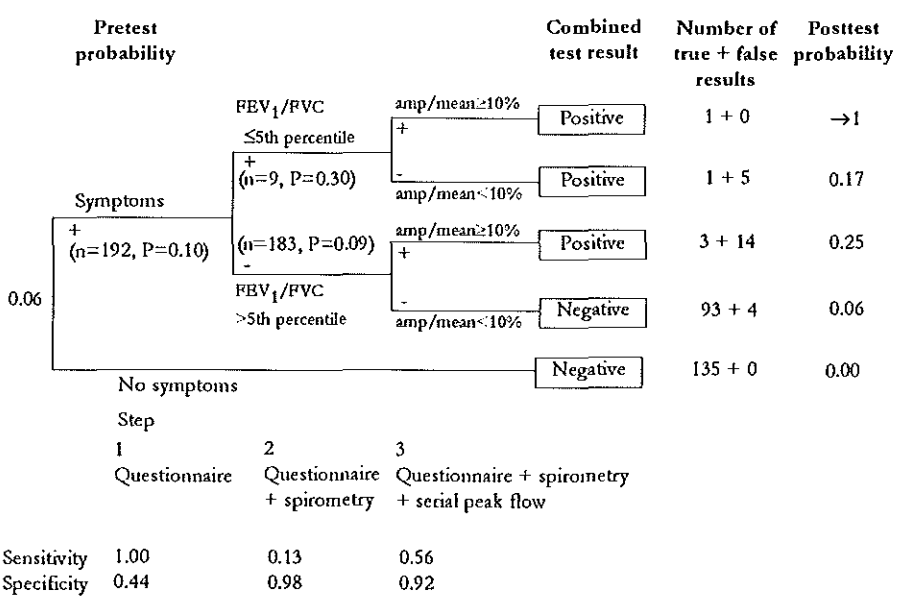

Figure 2 Stepwise health surveillance among workers with exposure to laboratory animals. Explanations as for figure 1.

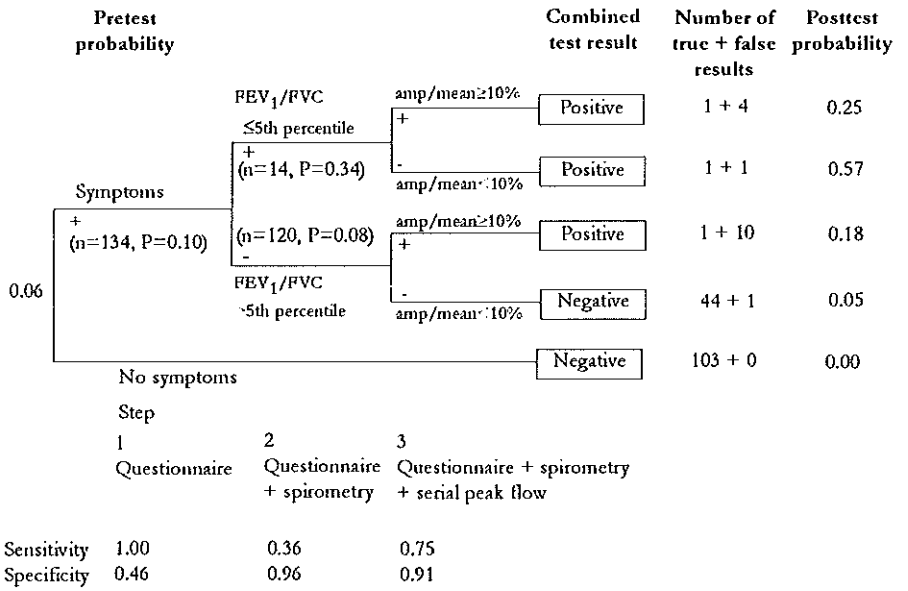

Figure 3 Stepwise health surveillance among workers with exposure to flour dusts. Explanations as for figure 1.

With relatively few truly diseased subjects, the false positive rate strongly affects the interpretation of a positive result; the lower the false positive rate of a test (or the higher the specificity), the higher the probability of disease after testing.

The aim of the current analyses was to evaluate screening instruments currently used in occupational health services on their usefulness to identify subjects with respiratory diseases - such as asthma and chronic bronchitis. The acid anhydride workers are probably more affected by chronic obstructive pulmonary disease induced by smoking. Among laboratory animal handlers asthma will presumably predominate, whereas among the flour worker a mixture of COPD and asthma is not unlikely. Although surveillance might be preferred for work related or even occupational respiratory disease in these occupational groups, we choose to identify NSBHR with the presence of BIS. We think that the first step in surveillance in occupational groups is to detect those subjects with disease, applying general diagnostic tests. Occupational physicians should be aware that identifying BIS in a working population does not mean that it is work related. In a second step, subjects with suspected disease should be tested with specific diagnostic tools to establish the likelihood of a causal relation with agents in the work environment.

In the three study groups, several diagnostic tests had been carried out, which could all be used as either a gold standard test or as part of the screening procedure.

Other researchers might have chosen another definition of gold standard or other tests as screening instruments, and we emphasise that the current study is only one possible approach for surveillance for respiratory disorders in occupational health care.

We used a gold standard defined as a positive histamine challenge test in subjects who reported bronchial irritability in the preceding four weeks - for example, wheeze and difficulty in breathing in defined circumstances such as sleep and exercise. Mortagy et al. studied bronchial irritability symptoms in combination with NSBHR, and named it the Bronchial Irritability Syndrome (BIS).[13]

They found that only 27% of subjects with BIS had been diagnosed asthmatic by their general practitioners. Almost 8% had been diagnosed as having other respiratory diseases. The current analysis gives no further insight into the relation between BIS and asthma or COPD. However, information on medication for chest or breathing and history of respiratory disease showed that BIS cannot be regarded as a gold standard for asthma alone, but that it can also be an indication of COPD.

We used a stepwise logical approach for surveillance of workers' health, anticipating a better characterization of BIS with the combination of different tests than with the same tests separately, as more information is used. Administration of the tests to be considered had to be feasible within occupational health care; a questionnaire on respiratory symptoms, spirometry, and serial peak flow measurements were chosen as instruments for screening.

Despite differences between the three occupational groups under study in age, smoking, sex, and atopy, the prevalence of BIS was similar and reporting of respiratory symptoms gave a surprisingly similar picture. The definition of symptoms in the current study was very broad, including chronic bronchitis-like symptoms (chronic cough and phlegm), upper respiratory symptoms (eye and nasal symptoms), and lower respiratory symptoms (wheezing, chest tightness and difficulty breathing). The sensitivity of reporting any of the respiratory symptoms was high, ranging between 88% and 100%, with a specificity around 46% in all three occupational groups. This means that almost all subjects with BIS were identified in the first step of the tree, together with many false positive subjects.

