Interplay between allergy and work

Jiska Annette Patiwael

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Interplay between allergy and work

Interplay Between Allergy and Work

De interactie tusssen allergie en arbeid

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Voor mijn moeder

Midnights in Winter
The glowing fire
Lights up your face in orange and gold
I see your sweet smile
Shine through the darkness
It's line is etched in my memory

So I'd know you by heart

Mornings in April
Sharing our secrets
We'd walk until the morning was gone
Mother and daughter
laughing for hours
The joy you gave me lives on and on

Because I know you by heart

I still hear your voice
On warm Summer nights
Whispering like the wind

You left in August
The leaves were turning
I walked down roads of orange and gold
I saw your sweet smile
I heard your laughter
You're still here beside me every day

Because I know you by heart,
Because I know you by heart

Vrij naar Eva Cassidy 'I know you by heart'

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1

General introduction

Background and definitions

Rhinitis is acknowledged to have both a health and a socio-economic impact[1-5]. Furthermore, the link between upper and lower respiratory tract - concerning rhinitis and asthma respectively - is being underlined[6-8]. The burden of occupational rhinitis seems to have been underestimated compared to e.g. occupational asthma[9-11]. However in the existing literature, only attention has been paid to occupational rhinitis.

Occupational rhinitis is an inflammatory disease of the nose, which is characterized by intermittent or persistent symptoms (*i.e.* nasal congestion, sneezing, rhinorrea, itching), and/or variable nasal airflow limitation and/or hypersecretion due to causes and conditions attributable to a particular work environment and not to stimuli encountered outside the workplace[12]. Low and high molecular weight agents as well as irritants may lead to occupational rhinitis.

When occupational rhinitis is caused by an IgE (antibody)-mediated allergic reaction due to an occupational allergen, it is called *IgE-mediated allergic occupational rhinitis*. An IgE-mediated allergic occupational rhinitis can be caused by a wide variety of high molecular weight (HMW) agents (*i.e.* proteins from vegetable and animal origin such as wheat flour, natural rubber latex, other plant allergens, laboratory animals, fish and seafood protein) and some low molecular weight agents (LMW) for example platinums salts, reactive dyes and acid anhydrides[12].

Occupational asthma is a subtype of work-related asthma characterized by variable airflow obstruction, airway hyperresponsiveness, and airway inflammation attributable to a particular exposure in the workplace and not due to stimuli encountered outside the workplace. Similar to occupational rhinitis, low and high molecular weight agents as well as irritants may cause occupational asthma and in particular HMW agents are known to induce occupational asthma through an IgE-dependent mechanism[13].

Occupational rhinitis and occupational asthma should be distinguished from the broader diseases work-related rhinitis and work-related asthma. Work-related rhinitis for example includes occupational rhinitis, but also pre-existing or concurrent disease worsened by workplace exposures[12].

The assumed sequence of events in developing an *IgE-mediated occupational allergy*, while working with HMW occupational allergens, is that individuals become sensitized to common inhalant allergens, then develop sensitization to an occupational allergen at work, subsequently occupational rhinitis, and finally occupational asthma[14-16]. Occupational asthma may become severe[17]. Furthermore, asthma can persist in subjects after cessation of exposure[18].

Epidemiology of occupational rhinitis

Prevalence and incidence

The prevalence figures of occupational rhinitis in workforces exposed to HMW agents vary widely (from 2% to 87%) depending on the occupational agent involved and on the definitions used 9. Compared to occupational asthma, occupational rhinitis due to HMW agents tends to be 3 times more prevalent[9].

Up to date, there are few reports on the incidence of work-related rhinitis. Similar to the prevalence figures, the incidence of work-related rhinitis depends on the occupational agent involved and varies from 0.3 to 13.1 per 100 person years[19].

Since only few studies have addressed the incidence of work-related rhinitis symptoms, there is a need for further information on this subject. Therefore, we investigated this topic in **chapter 2**. Subject of study were bell pepper employees, an occupational group associated with a high percentage of occupational IgE-mediated allergy since employees, while at work in greenhouses, are intensely exposed to bell pepper pollen (HMW) allergens.

Risk factors for occupational rhinitis

Three known possible risk factors for the development of occupational rhinitis are the level of exposure, smoking and atopy.

Level of exposure: The level of exposure to occupational allergens has shown to be a determinant for the development of an IgE sensitization to a variety of HMW agents[20-23]. Furthermore, IgE sensitization to some agents appears to be a risk factor for rhinitis/asthma symptoms[24-27].

Smoking: The association between smoking and work-related rhinitis and asthma symptoms is still disputable. No relationship between occupational rhinitis and smoking was found in working groups such as laboratory animal workers[28] and bakery employees[29]. Jeebhay *et al.* demonstrated that smoking is a risk factor for development of occupational asthma among saltwater fish processing workers[30]. Siracusa, however, showed that smoking was a negative determinant for development of asthma in working groups in British Colombia[31]. A review published in 2006 concluded that there is little to support the view that the risk of occupational asthma is increased in workers who are smokers[32].

Atopy: Atopic individuals have an increased risk of developing sensitization to a variety of HMW agents, while being exposed[32]. Atopy is also associated with occupational rhinitis due to HMW agents such as wheat flour and laboratory animals and natural rubber latex, although results of studies are sometimes inconsistent[33-34].

Since there is a need for additional characterization of risk factors for developing work-related allergic symptoms, we studied possible risk factors for the onset of work-related rhinitis together with asthma symptoms in bell pepper greenhouse employees in **chapter 2**.

The social burden of occupational rhinitis

Quality of life

It has been found that quality of life (QoL) is negatively affected by allergic diseases 1. Concerning the impact of occupational rhinitis on QoL, up to date only few studies have been performed[35-36]. In a previous study by our group, it was described how bell pepper pollen allergy has a negative impact on daily life[37].

The effect of avoidance on Quality of Life (QoL)

Avoiding exposure to the causative occupational allergen is one of the therapeutic options in occupational rhinitis[38]. The few studies that have been performed on the effect of avoidance on rhinitis indicate that rhinitis symptoms improve after cessation or reduction of occupational allergen exposure[39-42].

To our knowledge, just one study compared QoL of patients with occupational rhinitis, not exposed to occupational allergens anymore, with occupational rhinitis patients who were continuously being exposed. QoL was impaired among patients from the latter group, whereas the QoL among patients no longer exposed was mainly similar to that of the healthy controls[36].

Given the fact that there is scarce information on the effect of avoidance of occupational allergens on rhinitis-related QoL[35-36], this topic needs further exploration. In chapter 3, we investigated the effect on rhinitis-related quality of life of leaving work and subsequent occupational allergen avoidance in bell pepper employees.

The economic burden of occupational rhinitis

At present, it is well known that allergic rhinitis has economic implications[43-44]. On the contrary, little known is about the economic impact of occupational rhinitis[12].

Rhinitis in the general population has been shown to contribute to productivity loss through sick leave as well as on-the-job productivity loss[4-5, 45]. Since productivity loss leads to higher productivity costs, this particular loss has economic consequences. Because it is largely unknown what the influence of occupational rhinitis and occupational asthma is on productivity loss, including the resulting costs, this was subject of study in the bell pepper workforce. The results of this study are discussed in **chapter 4**.

Primary prevention of occupational rhinitis: reducing exposure

Since the level of exposure to occupational allergens appears to be the most important determinant of development of an IgE sensitization[20-23] and, in turn, IgE sensitization to some agents appears to be associated with rhinitis/asthma symptoms[25-27], reduction or elimination of workplace exposure to occupational allergens should be the most effective way of achieving primary prevention[19].

Data on successful reduction of exposure concern for example changes in the properties of natural rubber latex (NRL) gloves designated for health care

workers[46-47]. As the powder in NRL gloves appears to be the main cause of the airborne exposure to NRL, and thus playing an important role in the sensitization process, introducing powder-free NRL gloves should lower this exposure[23,47-48]. Consequently, the prevalence of NRL sensitization and allergy should also be diminished.

Although there are several studies that indicate that the introduction of powder-free NRL gloves seem to be effective in reducing the incidence of disease, sufficiency of the evidence has been a matter of debate[49-50]. We therefore addressed this issue in **chapter 5**. Subject of study were operating room employees from a university hospital.

New occupational allergens

Considering the fact that the level of exposure appears to be the most important determinant of sensitization and occupational rhinitis, an important reason for a new occupational allergy to develop is the *increase* in level of exposure. This is the case in, for instance, strawberry horticulture, where employees nowadays work in greenhouses and not in the open field anymore as they used to do. In **chapter 6**, first, we tried to estimate the prevalence of work-related symptoms in employees in strawberry greenhouses. Second, we aimed to prove the concept that an IgE mediated allergy to strawberry pollen could be responsible for work-related symptoms. Specific immunological tests, which are essential for the assessment of an IgE mediated sensitization to a new occupational allergen, are described, *i.e.* skin prick tests and specific IgE measurements (ELISA and immunoblotting). In addition, nasal provocations tests (NPT), to establish the biological activity of the new allergen and thereby confirming the diagnosis of occupational rhinitis, were performed.

In summary, the aims of this thesis are:

- To investigate to cumulative incidence of work-related rhinitis together with work-related asthma symptoms and sensitization to bell pepper pollen, and to establish risk factors for the onset of work-related symptoms among bell pepper employees (**Chapter 2**).

- To study the economic burden caused by productivity loss due to work-related rhinitis and work-related asthma symptoms in bell pepper employees (**Chapter 3**).

- To evaluate the social burden of disease by determining rhinitis-related quality of life and studying the effect of leaving work and subsequent occupational allergen avoidance in bell pepper employees (**Chapter 4**).

- To evaluate the preventive capacity of the introduction of sterile powder-free NRL gloves in the operating room from a university hospital, measured by the change in prevalence of NRL sensitization and allergy among operating room employees, 10 years after the introduction. To study the determinants of NRL sensitization and allergy (**Chapter 5**).

- To explore the presence of work-related allergic symptoms in strawberry greenhouse workers and to prove the concept that an IgE-mediated allergy could be responsible for work-related symptoms (**Chapter 6**).

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2

Occupational allergy to bell pepper pollen in greenhouses in the Netherlands, an 8-year follow-up study

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Abstract

Background

Pollen from bell pepper plants cultivated in greenhouses are known to cause occupational allergic disease. A cross-sectional study among 472 bell pepper employees in 1999 estimated prevalences for sensitization to bell pepper pollen of 28% and for work-related allergic symptoms of 54%. There is scarce information on the incidence of work-related allergy and its risk factors. Aims of the present study were: (1) to estimate the cumulative incidence of work-related symptoms and sensitization to bell pepper pollen, and (2) to determine risk factors for the onset of these symptoms and sensitization.

Methods

Bell pepper employees who participated in a cross-sectional survey in 1999 were asked to take part in a follow-up study in 2007. Information on demographic characteristics, job characteristics, and allergic symptoms was gathered by means of a questionnaire. Furthermore, skin tests were performed with *a.o.* bell pepper pollen.

Results

In total, 280 out of 472 employees were available for questionnaires and in 250 employees allergy tests were performed. During the 8-year follow-up, the cumulative incidence of sensitization to bell pepper pollen was 9% and of work-related rhinitis 19%. Atopy [odds ratio (OR) 5.60] and smoking (OR 3.53) were significantly associated with development of rhinitis. The cumulative incidence of work-related asthma symptoms was 8%. Again atopy (OR 5.03) and smoking (OR 11.85) were significant risk factors.

Conclusion

Cumulative incidences for sensitization to bell pepper pollen, work-related rhinitis and asthma symptoms were 9%, 19% and 8%, respectively. Atopy and smoking are risk factors for developing work-related respiratory symptoms among workers in bell pepper horticulture.

Introduction

The prevalence of occupational allergy and asthma has increased over the past few decades and an estimated 10-25% of all adult onset asthma can be attributed to the work place[1].

Occupational asthma and rhinitis may lead to substantial consequences for work, most notably productivity loss at work, sickness absence, and work disability[2-4]. Employees in horticulture are at risk for developing an occupational allergy[5]. The European Farmers' project demonstrated that working in a greenhouse was a risk factor for developing respiratory symptoms[5-7]. Kronqvist *et al.*[8] showed that upper and/or lower airway symptoms were present in 38% of workers in Swedish greenhouse cucumber and tomato growers.

Greenhouses for crop growing in the Netherlands, approximately 9000 in total, host a large workforce. The bell pepper cultivation in the Netherlands is an important branch of horticulture under glass with a size of 1 184 ha and the current workforce (2008) consists of approximately 9800 employees (Commodity Board of Horticulture, market and innovation). Furthermore, the bell pepper greenhouse is an environment characterized by a high prevalence of upper and lower airway symptoms. In a cross-sectional study among 472 employees from 85 greenhouses – nearly 10% of the bell pepper workforce at that time – work-related allergic symptoms were found in 54% of workers[9]. These symptoms consisted of rhinitis, conjunctivitis, and asthma in 49%, 30%, and 13% of individuals, respectively. Further analysis demonstrated sensitisation to the bell pepper plant in 35% of workers and 23% was sensitized to predatory mites which were used as a biologic control of the crops[9, 10]. Work-related symptoms among bell pepper employees were associated with sensitization to substances of the bell pepper plant (bell pepper pollen being the most important), age, and atopy.

In the general (unexposed) population the prevalence rates reported for rhinitis range from 19% to 30%[11, 12] and for both conjunctivitis and asthma prevalence rates of 15%-20% are found[13, 14]. It can thus be concluded that the prevalence of work-related symptoms (mainly rhinitis and conjunctivitis) and allergy among greenhouse workers is high. Up to present, studies have been cross-sectional of nature and no longitudinal studies on the natural course of occupational allergy in greenhouse horticulture have been performed. Therefore, there is no information

available on the cumulative incidences of work-related symptoms or allergy and its risk factors. To identify greenhouse employees who are at risk of developing sensitization and symptoms, more insight into these factors is needed. The obtained knowledge can be used to develop tools to detect occupational allergy in these employees in an early stage.

A longitudinal study was conducted based on follow-up of all participants in a previous cross-sectional study among bell pepper greenhouse workers[9]. Although only bell pepper employees were subject of study, this branch of industry may serve as a model for many other kinds of horticulture characterised by pollen exposure.

The aims of this study were twofold: (1) to estimate the cumulative incidence of sensitization to bell pepper pollen and work-related rhinitis and asthma symptoms, and (2) to establish risk factors for the onset of work-related symptoms and occupational allergy.

Material and Methods

From March until September 2007, a follow-study among bell pepper employees was performed. As many employees as possible of the 472 who participated in the first study were included in the follow-up study[9]. Bell pepper greenhouses who participated in the cross-sectional survey in 1999 were approached by telephone and asked to take part in a second survey. Subsequently, the investigators paid a visit to the greenhouses. Subjects that had left the job were traced and also asked for participation. If they agreed to take part, the investigators paid a visit to their new workplace or made a home visit. During the visits the former and current employees gave their informed consent. A questionnaire was administered on gender, age, smoking habit, current job characteristics, work history, atopic complaints, and allergic symptoms at work, *i.e.* work-related rhinitis and asthma symptoms. Questions did not specifically focus on the flowering season. Subjects were labeled as having work-related rhinitis symptoms if they reported any of the following items: sneezing, rhinorrhoea, nasal itching, or nasal obstruction after occupational exposure[9]. Similarly, if subjects reported either wheezing, coughing, sputum, or shortness of breath after occupational exposure, they were labeled as having work-related asthma symptoms[9]. Sensitization to occupational allergens

and common inhalant allergens was determined by means of skin prick tests. The study was approved by our Hospital Medical Ethical Committee. Confidentiality was maintained.

In this follow-up study, the cumulative incidence of sensitization to bell pepper pollen, work-related rhinitis and work-related asthma incidence were primary outcome measures. Work-related rhinitis and asthma incidence were defined, respectively, as newly reported rhinitis and asthma symptoms at work during follow-up that were not mentioned in the first study in 1999.

Skin tests

Skin prick tests were carried out according to international guidelines[15, 16] and performed by a skilled allergy nurse. In addition, reactions were expressed in mean wheal diameter of the longest diameter and the orthogonal diameter. A diameter of 3 mm or more was considered positive[17].

Allergens

Home made extracts: bell pepper pollen and Amblyseius cucumeris

As the bell pepper pollen appeared to be the substance of the bell pepper plant most strongly associated with allergic complaints, only pollen were used for skin prick testing during the follow-up study[9]. Pollen from bell pepper plants were collected in a greenhouse in the period February-March 2007. The flowers were in full blossom, and biological control by predatory mites (*Amblyseius cucumeris*) was not used yet. A 10% (w/v) extract was made in phosphate-buffered saline (PBS) pH 7.4, containing 0.03% human serum albumin (HSA) and 0.5% phenol[18]. The protein concentration, determined by the method of Watanabe *et al.*[19] was 0.62 g/L. Predatory mites (*Amblyseius cucumeris*) were kindly supplied by Koppert Biological Systems (Berkel en Rodenrijs, the Netherlands) and extracted according to Groenewoud *et al.*[10]. The protein concentration was 1.05 g/L[19]. Appropriate aliquots were stored at -20°C, defrosted 1 hour before skin test and mixed.

***Botrytis cinerea* and common inhalant allergens**

In addition, skin prick tests were performed with *Botrytis cinerea* (ALK Abello, SQ 412), one of the moulds found in greenhouses and with 6 common inhalant allergens from ALK Abelló (Nieuwegein, the Netherlands). The common inhalant allergens comprised *Dermatophagoides pteronyssinus* (SQ-503), grassmix (SQ-293) and tree mix (SQ-108), mugwort (SQ-312) and animal dander (dog, SQ-553 and cat, SQ-555). Dilution buffer served as a negative control, histamine chloride (10 mg/ml) as a positive control.

Statistical analysis

In the statistical analysis, baseline characteristics of subjects which were included in follow-up were compared to those lost to follow-up: Differences between continuous variables were tested with the unpaired Student τ-test and the differences between frequencies of categorical variables were tested with the chi-square test (χ^2).

A logistic regression model was used to study risk factors for primary dichotomous outcomes measures *i.e.* onset of work-related rhinitis, work-related asthma symptoms, and sensitization to bell pepper pollen during the follow-up period. For all three primary outcome measures the following independent variables from the baseline study were used; individual characteristics (gender, age, smoking), job characteristics (years of exposure, job classification) and atopy. Atopy was defined by the presence of a positive skin prick test result to at least one of the common inhalant allergens.

For the analysis, univariate associations were investigated and variables with a significance level of $P < 0.10$ were considered for inclusion in the multivariate models. In the final multivariate models only variables with a *P*-level below 0.05 were retained. The odds ratio (OR) was used as measure of association.

The statistical analysis was executed using the SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

In total, 280 out of 472 employees who participated in the first study were available for questionnaires and 250 of these 280 employees were available for both questionnaires and allergy testing. Among another 42 subjects it was possible to gather information on current employment status. Therefore, in total 322 subjects were included in the follow-up study (Figure 1).

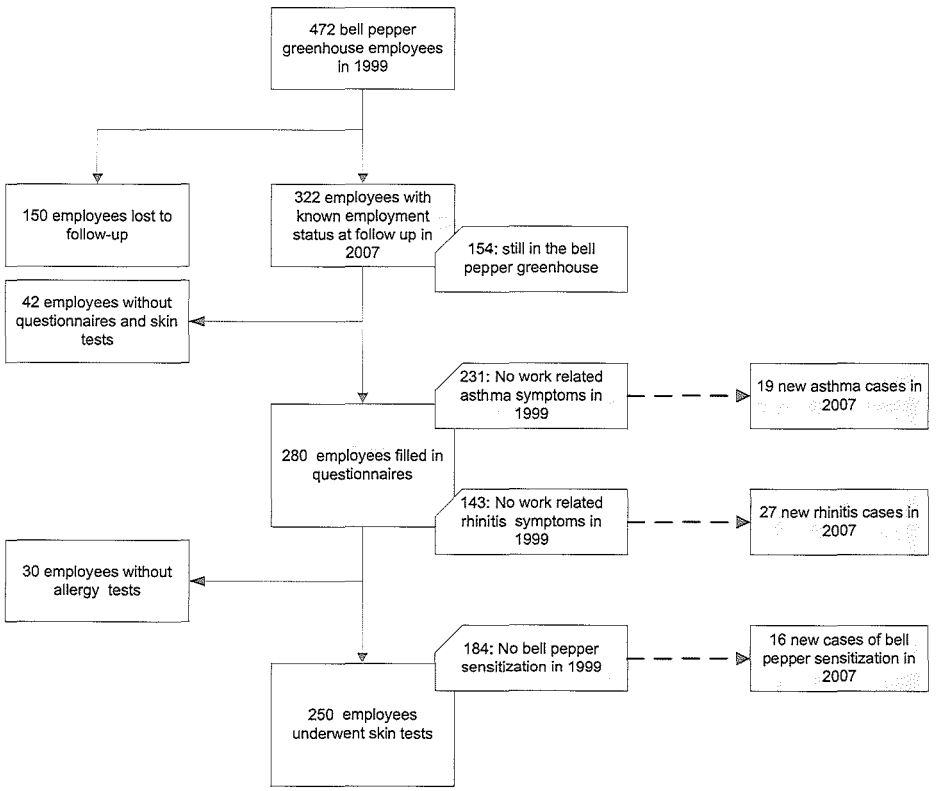

Figure 1. Overview of bell pepper employees at baseline (1999) and during follow-up in 2007: (participants and non-participants).

Information from the first study in 1999 on individual characteristics, job characteristics, allergy symptoms, and allergy test results were compared between the (former and current) employees included in the follow-up study in 2007 and those lost to follow-up (Table 1). No difference was found for gender, work-related rhinitis, work-related asthma symptoms, atopy, and sensitization for bell pepper pollen or for any of the occupational allergens between the two groups. There was a clear overlap between atopy and sensitization to bell pepper pollen.

Table 1. Individual and job characteristics and allergy (symptoms) at baseline (1999) of the group follow-up versus lost to follow-up in 2007.