In earlier studies the FVC, FEV_1, and FEV_1/FVC ratio have been found to be very specific to detect respiratory obstructive disease (90%-95%), but to have a low sensitivity (around 20%).[21,22] More recently, validation of the FEV_1/FVC for bronchial hyperresponsiveness yielded a sensitivity of 21%, with a specificity of 97%.[23] In our study, a low FEV_1/FVC was more likely to appear in symptomatic subjects with BIS, but except for the acid anhydride workers, its sensitivity was very low.

A probable explanation of this difference is the older age distribution of the acid anhydride workers, who are possibly more affected by chronic obstructive pulmonary diseases induced by smoking than the other groups. In patients with COPD there is a strong relation between baseline forced expiratory volume and bronchial hyperresponsiveness to methacholine or histamine.[24] The flour workers were older than the laboratory workers, and non-allergic mechanisms in these groups have been suggested in earlier cross sectional analysis of these two cohorts, which showed different associations with symptoms and skin reactivity against occupational allergens.[15] This might explain why FEV_1/FVC was slightly better in classifying subjects with BIS as abnormal among the flour workers than among laboratory workers.
The accuracy of peak flow measurements can also be related to the studied population. Among the laboratory workers subjects were at risk of developing asthma more than COPD and thus peak flow measurements yield a better performance than spirometry.

As a result of the high specificity of FEV_1/FVC, combining presence of respiratory symptoms and an abnormal FEV_1/FVC test resulted in a high specificity, and thus a drop in the number of false positive results and a higher probability of BIS if test results were positive. On the other hand, a rise in specificity can only occur at the expense of sensitivity, and therefore the number of false negative results increased. Because the specificity was so much higher than the sensitivity, less precise clinical information is required to confirm the diagnosis of BIS if the FEV_1/FVC is abnormal than is needed to exclude the diagnosis if the FEV_1/FVC is normal. Therefore, especially in subjects with respiratory symptoms and normal lung function, further testing is warranted.

We found that the laboratory workers without peak flow measurements had a somewhat higher prevalence of BIS. Despite the short recording period and low compliance that might have caused selection bias, peak flow recording seemed particularly worthwhile among symptomatic workers with a normal FEV_1/FVC. In our analysis, it does not seem necessary to do peak flow tests on those with positive symptoms and abnormal spirometry to further exclude or confirm the diagnosis of BIS. However, the few subjects in this particular step of the tree, should be borne in mind.

Combination of respiratory symptoms, spirometry, and peak flow variability to identify abnormal subjects had a sensitivity of 56% among laboratory workers and 75% among flour workers, which compares favourably with the sensitivity of peak flow measurements alone. The corresponding specificity was > 90% in both cases.

Another advantage of combined testing is an economy in the effort to screen for subjects with BIS. The use of a questionnaire is relatively simple and cheap and reduces the number of subjects who would have to perform peak flow measurements. As fewer people perform peak flow measurements, more effort can be put into a higher compliance with serial peak flow measurements. The moderate compliance with peak flow measurements is a disadvantage of this test for epidemiological studies. Furthermore, a combination of respiratory symptoms, spirometry and serial peak flow resulted in a more detailed estimation of probabilities of BIS after testing.

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8 General discussion

RESEARCH QUESTIONS

With collected information in sickness absence registrations, pre-placement medical examinations, and periodic medical examinations, several aspects of CNSLD are recorded on a routinely basis in occupational health services. A large amount of information on CNSLD, its impact and risk factors, is gathered. Despite the abundance of this information, it has hardly contributed to our knowledge of the impact of CNSLD on a worker's ability to cope with the routine activities at work. Nor has it led to improvement of the available diagnostic procedures for CNSLD in occupational health care.

In order to contribute to a sound basis for primary and secondary prevention of CNSLD in occupational health care, the thesis looks for the answers on the following questions:

1) Are workers in a number of occupational conditions more prone to develop CNSLD ?
2) How do workers with CNSLD cope in these work conditions with routine activities at work ?
3) Is it possible to improve the performance of health surveillance programmes for CNSLD with the use of currently available instrumentarium in occupational health care ?

OCCURRENCE AND IMPACT OF CNSLD

In the studies on the occurrence and impact of CNSLD different health endpoints are described; the 25-year cumulative incidence of CNSLD, the change in lung function over five years and loss-to-follow up, and the development of laboratory animal allergy. As is quite common in CNSLD studies, each study applied its own definition of disease, which hinders comparison across studies. The current debate on the contribution of hazardous agents at work to the development and aggravation of CNSLD can be partly attributed to the different modes of disease diagnosis.

The use of generally accepted definitions of CNSLD, asthma, COPD, and other associated health outcomes such as impaired lung function and bronchial hyperreactivity would greatly facilitate our knowledge of the occurrence and impact of respiratory disorders in occupational populations.

The study in chapter 2 demonstrated that almost 40% of the general population were ever occupationally exposed to hazardous agents. Exposure to at least one agent resulted in a significant risk ratio of 1.5, compared with workers without exposure. The attributable proportion of respiratory disease in the total population was estimated to be approximately 17%. This confirms previous estimates of the population attributable fraction of 11-19%[1] and 3-20%[2]. The estimated attributable risk strongly depends on the exposure distribution in the study population and the particular health outcome of CNSLD applied. This is illustrated in chapter 4 with the study on laboratory animal workers. It was estimated that subjects working with laboratory animals for more than 2 hours per week had a relative risk of 5 for respiratory allergy. The attributable fraction in this occupation was thus 31%.

Both studies also showed that the risk of developing CNSLD differed according to the time window applied in the longitudinal analysis. In the Zutphen Cohort in chapter 2 subjects whose first exposure to dust occurred more recently were at higher risk for developing CNSLD, as compared with subjects with the longest time since first exposure. A similar pattern was observed among the laboratory animal workers where some subgroups of workers developed laboratory animal allergy earlier than others. These analyses demonstrated the importance of applying various time windows when studying the risk of developing CNSLD in a longitudinal study.

Studies on the impact of CNSLD on work capacity are obscured by the occurrence of the healthy worker effect. But, the healthy worker effect by itself is also a measure of the impact of CNSLD: subjects with symptoms or risk factors for CNSLD are less likely to enter specific jobs and subjects are more likely to change job when CNSLD symptoms are developed or existing CNSLD symptoms get worse. In all studies on the impact of CNSLD (chapters 2 to 5) the healthy worker effect was observed. Among laboratory animal workers this effect probably explains the decrease in risk for workers exposed to laboratory animals for more than 15 hours per week when compared with those working less hours per week with laboratory animals. Furthermore, the proportion of people who were transferred to another task or job because of allergic symptoms was higher among workers exposed 15 hours or more per week to laboratory animals than those with less exposure.

Selection processes, either self-selection or through advice during the pre-placement medical examination, could also explain the fact that most atopic people were found in the unexposed category. In the grain processing and animal feed industry the healthy worker effect was again clearly present. First, longer exposure (duration of employment) was related to a smaller annual decline in FEV_1. Second, the presence of respiratory symptoms in the baseline survey was a strong predictor of subsequent loss-to-follow up. The study on relations between respiratory symptoms and sickness absence among workers in the animal feed industry showed that the proportion of office workers with respiratory complaints before entering their job was substantially larger than the proportion among blue collar workers.

CNSLD AND DISABILITY

The second research question on how workers with CNSLD cope with routine activities at work was addressed in chapters 4 and 5. These studies showed that workers with respiratory symptoms are at risk for temporary disability. Moreover, if these subjects are exposed to hazardous agents associated with CNSLD they are at even higher risk. Both among laboratory animal workers and workers in the animal feed industry absence from work because of allergic or respiratory symptoms was about sevenfold higher for exposed workers compared with workers with no or low exposure to allergens at the workplace. These studies suggest that workers with respiratory symptoms more easily survive in jobs with no or low(er) exposure than in jobs with higher exposure levels. Furthermore, in the animal feed industry workers with respiratory complaints were absent more often due to influenza and, among the blue-collar workers, also due to musculoskeletal symptoms. The first association is well-known, which is the rationale behind the influenza vaccination among people with CNSLD. The second association may be explained by the fact that respiratory complaints may affect stamina and endurance, and subsequently reduce the worker's capacity to perform heavy physical labour.

As sickness absence is registered industry-wide, registration of sickness absence due to respiratory symptoms provides an instrument of continuous surveillance in occupational populations. Spells of respiratory sickness could be used to identify subjects at risk. The relationship between CNSLD and absence is difficult to establish in the currently used sickness absence registers. These registers are oriented towards diagnosis rather than symptoms and in many situations broad disease categories are used that are not specific enough to identify those spells of sickness absence to which CNSLD has contributed as primary or secondary cause.

Furthermore, they comprise only information about a more specific diagnosis when the worker has been ill for a longer period. This again hampers an appropriate estimation of the contribution of CNSLD to sickness absence since a substantial part of the absence periods due to respiratory complaints is shorter than 2 weeks[4]. A requirement for sickness absence registers to be useful in studying the impact of CNSLD is to use self-reported health complaints at the start of a sick leave period, completed with a diagnosis at a later stage. This will greatly facilitate the study of morbidity and co-morbidity patterns of CNSLD in occupational populations.

SURVEILLANCE OF WORKERS WITH CNSLD

Despite generally accepted definitions of asthma and COPD, no gold standard test for these disorders is available[3]. Therefore, in some studies particular tests are used as gold standard, whereas in other studies these tests are evaluated as surveillance instruments against another gold standard. When choosing a surveillance instrument, one must be aware of the differences in performance between gold standard tests in validation studies and those tests in occupational populations. It is sometimes assumed that tests which perform well within a clinical setting will perform satisfactorily within occupational health practice. But the differences between populations cause different behaviour of the same test in different circumstances, since the disease outcomes in the study groups range between early stages to severely developed disease. Hence, results obtained in clinical studies, case-finding, screening, or surveillance in occupational health care cannot be easily compared.

In occupational health practice, the yield of surveillance programmes is largely unknown but expected to be poor. The daily practice of applying insensitive and non-specific surveillance tests, misapprehensions of test characteristics, and the incomplete exploitation of the capability of currently available diagnostic armamentarium in occupational health practice offer some explanation for the lack of well-established surveillance programmes for CNSLD. In chapters 6 and 7 three ways to improve surveillance of CNSLD are discussed: optimising cut-off points, sequential testing, and the concept of pre- and post-test probabilities.

In surveillance within occupational health services, questionnaires, spirometric lung function testing, peak flow measurements, and bronchial hyperresponsiveness may be used to detect subjects with CNSLD. Except for questionnaires, these tests do not involve a simple dichotomous choice, but test results show a continuous distribution with a certain range of values.

Any single cut-off point is by necessity arbitrary, with the consequence that subjects whose test results lie just below or above the cut-off point are more likely to be misclassified. Moving the cut-off point changes the test's sensitivity, specificity, and positive and negative predictive values, and, hence, the way in which the test may be used. The consequences of augmenting specificity at the expense of sensitivity have to be considered. This process starts with an unequivocal definition of the particular goal of a surveillance programme. The choice of a particular cut-off point between healthy and diseased should depend upon the disease prevalence in the population. For instance, in surveillance among laboratory animal workers with a considerable disease prevalence a cut-off point for FEV_1 less than 80% would be preferred in order to achieve a high sensitivity that only affects moderately the specificity. In occupational groups with a lower disease prevalence a cut-off point less than 70% is adviced since a higher specificity is preferred together with a reasonable sensitivity. Furthermore, as chapter 6 demonstrates, to determine the cut-off point for surveillance of CNSLD, the number of false-positive (FPR) and false-negative results (FNR) should be considered. The costs of these errors are interpreted in relative values assigned to the importance of true and false diagnosis by comparing the medical consequences and/or taking the economic costs into consideration. The relative costs of a false positive or a false negative result differ between the various settings, depending on test characteristics, disease prevalence, disease stage, and available medical treatment. The decision-analytic technique used in chapter 6 can easily be applied to data that is currently gathered in large numbers within occupational health services. Obviously, its application will necessitate more explicit thought about the costs and consequences of over-diagnosing and of cases being missed.

A potentially useful approach to overcome the limitation of a single cut-off point and associated sensitivity-specificity trade-off dilemma is the use of a stepwise health surveillance programme. The available diagnostic armamentarium does allow combinations of tests and, hence, presents a potential for better classification of subjects with and without CNSLD. The results of the analyses in chapter 7 show that combination of test outcomes does affect sensitivity and specificity as well as post-test probability of disease. It is clearly demonstrated that the choice for an individual test or combined tests depends on the goal of the surveillance programme. By means of sequential testing, either sensitivity, specificity, or post-test probability can be optimised and the number of false positives and false negatives minimised. An advantage of sequential testing is that subsequent tests are offered to those workers most likely to have CNSLD while simultaneously preventing large numbers of diagnostic tests among subjects without CNSLD.