	Participant 2007 ($n = 322$)	**Non-participant 2007 ($n = 150$)**
Determinants		
Gender (male)	263 (82%)	124 (83%)
Age (mean years)*	37.7	34.3
Smoking*	94 (29%)	59 (39%)
Job classification (owner)*	116 (36%)	17 (11%)
Duration of employment (mean years)*	8.98	7.51
Atopy	113 (35%)	64 (42%)
Sensitization to one of the occupational allergens#	133 (41%)	72 (48%)
Sensitization to the bell pepper plant°	112 (35%)	55 (36%)
Work-related rhinitis symptoms	156 (48%)	77 (51%)
Work-related asthma symptoms	43 (13%)	20 (13%)

* $P < 0.05$

occupational allergens: bell pepper plant, *Amblyseius cucumeris, Botrytis cinerea.*

° bell pepper plant: bell pepper stem, leaf, pollen, juice, stamen.

Owners were statistically more likely to be included in the follow-up study, compared to employees. The follow-up group had a smaller proportion of smokers compared to those lost to follow-up. This, however, appeared to be associated with job classification, since owners were less often smoker than employees. The mean age of the follow-up group was higher (38 *vs* 34 years) and also the mean duration of employment was higher in the follow-up group (8.89 *vs* 7.51 years).

Reasons for the owners to refuse participation (in the questionnaire survey and/or allergy tests) were lack of time or interest ($n = 5$) and the fact that they had quit the bell pepper cultivation or had changed to other crop growing ($n = 9$). Some owners could not be reached by telephone ($n = 6$) and one owner had died. Consequently, this hampered the recruitment of the (formerly) enlisted employees.

The cumulative incidence of sensitization to bell pepper pollen, work-related rhinitis, and asthma symptoms was 9%, 19%, and 8%, respectively (Table 2). There was a clear overlap among these incidences. Of the 27 workers who developed work-related rhinitis, 7 workers also developed work-related asthma symptoms, and 12 workers developed sensitization to bell pepper pollen. Furthermore, of the 19 workers who developed work-related asthma symptoms, all workers developed work-related rhinitis and 10 out of 19 were also newly sensitized to bell pepper

pollen. Finally, of the 16 workers who developed a bell pepper pollen sensitization, 13 also developed work-related rhinitis of which 3 developed work-related asthma symptoms as well.

At baseline work-related allergy symptoms were also strongly interrelated with 93.3% of subjects with asthmatic complaints also reporting rhinitis. Furthermore, atopy at baseline was associated with sensitization to occupational allergens at baseline, with 65% of the atopic subjects also being sensitized to the bell pepper plant and 80% of the atopic subjects to at least one of the occupational allergens (*i.e.* either to the bell pepper plant, to *Botrytis cinerea* or to *Amblyseius cucumeris*) (data not shown).

The cumulative incidence of sensitization to bell pepper pollen during 8-year follow-up was 9% (n = 16) (Table 2). With increasing age (OR 0.95) the risk of developing sensitization to bell pepper pollen decreased (Tables 3 and 4).

Table 2. Prevalence at baseline (1999) and cumulative incidence during follow-up (2007) of the three primary outcomes *i.e.* sensitization to bell pepper pollen, work-related rhinitis and work-related asthma symptoms.

	Prevalence at baseline % (95% CI)	**Number of workers for whom data was available during 8-year follow-up**	**Population-at-risk during 8-year follow-up**	**New cases during 8-year follow-up**	**Cumulative incidence % (95% CI)**
Sensitization to bell pepper pollen	27.3 (25.2-29.4)	250	184	16	8.7 (7.5-9.9)
Work-related rhinits symptoms	49.5 (46.2-52.5)	280	143	27	18.8 (16.1-21.7)
Work-related asthma symptoms	13.3 (12.2-14.5)	280	231	19	8.2 (7.2-9.2)

Table 3. Univariate analysis of individual and job characteristics and atopy at baseline (1999) on the cumulative incidence of sensitization to bell pepper pollen, work-related rhinitis symptoms and work-related asthma symptoms during follow-up in 2007.

Determinants (baseline in 1999)	New cases of sensitization to bell pepper pollen: 16/184 (9%) Odds Ratio (95 % CI)	New cases of work-related rhinitis symptoms: 27/143 (19%) Odds Ratio (95 % CI)	New cases of work-related asthma symptoms: 19/231 (8%) Odds Ratio (95 % CI)
Gender (male)	1.67 (0.54-5.11)	0.74 (0.23-2.37)	1.81 (0.65-5.05)
Age	0.95 (0.91-1.00)**	0.96 (0.92-1.00)**	0.98 (0.94 -1.02)
Smoking	1.50 (0.52-4.36)	2.34 (1.00-5.50)*	8.62 (2.96-25.07)**
Job classification (owner)	1.3 (0.46-3.65)	0.80 (0.34-1.91)	0.28 (0.08-0.99)**
Duration of employment	0.98 (0.90-1.07)	0.96 (0.90-1.03)	0.98 (0.90-1.06)
Atopy	1.86 (0.61-5.72)	4.29 (1.64-11.20)**	2.75 (1.07-7.10)**

* $P < 0.10$
** $P < 0.05$

The cumulative incidence of work-related rhinitis symptoms during the 8-year follow-up was 19% ($n = 27$). In the univariate analyses atopy (OR 4.29), smoking (OR 2.34), and age (OR 0.96) were associated with development of rhinitis symptoms ($P < 0.10$) (Table 3). In the final multivariate model only smoking (OR 3.53) and atopy (OR 5.60) were significantly associated with the development of rhinitis symptoms ($P < 0.05$) (Table 4).

Table 4. Multivariate analysis of individual and job characteristics and atopy at baseline on the cumulative incidence of sensitization to bell pepper pollen, work-related rhinitis symptoms and work-related asthma symptoms during follow-up in 2007.

Determinants (baseline in 1999)	New cases of sensitization to bell pepper pollen: 16/184 (9%) Odds Ratio (95 % CI)	New cases of work-related rhinitis symptoms: 27/143 (19%) Odds Ratio (95 % CI)	New cases of work-related asthma symptoms: 19/231 (8%) Odds Ratio (95 % CI)
Gender (male)	n/a	n/a	n/a
Age	0.95 (0.91-1.00)**	0.98 (0.94-1.02)	n/a
Smoking	n/a	3.53 (1.28-9.69)**	11.85 (3.59-39.11)**
Job classification (owner)	n/a	n/a	0.47 (0.12-1.78)
Duration of employment	n/a	n/a	n/a
Atopy	n/a	5.60 (1.77-17.75)**	5.03 (1.65-15.37)**

** $P < 0.05$
n/a, not applicable

The cumulative incidence of work-related asthma symptoms was 8% ($n = 19$). In the univariate analyses atopy (OR 2.75), smoking (OR 8.62) and job classification (owner) (OR 0.28) were associated ($P < 0.10$) with the development of asthma (Table 3). In the final multivariate model only smoking (OR 11.85) and atopy (OR 5.03) were significantly associated with the development of asthma symptoms (Table 4).

The duration of employment appeared not be a risk factor for either work-related rhinitis or work-related asthma symptoms.

At time of follow-up, 48% of workers was still employed in bell pepper horticulture. Job classification was the only determinant significantly associated with current employment in bell pepper horticulture. Compared to employees, owners were more likely to stay in the bell pepper greenhouse [OR (95% CI)]: 1.97 (1.21 - 3.20). Within the employee group who had left the greenhouse, rhinitis symptoms in 1999 were significantly ($P < 0.05$) more present than among the employees who stayed [61% (74/122) *vs* 38% (32/84)].

Discussion

During the 8-year follow-up the cumulative incidence of bell pepper pollen sensitization was 9% and the cumulative incidence of work-related rhinitis and asthma symptoms were 19% and 8%, respectively. Important individual risk factors were atopy and smoking.

The estimated prevalence of bell pepper pollen sensitization, work-related rhinitis, and asthma symptoms in the baseline study may be assumed to be the cumulative incidence due to the average duration of exposure of about 8 years. On the basis of these prevalence figures, it was expected that the cumulative incidence for bell pepper pollen sensitization and for work-related rhinitis and asthma symptoms during the 8 year follow-up would be in the same range as the prevalence found at baseline. However, the observed cumulative incidence was lower for all three measures. This finding can be partly explained by the fact that the peak of onset of sensitization and symptoms apparently occurs during the first several years of exposure and not in a later phase of prolonged exposure. The fact that sensitization to an occupational allergen occurs in the first years of exposure is also described for other occupational groups with occupational allergy. In laboratory animal workers

sensitization to occupational allergens and symptoms occur primarily in the first 2-3 years after starting exposure to laboratory animals[20]. In baker apprentices, the peak incidence of skin reactivity and work-related rhinoconjunctivitis was reached about 1-2 years after entering an educational programme[21]. Furthermore, one of the reasons for the cumulative incidence being lower than estimated is an healthy worker effect (HWE)[22]. In our study, a HWE seems to have occurred since rhinitis symptoms in 1999 were significantly more present in the group that had left the greenhouse during follow-up compared to the group still employed in the greenhouse, indicating that rhinitis could be an expelling factor. Sixteen out of 168 former employees explicitly mentioned that allergy symptoms were reason of their resignment. This points to a possible HWE and moreover it also indicates that work-related allergy possibly has economic consequences for both the industry and for the workers themselves. Another indication for a HWE was that at time of follow-up 8 years later, 48% of workers were still employed in bell pepper horticulture and owners were more likely to be still at work in the bell pepper greenhouse than employees. Another possible explanation for the lower cumulative incidence is the fact that the working environment in most bell pepper greenhouses has changed over the years, for example greenhouses are more spacious than before. It can be hypothesized that the pollen density nowadays is, therefore, less high. Personal sampling to measure pollen concentrations will be required to estimate the current exposure of the employees.

Taking the duration of the follow-up into account, the incidence of bell pepper sensitization, work-related rhinitis, and work-related asthma symptoms was 11, 24 and 10 cases per 1000 person-years, respectively. In 2001, the second Dutch National Study of General Practice reported an incidence of 'hay fever/allergic rhinitis' of 8.8 new cases per thousand individuals per year[23] and on the basis of data from five general practice data registration systems, the number of new asthma cases in the general population occurring in 2003 was 6.5 per thousand men and 7.9 per thousand women[23]. Thus, compared to the incidence of rhinitis in the general population, the cumulative incidence of work-related rhinitis in this group of bell pepper employees is considerably higher. The cumulative incidence of work-related asthma symptoms found in our study is comparable to the incidence of asthma in the general population. It is known that adult onset asthma can mainly be attributed to the workplace.

In the cross sectional survey in 1999, bell pepper pollen sensitization appeared to be the most important allergen (in the bell pepper greenhouse) associated with work-related symptoms[9]. Therefore, during follow-up the cumulative incidence of bell pepper sensitization was studied and not the cumulative incidences of sensitization to other occupational allergens or to the common inhalant allergens (including pollen allergy). The onset of the other allergens is most likely less relevant and therefore the limitation resulting from this approach seems to be marginal.

Risk factors

The cumulative incidence of bell pepper sensitization in our study decreased significantly by age. In general, it is known that the development of inhalant allergies diminishes when age increases[24, 25]. This could also hold true for occupational allergies and our finding points into that direction.

Risk factors found in this study for the cumulative incidence of work-related rhinitis and asthma symptoms were smoking and atopy.

Whether smoking is associated with development of work-related allergic symptoms has been a matter of debate. Jeebhay *et al.*[26] demonstrated that smoking is indeed a risk factor for development of occupational asthma among salt water fish processing workers. Siracusa, however, showed that smoking was a negative determinant for development of asthma in working groups in British Colombia[27]. A review from 2006 on studies on smoking and occupational asthma published from 1970-2005 showed that there is little support for the hypothesis that smoking is a risk factor for the development of occupational asthma[28]. In general, tobacco smoke impairs the innate immune system and in a recently published review Cagnani *et al.*[29] have concluded that active smoking is associated with current rhinitis and asthma symptoms and that it seems to be a risk factor for development of new asthma in rhinitis patients. Our study clearly showed that smoking is a risk factor for development of both work-related rhinitis and asthma symptoms in this particular branch.

Inhalant atopy as a whole (*i.e.* sensitization to at least one of the following common inhalant allergens: *Dermatophagoides pteronyssinus*, grass pollen, tree pollen, mugwort, dog or cat dander) appeared to be an important determinant of work-

related symptoms and sensitization to the bell pepper plant in the previous cross sectional study conducted in 1999[9]. Therefore, also in this longitudinal study the common inhalant allergens were not studied separately but grouped together as one possible risk factor. Furthermore, at baseline atopy and bell pepper pollen sensitization strongly overlapped and therefore it was not possible to estimate the separate role of these two factors[9]. The proposed sequence of events in developing occupational allergy while working with high molecular weight allergens is first atopy, then development of sensitization to an occupational allergen, subsequently the development of occupational rhinitis, and finally the onset of occupational asthma[30-32]. In our study, we found that atopy is indeed at the start of the series of events, since atopy was associated with the cumulative incidence of both work-related rhinitis and asthma symptoms in bell pepper employees. This finding corroborates earlier results showing that atopic people have an increased risk of developing work-related allergic symptoms while being exposed to high molecular weight antigens[30-32]. Our study also seems to confirm the hypothesis that occupational rhinitis precedes occupational asthma[33, 34] since work-related rhinitis was associated with the onset of work-related asthma symptoms. However, this association was partly explained by the fact that rhinitis and asthma had similar risk factors. With two measurements over time, the study design did not allow us to investigate the sequence in more detail. However, the clear overlap among the cumulative incidence of sensitization to bell pepper pollen, work-related rhinitis, and work-related asthma symptoms indicates that these outcomes are clustered. During the field visits to the greenhouses it was established that almost all cultivations were sweet bell pepper and, hence, capsaicin from *Capsicum annuum* will not have played an important role in the onset of work-related symptoms.

In future research, the exact sequence of events should be disentangled in order to facilitate better targeted prevention and early treatment strategies. The fact that occupational allergy may have a profound effect on work performance through productivity loss at work as well as sick leave emphasises the need for these prevention and early treatment strategies.

Conclusion

Cumulative incidences for sensitization to bell pepper pollen, work-related rhinitis and asthma symptoms were 9%, 19% and 8%, respectively. We found that smoking and atopy are risk factors for developing work-related rhinitis and asthma symptoms in bell pepper greenhouse workers.

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3

Occupational rhinitis in bell pepper greenhouse workers: determinants of leaving work and the effects of subsequent allergen avoidance on health-related quality of life

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Abstract

Background

Avoidance of occupational allergens or reduction of exposure has been advocated as the mainstay of the management of occupational rhinitis. Sparse data to the effect of allergen avoidance are available.

Objective

To identify factors which may lead to leaving work and to address the effect of subsequent allergen avoidance on quality of life.

Methods

A survey to the prevalence of occupational allergy to bell pepper performed in 1999 comprised 472 employees, of which 254 had work-related rhinitis and 228 completed the Rhinitis Quality of Life Questionnaire. After 8 years follow-up in 2007, 91 workers with rhinitis in 1999 were available to fill out the questionnaire again and were used to evaluate the course of nasal disease in terms of perceived severity and impact on daily life.

Results

Workers with rhinitis at baseline were more likely to leave their job in bell pepper cultivation for another job (OR =1.62, 95% CI 0.95-2.75). Among the 91 workers, 58 subjects were still at work, whereas 33 subjects had left work. The subjects who left jobs reported substantial improvement in quality of life. The magnitude of the changes ranged from - 0.31 to -1. The effect of quitting work on the mean quality of life score amounted – 0.76 ± 0.15.

Conclusions

The current study is the first large longitudinal studies showing that leaving work and subsequent occupational allergen avoidance has a beneficial effect on rhinitis-related quality of life. The study suggests that occupational rhinitis can be a reason to leave work.

Introduction

Occupational rhinitis is a disease of emerging relevance which has received little attention in comparison to occupational asthma[1]. The epidemiology of occupational rhinitis has been investigated less extensively, mainly because it is not considered such a serious disease[2]. Position papers focusing on occupational rhinitis became quite recently available[1]. Although underestimated, the prevalence of occupational rhinitis appears to be high. It has been suggested that the prevalence is 2-4 times higher compared to occupational asthma[2]. This is in line with previous studies performed in bell pepper greenhouses, showing that 49% of the workforce experiences work-related upper airway symptoms, whereas 13% reports symptoms suggestive for work-related asthma[3].

Reduction of exposure to occupational allergens or avoidance has been advocated as the mainstay of the management of occupational rhinitis[1]. Sparse data to the effect of allergen avoidance on occupational rhinitis are available. In some specific occupations, information is available on the effect of reduction in allergen exposure. Helmet respirators are effective[4] in natural rubber latex (NRL) allergy but not always feasible. A previous study in bell pepper greenhouses suggests that introduction of honey bees into these greenhouses may reduce exposure to bell pepper pollen resulting into a decrease of nasal symptoms[5]. Apart from these measures in the work place, complete avoidance by quitting work has not been the topic of many studies. Three longitudinal studies report reduction of rhinitis symptoms in patients with natural rubber latex allergy after lowering or cessation of exposure[6-8]. Other studies suggesting a favorable effect of leaving work on rhinitis are cross-sectional[9, 10] or retrospective[11, 12].

To address the effects of leaving work on rhinitis, we examined follow up data from a cohort of bell pepper greenhouse workers studied in 1999[3] and in 2007. The cross-sectional survey in 1999 among 472 employees from 85 greenhouses – nearly 10% of the national bell pepper work force at that time – showed that work-related allergic symptoms were found in 54% of workers[3]. Further analysis demonstrated sensitisation to the bell pepper plant in 35% of workers, whereas 23% was sensitized to predatory mites which were used as a biologic control of the crops[13]. Determinants associated with work-related symptoms among bell pepper employees were presence of sensitization to substances of the bell pepper plant (bell pepper pollen being the most important), age, and atopy[3].

In the baseline survey we demonstrated that rhinitis-related quality of life was mainly determined by sensitisation to bell pepper pollen and not to concomitant common inhalant allergies[14]. Eight years later in 2007, a follow-up study was performed to estimate the incidence of rhinitis, asthma and sensitization to occupational allergens in the same cohort of bell pepper greenhouse workers[15].

Questionnaires obtained in 1999[14] allowed us to identify factors that might lead to leaving work, whereas information on rhinitis-related quality of life obtained in 1999 and 2007 enabled us to evaluate the course of nasal disease in terms of perceived severity and impact on daily life. We hypothesized that greenhouse workers with nasal symptoms at baseline would express a better quality of life if they had left work in between 1999 and 2007.

Methods

From March until September 2007, a follow-up study among current and former bell pepper employees was performed. As many employees as possible of the 472 who participated in the first study were included in the follow-up study[3]. Bell pepper greenhouses who participated in the cross-sectional survey in 1999 were approached by telephone and asked to take part in a second survey. Subsequently, the investigators paid a visit to the greenhouses. Subjects that had left the job were traced and also asked for participation. If they agreed to take part, the investigators paid a visit to their new workplace or made a home visit. During the visits, the (former) employees gave their informed consent. A questionnaire was administered on gender, age, smoking habit, current job characteristics, work history, atopic complaints and allergic symptoms at work, *i.e.*, work-related rhinitis and asthma symptoms[3]. The criteria of work-related rhinitis comprised the presence of symptoms such as nasal congestion, sneezing, rhinorrea, itching (as mentioned by the recent position paper on occupational rhinitis)[1], elicited during work in the greenhouses[3, 14]. Also, the diagnosis of work-related asthma was questionnaire based. Subjects with one of the following symptoms: wheezing/coughing/sputum/shortness of breath at work were labeled as having work-related asthma. The study was approved by our Hospital Medical Ethical Committee. Confidentiality was maintained.

Rhinitis-related quality of life

Quality of life was measured using the approved Dutch translation of the Rhinitis-related Quality of Life Questionnaire (RQLQ) developed by Juniper *et al*[16]. This questionnaire more precisely describes the effect of rhinitis on different areas of the employees' day-to-day lives. It comprises 28 questions divided into the following domains: activities (n = 3), sleep (n = 3), non-rhinitis symptoms (n = 7), practical problems (n = 3), nasal symptoms (n = 4), eye symptoms (n = 4), and emotions (n = 4). In each item, they were asked how much they were troubled as a result of their nasal symptoms during the previous two weeks. The score ranged from 0 (not troubled) to 6 points (extremely troubled). In case of the items concerning activities, the employees were asked to identify activities that were limited because of their nasal symptoms. If more than three activities are identified, employees were asked to choose the three most significant. To ensure that all possible relevant items are considered, a list of 29 probe activities was provided as well. The investigators instructed the employees according to the guidelines, defined by the designers of the questionnaire. All employees filled in their questionnaires in the canteen of the greenhouse or at home in the presence of the investigators. In the analysis, the mean within-employee score of each RQoL domain was used (these mean domains scores were measured by calculating the mean of the items within each domain). Furthermore, all 28 items were used to calculate the mean RQoL score.

Missing values: subjects were excluded if Dutch was not their primary language. Missing values were also defined for domains consisting of 3 items if more than 1 item was missing. In case of domains with 4 or 7 items, a maximum of 2 missing items were allowed.

Sensitization to occupational allergens and atopic background

To characterize employees in terms of sensitization, skin tests with occupational and common inhalant allergens were carried out according to international guidelines[17]. Reactions were expressed in mean wheal diameter of the longest diameter and the orthogonal diameter. A diameter of 3 mm or more was considered positive. Skin prick test was performed with occupational allergens: a home-made extract of the leaf, stem, pollen, stamen, and juice of the bell pepper plant and a home-made extract of the predatory mite *Amblyseius cucumeris* as previously described[3, 13] and *Botrytis cinera* (SQ 412 from ALK Abelló, Nieuwegein, the Netherlands) as one of the moulds found in greenhouses. The allergenicity of the home-made extracts has been tested previously. With immunoblotting, major IgE-binding structures

were seen at 14, 29 and 69 kDa in sweet bell pepper pollen extract[18]. Allergenicity of predator mite extracts was tested with nasal provocation[13].
An atopic background was defined as having one or more positive skin reactions to common inhalant allergens: *Dermatophagoides pteronyssinus* (SQ 503), tree mix (SQ 108), grass mix (SQ 293), mugwort (SQ 312), dog dander (SQ553), and cat dander (SQ 555).