When starting with a highly sensitive test, further testing will not be necessary among those subjects with a negative test outcome. All those who are positive on the first test are evaluated more carefully by a specific second stage test. In the study of flour workers, it was noted that among workers with respiratory symptoms and an abnormal lung function additional peak flow measurements did not further distinguish between diseased and healthy subjects. Though the small number of subjects necessitates a cautious interpretation, this observation indicates that in some cases, given two positive tests, further testing among those individuals is not warranted. In many occupational health services different tests are routinely included in medical examinations. With respect to these large numbers of tests, protocols for sequential testing in different types of industries should be developed. This will require standardised testing and agreement about cut-off points and health outcomes. Moreover, as an extension of sequential testing, the longitudinal change in health outcomes might be considered as useful surveillance criterion. Studies evaluating surveillance programmes longitudinally within different occupational groups are strongly recommended and more longitudinal reference values should be developed.

Using pre- and post-test probabilities presents some quantitative, but imprecise, information about how much the probability of CNSLD has been changed by the test. The test result is thus used to raise or lower the probability of the disease of interest being present. In chapter 7, the post test probability on CNSLD at different cut-off points of the FEV1 was calculated with an estimated pre-test probability. In this study it is recognised that, rather than using a fixed estimate for all subjects in the target group, the pre-test probability should be adjusted for additional risk factors, such as age, smoking habit, atopic status, and past or family history of respiratory disease. Information on this risk profile can be obtained during clinical examination of the individual. Additional analyses demonstrated that the prevalence of the disease was affected by those determinants and, hence, inclusion of this information will result in a more precise estimate of individual pretest probabilities. However, the diagnostic decision trees remained largely unchanged after inclusion of these determinants as an additional step in the decision tree. This finding underlines that, at this moment, these determinants should not be used as job discriminants. It is proposed to inform individual workers with elevated risks for respiratory disease about their chances to develop CNLSD symptoms if they take up or stay in a job with certain exposure to hazardous agents.

CONCLUSIONS

1. The population attributable fraction of occupational exposure to hazardous agents for CNSLD in the general population was estimated as approximately 17%. In specific occupational populations this fraction may be substantially higher. Among laboratory animal workers the population attributable fraction for subjects working more than 2 hours per week with animals was approximately 30%.

2. Workers with respiratory symptoms are at risk for temporary disability. Both among laboratory animal workers and workers in the animal feed industry absence from work because of allergic or respiratory symptoms was about sevenfold higher for exposed workers compared with workers with no or low exposure to allergens at the workplace. The occurrence of CNSLD also has a strong impact on the healthy worker effect by forcing workers with CNSLD to change job.

3. The opportunities for diagnosis and surveillance of CNSLD in occupational health care are hardly put to proper use. Sequential testing with questionnaires, spirometry, and serial peak flow measurements will increase sensitivity and specificity of diagnosis. Application of a decision tree will avoid unnecessary testing among subjects with a negative test outcome on the first test. Individual characteristics such as age, atopy, and smoking habits, did not affect the decisions based on a sequential test procedure.

RECOMMENDATIONS

1. In longitudinal epidemiological studies the use of different time windows seems indispensable to study the relationship between exposure to hazardous agents at the workplace and the occurrence of chronic non-specific respiratory disease and the impact of CNSLD on a worker's ability to perform his job.

2. Extension of sickness absence registers with information on respiratory symptoms from the start of a sickness absence period offers additional opportunities to identify workers at risk for aggravation of their CNSLD and to study the impact of CNSLD on work ability.

3. Since the performance of diagnostic tests depends on the disease prevalence as well as the disease stage, test attributes such as sensitivity, specificity, and predictive value should be evaluated in relation to the expected characteristics of CNSLD in the study population, the particular goal of surveillance in occupational health care, and the medical and economic consequences of overdiagnosing and of cases being missed.

4. Individuals with elevated risks for CNSLD should be informed about their chances to develop CNSLD if they take up or stay in a job with certain hazardous exposure. Statistical models need to be developed that combine information on individual and work-related risk factors with test results into accurate estimates of pre- and post-test probabilities on CNSLD.

5. In occupational health care improvement of surveillance programmes can be obtained by optimising cut-off points of diagnostic tests, by combining diagnostic tests, and by assessing longitudinal changes in health status. Protocols should be developed (a) defining relevant health endpoints of CNSLD, (b) describing test procedures, and (c) outlining decision procedures. Development of different protocols for stepwise surveillance trees for asthma, chronic obstructive pulmonary disease, bronchial irritability, and allergy in specific exposure/occupational groups will greatly facilitate the surveillance of CNSLD in occupational health care.

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Summary

So far, little is known about the impact of Chronic Non Specific Lung Disease on the workforce. On the one hand, specific occupational exposures may cause CNSLD and attribute to temporary and permanent disability among workers. On the other hand, workers with CNSLD may encounter working conditions that aggravate their respiratory complaints and, consequently, affect their capabilities to perform their job. This thesis focuses on interrelationship between CNSLD and work by searching for answers on the following questions:

1) Are workers in a number of occupational conditions more prone to develop CNSLD ?
2) How do workers with CNSLD cope in these working conditions with routine activities at work ?
3) Is it possible to improve the performance of health surveillance programmes for CNSLD with the use of currently available instrumentarium in occupational health care ?

The first part of this thesis is dedicated to the occurrence of CNLSD in occupational populations and the impact of CNSLD on sickness absence and permanent disability (chapters two to five). The second part of this thesis targets the identification of workers with CNSLD in an occupational health care setting and the best application of available diagnostic tests (chapters six and seven).

Chapter two, **'Occupational exposures estimated by a population specific job exposure matrix and 25-year incidence rate of chronic non-specific lung disease (CNSLD): The Zutphen Study'** used detailed information about specific exposures in combination with job titles to construct a population-specific Job Exposure Matrix (JEM). The analyses of relationships among occupational exposures and CNSLD incidence confirmed results from other community-based studies that exposure to dust and solvents increases the incidence of CNSLD. Subjects exposed for up to 20 years to dust had a statistically significantly elevated risk for developing CNSLD.

However, subjects with longer duration of dust exposure showed a lower risk for developing CNSLD. This may indicate the presence of a healthy worker effect, forcing workers with CNSLD out of their job.

In chapter three, **'Occupational exposure to organic dusts and decline in lung function over five years'** a longitudinal analysis among workers in the animal feed industry is presented. A statistically significant drop in FEV_1 and MMEF was observed when comparing workers with high exposure to dust and endotoxin with workers with no or low exposure to these agents. Assuming an average exposure of 5 $mg.m^{-3}$ over 40 years the estimated effect on the FEV_1 would be a decline of 157 $ml.s^{-1}$, which is approximately 4% of the group mean FEV_1. The MMEF would decline by 473 $ml.s^{-1}$ which is approximately 12% of the group mean MMEF. Workers with a dust exposure exceeding 4 $mg.m^{-3}$ or endotoxin levels exceeding of 20 $ng.m^{-3}$ in the baseline survey had a significantly higher risk of rapid decline in FEV_1, with an OR of 3.3. Presence of the healthy worker effect was apparent from decreasing annual decline in FEV_1 and fewer individuals with rapid decline in FEV_1 with increasing duration of employment. The healthy worker effect was also demonstrated in the finding that the occurrence of respiratory symptoms at baseline was a strong predictor of subsequent loss-to-follow up. Baseline lung function did not predict subsequent loss-to-follow up. However, in the baseline survey the workers eventually lost-to-follow up had a stronger inverse relationship between lung function and duration of employment than was observed among those workers who completed the 5-year follow-up in their own job.

In chapter four, **'Respiratory allergy in laboratory animal workers: a prospective cohort study using pre-employment screening data'** Laboratory Animal Allergy (LAA) was studied. Among people working with laboratory animals prevalence rates of 10 to 30 percent have been observed and it has been suggested that most cases will develop LAA two to three years after first exposure to laboratory animals. In this retrospective cohort study based on pre-employment medical examinations almost 20 percent of the cohort reported LAA. Exposure to laboratory animals and atopy were significant determinants of LAA, whereas sex, age, and smoking were not associated. More people with asthmatic symptoms were found in the high exposure categories. The latency time for LAA symptoms was shorter with higher intensity of exposure, except for those workers exposed less than two hours per week. Almost twice as many atopics reported asthmatic symptoms compared with non-atopics and mean latency time for LAA was shorter among atopics than non-atopics.

An increased relative risk was found for non-atopics exposed to laboratory animal allergens for more than two hours/week. Atopics had an even higher risk when exposed to laboratory animal for more than two hours/week (RR above 7.3). Compared to non-atopics, more atopics had been absent from work for substantial periods or had been transferred to other job because of allergy complaints.

In chapter five, **'Relations between respiratory symptoms and sickness absence among workers in the animal feed industry'** determinants of sickness absence due to respiratory symptoms were studied among production workers and office clerks. Logistic regression analysis showed that workers with self-reported CNSLD were more likely to fall ill than those without CNSLD in the past 12 months. Adjusted for age and smoking, the odds ratio was 1.9 among office clerks, and 2.6 among blue-collar workers. Smoking increased the risk on sickness absence with 2.4 and 1.6, respectively. When restricting the analysis to sickness absence due to respiratory complaints, subjects with self-reported CNSLD had significantly higher risks on sickness absence (both prevalence and duration) than those without respiratory complaints. Workers with respiratory symptoms could more easily survive when performing administrative tasks than in production work, which is physically more demanding and entails considerable exposure to organic dusts.

In chapter six, **'Choosing optimal values for FEV_1 and FEV_1/FVC for diagnosing respiratory disorders in occupational populations'** the diagnostic performance of FEV_1 and FEV_1/FVC was evaluated in the community-based Zutphen Study. Both parameters showed a maximum sensitivity of 40% at a specificity of 95% relative to the physician's diagnosis of respiratory disorder (CNSLD). The application of Relative Operating characteristics Curves made it possible to investigate the optimal cut-off point at which the total costs of misclassification are minimised, given varying levels of the costs of false results. This study demonstrated the usefulness of clinical decision making techniques in optimising the performance of surveillance programmes in occupational health care. These techniques stimulate more explicit thought about the costs and consequences of over-diagnosing and of cases being missed and about the probability of developing CNSLD.

In chapter seven, **'Evaluation of the diagnostic performance of stepwise health surveillance for bronchial irritability syndrome (BIS) in occupational health care'** the most widely used tests in occupational health care (questionnaire, spirometric lung function test, and serial peak flow

measurement) were evaluated on their usefulness to diagnose bronchial irritability syndrome (BIS). This study clearly showed that a combination of respiratory symptoms, spirometry and peak flow variability resulted in a better sensitivity to identify abnormal subjects than individual tests alone. In addition, combination of respiratory symptoms, spirometry and serial peak flow resulted in a more detailed estimation of post-test probabilities of BIS. Combined testing will result in more efficient screening for subjects with BIS. The use of a questionnaire is relatively simple and cheap and its results may reduce the number of subjects who would have to perform peak flow measurements. It is suggested that a better selection of subjects with respiratory complaints will improve compliance with serial peak flow measurements and, thus, improve the applicability of this test for epidemiological studies and surveillance programmes.

In the final chapter, **'Discussion'**, the general conclusions are presented of the research in this thesis. Occupational exposures contribute to the occurrence of CNSLD. Workers with CNSLD may experience serious aggravation of their health problems in particular working conditions. Diagnosis and surveillance of workers with CNSLD is hardly developed in the dutch occupational health care. The thesis ends with five recommendations aimed at improving the identification of workers with CNSLD, extending knowledge of the impact of CNSLD on worker's ability to perform their regular work, and creating opportunities in occupational health care to implement effective surveillance programmes for CNSLD. I hope that this thesis will contribute to the establishment of a sound basis for occupational health programmes directed at secondary prevention of asthma and COPD.

Samenvatting

Tot op heden is er weinig bekend over het effect van CARA op de beroepsbevolking. Enerzijds kunnen specifieke beroepsmatige blootstellingen CARA veroorzaken en een bijdrage leveren aan tijdelijke en blijvende uitval van werknemers. Anderzijds kunnen de arbeidsomstandigheden waaronder werknemers met CARA werken de respiratoire aandoening verergeren en zo het vermogen om werkzaamheden uit te voeren beïnvloeden. Dit proefschrift richt zich op de relatie tussen CARA en werk en tracht de volgende vragen te beantwoorden:

1) Zijn werknemers onder bepaalde arbeidsomstandigheden of blootstellingen meer vatbaar voor het krijgen van CARA?
2) Hoe gaan werknemers met CARA om met de dagelijkse routine van hun werk?
3) Is het mogelijk het rendement van screeningsprogramma's voor CARA te verhogen met het huidige instrumentarium?

Het eerste deel van het proefschrift is gewijd aan het voorkomen van CARA in beroepsgroepen en het effect van CARA op ziekteverzuim en uitval (hoofdstukken twee tot en met vijf). Het tweede deel van dit proefschrift richt zich op het herkennen van werknemers met CARA binnen de bedrijfsgezondheidszorg en de best mogelijke toepassing van beschikbare instrumenten voor de diagnose van CARA (hoofdstuk zes en zeven).