Statistical analysis

In the analyses, two groups of respondents were compared, those who were still employed in the bell pepper cultivation after 8 years of follow-up and those who had changed job to employment outside the bell pepper cultivation.

Baseline RQLQ data from non-respondents were compared with responder data to evaluate the possibility that quality of life at baseline has an influence on lost to follow up.

A logistic regression was used to determine the factors that predicted leaving paid employment in the bell pepper cultivation. Independent factors were individual characteristics, years of work history in bell pepper greenhouses, and health factors related to allergy. Variables were coded in such a manner that an odds ratio above 1 indicates an increased likelihood of leaving paid employment in bell pepper cultivation. The analysis started with univariate association, and those independent factors with $P < 0.20$ were investigated in the multivariate analysis. In the final multivariate model, variables were retained when statistically significant ($P < 0.05$) or when remaining almost unchanged (change in regression coefficient < 10%).

The association of quitting work with changes in rhinitis-related quality of life was investigated with a mixed linear regression model for repeated measurements. This model takes account of the correlation between repeated measures on the same subject. In this model, change of job was included as fixed (categorical) effect, and the variances between and within workers were regarded as random effects under the assumption of a compound symmetry covariance structure[19]. All statistical analyses were performed using SAS V 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

In total, 269 out of 472 employees who participated in the first study, were available for questionnaires and 240 of these 269 employees were available for both questionnaires and allergy testing. However, because of language problems and handling of missing items, we could obtain eligible RQLQ data – filled in at baseline and in 2007 – from 228 employees.

The study population had a mean age of 46 years and 80% of the study population was male (Table 1). Forty percent was owner of a greenhouse. Ownership of a greenhouse and being male were strongly associated. Thirty-five percent had an atopic background, whereas 39% were sensitized to occupational allergens. Forty-five percent had rhinitis complaints.

Table 1. Baseline characteristics of the workers in bell pepper greenhouses ($n = 228$) at the start of the cohort study.

	All employees ($n = 228$)
Age (mean, SD) in 2007	45.7 ± 12.0
Male sex (*n*, %)	183 (80%)
Being owner of greenhouse (*n*, %)	92 (40%)
Years working in bell pepper greenhouses (mean, SD)	8.9 ± 5.9
Smokers (*n*, %)	59 (26%)
Subjects with atopic background (*n*, %)	79 (35%)
Subjects sensitized to occupational allergens (*n*, %)	90 (39%)
Rhinitis complaints (*n*, %)	102 (45%)

We evaluated the total group of bell pepper workers in 1999 in terms of lost to follow up ($n = 150$) or participation in the study ($n = 322$). The groups did not differ in the available RQLQ data; thus, quality of life at baseline did not have any influence on lost to follow-up.

Ninety-one of these subjects reported nasal symptoms in 1999. In 1999 and 2007, 41.7% and 26% of these 91 subjects used anti-allergic medication in 1999 and 2007. In 2007, 58 subjects were still employed in bell pepper greenhouses, whereas 33 subjects had left work (Figure 1).

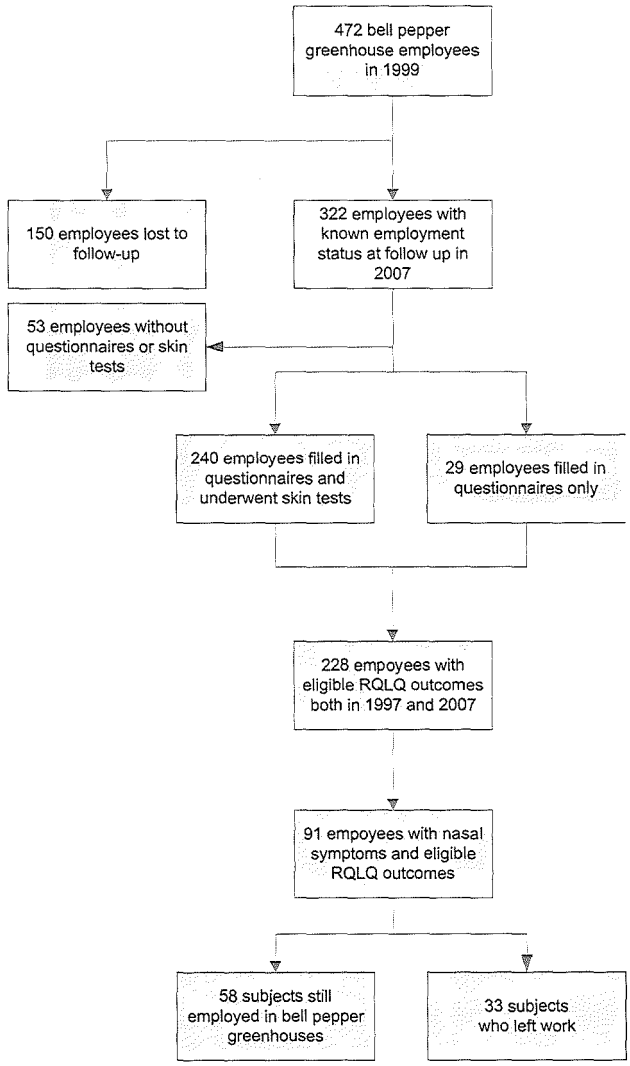

Figure 1. Flowchart of bell pepper employees with nasal symptoms and eligible rhinitis-related quality of life (RQLQ) data.

Table 2 shows that male workers and owners were less likely to quit working in bell pepper cultivation than others. Workers with rhinitis complaints at baseline were more likely to leave their job in bell pepper cultivation for a job in another branch (OR = 1.62, 95% CI 0.95-2.75).

Table 2. The influence of individual characteristics, rhinitis complaints, and occupational allergy on the likelihood of leaving bell pepper cultivation during a follow-up period of 8 years (logistic regression analysis).

	Left bell pepper cultivation (univariate model) Odds Ratio (95% CI)	**Left bell pepper cultivation (multivariate model) Odds Ratio (95% CI)**
Age (yrs)	1.00 (0.98-1.02)	-
Male	0.41 (0.21-0.81)**	0.50 (0.25-1.00)*
Being owner	0.43 (0.23-0.70)**	0.45 (0.26-0.80)**
Smokers	0.68 (0.37-1.25)	-
Years working in bell pepper	0.95 (0.90-0.99)**	-
Subjects with atopic background	0.85 (0.49-1.48)	-
Subjects sensitized to occupational allergens	0.64 (0.37-1.10)*	-
Rhinitis complaints	1.62 (0.95-2.75)*	1.55 (0.90-2.68)

** $P < 0.05$, * $P < 0.10$

The multivariate analysis showed that subjects with rhinitis complaints were more likely to have left paid employment in the bell pepper cultivation, whereas men and owners more often remained employed. The magnitude of the associations remained largely unchanged after mutual adjustment, although the influence of rhinitis complaints became statistically insignificant ($P = 0.11$). In the univariate analysis, workers sensitized to occupational allergens had a decreased risk of quitting their job, but this effect disappeared when adjusted for sex and owner. A similar effect was also observed for years working in bell pepper, primarily due to its strong association with ownership.

Figure 2 shows the mean RQLQ scores at baseline and in 2007 in subjects still at work. For some RQLQ domains, the mean scores decreased, but these differences were not statistically significant.

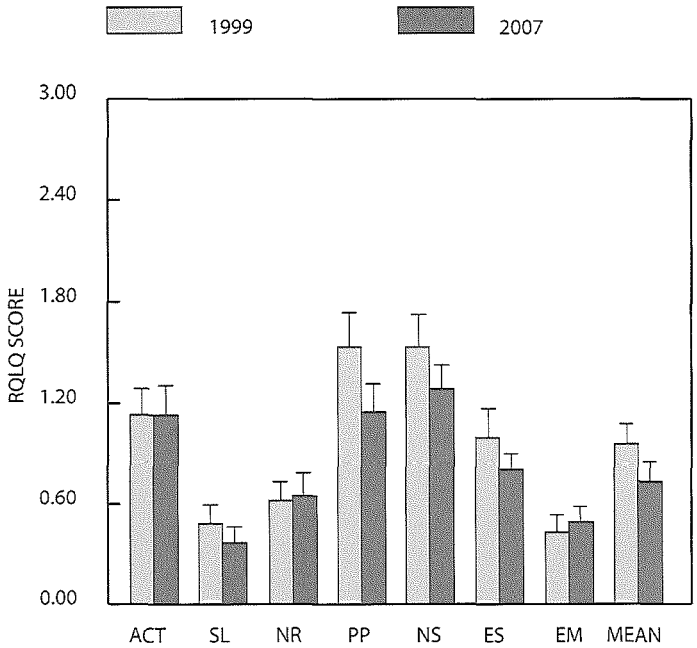

Figure 2. RQLQ scores obtained from subjects still at work (n = 58). Mean scores and S.E.M. for activities (ACT), sleep disorders (SL), non-rhinitis symptoms (NR), practical problems (PP), nasal symptoms (NS), eye symptoms (ES), emotions (EM) and mean RQL (MEAN).

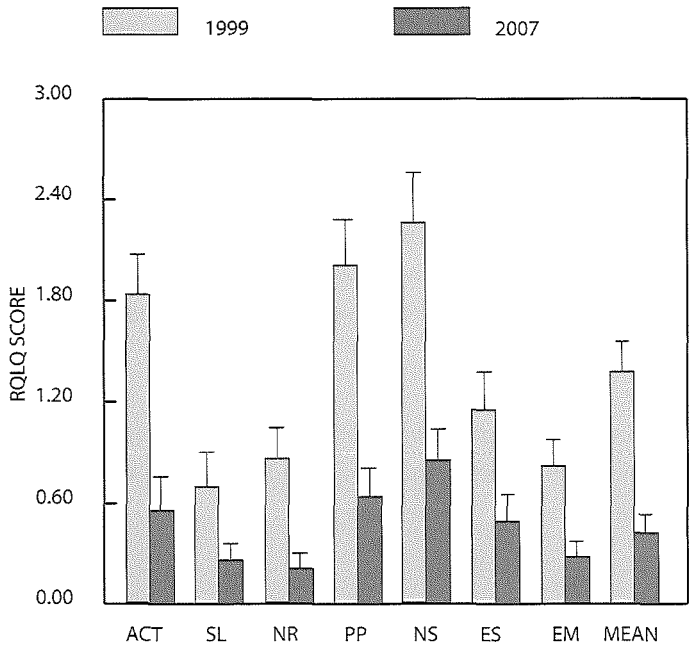

Figure 3. RQLQ scores obtained from subjects who left the job (n = 33).

From Figure 3, it can be seen that employees who left their work reported substantially lower RQLQ scores in 2007 compared with 1999.

Table 3 shows that quitting work in bell pepper cultivation had strong positive effects on the rhinitis-related quality of life, with an effect size varying from 0.31 to 1.09, indicating clinically relevant effects in most domains. The largest relative improvements were observed for mean RQoL and activities, whereas sleep disorders, eye problems, and emotional problems showed the smallest relative improvement.

Table 3. The influence of quitting work in bell pepper cultivation on the presence of rhinitis-related quality of life, adjusted for age and sex, among 91 workers at the end of the follow-up.

RQoL domain	Effect of quitting work in bell pepper cultivation (SD)
Activities	- 0.99 (0.21)*
Sleep disorders	- 0.31 (0.15)*
Non-rhinitic symptoms	- 0.56 (0.16)*
Practical problems	- 1.07 (0.24)*
Nasal problems	- 1.09 (0.24)*
Eye symptoms	- 0.55 (0.20)*
Emotional problems	- 0.40 (0.12)*
Mean RQoL	- 0.76 (0.15)*

* $P < 0.05$

Discussion

The relative backlog in research to occupational rhinitis compared with occupational asthma might be attributed to the opinion that occupational rhinitis is a trivial disease. However, our data suggest that rhinitis can be a reason to leave work. Examining the mean RQLQ scores, one might argue that the impairment in quality of life was mild. However, this may be due to a healthy worker effect. The mean duration of employment in the total study population amounted 8.5 ± 6.1 years in 1999[3]. It is conceivable that employees with more serious symptoms left the greenhouses at a much earlier stage.

Apart from the healthy worker effect, the RQLQ outcomes may also be influenced by the fact that assessment of occupational rhinitis was questionnaire-based. As this analysis was part of a large epidemiological study comprising almost 500 greenhouse workers, we were not able to establish a physician's diagnosis of

rhinitis and asthma. It is possible that subjects, who would not have been formally diagnosed of having occupational rhinitis, are included in this analysis. Moreover, no validated questionnaires for assessment of occupational rhinitis are available. However, in our previous study, bell pepper workers with rhinitis at work reported in 81.5% of the cases substantial improvement or complete remission of symptoms during holidays or weekends [3]. In addition, removal of bell pepper plants resulted in remission of symptoms (expressed in changes of rhinitis-related quality of life)[14]. Finally, in this study, population sensitization to bell pepper pollen appeared to be the only significant factor determining the level of rhinitis-related quality of life[14]. Although, the data do not provide us with a definite diagnosis of occupational rhinitis based on challenge tests, we believe that our study population meets the criteria of a probable occupational rhinitis (suggestive history plus sensitization)[1].

In recent years, the effectiveness of measures to change the indoor environment in the treatment of allergic rhinitis and asthma has been challenged[20]. It is a matter of debate as to whether effective allergen avoidance can be achieved in daily life. In contrast, in occupational allergy, there is general consensus that subjects should completely avoid the occupational agent when the patient is sensitized[21]. Cessation of occupational allergen exposure can be achieved by leaving work. The effect of complete allergen avoidance has been studied in occupational asthma. A systematic review with 38 longitudinal studies on the symptomatic and functional outcomes of occupational asthma after avoidance of exposure to the causative agent was carried out. Proportions of symptomatic recovery varied from 0% to 100%, with a pooled estimate of 32% (95% CI 26% to 38%). Patients with the shortest durations of exposure had the highest recovery (36%; 95% CI 25% to 50%), but the effect was not linear[22].

In contrast, sparse data are available on the effect of cessation of allergen exposure on occupational rhinitis. In a small retrospective study among 39 health care workers allergic to natural rubber latex, over 90% of the participants reported that their nose and eye symptoms had no longer impact on their quality of life after removal of latex from their work environment[12]. The same observation was seen in another retrospective latex study[11]. A cross-sectional study among 119 subjects with occupational rhinitis indicated that those with continuing occupational exposure had worse health-related quality of life when compared to subjects with decreased or eliminated exposure to allergens[10]. As previous allergen exposure at the time of the occupational rhinitis diagnosis (on average 10 years before) was retrospectively

estimated using a visual analogue scale, this study could be subject to recall bias. To our knowledge, only three longitudinal studies – all focused on natural rubber latex allergy – have been published. One study focused on occupational asthma to natural rubber latex. It appeared that 36 subjects with concomitant rhinitis experienced reduction in rhinitis severity after cessation of latex exposure or under reduction of exposure[7]. In another longitudinal study among 1040 health care workers, 20 subjects with occupational rhinitis due to natural rubber latex allergy were identified. Changeover to the use of powder free gloves resulted in improvement of symptoms in 16 out of 20 subjects. In neither study, however, a control group of employees continuously exposed to latex was included. A recent study reported that ten out of 34 latex sensitized health-care workers left their job. This resulted in a significant decrease in the prevalence of work-related rhinitis[6].

The current study clearly shows that bell pepper greenhouse workers with work-related nasal symptoms experience a substantial improvement in rhinitis-related quality of life after leaving the work environment. In a previous study, we demonstrated that rhinitis-related quality of life in these subjects is predominantly associated with sensitization to bell pepper pollen and not to other concomitant sensitizations to common inhalant allergens[14]. Therefore, we consider the improvement in quality of life as a result of cessation of bell pepper exposure. Interestingly, the greenhouse workers reported the most impairment and the largest effects of leaving work in the domains of activities, practical problems, and nasal symptoms. Apparently, these subscales are the most important domains with the largest room for improvement. We already demonstrated that patients with perennial allergic rhinitis to common inhalant allergens perceive sleep disorders and emotions as more important than greenhouse workers do[14]. Possibly, this can be attributed to differences in cultural and social background. Very few studies focus on quality of life in occupational rhinitis[10, 14]. The advantage of quality of life assessment is that an estimation of the burden of occupational disease is provided. Moreover, in allergic rhinitis, quality of life instruments are the best validated outcome measures available. Finally, the use of the RQLQ introduced by Juniper[16] allowed us to evaluate the clinical significance of the changes in quality of life. For those leaving the job, the magnitude of the change exceeded the minimal clinically important difference (MCID) of 0.5[23] in all domains except the subscale of sleep disorders and emotions. The magnitude of the effect of leaving work was comparable to that reported in a previous grass pollen subcutaneous immunotherapy study corrected for the placebo-effect[24] and superior to that

reported in studies investigating the effect of sublingual immunotherapy[25, 26] or antihistamines[27, 28].

In conclusion, the current study is one of the first large longitudinal studies showing that occupational allergen avoidance has a beneficial effect on health-related quality of life in workers with occupational rhinitis. The study suggests that occupational rhinitis can be a reason to leave work.

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4

Influence of occupational allergy in bell pepper horticulture on productivity loss

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Submitted

Abstract

Purpose

Occupational allergy is a health condition that may have a profound effect on work performance through productivity loss at work as well as sick leave and, hence, may result in higher productivity costs. There is limited information on the magnitude of these productivity costs. The aim of this study is to estimate productivity loss and associated costs due to occupational allergy in bell pepper horticulture.

Methods

A cross sectional study was conducted among bell pepper employees in 2007. Information on demographic characteristics, current job characteristics, productivity loss at work on the last regular working day, sick leave in the past 6 months, (work-related) rhinitis, (work-related) asthma symptoms, severity of rhinitis symptoms (through visual analogue scale) was gathered by means of a questionnaire.

Results

In total, 142 bell pepper employees participated. The prevalence of rhinitis, moderate to severe rhinitis, and asthma symptoms was 52.9%, 11.4%, and 20.3%, respectively. Productivity loss at work and sick leave was found in 16.9% and 19.1% of subjects, respectively. Moderate to severe rhinitis symptoms were significantly associated with productivity loss at work (Odds Ratio (OR) = 1.95) and asthma symptoms were significantly associated with both productivity loss at work (OR = 4.55) and sick leave (OR = 5.30). The total productivity loss amounted to 4.6% time lost. In total, the productivity costs of productivity loss per person-year were €1,122.

Conclusion

Occupational allergy can cause substantial productivity loss and, therefore, may result in a significant reduced work performance and higher productivity costs that prompts for interventions to prevent the onset of occupational allergy and treatments that reduce the negative consequences for work among those with occupational allergy.

Introduction

Occupational allergy is a health condition that may have consequences on work performance through productivity loss. Productivity loss is a combination of productivity loss at work due to presence of health problems and of days absent from work due to health problems[1-2].

This productivity loss has economic consequences, since it causes higher productivity costs. Moreover, these costs may even exceed the direct medical costs of occupational allergy[3]. Both asthma and rhinitis have shown to contribute to productivity loss due to sick leave as well as on-the-job productivity loss[4-10]. However, the contribution of occupational rhinitis and asthma to productivity loss is largely unknown, since earlier studies on productivity loss were focused on rhinitis and asthma in general and not on occupational airway diseases. Focusing on the latter would give a more precise indication of the actual productivity loss in a specific population at work. Therefore, it is essential to study the influence of occupational allergy (rhinitis and asthma symptoms) on productivity loss in a specific workforce.

Since it is known that the prevalence of occupational allergy (sensitization and symptoms) among bell pepper employees is high[11], this occupational group is evidently suitable to study possible productivity loss due to an occupational allergy. A cross sectional analysis (which was part of a larger longitudinal study[11-12]) was performed among 142 bell pepper employees. Allergy characteristics (*i.e.* atopy and sensitization to bell pepper pollen) of subjects participating in this cross sectional analysis were comparable with the population at baseline in 1999 (31.4% *vs* 37.5% and 29.9% *vs* 27.5%). Although a healthy worker effect (HWE) seemed to have occurred[11], the prevalence of sensitization to bell pepper pollen was still high in the present study population.

The aims of this study were twofold: (1) to study productivity loss due to occupational allergy (work-related rhinitis and work-related asthma symptoms) in bell pepper employees expressed as productivity loss at work and sickness absence, and (2) to estimate the productivity costs associated with this productivity loss.

Material and Methods

Study population and design

From March to September 2007, a cross-sectional study was conducted among 142 bell pepper employees. This study was part of a larger longitudinal study in bell pepper horticulture in the Netherlands[11-12]. Bell pepper greenhouses who participated in the cross-sectional survey in 1999 were approached by telephone and asked to take part in a second survey. Subsequently, the investigators paid a visit to the greenhouses. During the visits the employees gave their written informed consent. The study was approved by our Hospital Medical Ethical Committee. Confidentiality was maintained.

Questionnaire

A questionnaire was administered on gender, age, smoking habit, job characteristics (owner *vs* employee - full time/part-time/seasonal employment, duration of employment), productivity loss (productivity loss at work, sickness absence), work history, (work-related) rhinitis and asthma symptoms. Subjects were labeled as having work-related rhinitis symptoms if they reported any of the following items: sneezing, rhinorrhoea, nasal itching, or nasal obstruction after occupational exposure. Similarly, if subjects reported either wheezing, coughing, sputum, or shortness of breath after occupational exposure, they were labeled as having work-related asthma symptoms[11]. Severity of nasal symptoms was assessed by rating overall nasal symptoms over a 1-week period on a visual analogue scale (VAS) (0-10 cm, 0 representing absence of symptoms and 10 representing a high intensity of symptoms). In accordance with Bousquet *et al.* the visual analogue scale was also used to discriminate between mild and moderate/severe allergic rhinitis, by using a cut-off level of 5 cm[13-14].

Productivity loss at work and sick leave were primary outcome measures. Productivity loss at work was measured with the quantity scale of the Quantity and Quality (QQ) method, by a question about productivity loss at work on the last regular working day[15-17]. Respondents were asked to indicate, on a 10-point numerical scale, how much work they had actually performed during regular hours as compared with normal (0 representing 'nothing' and 10 representing 'normal quantity'). The productivity loss on the last working day for each employee was expressed as proportion relative to the normal production (0/10, 1/10 etcetera) and the total productivity loss (%) was subsequently calculated by adding up

the losses of all employees. Since not all employees were employed at full time base, the different types of jobs had to be taken into account (full time employee, part-time employee, and seasonal employee) by multiplying these productivity losses by 1.0, 0.4, and 0.5, respectively (these figures were estimated by means of a telephonic survey done by the Commodity board horticulture 2007). The total on-the-job productivity loss was expressed as percentage of time lost per person-year of work in the bell pepper horticulture. In their study Meerding *et al.* showed that the self-reported productivity in the QQ instrument correlated significantly with objective work output ($r = 0.48$)[18].