In hoofdstuk twee, **"Occupational exposures estimated by a population specific job exposure matrix and 25-year incidence rate of chronic non specific lung disease (CNSLD): The Zutphen Study"**, wordt gedetailleerde informatie over specifieke blootstellingen gecombineerd met beroepscodes tot een bevolkingsspecifieke beroepsmatige blootstellingmatrix (Job Exposure Matrix, JEM). De analyses van de relatie tussen beroepsmatige blootstelling en de CARA incidentie bevestigden de resultaten van andere bevolkingsstudies. Personen met een blootstelling aan stof gedurende één tot twintig jaar hadden een duidelijk, statistisch significant, verhoogd risico op het verkrijgen van CARA terwijl personen die langer aan stof waren blootgesteld een lager risico op het verkrijgen van CARA hadden. Dit wijst op het bestaan van het zogeheten healthy worker effect, wat werknemers met CARA dwingt het beroep te verlaten.

In hoofdstuk drie, **"Occupational exposure to organic dusts and decline in lung function over five years"**, wordt een longitudinale studie van werknemers in de mengvoeder industrie gepresenteerd. Vergelijking van werknemers met de hoogste blootstellingniveaus met werknemer met geen of lage blootstelling aan stof en endotoxine leerde dat de eerste groep een statistisch significante verlaging van de FEV_1 en de MMEF had. Uitgaande van een cumulatieve blootstelling over 40 werkjaren met een stofblootstelling van 5 $mg.m^{-3}$, is het verwachte effect op de FEV_1 een verlaging van 157 $ml.s^{-1}$, vergelijkbaar aan ongeveer 4% van de gemiddelde FEV_1. The MMEF zou met 473 $ml.s^{-1}$ afnemen, vergelijkbaar aan ongeveer 12% van de gemiddelde MMEF. Werknemers met een stofblootstelling groter dan 4 $mg.m^{-3}$ of een endotoxineblootstelling groter dan 20 $ng.m^{-3}$ tijdens het onderzoek in 1986, 1988 hadden een significant hoger risico op een verhoogde afname in FEV_1 met een Odds Ratio van 3,3. Het optreden van het healthy worker effect bleek uit de verminderde jaarlijkse afname in FEV_1 en het geringere aantal personen met een versnelde afname in FEV_1 naarmate het aantal werkjaar toenam. Het healthy worker effect bleek ook uit het feit dat het hebben van klachten aan de luchtwegen tijdens het eerste onderzoek een sterke voorspeller was voor het verdwijnen uit het bedrijf. De tijdens het eerste onderzoek gemeten longfunctie voorspelde deze uitval niet, alhoewel bij de uitvallers het aantal werkjaren een sterkere negatieve relatie vertoonde met de longfunctie dan bij de werknemers die na vijf jaar nog steeds de werkzaamheden in de mengvoederindustrie uitvoerden.

In hoofdstuk vier, **"Respiratory allergy in laboratory animal workers: a prospective cohort study using pre-employment screening data"**, wordt proefdierallergie bestudeerd. Onder proefdierwerkers zijn prevalentiecijfers van 10 tot 30 procent gevonden en is gesuggereerd dat in de meeste gevallen proefdierallergie twee tot drie jaar na het eerste contact met proefdieren optreedt. In deze retrospectieve studie met follow-up vanaf de aanstellingskeuring rapporteerde bijna 20% van de onderzoeksgroep het ontstaan van proefdierallergie. De analyse toonde aan dat blootstelling en een atopische constitutie significante determinanten zijn voor proefdierallergie. Geslacht, rookgewoonten en leeftijd bleken geen risicofactor te zijn. Meer personen met astmatische klachten bevonden zich in de hoge blootstellings-categorie. De tijd tot het ontwikkelen van symptomen van proefdierallergie was korter bij een hogere blootstellingintensiteit, behalve bij personen met een blootstelling van minder dan twee uur per week. Bijna twee maal zoveel personen met een atopische constitutie meldde astmatische klachten dan personen zonder atopie.

Een verhoogd relatief risico is gevonden voor personen zonder atopie die meer dan twee uur per week in contact kwamen met proefdieren. Atopische personen hadden een hoger risico indien zij meer dan twee uur per week in contact kwamen met proefdieren (RR groter dan 7,3). Personen met atopie bleken, in vergelijking met personen zonder atopie, vaker te verzuimen of van baan te veranderen ten gevolge van allergische verschijnselen.

In hoofdstuk vijf, **"Relations between respiratory symptoms and sickness absence among workers in the animal feed industry"**, worden determinanten van ziekteverzuim ten gevolge van luchtwegklachten bestudeerd. Logistische regressie analyse liet zien dat werknemers met zelfgerapporteerde CARA een grotere kans op ziekteverzuim hadden dan werknemers zonder CARA in de voorafgaande 12 maanden. Gecorrigeerd voor leeftijd en roken was de Odds ratio 1,9 onder de kantoormedewerkers en 2,6 onder de productiemedewerkers. Roken verhoogde het risico van ziekteverzuim met 2,4 respectievelijk 1,6. Indien alleen naar ziekteverzuim ten gevolge van luchtwegklachten werd gekeken hadden werknemers met zelfgerapporteerde CARA significant hogere risico's op verzuim dan werknemers zonder luchtwegklachten. Werknemers met luchtwegklachten konden gemakkelijker 'overleven' indien zij een kantoorfunctie hadden dan de collegae in de productie, wiens lichamelijke belasting en blootstelling aan organisch stof hoger zijn.

In hoofdstuk zes, **"Choosing optimal values for FEV_1 and FEV_1/FVC for diagnosing respiratory disorders in occupational populations"**, wordt het testen van de FEV_1 en FEV_1/FVC met spirometrie geëvalueerd in de algemene bevolkingsstudie, de Zutphen Studie. Beide parameters lieten tegenover de klinisch diagnose van CARA een maximale sensitiviteit van 40% bij een specificiteit van 95% zien. Het toepassen van Relative Operating Characteristic (ROC) curven maakten het mogelijk het optimale afkappunt te bepalen bij bepaalde waarden voor de kosten van misclassificatie, waarbij de totale kosten van die misclassificatie waren geminimaliseerd. De studie toonde aan dat deze technieken, afkomstig van de klinische besliskunde een belangrijke bijdrage kunnen leveren aan de evaluatie van screeningsprogramma's en deze programma's kunnen optimaliseren. Deze benadering stimuleert het expliciet maken van de kosten en consequenties van een onjuiste diagnose en van de kans op het ontwikkelen van CARA.