Sick leave was measured by a question on the duration of sick leave for any disease in the past 6 months[16]. For the duration of sick leave, patients reported on a 4-point scale whether they experienced no sick leave, 1-7 days, 8-14 days, or >2 weeks of sick leave. These questions have shown high specificity (91%), high sensitivity (79%), and moderate agreement with registry data (K = 0.50 and 0.54, respectively). A crude estimate of the total sick leave in the last (calendar) year was made by using the mid-point values of each category of sick leave duration (these were 0, 4, 11, and 21 days, respectively) for each individual employee, counting up those values and multiplying it by 2. Again, multipliers were used for full time employee (1.0), part-time employee (0.4), and seasonal employee (0.5) to estimate the total sick leave per calendar year. The total sick leave was expressed by the number of days of sick leave per person-year and subsequently converted into a percentage of time lost per person-year of work in the bell pepper horticulture.

The total productivity loss as percentage of time lost per person-year, the result of both on-the-job productivity loss together with sick leave, was calculated by counting up both percentages of time lost.

Statistical analysis

Descriptive statistics were used and the spearman correlation coefficient was used for the correlation between productivity loss at work and sick leave.

The variable 'productivity loss at work' was not normally distributed and, therefore, dichotomised. A productivity score of 10 was labelled as having no productivity loss at work. A productivity score of 9 or less was labelled as productivity loss at work[17-18].

Duration of sick leave was also not normally distributed and, thus, dichotomised into those subjects with any sick leave in the past months and those workers without sick leave.

A logistic regression analysis was applied to study determinants for the primary dichotomous outcomes measures, *i.e.* productivity loss at work and sick leave. The odds ratio (OR) was used as measure of association. For these primary outcome measures the following independent variables were used: individual characteristics (gender, age, smoking), job characteristics (job classification, duration of employment), (work-related) rhinitis symptoms, VAS rhinitis (dichotomised into mild versus moderate to severe), and presence of (work-related) asthma symptoms. In the first step in the analysis, all possible univariate associations were investigated. In the second step with multivariate models, univariate associations with a *P* - value below 0.10 were considered and only variables with a *P* - level below 0.05 were retained. The statistical analysis was executed using the SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA).

The proportion of productivity loss (productivity loss at work and sick leave) at population level attributable to (work-related) rhinitis and asthma symptoms was estimated by population attributable fractions. These population attributable fractions (PAFs) were calculated using the formula PAF=Pe (OR-1)/(1+Pe(OR-1)), whereby Pe is the prevalence of rhinitis or asthma in the study population and OR is the association of rhinitis or asthma with productivity loss at work or sick leave[19-20].

Economic analysis on productivity costs

The costs of productivity loss at work and sick leave were expressed per person-year of work in bell pepper horticulture. First, the salary costs per person-year were calculated by multiplying the average employee salary costs per hours (€12.24) by the total hours during a regular working week (38 hours) and by the number of weeks per year (52) (Salary information, collective agreement, Commodity Board, 2007). These salary costs do not cover the employer's premiums for social security and pension scheme, which amount to at least 38% on top off the direct salary costs. Second, the productivity costs were estimated by calculating the salary costs for on-the-job productivity time lost and sickness days per person-year of work in bell pepper horticulture.

Results

The baseline population in 1999 consisted of 472 subjects. In 2007, 154 subjects who were still at work in bell pepper horticulture could be traced. In total, 142 out of those 154 subjects were willing to participate in the study (Table 1). Reasons to refuse participation were lack of time or interest. Most workers were male (86%) and their mean age was 46.2 years, ranging from 21 to 78 years. The mean duration of employment was 17.8 years (9-47 years) and 67 (46%) were owners. Rhinitis, moderate to severe rhinitis, and asthma symptoms were reported by 52.9%, 11.4%, and 20.3%, respectively. In total, 16.9% of subjects (n = 24) experienced reduced productivity at work on the last working day and 19.1% of subjects (n = 27) reported sickness absence during the last 6 months. The total on-the-job productivity loss per person-year in this occupational group was 3.8% and total number of days of sick leave per person-year was 2.2 days (0.8%). A weak correlation of 0.22 (P = 0.008) was found between sick leave and productivity loss at work, indicating that these two variables were correlated to some extent.

Table 1. Population characteristics.

	Employees ***n*** **= 142**
Gender (male)	122 (85.9%)
Age (mean years)	46.2
Smoking	29 (20.4%)
Job classification (owner)	67 (47.2%)
Duration of employment (mean years)	17.8
Moderate to severe rhinitis	16 (11.4%)*
Rhinitis symptoms	74 (52.9%)*
Asthma symptoms	28 (20.3%)#
Productivity loss at work	24 (16.9%)
Sick leave	27 (19.1%)$

*2 missing, #4 missing, $1 missing

In the univariate analyses duration of employment (OR = 0.93), moderate to severe rhinitis symptoms (OR = 2.73) and asthma symptoms (OR = 3.32) were associated with productivity loss at work (Table 2). When controlled for duration of employment and job classification, both moderate to severe rhinitis symptoms (OR = 1.95) and asthma symptoms (OR = 4.55) were still significantly associated with productivity loss at work (Table 3). In the univariate analyses duration of employment (OR = 0.91), job classification (owners OR =0.10) and asthma symptoms (OR = 2.68) were associated with sick leave (Table 2). When controlled

for duration of employment and job classification, asthma symptoms (OR = 5.3) were still significantly associated with sick leave (Table 3).

Table 2. Univariate analysis of individual and current job characteristics and allergy symptoms on productivity loss at work and sick leave.

Determinants	Productivity loss at work Odds Ratio (95% CI)	Sick leave Odds Ratio (95% CI)
Rhinitis	1.78 (0.82-43.89)	1.10 (0.56-2.17)
Moderate / Severe rhinitis	2.73 (1.26-5.92)**	0.64 (0.17-2.46)
Asthma symptoms	3.32 (1.67-6.62)**	2.68 (1.40-5.10)**
Gender (male)	1.28 (0.39-4.22)	2.04 (0.70-5.93)
Age	1.03 (0.99-1.08)	0.99 (0.95-1.04)
Smoking	1.91 (0.70-5.21)	1.54 (0.58-4.12)
Job classification (owner)	0.62 (0.25-1.53)	0.10 (0.03-0.34)**
Duration of employment	0.93 (0.85-1.01)*	0.91 (0.84-0.99)**

** $P < 0.05$, * $P < 0.10$

Table 3. Multivariate analysis of rhinitis and asthma symptoms (at work) on productivity loss at work and sick leave.

Determinants	Productivity loss at work Odds Ratio (95% CI)	Sick leave Odds Ratio (95% CI)
Moderate / Severe rhinitis	1.95 (1.09-3.48)*	1.04 (0.42-2.62)
Duration of employment	0.93 (0.86-1.02)	0.94 (0.85-1.02)
Job classification	0.78 (0.30-2.07)	0.12 (0.03-0.43)*
Asthma symptoms	4.55 (1.70-12.20)*	5.30 (1.72-16.31)*
Duration of employment	0.966 (0.88-1.04)	0.95 (0.87-1.05)
Job classification (owner)	0.67 (0.25-1.81)	0.085 (0.02-0.33)*

* $P < 0.05$

The contributions of (moderate to severe) rhinitis and asthma to productivity loss at work were 0.09 and 0.42, respectively. The respective population attributable fractions of sick leave were 0.02 and 0.46.

The total productivity loss amounted to 4.6% time lost. The total productivity costs per person-year of work in bell pepper horticulture were estimated at €1,122 and comprised of 82% productivity loss at work and 18% productivity loss due to sick leave. On top of these productivity costs the employer's premiums for social security and pension scheme of about €440 per person-year must be taken into account. About half of the productivity loss could be attributed to work-related rhinitis and asthma symptoms.

Discussion

In this study the prevalence of on-the-job productivity loss and sick leave was 16.9% and 19.1%, respectively, which resulted in a total time lost of 4.6%, being approximately €1,100 per person-year work in the bell pepper horticulture. About half of the productivity loss could be attributed to work-related rhinitis and asthma symptoms.

Earlier studies on on-the-job productivity loss in other occupational groups reported various levels of productivity loss. For example, Meerding *et al.* showed that a reduced productivity at work due to health problems was prevalent in 5-12% of construction workers and industrial workers. They reported an on-the-job productivity loss of 1-3% of total work time, which is somewhat lower compared to our study (3.8%)[18]. Also higher levels of on-the-job productivity loss have been reported. A study among 2252 workers in 24 different companies in the Netherlands on self reported productivity loss, about 45% of the workers reported some degree of productivity loss on the previous working day[21], resulting in a total time lost in the population of about 5.0%. Thus, the level of on-the-job productivity loss of our study population lies within the range of reported productivity losses due to illness in other occupational groups.

It is, however, remarkable that rhinitis and asthma appear to be largely responsible for the specific productivity loss found in our study. The high OR together with the high prevalence of rhinitis and asthma in this specific workforce (resulting in the high PAFs) accounts for this substantial contribution. Since rhinitis symptoms and asthma symptoms appeared to be work-related in respectively 93% and 75% of the cases, we hypothesize that the PAFs mainly concerns work-related rhinitis and asthma symptoms.

The questions used to identify subjects with occupational allergy do not strictly distinguish between (the broader issue of) work-related symptoms and occupational allergy. However, work-related symptoms together with the high prevalence of sensitization to bell pepper pollen in this study population support the hypothesis that symptoms mentioned are mainly due to a true IgE-mediated occupational allergy. Other (temporary) airway complaints, for example airway irritation or influenza, could possibly form a bias. Again, the high prevalence of

sensitization to bell pepper pollen, provides evidence for the assumption that mainly occupational allergy is responsible for symptoms at work.

Notably, the average sick leave per person-year of 2.2 days is lower than reported for other occupational groups. For example, the Netherlands Working Conditions Survey of 2007 showed that 50% of employees reported sick leave during the past year with an average sick leave of 7.5 days per person-years[22]. Goetzel *et al.* have described an average sick leave of 8.2 and 12.0 days per person-year for respectively allergy and asthma[3]. Lamb *et al.* found that the number of days of sick leave due to allergic rhinitis mounted 3.57 days per person-year[3]. Since both Goetzel and Lamb focus on specific patient groups instead of occupational groups (with a substantial number of healthy subjects) it is to be expected they find a higher level of sick leave per person-year. The low sick leave in our study population may also be explained by the fact that almost half of our study population was owner of the greenhouse and this reduced sick leave substantially as can be seen from both the univariate and multivariate analysis. Furthermore, although (work-related) rhinitis and asthma contributed to productivity loss, this effect might be lessened by a HWE since the mean duration of employment was 17.8 years. It is conceivable that greenhouse workers with severe occupational rhinitis or asthma already left their job. The ORs of 0.93 and 0.91 representing the association between duration of employment and productivity loss at work and sick leave in the univariate analysis indeed strongly suggest the presence of a HWE. Moreover, it is known from our previous study that bell pepper employees will not easily admit to their impairment because of commitment to the job[11]. Apparently, they do not report sick but for the greater part keep on working in spite of their symptoms.

We found that asthma is associated with both on-the-job productivity loss and sick leave. These findings are compatible with earlier reports in literature[4-5, 7, 10]. Rhinitis on the other hand does have an impact on the on-the-job productivity loss without any effect on sick leave. Other studies have also described stronger associations between allergy and on-the-job productivity loss than between allergy and sick leave[3, 8]. We further demonstrated that moderate to severe rhinitis but not mild rhinitis is associated with on-the-job productivity loss. Similarly, Bunn and colleagues found that on-the-job productivity loss for workers with modest allergy did not differ from healthy subjects, but the productivity consistently and progressively declined as severity of allergy symptoms increased[23].

In this study we estimated the costs of productivity loss among bell pepper workers. In total, the productivity costs of productivity loss per person-year were €1,122 and comprised of €919 for productivity loss at work and €203 for sick leave. About half of costs of productivity loss could be attributed to work-related rhinitis and asthma symptoms (€566). These findings are in line with the estimated costs for productivity loss at work of $222 per person-year by Goetzel *et al.*, for sick leave and productivity loss at work of $593 per person year by Lamb *et al.*, and for sick leave ($597 - $1,024) and for on-the-job productivity loss ($ 658 - $1,808) per person year by Joshi *et al.*[3, 7-8]. One has to bear in mind that our estimates are based on workers with a long working history in bell pepper cultivation. Since rhinitis and asthma may be a cause to change jobs outside this particular cultivation[11], these costs may underestimate the economic consequences of occupational allergy among workers with shorter employment.

Conclusion

In this specific bell pepper cultivation workforce total time lost per person-year mounted to 4.6%. In total, the productivity costs of productivity loss per person-year were €1,122. About half of the productivity loss could be attributed to work-related rhinitis and asthma symptoms.

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5

Natural rubber latex allergy among health care workers: significant reduction of sensitization and clinical relevant allergy after introduction of powder-free latex gloves

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Submitted

Abstract

Background

An IgE mediated allergy to natural rubber latex (NRL) is a serious occupational health problem. Health care workers (HCWs) are especially at risk due to their frequent contact with rubber gloves. The aim of the study was to estimate the prevalence of NRL sensitization and NRL allergy, among operating room employees, before and 10 years after the introduction of powder-free low protein NRL gloves.

Methods

Surgical NRL glove wearing operating room employees were asked to participate in a cross sectional study at two occasions (1998 and 2009). Information on demographic and job characteristics and (work-related) respiratory allergy symptoms were gathered by means of a questionnaire. Skin prick tests with allergen extracts were performed including NRL glove extract(s) used in the operating rooms and cross-reacting foods such as kiwi, avocado, banana; and common inhalant allergens. Blood samples were taken for specific IgE analysis.

Results

In 1998 and in 2009, respectively, 163 and 178 employees participated in the study. The two groups were comparable concerning gender, smoking habits, job classification, work-related symptoms and atopy. In 2009, the prevalence of sensitization to NRL was significantly lower compared to 1998 (4.5% *vs* 14.1%). Also, NRL allergy was significantly less present in 2009 compared to 1998 (2.8% *vs* 9.8%). The same trend was seen in a subgroup ($n = 49$) which participated in both 1998 and 2009. Atopy was significantly associated with the development of sensitization to NRL.

Conclusion

This study provides a clear indication that the introduction of powder-free low protein NRL surgical gloves in 1998 is most likely responsible for the reduction in NRL sensitization and NRL allergy prevalence found in 2009.

Introduction

Natural rubber latex (NRL) hypersensitivity among healthcare workers is a well-known and acknowledged occupational disease. An IgE mediated allergy to NRL can induce reactions ranging from (work-related) urticaria and rhinoconjunctivitis to asthma and even anaphylactic shock and is therefore a serious health problem. Healthcare workers (HCWs) and especially employees in operating rooms, are at risk due to their frequent contact with rubber gloves[1-6].

Powder (from maize meal) in powdered NRL gloves plays an important role in the sensitization process in glove wearing employees, since latex allergen can bind to it. When this powder subsequently becomes airborne, employees are exposed to latex allergen and sensitization can occur via inhalation[7-10].

The use of protective gloves by HCWs has increased since the era of acquired immunodeficiency syndrome (AIDS). This increase has led to numerous undesirable cutaneous and mucosal effects, such as IgE mediated reactions to NRL gloves. In the 1990s, the reported prevalence of NRL allergy in HCWs was high, ranging up to 15%[1, 4, 6, 11-12].

Several studies have shown that in recent years the incidence of (suspected) NRL allergy among HCWs has decreased[4, 12-15]. This decrease in new cases has been attributed to an overall reduction in NRL exposure by the large-scale introduction of low-allergen (often powder-free) NRL gloves or non NRL gloves in health care facilities[4, 12-15].

Few studies have compared the prevalence of NRL allergy among HCWs before and after the introduction of powder-free NRL gloves[16-17]. If the NRL allergy prevalence among a group of HCWs is nowadays significantly lower compared to the period when powdered NRL gloves were used, this would accumulate evidence to support the effectiveness of the introduction of powder-free low protein NRL gloves.

The first cross-sectional studies among personnel from the Erasmus MC, a university hospital in Rotterdam, the Netherlands, were conducted in 1998. Among employees of the immunology department, wearing powdered examination gloves, a prevalence of NRL sensitization of 8.3% was found[11]. A second survey was conducted among employees in the operating rooms, showing a prevalence

of NRL allergy of 9.8%[18]. On account of these results throughout the hospital, powdered NRL examination gloves were replaced by powder-free low protein NRL gloves and non NRL (nitrile) examination gloves. For specific personnel of operating rooms the powdered NRL sterile surgical gloves were replaced by powder-free low protein NRL gloves. These changes took place in the period 1998 to 1999.

The aim of the current study was to estimate the change in prevalence of NRL sensitization and allergy among operating room employees from the Erasmus MC 10 years after the introduction of sterile powder-free low protein NRL gloves (1998 and 2009). In addition, possible determinants of NRL sensitization and allergy were investigated.

Material and Methods

This study evaluates the effect of the intervention throughout repeated cross-sectional surveys pre and post intervention with a 10 year time lag. In 1998[18] and 2009, two cross-sectional studies were performed among operating room employees (*i.e.* operating room nurses, nurse anaesthetists and anaesthetists) from the Erasmus MC. Part of the study population in 2009 also participated in the first cross-sectional study in 1998. During the visits, the employees gave their informed consent. An extensive questionnaire was administered on gender, age, smoking habit, job characteristics, atopic complaints, and allergic symptoms at work, *i.e.* work-related urticaria, angioedema, rhinitis and asthma symptoms (including symptoms related to NRL glove use). Subjects were labeled as having work-related rhinitis symptoms if they reported any of the following items: sneezing, rhinorrhoea, nasal itching, or nasal obstruction after occupational exposure 18. Similarly, if subjects reported either wheezing, coughing, sputum, or shortness of breath after occupational exposure, they were labeled as having work-related asthma symptoms[18]. Questions were asked on complaints following eating foods known for crossreactivity with NRL. Sensitization to NRL allergen, cross reacting fruits (kiwi, avocado, and banana) and common inhalant allergens was determined by means of skin prick tests. Blood samples were taken for CAP-FEIA tests. The study was approved by our Hospital Medical Ethical Committee. Confidentiality was maintained.

Primary outcome measures were the prevalence of NRL sensitization and the prevalence of clinical relevant NRL allergy in 1998 and 2009, respectively. Clinically relevant NRL allergy was defined as NRL sensitization in combination with allergic symptoms at work, *i.e.* urticaria, angioedema, rhinitis, asthma symptoms and/or anaphylaxis.

In 1998 the operating room nurses, the anaesthetists and the nurse anaesthetists all used NRL powdered (sterile and/or examination) gloves. In 2009 the operating room nurses and the anaesthetists used the sterile surgical powder-free low protein NRL gloves as well as the nitrile (non NRL) examination gloves, whereas the nurse anaesthetists only used the nitrile (non NRL) examination gloves.

Skin tests

Skin prick tests were carried out according to international guidelines[19-20] and performed by a skilled allergy nurse. In addition, reactions were expressed in mean wheal diameter of the longest diameter and the orthogonal diameter. A diameter of 3 mm or more was considered positive[21].

Allergens

The NRL allergens for prick testing were prepared by extracting pieces, cut from a pair of gloves, in phosphate-buffered saline (PBS), pH 7.4, containing 0.03% human serum albumin and 0.5% phenol during 72 hours at 4°C. After centrifugation at 3000 g, 15 min, supernatants were collected and dialysed with a 3,500 d molecular weight cut-off membrane (Molecularpouros Dialyses Membrane, Spectrum, California) against deionized water for 72 hours. The dialysate was centrifuged at 13000 g for 15 minutes, and the supernatants were sterilized with a 0.22 microm Millex GS filter (Millipore, the Netherlands) and freeze-dried. A 1% solution in PBS was made of the freeze-dried material[34].

Five types of gloves were used for skin testing in 1998 and one type (Latex Examination Glove (powdered), Romed) was tested in 2009, since this glove appeared to be associated most strongly with sensitization to NRL allergens in 1999 18. These gloves included:

- Latex Examination Gloves (powdered), Romed, Omnilabo, the Netherlands (1998 and 2009);
- Sterile Latex Surgeon's Gloves (powdered), Baxter Healthcare Corporation, Valencia, USA (1998);

- Sterile Latex Surgeon's Gloves (unpowdered), Nutex, Ansell Medical Lameris Veenendaal, The Netherlands (1998);
- Sterile Latex Surgeon's Gloves (unpowdered), Regent Hospital Products, Medeco, Oud Bijerland, The Netherlands (1998);
- Latex Examination Gloves (unpowdered), Ansell Medical Lameris Veenendaal, the Netherlands (1998).

The protein content was determined by the method of Watanabe using Pyrogallol Red Molybdate complex[35]. The protein concentrations of the five gloves extracts (1% w/v), used in skin prick testing, were in the range of 5.5 - 7.4 g/L.

From the glove powder (Absorbable Dusting Powder, Keoflo 7136P-USP, van der Bend BV, Brielle, the Netherlands), a 10% extract (w/v) was made in PBS. After 1 hour the extract was centrifuged for 10 minutes at 2000 g and supernatant was passed through a 0.22 microm filter.

Kiwi, avocado and banana extracts were prepared from small ripe pieces of the fruits without peel or core. The pulps were homogenized in a food processor and the slurries were passed through a 0.22 µm Filter Unit. All extracts were stored in appropriate aliquots at -20°C until use in skin prick tests. Before use, extracts were defrozen during 1 hour before the skin test and centrifuged for 45 seconds at 3200 g.

Also prick tests were performed with common inhalant allergens from ALK Abello (Nieuwegein, the Netherlands): grass mix (SQ 293), tree mix (SQ 108), *Dermatophagoides pteronyssinus* (SQ 503), cat dander (SQ 555) and dog dander (SQ 553). Dilution buffer served as a negative control, histamine chloride (10 mg/ml) as a positive control.

CAP-FEIA

Allergen specific IgE was determined by the CAP-FEIA (k82 *Hevea braziliensis*).

Statistical analysis

In the statistical analysis, the primary outcomes in both cross-sectional studies (NRL sensitization and clinical relevant NRL allergy) were compared. In addition, it was analyzed whether the 2 studies were comparable with regard to potential determinants of NRL sensitization and clinical NRL allergy (*i.e.* individual and job

characteristics, atopy, work-related symptoms, sensitization to cross-reacting fruits).

Differences between continuous variables were tested with the unpaired Student t-test. Differences between frequencies of categorical variables were tested with the chi-square test (χ^2). The significance level α was set at 0.05. All statistical analyses were executed using the SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

In both cross-sectional studies, approximately two third of the operating room work force participated: 163 employees took part in 1998 and 178 employees participated in 2009. Reasons for non-response were lack of time or interest, fear for skin prick tests or for drawing blood for specific IgE analysis, or absence because of holiday, illness or duty-schedule.

Information on possible determinants for NRL sensitization and for clinical NRL allergy (*i.e.* individual characteristics, job characteristics, atopy, work-related symptoms and on sensitization to cross-reacting fruits) was compared between the first cross-sectional study and the second cross-sectional study (Table 1). No significant difference was found for the determinants gender, smoking habits, job classification, work-related symptoms and atopy. The average age was significantly higher in the second cross-sectional study (40.7 years *vs* 37.6 years).

Table 1. Individual and job characteristics and allergy (symptoms) of participants in 1998 *vs* 2009.

	Participants 1998 ***n* = 163**	**Participants 2009** ***n* = 178**
Gender (female)	133 (81.6%)	144 (80.9%)
Age (mean years)*	37.6	40.7
Smoking – yes	42 (25.8%)	41 (23.0%)
Job classification	Operating room nurse: 98 (60.1%)	Operating room nurse: 99 (55.6%)
	Anaesthetist: 13 (8.0%)	Anaesthetist: 21 (11.8%)
	Nurse anaesthetist 52 (31.9%)	Nurse anaesthetist 58 (32.6%)
Work-related symptoms	57 (35.0%)	50 (28.1%)
Atopy	73 (44.8%)	88 (49.4%)

* $P < 0.05$

The prevalence of NRL sensitization and clinical relevant NRL allergy in the two cross-sectional studies were compared (Table 2). In 2009, significantly fewer employees were sensitized to NRL (4.5% *vs* 14.1%) and significantly fewer employees had NRL allergy compared to 1998 (2.8% *vs* 9.8%). Furthermore, fewer employees were sensitized to 1 or more of the cross reacting fruits ($P = 0.057$) (Table 2). Among the complete study population ($n = 292$) subjects with atopy had increased risks for NRL sensitization (Odds Ratio (OR) 3.9, $P = 0.003$) and clinical NRL allergy (OR 2.6, $P = 0.058$). Job classification was not significantly associated with NRL sensitization or clinical relevant NRL allergy in both surveys.

Table 2. Primary outcomes of participants in 1998 versus 2009.

	Participants 1998 $n = 163$	**Participants 2009 $n = 178$**
Sensitization to NRL**	23 (14.1%)	8 (4.5%)
NRL allergy **	16 (9.8%)	5 (2.8%)
Sensitization to * cross reacting fruits	43 (26.4%)	32 (18.0%)

** $P < 0.05$
* $P < 0.10$ ($P = 0.057$)

Forty nine employees participated in both cross-sectional studies. The prevalence of NRL sensitization and NRL allergy among these employees was respectively 12% ($n = 6$) and 10% ($n = 5$) in 1998 and 6% ($n = 3$) and 4% ($n = 2$) in 2009. In 2009, 5 out of 6 employees had lost their NRL sensitization and 2 employees had developed a new NRL sensitization.

Discussion

In this study a significant reduction of sensitization to NRL among operating room personnel was found in 2009 compared to 1998 (4.5% *vs* 14.1%). Also, NRL allergy was significantly less prevalent in 2009 compared to 1998 (2.8% *vs* 9.8%). As expected, atopy appeared to be a risk factor for NRL sensitization.

Before the introduction of powder-free low-NRL protein gloves, the prevalence of sensitization to NRL among the operating room personnel was 14.1% (1998). This percentage is in line with other studies on the prevalence of NRL allergy performed in the (early) nineties. In a large epidemiologic study among 1351 hospital workers, Liss *et al.* found a prevalence of NRL sensitization of 12.1%[4]. In a study among 101

employees of an Institute of Anesthesiology, 16 (15.8%) persons had a positive skin test to NRL[22]. Lagier *et al.* reported positive skin tests to latex allergen among 21 of 197 (10.7%) operating room nurses[6]. Mace *et al.* also tested operating room nurses (n = 274); 6.9% had positive skin prick tests to latex extracts[1].

When it became apparent that powder in NRL gloves played an important role in the sensitization process in glove wearing employees[7-8, 10], several studies were performed to demonstrate that the use of powder-free NRL gloves could reduce the airborne NRL component and thus reduce the risk for NRL sensitization. For example, Allmers *et al.* found that substitution of powdered NRL gloves by powder-free NRL gloves or synthetic non NRL gloves caused a fast reduction (within 24 hours) of NRL aero allergen levels (below detection level)[23]. Likewise, Tarlo and colleagues[7] showed that NRL levels were below the level of detection in a hospital haematology laboratory, where employees used powder-free NRL gloves. Furthermore, Baur *et al.* indeed found that sensitization to NRL in a group of hospital workers only occurred when they had worked in areas where the aerosol concentration exceeded certain levels (0.6 ng/m^3)[24]. A longitudinal study among dental school students using powder-free NRL gloves also demonstrated that no student developed new NRL sensitivity during 5 years of study[13]. Also, population based studies describe a correlation between the introduction of powder-free NRL gloves and a decline of (suspected) occupationally caused NRL allergy. For example, Allmers *et al.* found that the suspected new occupational NRL allergy cases in Germany steadily declined since 1998, the year that the purchase of powder-free NRL examination gloves exceeded that of powdered gloves for the first time[14]. Tarlo and Liss reported that despite the effect of increasing recognition, the introduction of gloves with reduced powder, protein, or both, as well as other interventions, was associated with a decline in the number of cases of NRL-caused occupational asthma in Ontario, Canada[25]. Tarlo *et al.* described that the number of workers from a teaching hospital in Ontario identified with NRL allergy rose annually until 1994, but decreased markedly after a change to powder-free lower protein NRL examination gloves (1995) and sterile gloves (1997)[15].

Bearing this in mind, we hypothesize that the reduction in prevalence of NRL sensitization and allergy among the operating room personnel, found in our study, is (for the greater part) caused by the introduction of powder-free low protein NRL gloves in 1998. Another repeated cross-sectional study on the prevalence of NRL sensitization among HCWs, performed by Saary *et al.*, also showed a significant

reduction in the prevalence of NRL sensitization after the introduction of powder-free gloves[16]. Students and staff members from a dental school were subject to allergy testing twice, before and after changes in NRL gloves. Of 97 subjects who underwent skin prick testing, 3 (3%) had positive skin prick test responses to NRL in 2000; this compared with 13 (10%) of 131 subjects in 1995. The prevalence of NRL sensitization found in our study in 2009 (4.5%) is in accordance with this study.

On the other hand, Schmid *et al.* observed a significant increase in NRL sensitization among dental students, *i.e.* from 8.7% in 1990 to 17.3% in 2000 despite the introduction of NRL powder-free gloves[17]. They ascribed this rise to an increasing non-occupational sensitization to NRL since the preclinical sensitization rate was high and no dependency on occupational NRL contact during education was found. Since the clinical relevant NRL allergy percentage decreased from 5.3% to 1.3%, they concluded that although the use of NRL powder-free gloves may not prevent sensitization, the appearance of complaints can however be prevented.

As expected, atopy appeared to be a risk factor for NRL sensitization, which corroborates other studies on the role of atopy in NRL sensitization[1, 4, 22, 26]. Furthermore, sensitization to 1 or more of the cross-reacting fruits was associated with NRL sensitization. This finding has been frequently reported in the literature[1, 4, 27-31].

Job classification (1998 and 2009) was not significantly associated with NRL sensitization or NRL allergy, indicating that an operating room nurse, who nowadays mainly wears NRL powder-free gloves, does not have a significant higher risk for developing NRL sensitization compared to a nurse anaesthetist, who nowadays mainly uses NRL-free nitrile (examination) gloves.

Interestingly, in the small sample of 49 workers with repeated participation 2 employees developed a NRL sensitization. The first case was an anaesthetist who had worked with NRL gloves for 20 years already. The second employee, an operating room nurse, not only developed a NRL sensitization, but also reported symptoms upon contact with NRL and was thus considered to be NRL allergic. She had been working with NRL gloves for 35 years in total. An explanation for the fact that both employees eventually became sensitized to NRL can be the accumulating exposition (of many years) to NRL. Although this argument can hold true for these individual cases, no significant association however was found

between years of exposure and NRL sensitization or allergy in the first part of the cross-sectional study (1998).

A systematic review from 2006[5] did not present clear evidence for the effect of the use of powder-free NRL gloves in terms of protection against development of NRL allergy. A recently published review[32] concluded that the use of low-protein, low- allergenic, powder-free gloves is associated with a significant decrease in the prevalence of type I allergic reactions to NRL among HCWs. The results of our study support the conclusion that the risk for NRL sensitization is strongly diminished by using powder-free low protein NRL gloves.

This study has some limitations. As the analysis of the first cross-sectional study was based on skin test results only, we also used skin tests as our main diagnostic tool to estimate the prevalence of sensitization to NRL in the study group of the second cross-sectional study. In the first study only 2 out of 23 subjects with a positive skin test showed specific IgE to NRL, whereas 1 patient with specific IgE did not react to a skin test with NRL extract. We also encountered such discrepancies in the second cross-sectional study (data not shown), and thus we restricted ourselves to the analysis of skin tests. This strategy is in line with previous observations underwriting the better diagnostic performance of skin tests with NRL extract[33]. However, the discrepancies in both cross-sectional studies warrant further investigation to understand the relationship between the different diagnostic tools.

In conclusion, we found a significant reduction of both NRL sensitization and clinical relevant NRL allergy among operating room personnel of an academic hospital, 10 years after the large-scale introduction of powder-free low protein NRL gloves. Although the risk for NRL sensitization or allergy has not entirely been banned out, this study provides a clear indication that the risk for sensitization is strongly diminished by using powder-free low protein NRL gloves.

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6

Occupational allergy in strawberry greenhouse workers

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Abstract

Background

Employees in strawberry greenhouses are highly exposed to several (potential) allergenic agents. However, no occupational allergy in this branch has been described before. First, the presence of work-related allergic symptoms in strawberry workers was explored. Second, we aimed to prove the concept that an IgE mediated allergy could be responsible for work-related symptoms. To test the possibility of an IgE response secondary to cross-reactivity to birch or grass pollen, inhibition experiments were additionally performed.

Methods

First, a questionnaire survey concerning work-related allergic symptoms among strawberry workers in the Netherlands was carried out. Second, 3 workers with work-related symptoms were investigated in detail. Skin tests, serum-specific IgE tests with home made extracts of strawberry pollen and other possible allergenic agents of the strawberry glasshouse environment were executed. Furthermore, immunoblots and nasal provocations with strawberry pollen extract were performed. In addition, inhibition experiments were performed.

Results

29 of 75 questionnaire respondents (38.7%) reported work-related symptoms. Sensitization to strawberry pollen was found in skin tests in all 3 employees with work-related symptoms. ELISA and immunoblotting with strawberry pollen showed positive results in 2 employees. Birch and grass pollen failed to inhibit IgE binding to strawberry pollen in 1 of 2 employees. Partial inhibition was seen in the second employee. Nasal provocation validated clinically relevant allergy to these pollen in 2 of 3 subjects.

Conclusions

Allergic symptoms attributable to the workplace are present among a proportion of strawberry greenhouse employees. An IgE mediated occupational allergy to strawberry pollen may contribute to these symptoms.

Introduction

The prevalence of occupational allergy has increased over the past few decades[1]. Pollen from flowers and bell pepper plants cultivated in greenhouses are known causes of this type of allergy[2-6].

In the last 10 years, strawberry cultivation in the Netherlands shifted from open field horticulture towards greenhouses. In 2006, the size of strawberry horticulture was estimated at 245 ha, divided among 710 greenhouses. The workforce consists of approximately 3500 people.

Strawberry plants grow in rows in boxes at 150 cm height. Work activities comprise pulling blossoms of a plant towards the pathway to improve exposure to light and to facilitate harvesting. These activities take place from April to June and from October to December. While performing these particular activities, large amounts of pollen are released. Though bumblebees and honeybees used for pollination, reduce exposure[7], workers are likely to inhale a substantial number of pollen. Employees are also exposed to the predatory mite *Amblyseius cucumeris*, which serves as biological pest control agent[4]. Furthermore, greenhouse humidity favors exposure to moulds, such as *Botrytis cinerea*[4, 8].

Despite potential allergen exposure, no occupational allergy in this branch of horticulture has been described before.

As some strawberry greenhouse workers reported symptoms suggestive for an occupational allergy to their occupational physician, an investigation to these symptoms and possible causes was carried out. First, we tried to estimate the prevalence of work-related symptoms in strawberry green houses using questionnaires. Second, we aimed to prove the concept that an IgE mediated allergy could be responsible for work-related symptoms. Therefore, we tried to assess an IgE response to strawberry pollen in a few selected employees. In addition we used a nasal provocation test, the golden standard in the diagnosis of occupational rhinitis[9], to test the clinical relevance of sensitization to strawberry pollen.

At this stage, we considered a positive challenge in a few patients being sufficient to confirm the existence of a clinically relevant allergy. To test the possibility of

an IgE response secondary to cross-reactivity to birch or grass pollen, additional inhibition experiments were performed. Confirmation of a new IgE-mediated allergy to strawberry pollen would be the starting point of future research to the contribution of this allergy to work-related symptoms.

Material and Methods

Questionnaire

A questionnaire survey was conducted among strawberry greenhouse employees in Brabant, a region in the south of the Netherlands from October until December 2004. Strawberry growers from a list of addresses were at random contacted by telephone by trained personnel and asked to participate in the study. When an owner agreed upon participation, he or she was asked to record the number of employees enlisted who mastered the Dutch language. Subsequently, the questionnaires were sent by surface mail and distributed by the owners among all potential participants. In an attached letter, the aim of the study was explained, employees were asked for participation, and instructions were given on how to fill in the questionnaire. A response envelope was enclosed to return the questionnaire afterwards.The contents of the self-administered questionnaires were derived from an authorized practice guideline 'management of workers with asthma or COPD' issued by the Netherlands Society of Occupational Medicine[10] and supplemented with strawberry cultivation-specific questions. Questions concerned gender, age, smoking habit, job (characteristics), work history, symptoms at work, atopic symptoms, (chronic) airway symptoms, family history of atopy. Symptoms present after occupational exposure comprised the following categories: itching, redness and swelling of the skin, rhinitis (sneezing/rhinorrhoea/itching/obstruction), conjunctivitis (redness/itching/watery eyes), and asthma (wheezing/coughing/sputum/shortness of breath). Symptoms or exacerbation of symptoms during work were assumed to be related to work. Furthermore, regression upon homecoming, in weekends and holidays were considered to strengthen the possible relation with work. Confidentiality was maintained.

Statistical Analysis

Data were saved and handled statistically using Statistix for Windows, version 8.0 (Microsoft, the Netherlands). In statistical analysis, differences between continuous variables were tested with the unpaired Student t-test. Differences between

frequencies of categorical variables were tested with the chi-square test. The significance level α was 0.05.

In the second part of the study, 3 strawberry greenhouse employees, selected by the occupational physician because of a strongly suggestive history of an occupational allergy, were studied in detail. These 3 employees were included because of symptoms of rhinitis (*i.e.*, nasal blockage, sneezing and watery discharge) during work and regression of these symptoms while being away from work. The medical history of these employees was recorded and allergy tests were performed.

Medical History

Patient A, a 46-year-old-female joint owner of a strawberry greenhouse, with a history of respiratory symptoms after contact with dogs, was referred with work-related rhinoconjunctivitis, asthma and itchiness of the air-exposed skin. She had been performing production activities in the glasshouse since 1994, but because of the aforementioned symptoms she discontinued her occupation from 1998 until 2004. After returning to work, she switched to cleaning up the office and canteen, while wearing a mask. The symptoms subsided and she scarcely needed anti-allergic medication.

Patient B, a 52-year-old female employee has been performing production activities since 1999. In 2003, she developed rhinoconjunctivitis on working days and itchiness of the skin upon contact with a strawberry plant. Symptoms partially improved when using antihistamines, which she obtained from the drugstore. Additionally, she mentioned oral allergy while eating strawberries and mild conjunctivitis due to grass.

Patient C, a 50-year-old-woman, who has been an employee since 1993, presented with a 8 year-history of work-related rhinoconjunctivitis, red itchy macula of air-exposed skin and rarely symptoms of coughing at work, but no dyspnea. Treatment with antihistamine tablets, prescribed by her family doctor, gave no clear improvement.

Both patient B and C mentioned having work-related symptoms during periods of pulling blossoms: *i.e.* from April to June and from October to December.

Allergy Tests

Skin Tests

Skin tests were carried out according to international guidelines[11, 12] and performed by skilled allergy nurses. Test results were scanned with a standard scanning device and the wheal size in mm^2 was calculated by a software application[13]. Skin reactivity was expressed as a ratio between allergen and histamine wheal size (histamine equivalent wheal size). Histamine equivalent wheal size > 0.22 in skin prick test (SPT) and > 0.55 in intracutaneous test (ICT) was regarded as positive. This classification is a modification of the grading system described by Niemeijer *et al.*[14]. In addition, reactions were expressed in mean wheal diameter (adding the longest diameter to the orthogonal diameter and dividing it by 2). A diameter of 3 mm or more was considered positive[15]. The skin test had to be positive using both methods.

Allergen Extracts

Pollen from strawberry plants were collected in a greenhouse and since this activity was highly labor-intensive, the essential material was collected at several occasions. Strawberry pollen extracts were made in phosphate-buffered saline (PBS) pH 7.4, containing 0.03% human serum albumin (HSA) and 0.5% phenol[2]. To prepare strawberry juice, strawberries were homogenized in a food processor, the slurry was filtered, and the fluid was subsequently passed through a 0.22 µm filter (Millex GS, Millipore, the Netherlands). Protein concentrations were determined by the method of Watanabe *et al.*[16]. The concentrations of the strawberry pollen extract and strawberry juice were 0.25 and 1.1 g/L respectively.

Predatory mites (*A. cucumeris*) were kindly supplied by Koppert Biological Systems (Berkel en Rodenrijs, the Netherlands) and extracted according to Groenewoud *et al.*[4]. Appropriate aliquots were stored at -20°C, defrosted 1 hour before skin test and mixed. Protein concentration was 1.05 g/L. All homemade extracts were skin prick tested.

In addition, skin tests were performed with *B. cinerea* (SPT: SQ 412), 1 of the moulds found in greenhouses and with 6 common inhalant allergens (ICT) from ALK Abelló (Nieuwegein, the Netherlands). The common inhalant allergens comprised *Dermatophagoides pteronyssinus*, pollen from grass and birch, mugwort and animal dander (dog and cat). Dilution buffer served as a negative control, histamine chloride (10 mg/ml) as a positive control.

Control Group

Ten control subjects allergic to grass pollen (9 of whom were also allergic to birch pollen), who had never been in contact with strawberry plants, were skin tested with strawberry pollen extract to investigate possible nonspecific irritative reactions of the strawberry pollen extract or cross reactivity of strawberry pollen with grass or birch pollen.

ELISA (Inhibition)

Allergen-specific IgE to strawberry pollen was determined by ELISA.
100 mg strawberry pollen were incubated for 2 hours at room temperature with 1 ml PBS. After 10 minutes centrifugation at 1700g, the supernatant was frozen at -20°C. The protein content of this supernatant was 2.18 g/l. 0.1 ml of a 1/100 dilution of this extract in coating buffer (50 mM carbonate buffer, pH 9.5, 0.1% NaN_3) was incubated in wells of a microtiterplate for 48 hours at 4°C. After 3 washes with PBS, 0.05% Tween 20 (PBST), 0.1 ml of PBST, 1% BSA, was added to each well. After 1 h incubation at room temperature, and three subsequent washes with PBST, 0.1 ml of the patient sera was added. After 2 h incubation at room temperature under rotation, and 3 subsequent washes with PBST, 0.1 ml alkaline phosphatase labeled anti-IgE (BD Science San Diego Ca, USA), diluted 1/1000 in PBST, 1% BSA, was added to each well. After 2 h incubation at room temperature under rotation, and 3 subsequent washes with PBST, 0.1 ml p-Nitrophenyl phosphate substrate was added. After 2 h incubation in the dark, the absorbance was read at 405 nm. For ELISA - inhibition, birch pollen and *D. glomerata* grass pollen (Allergon, Sweden) were extracted as described above for strawberry pollen. The protein content of these extracts was 0.69 g/L and 0.71 g/L respectively. For inhibition of the strawberry pollen ELISA, the 3 extracts were diluted in PBST to a final concentration of 0.1 g/L. 0.05 ml of these extracts were incubated with 0.05 ml serum for 90 minutes at room temperature under continuous rotation. 0.1 ml of this mixture was tested in the strawberry pollen ELISA as described above.

Ten sera with diverse levels of IgE against birch and/or grass pollen (as determined by CAP-RAST) were also tested in the strawberry pollen ELISA. A number of wells of the microtiterplate were not coated with strawberry pollen extract, but with birch pollen extract. These wells were incubated with serial dilutions of a serum with a known level of specific IgE against birch pollen, quantitated by the Immuno CAP system. This dilution curve was used as standard curve, and made it possible to convert the ELISA signals into kU/l.

RAST

Allergen-specific IgE to *A. cucumeris* was determined by RAST by use of agarose beads as allergen support, with a modification of the procedure described previously[17].