In hoofdstuk zeven, **"Evaluation of the diagnostic performance of stepwise health surveillance for bronchial irritability syndrome (BIS) in occupational health care"**, worden de binnen de bedrijfsgezondheidszorg, meest toegepaste instrumenten geëvalueerd op hun bruikbaarheid bij gecombineerd testen op de aanwezigheid van het zogeheten BIS (bronchial irritability syndrome). De geëvalueerde testen waren vragenlijsten, spirometrie en piekstroommetingen. De studie liet verder zien dat het gecombineerd gebruik van verschillende testen in een efficiëntere wijze van screenen resulteert. Bovendien gaf het gecombineerde gebruik een meer gedetailleerde schatting van de waarschijnlijkheid van BIS. Het gecombineerd gebruik van verschillende testen resulteert in een efficiëntere wijze van screenen op personen met BIS. Het gebruik van een vragenlijst is relatief eenvoudig en goedkoop en vermindert het aantal personen dat piekstroom-metingen dient te ondergaan. Gesteld is dat een betere selectie van personen met respiratoire klachten de uitvoering van seriële piekstroommetingen verhoogd en, op deze wijze, eveneens de toepasbaarheid van dit instrument voor epidemiologisch onderzoek en screeningsprogramma's verhoogd.

Het laatste hoofdstuk, de discussie, geeft de algemene conclusies van de onderzoeken uit het proefschrift. Beroepsmatige blootstelling draagt bij tot het voorkomen van CARA. Werknemers met CARA kunnen een ernstige verslechtering van hun gezondheidsklachten ervaren onder specifieke arbeidsomstandigheden. De herkenning en het monitoren van werknemers met CARA zijn nauwelijks ontwikkeld binnen de Nederlandse bedrijfsgezondheidszorg. Het proefschrift eindigt met vijf aanbevelingen gericht op het optimaliseren van de herkenning van werknemers met CARA, het vergroten van de kennis over het effect van CARA op het vermogen van de werknemer om zijn dagelijkse werkzaamheden uit te voeren en het creëren van mogelijkheden binnen de bedrijfsgezondheidszorg om effectieve monitoringsprogramma's voor CARA te verwezenlijken. Ik hoop met deze aanbevelingen een bijdrage te leveren aan een gezonde basis voor de secundaire preventie van astma en COPD in de bedrijfsgezondheidszorg.

Dankwoord

Men neme: een aantal artikelen, twee lieve, maar aandacht opeisende kinderen, een relatie die anders uitpakte dan gewenst, een fulltime baan bij een Arbo-dienst en, op de valreep, opnieuw een zwangerschap. Dus is het duidelijk waarom de afronding van dit proefschrift jaren in beslag heeft genomen. Sterker nog, bovenstaand recept zal wellicht de vraag doen rijzen hoe dat proefschrift er ooit gekomen is. Dat laatste is te verklaren aan het meeste essentiële ingrediënt dat nog niet genoemd is, namelijk Lex Burdorf. Naar Lex gaat mijn grootste dank uit. Lex, het feit dat ik ooit zo ver ben gekomen getuigt van jouw inzettingsvermogen en enthousiasme. De overstap van de Landbouw Universiteit Wageningen naar de Erasmus Universiteit te Rotterdam was ook best wel een beetje eng, want ik wist al dat ik bij één van Nederlandse beste arbeidsepidemiologische onderzoekers kwam te werken. Immers, ik heb je voor het eerst ontmoet toen je deel uit maakte van het zeer selecte panel top arbeidshygiënisten dat ik had uitgenodigd te participeren in een afstudeervak. Dat je tevens een zeer prettig en begripvol persoon bent om voor te werken bleek onder meer uit al die keren dat ik je geduld toch behoorlijk op de proef stelde. In oktober 1993 kwam je met het voorstel in april 1994 naar Engeland te gaan voor een onderzoek. Jij zag het al helemaal voor je en tegenover jouw enthousiaste uiteenzetting van de plannen moet mijn reactie behoorlijk lauw zijn geweest. Ik zat me voortdurend af te vragen of ik je nu wel of niet zou vertellen dat ik 1 april 1994 uitgerekend was en dat dat geen grapje was. Typerend was je reactie: nou, dan ga je toch gewoon later met het kind onder je arm!

Op een gedeelde tweede plaats komen Ilse Phillips en mijn vader. Ilse vanwege de grote hoeveelheid werk die zij verzet heeft in de opmaak van het proefschrift, waarmee zij mij een enorme portie werk uit handen heeft genomen. En mijn vader, omdat hij, naast Lex, een stok achter de deur betekende. Papa, ik weet dat je er bijna niet meer op durfde te hopen, maar hier ligt het dan toch.

Uiteraard hebben verschillende mensen een positieve bijdrage geleverd aan het tot stand komen van mijn proefschrift. Paul van der Maas leerde ik, in het bijzonder in het eindstadium, kennen als een zeer vakkundig en kritisch persoon.

Zijn bijdrage heeft een zeer gunstig effect gehad op de inhoud van verschillende delen van het proefschrift. Mijn co-promotoren, Dick Heederik en Lex, waren van begin tot eind bij alle delen van het proefschrift betrokken, zowel tijdens de uitvoering als de verslaglegging. Ik heb veel van jullie geleerd, maar vooral, onder jullie begeleiding, altijd met veel plezier aan de verschillende onderzoeken gewerkt.

De tijd in Londen, bij het National Hearth and Lung Institute, was in dit alles een bijzondere periode. De daar verzamelde gegevensbestanden door Kate Venables en haar collega's leverden mij een schat aan informatie, waarmee ik vrijwel grenzeloos kon stoeien. Mijn zus, Jildo Post en haar familie, mag ik hierbij niet ongenoemd laten. Jildo zorgde gedurende negen maanden overdag voor mijn dochtertje, Aminata, die opgroeide met haar nichtjes Melissa en Daniëlle, twee jaar ouder respectievelijk drie maanden jonger dan Aminata. Aminata had in die periode de leeftijd van vijf maanden tot ruim een jaar. Jildo, nu ik zelf meer dan één kind heb, kom ik meer en meer tot de ontdekking hoeveel je toen voor me hebt gedaan. Niet dat ik het achteraf anders had willen doen, want het contact met jou en je familie maakt de periode in Engeland zo waardevol voor me.