CAP-RAST

Total IgE and Specific IgE to common inhalant allergens, *B. cinerea* and strawberry juice were determined by the ImmunoCAP-system (Phadia, Uppsala, Sweden).

Immunoblotting

Immunoblotting with strawberry pollen extract (100 mg extracted/ml phosphate buffered saline) was performed with a modification of the procedure as described previously[17]. Bound IgE was visualized with alkaline phosphatase labeled anti-human IgE antibodies (BD Science San Diego Calif., USA) and BCIP/NBT substrate (Sigma Biochemicals, Zwijndrecht, Netherlands).

For immunoblot inhibition, 4-fold dilutions of serum both patient B and C in PBS were mixed with an equal volume of the pollen extracts that we used in ELISA (*i.e.* strawberry pollen, birch pollen and grass pollen), diluted in PBS to a final concentration of 0.1 g/L. Diluted sera were incubated for 90 minutes at room temperature under continuous rotation. Subsequent immunoblotting was performed as described above.

Nasal Provocation with Strawberry Pollen Extract

To determine the clinical relevance of sensitization to strawberry pollen, nasal provocations with strawberry pollen were performed as described by de Graaf in 't Veld[18]. Medication for rhinitis was withdrawn: nasal corticosteroids 3 weeks and antihistamines 3 days before the provocation. Nasal provocations were performed with 8 increasing doses of strawberry pollen extract (0.0000001% to 1%) at ten-minute intervals after sham-challenge with PBS, containing HSA 0.03% and benzalkonium chloride 0.05% (ALK Abello, Nieuwegein, the Netherlands). The strawberry pollen extract was sprayed into each nostril with a nasal pump spray delivering a fixed dose of 0.125 ml solution. The nasal response was measured ten minutes after each step in the challenge by a symptom score according to Lebel *et al.*[19]. This scoring system was graded in points and the total score ranged from 0 to 11 points. The various items were scored in the following manner: sneezing (0-2 times sneezing: 0 points; 3-4 times sneezing: 1 point; > 5 times sneezing: 3

points), rhinorrhoea (anterior rhinorrhoea: 1 point, posterior rhinorrhoea: 1 point, both rhinorrhoea anterior and posterior: 2 points), difficulty in breathing (difficulty in breathing: 1 point; one blocked nostril: 2 points; both nostrils blocked: 3 points), and pruritus of nose (1 point), palatum or ear (1 point) and conjunctivitis (1 point).

A score ≥ 3 (progressive) above PBS provocation was considered positive.

Three nonatopic volunteers, who had never been in contact with strawberry plants, were challenged intra-nasally with strawberry pollen extract to rule out an irritative reaction.

Results

Questionnaire

Population Characteristics

13/19 approached greenhouses (68%) agreed to participate. Reasons for refusal were lack of interest and absence of work-related symptoms. With 75/149 dispatched questionnaires returned, the response rate was 50.3%. Fifty-two of these subjects (69.3%) were female and the mean age was 43.7 years (range 13-74). The majority (80%) of workers was engaged as employee and the mean duration of employment was 8.6 years, with a mean working week of 24 hours. Twenty-nine of 75 respondents (38.7%) reported 1 or more symptoms attributable to the workplace. Population characteristics between this group and the group without these symptoms were not significantly different, except for the mean hours of work per week, which were 17.3 and 28.4 h respectively ($p<0.001$).

Presence of Work-Related Allergic Symptoms

Work-related symptoms consisted of rhinitis (30.7%), conjunctivitis (23.3%), asthma (4.2%) or skin symptoms (16.7%). 77.8% noted an improvement while being away from work. As a possible cause of symptoms, the strawberry plant, strawberry pollen, sulphur, or biological control agents were mentioned by the respondents. Pulling blossoms of a strawberry plant towards the pathway and picking strawberries were 2 of the activities, held responsible for symptoms.

Determinants of work-related allergic symptoms

The variables seasonal or perennial rhinoconjunctivitis, were statistically associated with work-related symptoms ($P < 0.001$). Smoking, (chronic) airway symptoms, family history of atopy on the other hand, were not significantly associated with work-related symptoms.

Skin Tests

All 3 employees, who were studied in detail in the second part of the investigation, showed positive reactions in SPT with homemade strawberry pollen extract. Histamine-equivalent wheal size and mean wheal diameter were 1.54, 0.33, 1.62 and 9, 5 and 8 mm in patient A, B, and C respectively. SPT with strawberry pollen were negative in all control subjects.

ELISA and Immunoblotting

Strawberry pollen-specific IgE could be demonstrated by ELISA in 2 cases (patient B and C) (Figure 1). Nine of 10 sera with diverse levels of IgE against birch and/or grass pollen (range 0.1 to 96.9 kU/L in the grass pollen CAP-RAST, range 0.1 to 54.9 kU/L in the birchpollen CAP-RAST) scored less than 0.35 kU/L in the strawberry pollen ELISA; 1 serum with < 0.1 kU/L IgE against grass pollen, 7.08 kU/L against birch pollen and a total IgE of 71 kU/L scored 0.50 kU/L in the strawberry pollen ELISA. When quantifying the Elisa measurements, sera of patient A, B and C were found to contain respectively <0.10, 1.21 and 6.67 kU/L of specific IgE against strawberry pollen. The sera of patient B and C revealed a positive IgE response to strawberry pollen in immunoblotting with molecular weight bands between 18-50 kDa (Figure 2). ELISA and immunobotting were negative in the control sera (Figure 1, 2 respectively).

ELISA inhibition (Figure 3). IgE binding to strawberry pollen in serum from both patient B and C could almost completely be inhibited by preincubation with strawberry pollen extract. In serum from patient C, no inhibition was observed after preincubation with grass or birch pollen, whereas preincubation of serum from patient B with grass and birch pollen extract gave more than 50% inhibition of IgE- binding.

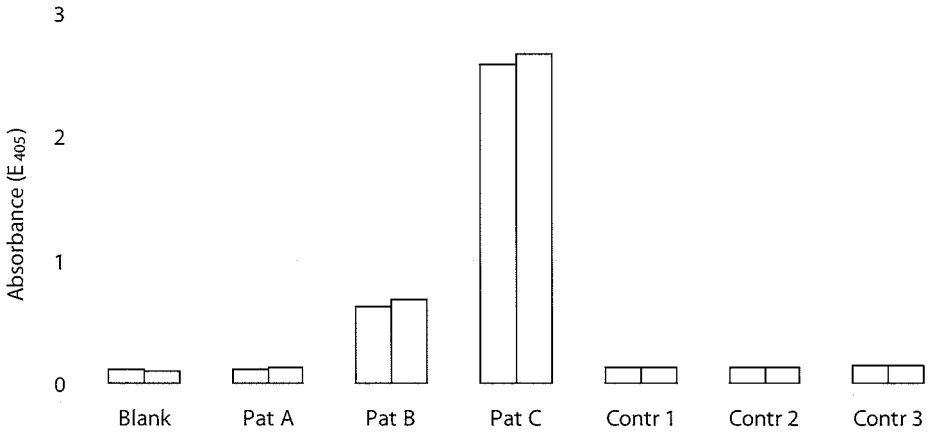

Figure 1. IgE binding to strawberry pollen in ELISA. From left to right in duplo respectively. Blank; patient A (total IgE 17 kU/L); patient B (total IgE 187 kU/L); patient C (total IgE 670 kU/L); negative control subject 1 (total IgE 14 kU/L); negative control subject 2 (total IgE 209 kU/L); negative control subject 3 (total IgE 785 kU/L). The absorbance was read at 405 nm.

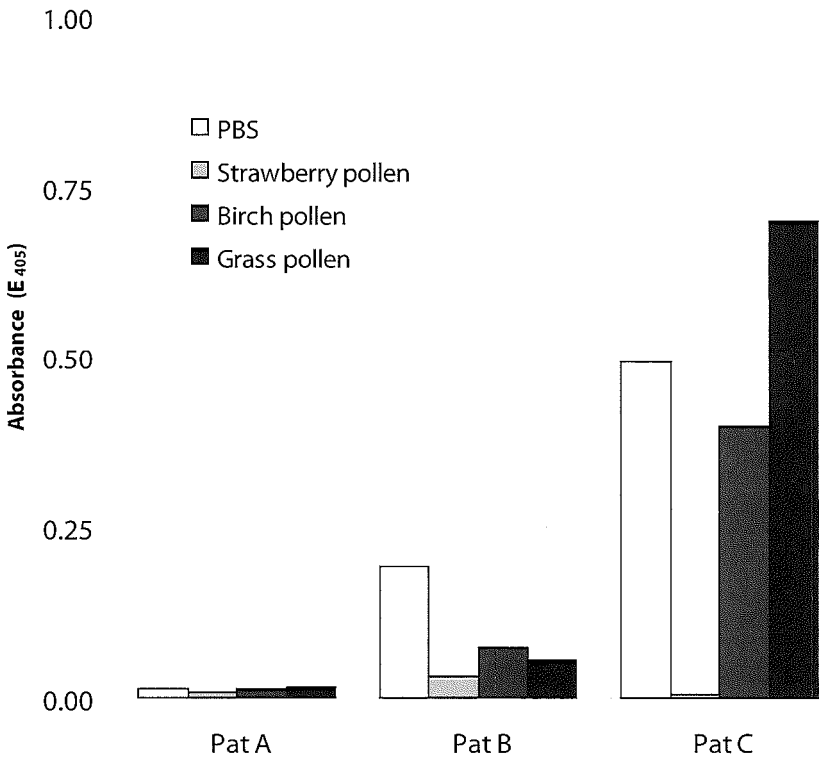

Figure 3. ELISA inhibition experiments Inhibition experiments are shown from left to right in patient A-C, respectively. The sera were inhibited with PBS, strawberry pollen extract, birch pollen and grass pollen. The absorbance was read at 205 nm.

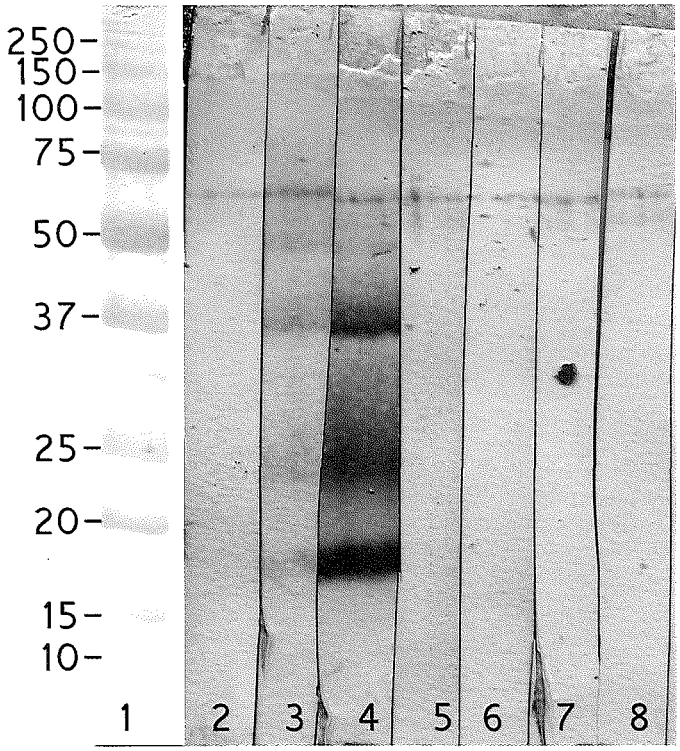

Figure 2. Immunoblotting with strawberry pollen extract. Molecular weight bands are shown to the left (kD); lane 1: molecular weight standard; lane 2: serum of patient A (total IgE 17 kU/L); lane 3: serum of patient B (total IgE 187 kU/L); lane 4: serum of patient C (total IgE 670 kU/L); lanes 5 -8: serum of 4 subjects without an occupational history in strawberry horticulture and with total IgE scores of 18, 153, 1586, 1670 kU/L in patient 5,6,7,8 respectively.

Immunoblot inhibition. Whereas the IgE binding to serum of patient C could completely be inhibited after preincubation of this serum with strawberry pollen extract, no inhibition was seen after preincubation with grass- and birchpollen extract (Figure 4). Immunoblot- inhibition experiments with serum of patient B, which gave a rather weak binding in the strawberry immunoblot, were inconclusive (data not shown).

Nasal provocation

Nasal provocation with strawberry pollen was positive in 2 employees (Figure 5; patients A and C). Symptoms during provocation were comparable with symptoms at work. Nasal allergen provocation was negative in 3 non-atopic volunteers (Figure 5; control 1-3).

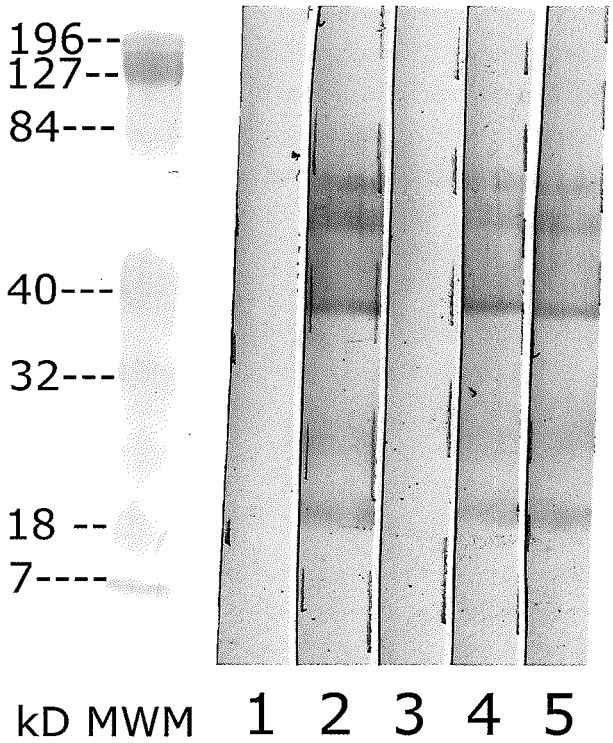

Figure 4. Immunoblot inhibition experiment in patient C. Molecular weight bands are shown to the left (kD); lane 1: PBS; lanes 2-4: serum of patient C with immunoblotting with strawberry extract after preincubation with PBS (2), strawberry pollen extract (3), birch pollen extract (4) and grass pollen extract (5) respectively. MWM = Molecular weight marker.

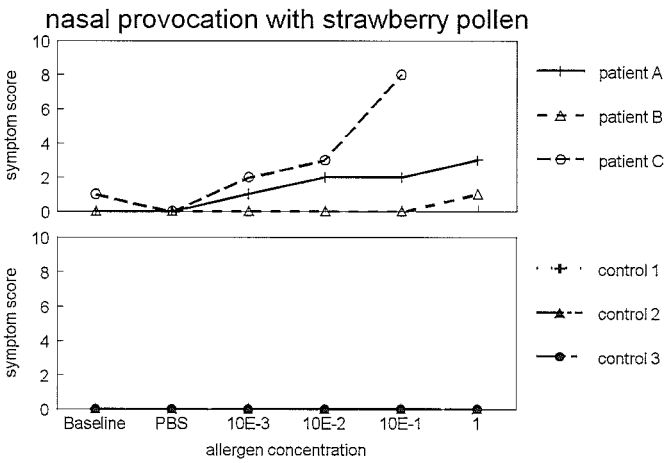

Figure 5. The upper part shows the response to nasal provocation with increasing doses of strawberry pollen in patient A-C and the lower part shows the response of 3 non-atopic volunteers; control 1, 2 and 3. Eight increasing doses of strawberry pollen extract (10^{-7} to 10^{0}) were used.

All 3 employees were atopic; 1 of the employees exhibited a positive IgE response to dog dander (patient A) whereas the other 2 employees were sensitized to grass pollen (patient C) or to both grass and birch pollen (patient B). Additionally, patient B and C revealed a positive response to strawberry juice in both SPT and CAP-RAST (2.36 and 1.93 kU/L, respectively). No sensitization to *A. cucumeris* or *B. cinerea* was found.

Lung Function Tests

Spirometry and histamine bronchial challenge was performed in all 3 employees and no bronchial obstruction or airway hyperresponsiveness was found.

Discussion

Due to a shift from open-field horticulture towards greenhouses employees in strawberry horticulture are highly exposed to several (potential) allergenic agents[20]. However, besides 2 case-reports on contact urticaria in strawberry pickers[21, 22], no occupational allergy in this branch of crop-growing has been described before.

The strawberry plant (*Fragaria ananassa*) is a member of the Rosaceae family. Allergic symptoms to another member of this family, *i.e.* rose (and its pollen), among villagers cultivating roses, have been described by Demir *et al.*[23]. Food allergy to related fruits, for example apple and peach, is better known[24].

This study concerned the initial research phase regarding a possible occupational allergy in the strawberry greenhouse environment. It comprised two parts; first, the questionnaire survey demonstrated that work-related symptoms suggestive for an occupational allergy occur among employees. The allergy tests, especially the nasal provocation tests, in the second part of the study, showed that symptoms can be caused by a strawberry pollen allergy.

Another research phase is required to determine disease prevalence and incidence, by means of a larger cross sectional study and a longitudinal study among apprentices, and to demonstrate pollen in the air of the strawberry greenhouse environment.

Although questionnaires concerning occupational (allergy and) asthma have not been validated yet[1, 25], questionnaires in general are a fundamental tool to determine health outcomes and exposure to external agents in epidemiologic studies[26]. In the epidemiological part of the study, 38.7% of respondents mentioned work-related allergic symptoms, and also insight into the strawberry greenhouse environment with its possible allergenic agents was provided.

Thus, the questionnaire shows that work-related allergic symptoms possibly due to an occupational allergy are present among strawberry greenhouse workers in the Netherlands. On the basis of these data, it is, however not possible to estimate the true prevalence of these symptoms. First, the response rate of the questionnaire was 50.3%, and therefore nonresponse bias could have occurred. Not only the low response rate, but also the cross-sectional design of the study can cause selection-bias. In contrary to a longitudinal study, symptoms can be underestimated[1]. Furthermore, the sensitivity of medical questionnaires (in general) is high, whereas specificity is low and false positive results can occur[1, 25, 27].

Symptoms of the upper airway system are more pronounced than complaints of the lower airway system. This matches with findings of earlier reports in literature[3, 6, 28, 29]. A possible explanation for the finding that workers with symptoms work significantly less hours per week than those without, is that the former group shortens the workweek to avoid exposure thereby reducing the symptoms. Further, atopic people have an increased risk of developing work-related symptoms while being exposed to high-molecular-weight antigens[3, 30]. The association between 'complaints of seasonal or perennial rhinoconjunctivitis' and work-related complaints supports this statement. However, occurrence of seasonal or perennial rhinoconjunctivitis does not differentiate between manifestation of atopy or work-related complaints, and therefore caution is required when drawing a conclusion from this finding.

In the second part of the study, sensitization to strawberry pollen in all 3 strawberry greenhouse employees with work-related allergic symptoms was demonstrated with skin prick tests. Furthermore, ELISA and immunoblotting showed positive results in 2 out of 3 employees. Moreover, the intensity of the bands were in correspondence with the level of specific IgE.

Since none of the birch pollen-allergic and grass pollen-allergic control subjects showed a positive reaction in skin prick testing with strawberry pollen, irritative reactions were ruled out and cross reactivity was considered unlikely. Furthermore 9 of 10 sera with IgE against birch and/or grass pollen were negative in the strawberry pollen IgE Elisa; 1 serum was borderline positive.
In patient C, neither the ELISA nor the immunoblot were inhibited by grass and or birch pollen, indicating that the sensitization to strawberry pollen in this specific patient is not caused by a sensitization to birch or grass pollen originally but that there is a true primary sensitization to the strawberry pollen. In patient B, the ELISA shows partial inhibition and partial cross reactivity may be conceivable in this patient. Taken together, the experiments point at primary sensitization to strawberry pollen. This is also underlined by the absence of skin reactions to strawberry pollen in control subjects sensitized to birch or grass pollen and by the absence of IgE binding to strawberry pollen in sera with IgE against birch/and or grass pollen. On the other hand, partial cross-reactivity with other pollens in some subjects might be possible.

The intra- and inter-individual differences in different allergy tests could possibly be partly explained by the fact that standardized strawberry extracts were not available. Pollen from flowers of strawberry plants were obtained from a greenhouse at several occasions. During 1 of these visits, collecting pollen for subsequent testing was hampered by the fact that climate conditions in the greenhouse were suboptimal, *i.e.*, greenhouse temperature was below normal and humidity was high.

Measurements of airborne pollen were not performed. Symptoms were, however, specifically mentioned during periods with pollen release, *i.e.* from April to June and from October to December.

Two patients in our study exhibited positive IgE responses to strawberry juice, and this sensitization was clinically relevant in 1 patient, as she mentioned symptoms of oral allergy while eating strawberries (patient B). The same patient was also sensitized to birch pollen. Musidlowska-Persson *et al.*[31] described homology between Bet v 1 and Fra a 1 allergen in strawberry juice. Since no RAST inhibition experiment with Bet v 1 and strawberry juice has been performed, cross-reactivity between birch pollen and strawberry juice has not been ruled out in this particular patient.

Because of the differences in sensitization route, an inhalation allergy presumably leads to a different sensitization pattern than food allergic reactions[3, 17]. Corecognition between strawberry pollen and strawberry juice is, however, conceivable. Zuidmeer *et al.*[32] demonstrated that strawberry also contains allergens with high molecular weight (20-28, 40 – 80 kDa).
The strawberry pollen immunoblots in our patients showed comparable weight bands. Since inhibition studies have not been performed, no conclusion can be drawn on cross-reactivity between strawberry pollen and juice.

In conclusion, we demonstrated that work-related symptoms are clearly present among strawberry greenhouse workers. An IgE mediated occupational allergy to strawberry pollen may contribute to these symptoms.