Alle andere personen met wie ik, direct of indirect, heb samengewerkt bij de vakgroep Humane Epidemiologie en Gezondheidsleer van de Landbouw Universiteit en bij het instituut Maatschappelijk Gezondheidszorg van de Erasmus Universiteit wil ik bedanken voor hun inzet. Bij de directe samenwerking bedoel ik de co-auteurs, met wie ik bij de verschillende onderzoeken heb samengewerkt. Dankzij Ton Bruggeling, Pieter de Jongh en Bart Naaktgeboren, allen werkzaam als bedrijfsarts in opleiding bij een Arbodienst, dank ik de wetenschap dat kwaliteit, wetenschap en bedrijfsgezondheidszorg wel degelijk hand in hand kunnen gaan.

Bij de indirecte samenwerking denk ik aan al die andere medewerkers van de vakgroep Gezondheidsleer en MGZ uit de periode dat ik daar werkte. Al die collega's zorgden voor de gezellige en ontspannen sfeer tijdens het werken bij de universiteit waar ik nu met enige mate van weemoed op terug kijk. Bij het noemen van de collega's gaat een speciaal woord van dank uit naar Sonja Deurloo die veel zaken voor me geregeld heeft en zo zorgde voor een soepele afrondingsfase.

Mijn collega's bij Arbo Unie Midden Nederland, Gouda BV verdienen toch een vermelding in dit dankwoord. Dankzij hen heb ik, in een zeer prettige sfeer, een goed beeld gekregen van de arbeidshygiënische praktijk. Ondanks een opmerking van een collega, vrij vlot naar mijn aanstelling, dat ik 'die wetenschap nu maar snel moet vergeten' ben ik meer en meer tot de overtuiging gekomen

dat de wetenschapswereld en de bedrijfsgezondheidszorg elkaar helemaal niet hoeven te bijten, maar dat zij samen borg kunnen staan voor een hoogwaardige kwaliteit van dienstverlening.

En nu eindig ik heel geijkt met het noemen van mijn kinderen. Echter, een reden om hen te bedanken ontbreekt en ook het stellen dat zonder hen het proefschrift veel eerder klaar zou zijn geweest voert me ook te ver. Toch drijft mijn moederlijke trots me er toe hen niet ongenoemd laten. Voor hen is onderstaand verhaaltje opgenomen - de boodschap en link naar mijzelf mag men zelf afleiden - (Guus Kuijer. 'Met poppen gooien').

"Als ik groot ben, dan word ik heel dik. Dan lopen ze me niet meer omver", zegt Roos. Ze zit met Madelief op een zandberg op het bouwterrein voor de deur.
"Dan nemen we een huis met een plat dak waar je bovenop kunt zitten. Dan zie je alles".
"Wie we?" vraagt Madelief.
"Ik en mijn meneer".
"Je mán, bedoel je".
"Ja. Dan durven we dicht bij het randje. Want mijn man, die is nergens bang voor. Ik ook niet natuurlijk. Ik ga altijd op de weegschaal."
"Nou, ik neem geen man hoor", zegt Madelief. "Mijn niet gezien. Dan moet je altijd afwassen. Mijn moeder heeft er ook geen."
Roos knikt. Dat was zo. Zonder man kon het ook.
"Maar ze wast wel altijd af", zegt ze.
"Logisch", antwoord Madelief. "Wie moet het anders doen?".
"Hij moet wel sterk zijn. Met van die spierballen. Maar niet sterker dan ik. Dat hoeft niet. Hij moet me niet omduwen, dan word ik kwaad. Dan moet 'ie naar kantoor".
"Daar ben je toch veel te zwaar voor, om je omver te duwen?"
Roos knikt heftig. "Ja, net zo zwaar als onze klok".
"De klok op de schoorsteen of de zevengeitjesklok?"
"De zevengeitjesklok".
"Oei", zegt Madelief. Want die klok is onmenselijk zwaar. Daar zijn twee verhuismannen aan te pas gekomen om die op z'n plaats te zetten. Ze kijken naar een bouwvakker die met balken sjouwt. Hij heeft er wel vijf op zijn schouder. Hij loopt er een beetje krom van.
"Misschien", zegt Madelief, "neem ik toch een man. Want als je dan verhuist, kan die de klok in de gang zetten".

Dus, kinderen, ik hoop dat jullie later toch met enige trots kunnen zeggen 'Jawel, ik lijk wel om mijn moeder, al is het niet qua uiterlijk'. Want, my oh my, het heeft lang geduurd, maar ik heb het toch gered.

About the author

Wendel Karyn Post werd geboren op 9 mei 1966 te Gorredijk, Friesland. Zij volgde het VWO aan het Bogerman College te Sneek. Aan de Landbouw Hogeschool te Wageningen studeerde zij vanaf 1984 milieuhygiëne, de richting milieu-effect-analyse. Deze studie betrof de effecten van het milieu op de mens, enerzijds gericht op de tropen, anderzijds gericht op het arbeidsmilieu. Na een laatste praktijkjaar in Ivoorkust, kwam zij bij de vakgroep Humane Epidemiologie en Gezondheidsleer terecht. Vanaf mei 1990 was zij hier betrokken bij een evaluatie van een praktijkproef voor bedrijfsgezondheidszorg voor de agrarische sectoren. In augustus 1990 studeerde ze af bij de Landbouw Universiteit te Wageningen.

Vanaf 1991 werd de onderzoeksrichting verlegd naar de aan beroepsmatige blootstelling gerelateerde CARA-problematiek. Dit onderzoek startte bij de vakgroep Humane Epidemiologie en Gezondheidsleer aan de Landbouw Universiteit te Wageningen onder begeleiding van Dick Heederik. Na enige tijd werd het onderzoek tevens uitgevoerd vanuit het instituut Maatschappelijke Gezondheidszorg aan de Erasmus Universiteit te Rotterdam onder leiding van Lex Burdorf. Een deel van het onderzoek werd gefinancierd door het Nederlands Astma Fonds. Na een onderbreking van ruim een half jaar in 1994, verhuisde zij, met kind onder de arm, naar Engeland. Deze verhuizing was financieel mogelijk door steun van het NAF, de Europese Gemeenschap en beide universiteiten. Doel van deze verhuizing was een negen maands-onderzoek bij het National Hearth & Lung Institute in Londen, onder begeleiding van Kate Venables.

Na terugkomst in Nederland in de zomer van 1995 was zij nog gedurende een half jaar werkzaam voor het instituut Maatschappelijke Gezondheidszorg. Eind 1995 nam zij afscheid van het onderzoeksleven en verlegde haar werkterrein naar het huisfront waar een tweede kind haar intrede nam. Na een jaar van 'niets doen' begon zij in februari 1997 als arbeidshygiënist bij Arbo Unie Midden Nederland, Gouda BV. Hier werkt zij nog steeds, zij het met een onderbreking van 16 weken vanaf 11 oktober 1999 voor de komst van, jawel, kindje nummer drie.