Acknowledgements
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7

General discussion

Introduction

The year 1998. Imagine being at work in a hospital as an operating room nurse. You have been working in the operating room for 10 years already, with much pleasure, only now you start to develop sneezing attacks and you have complaints of red itchy eyes while being at work. You find this very annoying (since you cannot blow your nose or rub in your eyes while being sterile) and it clearly affects your mental state in a negative way. At first, the fact that symptoms are work-related is not that clear, but when it strikes you that symptoms diminish in the weekends and totally disappear on vacations, you start to suspect a relation with your work in the operating room. Meanwhile, you have also developed shortness of breath, each time several hours after finishing work. You visit the Allergology department where allergy tests are performed. You turn out to be allergic to the natural rubber latex (used in surgical gloves). Consequently you are advised to avoid latex (gloves) and appropriate medicines are prescribed. After initial improvement, symptoms unfortunately return. Recurrence of allergy symptoms return can be explained by the fact that although you have stopped wearing latex gloves, your colleagues have not. Since latex allergens can become airborne through the powder present in latex gloves, you are still exposed to these allergens in the operating room.

The symptoms are very bothersome and despite increasing the dose of your medication, you often have to report ill. Finally, you are not able to keep on working in the operating room anymore and you have to quit the job. Although you cannot do the work you like most, your mental state is not affected anymore by allergy complaints.

The year 2009. You learn that powdered latex gloves nowadays are no longer used in the operating room; they have been replaced by powder-free latex gloves. You also learn that this implies a strong reduction in airborne latex exposure. Since you most of all want to work in the operating room, you realise that the current conditions may allow you to do so. And indeed, while being at work in the operating room again, this time you do not encounter symptoms of sneezing, shortness of breath or eye symptoms.

This visual image clearly shows that in *individual* cases an occupational allergy can be very bothersome, can become severe and can eventually lead to loss of a job. It further shows that appropriate interventions can enable someone to return to his or her job.

But what about occupational allergy at *population level*? How many people -in populations at risk- actually suffer from an occupational allergy? Why do some people develop an occupational allergy while others do not? Does an occupational allergy normally have an effect on someone's mental state, as described above? And, while staying at work despite symptoms, is someone usually still able to perform his or her normal activities? How can occupational allergies be prevented?

In this thesis, we have tried to find some answers to the questions raised above. We have aimed to focus mainly on IgE-mediated occupational rhinitis and allergy. Furthermore, we have chosen three Dutch occupational settings with a large workforce, where employees are at risk for developing an occupational allergy, *i.e.* the bell pepper industry, strawberry horticulture and the hospital operating room.

Epidemiology of occupational rhinitis and allergy

Prevalence and incidence figures from previous research

The prevalence figures of occupational rhinitis in workforces exposed to high molecular weight (HMW) allergens vary widely (from 2% to 87%) depending on the occupational agent involved and on the definition used when diagnosing occupational rhinitis[1].

Previous research among bell pepper employees and operating room employees showed high prevalence figures on occupational allergy in both occupational settings: in 1999 the prevalence of work-related rhinitis symptoms among bell pepper employees appeared to be 49%[2]. Work-related symptoms among bell pepper employees were associated with sensitization to substances of the bell pepper plant (bell pepper pollen being the most important), age, and atopy[2]. Among operating room personnel the prevalence of natural rubber latex (NRL) allergy in 1998 was found to be 9.8%[3].

Risk factors

To understand why some people develop an occupational allergy while others do not, insight in risk factors is necessary. Three known possible risk factors for the development of occupational rhinitis are exposure, smoking and atopy[4].

Whether smoking is associated with development of work-related allergic symptoms has been a matter of debate. No relationship between occupational rhinitis and smoking was found in working groups such as laboratory animal workers[5] and bakery employees[6]. Jeebhay *et al.* demonstrated that smoking is a risk factor for development of occupational asthma among saltwater fish processing workers[7]. A review published in 2006 however concluded that there is little evidence to support the view that the risk of occupational asthma is increased in workers who are smokers[8]. In general, tobacco smoke impairs the innate immune system and in a review by Cagnani *et al.* it was concluded that active smoking is associated with current rhinitis and asthma symptoms and that it seems to be a risk factor for development of new asthma in rhinitis patients[9]. Our follow-up study in 2009 clearly showed that smoking is a risk factor for development of both work-related rhinitis and asthma symptoms in the bell pepper industry.

The assumed sequence of events in developing an occupational IgE-mediated allergy while working with HMW occupational allergens is that individuals become sensitized to common inhalant allergens, then develop sensitization to an occupational allergen at work, subsequently occupational rhinitis, and finally occupational asthma[10-12]. In our study, we confirmed that in general this series of events starts with atopy, since atopy was associated with the cumulative incidence of both work-related rhinitis and asthma symptoms in bell pepper employees.

The bell pepper follow-up study also seems to confirm the hypothesis that occupational rhinitis precedes occupational asthma[13-14] since work-related rhinitis was associated with the onset of work-related asthma symptoms. However, this association was partly explained by the fact that rhinitis and asthma had similar risk factors. With two measurements over time, the study design did not allow us to investigate the sequence in more detail. However, the clear overlap among the cumulative incidence of sensitization to bell pepper pollen, work-related rhinitis, and work-related asthma symptoms indicates that these outcomes are clustered.

Now that the first risk factors for development of work-related rhinitis and asthma in bell pepper horticulture (smoking, atopy) have been identified, this information can be of use for screening purposes in the future. Also the fact that occupational rhinitis seems to precede occupational asthma in bell pepper horticulture can be used for better targeted secondary prevention. In order to identify other risk factors and to disentangle the exact sequence of events in the development of an occupational allergy in this branch, the need for a longitudinal study from the start of employment is emphasized. Consequently, prognostic models to detect subjects at risk for occupational allergy can be designed. These models may be converted into a prediction score chart for easy tailoring of advice by physicians.

Current prevalence and incidence figures for different occupational settings

To discuss the *prevalence* and *incidence* of occupational rhinitis and allergy we could differentiate between occupational settings where a comprehensive intervention has been made to reduce exposure to occupational allergens (for primary prevention purposes) and occupational settings where no intervention has been made so far. The level of exposure appears to be the most important risk factor for development of an IgE sensitization to a variety of HMW allergens including NRL[15-18]. In turn, IgE sensitization to some agents, also including NRL, appears to be associated with rhinitis/asthma symptoms[19-21]. Therefore, one would expect the incidence and prevalence of occupational allergy in the first group being low. The operating room, where airborne exposure to NRL is substantially reduced by the introduction of powder-free NRL gloves is an example of such an occupational environment.

Indeed in the repeated cross-sectional study among operating room employees, the *prevalence* of NRL allergy in 2009 was significantly lower compared to the first study in 1998 (2.8% *vs* 9.8%). In addition, the *incidence* of NRL allergy in 2009 in a subpopulation of this study (n = 49) also appeared to be low (2%, n = 1). We concluded that although the risk for NRL sensitization and allergy in operating room employees has not entirely been banned out, our study provides a clear indication that the risk is strongly diminished by using low-NRL protein, powder-free gloves.

Another repeated cross-sectional study, among students and staff members from a dental school, showed a significant reduction in the prevalence of NRL sensitization after the introduction of powder-free gloves too[22]. Population based

studies further also describe a correlation between the introduction of powder-free NRL gloves and a decline of (suspected) occupationally caused NRL allergy[23-25].

On the other hand, Schmid *et al.* observed a significant increase in NRL sensitization among dental students, *i.e.* from 8.7% in 1990 to 17.3% in 2000 despite the introduction of NRL powder-free gloves[26]. Furthermore, a systematic review from 2006[27] did not present clear evidence for the effect of the use of powder-free NRL gloves in terms of protection against development of NRL allergy. A recently published review[28] however concluded that the use of low-protein, low- allergenic, powder-free gloves is associated with a significant decrease in the prevalence of type I allergic reactions to NRL among health care workers. The results of our study support the conclusion that the risk for NRL sensitization is strongly diminished by using powder-free low protein NRL gloves, which is reflected by the low prevalence of NRL allergy found in our study.

To date, in bell pepper horticulture no comprehensive interventions to reduce exposure to bell pepper pollen, have been performed. In a cross-sectional study in 1999, among 472 employees from 85 greenhouses (nearly 10% of the bell pepper workforce at that time), work-related rhinitis symptoms were found in 49% of workers. During the 8-year follow-up in 2007, the cumulative *incidence* of work-related rhinitis appeared to be 19%. The mean duration of employment among the employees who participated in the follow-up study was 17 years.

Taking the duration of the follow-up into account, the incidence of work-related rhinitis was 2.4 cases per 100 person-years. This figure lies within the range (0.3 to 13.1 per 100 person-years) described for other occupations at risk for occupational allergy[4]. The fact that the peak of onset of sensitization and symptoms apparently occurs during the first several years of exposure and not in a later phase of prolonged exposure, could explain why the incidence lies in the lower segment of the aforementioned range[29-30]. Furthermore, one of the reasons for the incidence being in the lower part of the range can be a healthy worker effect (HWE)[31]. A HWE seemed to have occurred since rhinitis symptoms in 1999 were significantly more present in the group that had left the greenhouse during follow-up compared to the group still being employed in the greenhouse, indicating that rhinitis could be an expelling factor.

Compared to the incidence of rhinitis in the general population, the second Dutch National Study of General Practice reported an incidence of 'hay fever/allergic rhinitis' of 8.8 new cases per thousand individuals per year (*i.e.* 0.88 new cases per 100 person-years). The cumulative incidence of work-related rhinitis in this group of bell pepper employees is considerably higher. Thus, our study results clearly indicate that the development of new work-related rhinitis in bell pepper pollen employees, also in those employees with a long duration of employment, is still a substantial health problem.

It is clear that one cannot directly extrapolate the findings from the repeated cross-sectional study among operating room employees to another industry, for example the bell pepper horticulture with exposure to another type of occupational allergen, with other working activities and surroundings. However, it is to be expected that if exposure to bell pepper pollen in the bell pepper industry is sufficiently reduced, the incidence and prevalence of sensitization and symptoms will thereafter diminish. In a previous pilot study, it was already found that by using honeybees in the greenhouses pollen exposure is reduced. This study also suggested that there was a reduction in nasal complaints. Honeybees and bumble bees are already commonly used in greenhouses to promote pollination. A longitudinal intervention study is necessary in order to investigate whether the prevalence and incidence of sensitization and nose and asthma symptoms are indeed reduced by introducing a dense population of honeybees or bumblebees.

The number of listed occupational allergens is still increasing (Sastre, June, 2010, http://eaaci.net).
Considering the fact that the level of exposure appears to be the most important determinant of sensitization and occupational rhinitis, an eminent reason for a new occupational allergy to develop is the increase in level of exposure. This is the case in strawberry horticulture, where employees nowadays work in greenhouses and not in the open field as they used to do. We found that allergic symptoms attributable to the workplace are present among a proportion of strawberry greenhouse employees. Furthermore, an IgE response to strawberry pollen was demonstrated in a few selected employees by means of skin prick tests, ELISA and immunoblotting. In addition, a nasal provocation test in 2 out of 3 subjects validated the clinical relevance of sensitization to strawberry pollen.
The results of this study underline the importance of the level of exposure in the development of an occupational allergy.

The social and economic burden of occupational rhinitis

The question whether occupational rhinitis affects someone's mental state, someone's capability to work and as a consequence of the latter also someone's (*i.e.* the employee's, the employer's, society's) 'wallet' has been addressed in this thesis.

Quality of life

The emotional impact that a disease can have on a patient's life can be assessed by measuring health-related quality of life (HRQL)[32].

Quality of life (QoI) can be defined as the person's functioning in physical, psychological and social context, as perceived by the person him or herself[33]. QoL can only be investigated by means of a self-reportage-questionnaire[33]. Many factors - such as finances, spirituality, and *health* - contribute to QoL, and also affect each other[32].

Although not everyone may be familiar with the term QoL, the term *happiness* - the degree to which a person evaluates the *overall quality of his present life-as-a-whole positively* - is well known to all. Happiness is one of the indicators of the (apparent) quality of life[34].

One of most important sources of happiness is an absence of health problems[35]. A study among Dutch inhabitants showed that having a chronic disease makes someone less happy[36]. It is therefore evident that good health without chronic illness is beneficial for happiness and thus for the (apparent) quality of life. Also, good health is on top of the list of happiness factors of many people.

Bearing this in mind, we can reflect on the meaning of HRQL: HRQL is the component of overall quality of life that is determined primarily by a person's health and that can be influenced by clinical interventions[32]. A definition of HRQL is "The functional effects of an illness and its consequent therapy upon a patient, as perceived by the patient." Since two individuals can have identical clinical rhinitis or any other disease, HRQL in the one patient can be different from the other and this one patient can be more impaired compared to another[32]. Therefore HRQL has to be investigated separately.

Rhinitis-related quality of life: the social burden of occupational rhinitis

It has been found that the Rhinitis-related quality of life (RQoL) is negatively affected by allergic diseases[37].

Up to date, only few studies have been performed on the impact of occupational allergy on daily life[38-39]. In a previous study by our group, it was described how bell pepper pollen allergy has a negative impact on daily life[40].

Furthermore, to our knowledge just one study compared QoL of patients with occupational rhinitis, not being exposed to occupational allergens anymore, with occupational rhinitis patients who were continuously being exposed. QoL was impaired among patients from the latter group, whereas the QoL among patients no longer exposed was mainly similar to that of the healthy controls[38]. The current study clearly shows that bell pepper greenhouse workers with work-related nasal symptoms experience a substantial improvement in RQoL after leaving the work environment (with subsequent allergen avoidance). In our previous study we demonstrated that RQoL is predominantly associated with sensitization to bell pepper pollen and not to other concomitant sensitizations to common inhalant allergens[2]. Therefore, we considered the improvement in RQoL as a result of cessation of bell pepper pollen exposure. We also concluded that work-related rhinitis could be a reason the leave work.

Although the RQoL of these subjects is improved after quitting the job, one can imagine that the overall quality of life may not necessarily improve, since loss of job might possibly implicate loss of income and loss of appropriate perceived participation in society.

It is essential to keep employees at work. One way of achieving this, is by lowering exposure levels to occupational allergens at the workplace and thereby reducing (the onset of) rhinitis symptoms and raising RQoL in employees with occupational rhinitis. As stated previously, we recommend a large scale study to the effects of honeybees or bumblebees on occupational pollen exposure and symptoms. Such an intervention should also be evaluated in terms of cost-effectiveness.

The economic burden of occupational rhinitis: Productivity loss and costs

Next we will discuss whether an occupational allergy not only has an impact on someone's emotional life but also on work productivity and therefore causes higher productivity costs.

Rhinitis in the general population has been shown to contribute to productivity loss through sick leave as well as on-the-job productivity loss[41-43]. On the contrary, up to date there is little known about the economic impact of occupational rhinitis[4].

In the bell pepper follow-up study, we found that work-related rhinitis and asthma symptoms caused half of the productivity loss found. The prevalence of on-the-job productivity loss and sick leave was 16.9% and 19.1%, respectively, which resulted in a total time lost of 4.6%, being approximately €1,100 per person-year work in the bell pepper horticulture. Rhinitis appeared to have an impact on the on-the-job productivity loss without having any effect on sick leave. Other studies have also described stronger associations between allergy and on-the-job productivity loss than between allergy and sick leave[41, 44]. Apparently, employees with work-related rhinitis usually do not report sick in spite of their symptoms. Furthermore, it was demonstrated that moderate to severe rhinitis but not mild rhinitis was associated with on-the-job productivity loss. This is in line with a previous report by Bunn *et al.*[45].

We concluded that work-related rhinitis and asthma can cause substantial productivity loss which may consequently result in higher productivity costs. We also stated that since rhinitis and asthma may be a cause to change jobs outside this particular cultivation, the costs calculated might underestimate the economic consequences of occupational allergy among workers with shorter employment.

Thus, it is clear that not only from an employee's point of view, but also from the perspective of the employer and society, interventions to reduce the development and deterioration of occupational allergy have to be investigated.

Conclusions and final notes

1. The development of work-related rhinitis in bell pepper employees is, even in case of prolonged exposure, still a substantial health problem; smoking and atopy have been identified as risk factors.

2. Work-related rhinitis in bell pepper employees appears to have economic and social consequences through on-the-job productivity loss and impairment of RQoL. Employees experience a substantial improvement in RQoL after leaving the work environment. Moreover, work-related rhinitis can be a reason to leave work.

The need for a longitudinal study, from the start of employment, to identify other risk factors, is emphasized in order to develop a prediction score chart for easy tailoring of advice by physicians together with the need for a study to the cost effectiveness of honeybees or bumblebees on occupational pollen exposure and symptoms.

3. The introduction of powder-free low protein NRL surgical gloves in 1998 is most likely responsible for the reduction in NRL sensitization and NRL allergy prevalence among operating room personnel of an academic hospital in 2009.

4. Allergic symptoms attributable to the workplace are present among a proportion of strawberry greenhouse employees. These symptoms can be caused by a strawberry pollen allergy and can possibly result from increased exposure due to the change in working environment.

We feel that another research phase is required to determine the exact disease prevalence and incidence in strawberry horticulture by means of a larger cross-sectional study and a longitudinal study among apprentices.

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8

Summary

Samenvatting

Dankwoord

Curriculum Vitae

Portfolio

Chapter 1 provides a general introduction. It starts with defining occupational rhinitis, occupational asthma and occupational IgE-mediated allergy. Data regarding the epidemiology of occupational rhinitis are described. These data include the scarce available information on the incidence of work-related rhinitis, varying from 0.3 to 13.1 per 100 person-years, depending on the occupational agent involved. It is discussed that the evidence of smoking and atopy being risk factors for the development of occupational rhinitis is inconsistent. Furthermore, little is known about health-related quality of life in relation to (avoiding) exposure, in occupational rhinitis. Even less is known about the productivity loss due to the disease. Since there is a need for further information on the incidence, the risk factors and the socio-economic burden of work-related rhinitis, these topics are addressed in this thesis. To study this, a bell pepper workforce in the Netherlands was investigated. This occupational group is associated with a high percentage of occupational IgE-mediated allergy due to high exposure to bell pepper pollen allergens.

Since the level of exposure appears to be the most important determinant of sensitization and occupational rhinitis, reduction or elimination of workplace exposure to occupational allergens should be the most effective way of achieving primary prevention. It is discussed that data on successful reduction of exposure concern for example changes in the properties of natural rubber latex (NRL) gloves designated for health care workers. The powder in NRL gloves appears to be the main cause of the airborne exposure to NRL and thus plays an important role in the sensitization process (via inhalation). It is found that the airborne NRL levels are indeed successfully diminished after a substitution of powdered NRL gloves for powder-free NRL gloves. There has however been controversy on the evidence of the effectiveness of this measure in terms of primary prevention *i.e.* development of NRL sensitization and allergy. This topic is addressed in this thesis and subject of study were operating room employees from a university hospital.

The introduction also contains a description of the strawberry horticulture, where employees nowadays work in greenhouses and not in the open field as they used to do. It is because of this change in working environment that the overall exposure to strawberry pollen has increased.

Considering the fact that the level of exposure appears to be the most important determinant of sensitization and occupational rhinitis, the development of an

occupational allergy is plausible. For this working group we aimed 1) to explore the presence of work-related allergic symptoms in strawberry greenhouse employees and 2) to prove the concept that an IgE-mediated allergy to strawberry pollen could be responsible for work-related symptoms.

Chapter 2 presents the results of an 8-year follow-up study on occupational allergy to bell pepper pollen in greenhouses. Pollen from bell pepper plants cultivated in greenhouses are known to cause occupational allergic disease. A cross-sectional study, among 472 bell pepper employees in 1999, estimated prevalences for sensitization to bell pepper pollen of 28%, and for work-related rhinitis symptoms of 49%. Work-related symptoms among bell pepper employees were associated with sensitization to substances of the bell pepper plant (bell pepper pollen being the most important), age, and atopy. The mean duration of employment at that time was 8 years.

The investigation presented in this thesis is based on follow-up of all participants of that previous cross-sectional study. Aim of the study was to investigate the incidence and risk factors for work-related rhinitis. In total, 280 of 472 employees were available for questionnaires and in 250 employees allergy tests were performed. During the 8-year follow-up, the cumulative incidence of work-related rhinitis was 19% and of sensitization to bell pepper pollen 9%. Atopy and smoking were significantly associated with development of rhinitis. The cumulative incidence of work-related asthma symptoms was 8%. Again atopy and smoking were significant risk factors.

The estimated prevalences in the first study may be assumed to approach the cumulative incidence due to the average duration of exposure of about 8 years. On the basis of these prevalence figures, it was expected that the cumulative incidence figures during the 8 year follow-up would be in the same range as the prevalence found in the first study. However, the observed cumulative incidences were lower. The fact that the peak of onset of sensitization and symptoms apparently occurs during the first several years of exposure, and not in a later phase of prolonged exposure, could explain why the incidence of work-related rhinitis lies below the prevalence found in the first cross-sectional study. Furthermore, one of the reasons for the incidence being lower could be a healthy worker effect (HWE). In our study a HWE seemed to have occurred since rhinitis symptoms in 1999 were significantly more present in the group that had left the greenhouse during follow-up compared

to the group still employed in the greenhouse, indicating that rhinitis could be an expelling factor. Sixteen out of 168 former employees explicitly mentioned that allergy symptoms were the main reason of their resignment. Taken these factors into account, the incidence of work-related rhinitis found is still substantial.

Smoking and atopy appeared to be risk factors for both work-related rhinitis and asthma symptoms. Furthermore the follow-up study also seemed to confirm the hypothesis that occupational rhinitis precedes occupational asthma, since work-related rhinitis was associated with the onset of work-related asthma symptoms. The exact sequence of events should be disentangled in order to facilitate better targeted prevention and early treatment strategies.

A part of the follow-up study among bell pepper employees aimed to 1) identify factors that may lead to leaving work and to 2) study the effect of subsequent allergen avoidance on quality of life. The results of this part of the follow-up study are discussed in **chapter 3**. In 1999, 254 out of the 472 employees had work-related rhinitis and 228 out of 254 completed the Rhinitis-related Quality of Life Questionnaire at that time. After 8-year follow-up in 2007, 91 workers with rhinitis in 1999 were available to fill out the questionnaire again. These questionnaires were used to evaluate the course of nasal disease in terms of perceived severity and impact on daily life. Workers with rhinitis at baseline were more likely to leave their job in bell pepper cultivation for another job. Among the 91 workers, 58 subjects were still at work, whereas 33 subjects had left work. The subjects who left jobs reported substantial improvement in quality of life. In a previous study we demonstrated that rhinitis-related quality of life (RQoL) was predominantly associated with sensitization to bell pepper pollen and not to other concomitant sensitizations to common inhalant allergens. Therefore, we considered the improvement in RQoL in this follow-up study as a result of cessation of bell pepper exposure. We also concluded that work-related rhinitis can be a reason to leave work.

Occupational allergy is a health condition that may have a profound effect on work performance through productivity loss at work as well as sick leave and, hence, may result in higher productivity costs. Up to date, there is limited information on the magnitude of these productivity costs. **Chapter 4** comprises the results of the third part of the follow-up study in which productivity loss and associated costs due to occupational allergy in bell pepper horticulture were investigated.

In total, 142 bell pepper employees, who were still employed in bell pepper horticulture, participated. The prevalence of rhinitis, moderate to severe rhinitis, and asthma symptoms among these employees was 52.9%, 11.4%, and 20.3%, respectively. Productivity loss at work and sick leave was found in 16.9% and 19.1% of subjects, respectively. The total on-the-job productivity loss per person-year in this occupational group was 3.8% and total number of days of sick leave per person-year was 2.2 days (0.8%). Moderate to severe rhinitis symptoms were significantly associated with productivity loss at work and asthma symptoms were significantly associated with both productivity loss at work and sick leave. The total productivity loss amounted to 4.6% time lost and the productivity costs of productivity loss per person-year were €1,122. About half of the productivity loss could be attributed to work-related rhinitis and asthma symptoms. Rhinitis appeared to have an impact on the on-the-job productivity loss without having any effect on sick leave. Apparently, employees with work-related rhinitis usually do not report sick in spite of their symptoms. Furthermore, it was demonstrated that moderate to severe rhinitis but not mild rhinitis was associated with the on-the-job productivity loss.

It was concluded that work-related rhinitis and asthma can cause productivity loss which may consequently result in higher productivity costs. We also stated that since rhinitis and asthma may be a cause to change jobs outside this particular cultivation, the costs calculated might underestimate the economic consequences of occupational allergy among workers with shorter employment. Considering the economic impact, it is essential to develop interventions aimed to prevent the new onset of occupational allergy in these employees.

In **chapter 5** the change in prevalence of NRL sensitization and allergy among operating room employees from a university hospital was estimated 10 years after introduction of sterile powder-free NRL gloves. In 1998 and in 2009, respectively 163 and 178 employees participated in the study. The two groups were comparable concerning gender, smoking habits, job classification, work-related symptoms and atopy. In 2009, the prevalence of sensitization to NRL was significantly lower compared to 1998 (4.5% *vs* 14.1%). Also, NRL allergy was significantly less present in 2009 compared to 1998 (2.8% *vs* 9.8%). The same trend was seen in a subgroup (n = 49) which participated both in 1998 and in 2009. Atopy was significantly associated with the development of sensitization to NRL. This study provided a clear indication that the introduction of sterile powder-free NRL gloves in 1998

is most likely responsible for the reduction in NRL sensitization and NRL allergy prevalence found in 2009.

Due to a shift from open field horticulture towards greenhouses, employees in strawberry horticulture are nowadays highly exposed to several potential allergenic agents. However, no occupational allergy in this branch has been described before. In **chapter 6** the presence of work-related allergic symptoms in strawberry workers was explored first. Secondly, the prove of concept that an IgE-mediated allergy could be responsible for work-related symptoms was described by investigating 3 employees in more detail. 29 of 75 questionnaire respondents (38.7%) reported work-related symptoms, the main symptom being rhinitis (30.7%). Sensitization to strawberry pollen was found in skin tests in the 3 employees with work-related symptoms who were studied in detail. ELISA and immunoblotting with strawberry pollen showed positive results in 2 employees. Birch and grass pollen failed to inhibit IgE binding to strawberry pollen in 1 of 2 employees, indicating that the sensitization to strawberry pollen in this specific employee was not caused by birch or grass pollen originally, but that there is a true primary sensitization to the strawberry pollen. Partial inhibition was seen in the second employee, therefore partial cross-reactivity may be conceivable in this patient. Nasal provocation with strawberry pollen validated clinically relevant allergy to these pollens in 2 of 3 subjects. It was concluded that allergic symptoms attributable to the workplace are present among a proportion of strawberry greenhouse employees. An IgE-mediated occupational allergy to strawberry pollen may contribute to these symptoms. A next research phase is required to determine disease prevalence and incidence, by means of a larger cross-sectional study and a longitudinal study among employees from the start of employment in strawberry horticulture.

Chapter 7 is a general discussion of the results described in the previous chapters. It is concluded that in bell pepper horticulture, the incidence (even after prolonged exposure) and burden of occupational rhinitis/allergy are significant. The first risk factors have been identified. The need for a longitudinal study from the start of employment is emphasized, in order to identify other risk factors and to disentangle the exact sequence of events in the development of an occupational allergy in this branch. Future research should also include studies aimed at the development of interventions to prevent the new onset of occupational allergy in these employees. Furthermore, the prevalence of NRL sensitization and allergy among operating

room employees nowadays is low, most likely due to a substitution of powdered NRL gloves for powder-free NRL gloves. Finally we concluded that allergic symptoms are present among strawberry greenhouse workers and symptoms can be caused by a strawberry pollen allergy. Another research phase is required to determine disease prevalence and incidence, by means of a larger cross-sectional study and a longitudinal study among employees from the start of employment in strawberry horticulture.

Samenvatting

Hoofdstuk 1, de algemene inleiding, begint met het definiëren van beroepsrhinitis (neusklachten), beroepsastma en IgE-gemedieerde beroepsallergie. Enkele data aangaande de epidemiologie van beroepsrhinitis worden weergegeven. Deze gegevens betreffen ook de incidentie van werkgerelateerde rhinitis, waarover weinig bekend is. Afhankelijk van het betrokken beroepsallergeen, varieert de incidentie van 0,3 tot 13,1 per 100 persoonsjaren. Het bewijs voor het feit dat roken en atopie risicofactoren zijn voor het ontstaan van een beroepsrhinitis, is inconsistent. Verder wordt beschreven dat er tot op heden ook weinig bekend is over de gezondheidsgerelateerde kwaliteit van leven (in relatie tot blootstelling) van deze aandoening en nog minder over productiviteitsverlies als gevolg van deze ziekte. Omdat er behoefte is aan meer kennis over de incidentie, de risicofactoren en de socio-economische belasting van werkgerelateerde rhinitis, zijn deze onderwerpen bestudeerd in dit proefschrift. De onderzoekspopulatie betrof een groep paprikakasmedewerkers in Nederland. Deze beroepsgroep is geassocieerd met een hoog percentage aan IgE-gemedieerde beroepsallergie, als gevolg van de hoge expositie aan paprikastuifmeel in de kas.

Omdat de mate van blootstelling de meest belangrijke determinant van sensibilisatie (het ontstaan van allergische antistoffen) en beroepsrhinitis blijkt te zijn, zou vermindering of eliminatie van de bloostelling aan beroepsallergenen de meest effectieve vorm van primaire preventie moeten zijn.
Een voorbeeld van succesvolle vermindering van blootstelling betreft het beroepsallergeen 'natuur rubber latex' (NRL), dat ondermeer in handschoenen, bestemd voor gezondheidszorgmedewerkers, wordt verwerkt. Het poeder in de NRL handschoen blijkt de belangrijkste oorzaak te zijn van aerogene blootstelling aan NRL en speelt daarom een belangrijke rol in het sensibilisatie proces (via inhalatie). Uit diverse studies is gebleken dat het vervangen van gepoederde NRL handschoenen door poedervrije NRL handschoenen inderdaad zorgt voor een aanzienlijke verlaging van de aerogene blootstelling. Er is echter controverse over het bewijs voor de effectiviteit van deze maatregel met betrekking tot primaire preventie, d.w.z. de ontwikkeling van een NRL (latex) sensibilisatie en allergie. Dit onderwerp wordt daarom behandeld in dit proefschrift. Daartoe werden operatiekamermedewerkers, die veelvuldig (steriele) NRL handschoenen dragen, onderzocht.

De inleiding bevat ook een beschrijving van de aardbeienteelt, waar medewerkers tegenwoordig werkzaam zijn in kassen en niet meer in het open veld, zoals

voorheen. Vanwege deze verandering in de werkomgeving, is de blootstelling aan aardbeistuifmeel toegenomen.

Gezien het feit dat de mate van blootstelling de belangrijkste determinant van sensibilisatie en beroepsmatige rhinitis lijkt te zijn, is de ontwikkeling van een nieuwe allergie in deze branche goed denkbaar. Het voorkomen van werkgerelateerde klachten onder aardbeienkasmedewerkers is in dit proefschrift onderzocht. Tevens is getracht te bewijzen dat een IgE-gemedieerde allergie voor aardbeistuifmeel de oorzaak zou kunnen zijn voor de werkgerelateerde klachten.

Hoofdstuk 2 presenteert de resultaten van een vervolgonderzoek naar allergie voor paprikastuifmeel bij paprikakasmedewerkers. Het is bekend dat het stuifmeel van de paprikaplant, gekweekt in kassen, een beroepsallergie kan veroorzaken. Een dwarsdoorsnede studie onder 472 paprikakaswerknemers uit 1999 liet prevalenties van sensibilisatie voor paprikastuifmeel zien van 28% en voor werkgerelateerde rhinitis van 49%. De gemiddelde duur van dienstverband betrof 8 jaar. Werkgerelateerde symptomen waren geassocieerd met sensibilisatie voor bestanddelen van de paprikaplant (voornamelijk paprikastuifmeel), leeftijd, en atopie. Het onderzoek dat gepresenteerd wordt in dit proefschrift is gebaseerd op de follow-up van alle deelnemers van die eerdere dwarsdoorsnede studie. Het doel van de huidige studie was de incidentie en de risicofactoren van werkgerelateerde rhinitis te onderzoeken. In totaal waren 280 van de 472 medewerkers beschikbaar voor vragenlijsten en bij 250 werknemers werden opnieuw allergietesten uitgevoerd.

Tijdens de 8-jaar follow-up bleek de cumulatieve incidentie van werkgerelateerde rhinitis 19% en van sensibilisatie voor het paprikastuifmeel 9%. Atopie en roken waren significant geassocieerd met de ontwikkeling van rhinitis. De cumulatieve incidentie van werkgerelateerde astma symptomen bleek 8%. Wederom bleken atopie en roken significante risicofactoren.

Vanwege het gemiddelde dienstverband van 8 jaar in de eerste studie werd verondersteld dat de prevalentiecijfers van 1999 de cumulatieve incidentie zouden benaderen en daarom werd verwacht dat de incidentiecijfers in 2007 vergelijkbaar zouden zijn met de prevalentiecijfers uit 1999. Echter, het feit dat de piek van ontwikkeling van sensibilisatie en symptomen blijkbaar optreedt in de eerste jaren van een dienstverband, en niet in een latere fase van langdurige

blootstelling, kan verklaren waarom de incidentie van werkgerelateerde rhinitis lager ligt dan de prevalentie die gevonden werd in de eerste studie. Bovendien is een Healthy worker-effect (HWE) een andere mogelijke verklaring. In onze studie lijkt een HWE te zijn opgetreden omdat rhinitis symptomen in 1999 significant meer aanwezig waren in de groep werknemers die de kas had verlaten tijdens de follow-up, vergeleken met de groep die nog werkzaam was in de kas. Dit duidt erop dat rhinitis een "uitdrijvende" factor kan zijn. Zestien van de 168 ex-werknemers vermeldden expliciet dat allergische symptomen de hoofdreden was voor hun vertrek. Hiermee rekening houdend, is de incidentie van sensibilisatie en werkgerelateerde rhinitis die gevonden werd, nog steeds aanzienlijk.

Roken en atopie bleken risicofactoren te zijn voor zowel werkgerelateerde rhinitis als voor astma symptomen. Bovendien lijkt deze studie ook de hypothese te bevestigen dat beroepsrhinitis voorafgaat aan astma, omdat werkgerelateerde rhinitis geassocieerd was met het ontstaan van werkgerelateerde astma symptomen. In toekomstig onderzoek moet de exacte volgorde van ontwikkeling van een beroepsallergie in deze branche worden opgespoord om beter gerichte preventie en vroege behandelingstrategieën te kunnen ontwikkelen.

Tevens is in het vervolgonderzoek getracht 1) factoren te identificeren die kunnen leiden tot het opzeggen van een baan en 2) het effect, van het erop volgende vermijden van beroepsallergenen, op de kwaliteit van het leven te bestuderen. De resultaten van dit onderdeel van de studie worden besproken in **hoofdstuk 3**. In 1999 hadden 254 van de 472 werknemers werkgerelateerde rhinitis en 228 van de 254 vulden destijds de 'rhinitis specifieke kwaliteit van leven' vragenlijst in. Na 8 jaar follow-up in 2007, waren 91 werknemers met rhinitis in 1999 beschikbaar voor het opnieuw invullen van de vragenlijst en werd bij deze werknemers het verloop van nasale ziekte beoordeeld in termen van gepercipieerde ernst en de impact op het dagelijks leven. Werknemers met rhinitis in 1999 verlieten vaker hun baan in de paprikateelt voor een andere baan. Van de 91 werknemers, waren 58 nog aan het werk, terwijl 33 proefpersonen het werk hadden verlaten. De proefpersonen die vertrokken waren, vermeldden substantiële verbetering van kwaliteit van leven. In de vorige studie is aangetoond dat de rhinitis specifieke kwaliteit van leven voornamelijk is geassocieerd met sensibilisatie voor paprikastuifmeel en niet met gelijktijdige sensibilisatie voor andere gewone inhalatie allergenen. Geconcludeerd werd dat de verbetering in de rhinitis specifieke kwaliteit van leven een gevolg is van het elimineren van blootstelling aan paprikastuifmeel.

Bovendien werd geconcludeerd dat werkgerelateerde rhinitis een reden kan zijn om het werk in de paprikateelt te verlaten.

Een inhalatieallergie kan een diepgaand effect hebben op de arbeidsproductiviteit door zowel productiviteitsverlies op het werk als ziekteverzuim. Tot op heden is er beperkte kennis over de omvang van dit verlies en de daarmee gepaard gaande productiviteitskosten. **Hoofdstuk 4** bevat de resultaten van het derde deel van het vervolgonderzoek, waarin het productiviteitsverlies en de bijbehorende kosten, als gevolg van een allergie in de paprikateelt, werden onderzocht. In totaal namen 142 paprikakasmedewerkers deel aan de studie. Al deze werknemers waren nog steeds werkzaam waren in paprikateelt. De prevalentie van rhinitis, matige tot ernstige rhinitis en astmasymptomen bij deze medewerkers was respectievelijk 52,9%, 11,4% en 20,3%. Productiviteitsverlies op het werk en ziekteverzuim werden gevonden in respectievelijk 16,9% en 19,1% van de proefpersonen. Het totale productiviteitsverlies op het werk per persoonsjaar in deze beroepsgroep bedroeg 3,8% en het totale aantal dagen ziekteverzuim per persoonsjaar bedroeg 2,2 dagen (0,8%). Matige tot ernstige rhinitis symptomen bleken significant geassocieerd met productiviteitsverlies op het werk en astma symptomen waren significant geassocieerd met zowel productiviteitsverlies op het werk als ziekteverzuim. Het totale productiviteitsverlies bedroeg 4,6% aan verloren tijd en de daarmee gepaard gaande productiviteitskosten bedroegen €1.122. Ongeveer de helft van het productiviteitsverlies kon worden toegeschreven aan werkgerelateerde rhinitis en astma symptomen. Geconcludeerd werd dat werkgerelateerde rhinitis en astma substantieel productiviteitsverlies kunnen veroorzaken en daarom kunnen resulteren in significante productiviteitskosten. Omdat rhinitis en astma kunnen leiden tot het vertrek uit de paprikateelt, zouden de economische consequenties voor werknemers met een korter dienstverband wel eens onderschat kunnen worden. Gezien de economische impact is het noodzakelijk om interventies te ontwikkelen, die gericht zijn op het voorkomen van allergie.

In **hoofdstuk 5** wordt de verandering in prevalentie van NRL sensibilisatie en allergie onder operatiekamermedewerkers van een academisch ziekenhuis (Erasmus MC), 10 jaar na introductie van poedervrije NRL handschoenen, beschreven. In 1998 en in 2009, namen respectievelijk 163 en 178 medewerkers deel aan het onderzoek. De twee groepen waren vergelijkbaar met betrekking tot geslacht, rookgewoonten, arbeidskarakteristieken, werkgerelateerde klachten en atopie. In 2009 was de prevalentie van sensibilisatie voor NRL significant lager

in vergelijking met 1998 (4,5% versus 14,1%). Ook NRL allergie werd significant minder vaak aangetoond in 2009 ten opzichte van 1998 (2,8% versus 9,8%). Dezelfde trend werd gezien in een subgroep (n = 49) werknemers die zowel in 1998 als in 2009 deelnamen aan de studie. Atopie bleek significant geassocieerd met de ontwikkeling van NRL sensibilisatie en allergie. De resultaten van deze studie wijzen erop dat de invoering van steriele poedervrije NRL handschoenen in 1998 zeer waarschijnlijk geleid heeft tot een daling van de prevalentie van NRL sensibilisatie en allergie in 2009.

Als gevolg van een verschuiving van het kweken van aardbeien in het open veld richting de kassen, worden de werknemers tegenwoordig in hoge mate blootgesteld aan verschillende (potentiële) allergene stoffen. Tot op heden is er echter nog geen beroepsallergie in deze branche beschreven. In **hoofdstuk 6** is allereerst onderzocht of aardbeienkasmedewerkers werkgerelateerde allergische symptomen ervaren. Ten tweede werd getracht te bewijzen dat een IgE-gemedieerde allergie de oorzaak zou kunnen zijn van werkgerelateerde klachten, door 3 werknemers uitgebreider te onderzoeken. Van de 75 vragenlijst respondenten vermeldden 29 (38,7%) werkgerelateerde symptomen. Rhinitis werd het meest genoemd (30,7%). Sensibilisatie voor aardbeistuifmeel werd aangetoond bij de 3 werknemers met werkgerelateerde klachten die uitgebreider werden onderzocht. ELISA en immunoblotting met aardbeistuifmeel lieten positieve resultaten zien bij 2 medewerkers. IgE-binding aan stuifmeel kon niet geremd worden door berken- of graspollen bij 1 van deze 2 medewerkers. De sensibilisatie voor aardbeistuifmeel bij deze specifieke werknemer wordt dus niet veroorzaakt door een boom- of graspollen allergie (kruisreactiviteit), maar er is sprake van een primaire sensibilisatie voor het stuifmeel van de aardbeiplant. Gedeeltelijke remming werd gezien bij de tweede werknemer en daarom is gedeeltelijke kruisreactiviteit bij deze werknemer nog mogelijk. Nasale provocatie met aardbeistuifmeel toonde de klinische relevantie van de sensibilisatie voor deze pollen aan bij 2 van de 3 medewerkers. Er werd geconcludeerd dat werkgerelateerde allergische symptomen aanwezig zijn bij een deel van de aardbeienkasmedewerkers. Een IgE-gemedieerde allergie voor aardbeistuifmeel kan bijdragen aan deze symptomen. Een volgende onderzoeksfase is nodig om de ziekteprevalentie en ziekte-incidentie vast te stellen door middel van een grootschaliger dwarsdoorsnede onderzoek en een longitudinale studie onder medewerkers vanaf het moment van in dienst treden in de aardbeienteelt.

Hoofdstuk 7 is een algemene discussie van de resultaten beschreven in de voorgaande hoofdstukken. Geconcludeerd wordt dat de incidentie (zelfs na langdurige blootstelling) en de ziektelast van beroepsrhinitis in de paprikateelt significant zijn. De eerste risicofactoren zijn geïdentificeerd. Het belang van grootschalig longitudinaal onderzoek onder werknemers vanaf het moment van in diensttreden wordt benadrukt, zodat andere risicofactoren geïdentificeerd kunnen worden en de precieze volgorde in de ontwikkeling van een beroepsallergie in deze branche opgespoord kan worden. Toekomstig onderzoek zou ook studies moeten bevatten die gericht zijn op het ontwikkelen van een interventie met als doel een beroepsallergie bij deze werknemers te voorkomen.

De prevalentie van NRL sensibilisatie en allergie onder operatiekamermedewerkers van het Erasmus MC, is tegenwoordig laag. De meest waarschijnlijke oorzaak van deze lage prevalentie is de vervanging van gepoederde NRL handschoenen door poedervrije NRL handschoenen.

Tot slot wordt geconcludeerd dat werkgerelateerde allergische symptomen vermeld worden door aardbeienkasmedewerkers en dat deze symptomen mogelijk verklaard kunnen worden door een aardbeistuifmeelallergie. Een volgende onderzoeksfase is aangewezen om de ziekteprevalentie en ziekte-incidentie te bepalen, door middel van een grootschaliger dwarsdoorsnede onderzoek en een longitudinale studie onder medewerkers vanaf het moment van in dienst treden in de aardbeienteelt.

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als een tweede huis (ik zie uit naar de Jiska sticker op de stoel:-). Ik ben ongelooflijk blij met jou en wat fijn dat je mijn paranimf wilt zijn!

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Marc, mijn lieve grote broer. Je leven speelt zich de afgelopen jaren af in Amsterdam, Antwerpen en Pijnacker. Ondanks je drukke bestaan, weet je steeds weer tijd (in de auto van Amsterdam naar Antwerpen of andersom) te vinden om te horen hoe het is met je kleine zusje. Heel veel dank voor je zorgzaamheid! Jij en vooral ook Reshma weten ons altijd weer te verrassen met exotische lekkernijen en lieve kadootjes uit verre oorden.

Ruud, lieve oom. Door jou heb ik Amsterdam op een andere manier leren kennen. Op de fiets door een stadsdeel dat nog onbekend was voor mij (maar waarin ik later zou gaan wonen!), op zoek naar mooie gevels in de stijl van de Amsterdamse school. Nog niet ontdekte eettentjes uitproberen of voor de zoveelste keer aanschuiven bij de Surinamer:-). Ik zie uit naar nog veel meer leuke citytripjes!

Tante Evie: dank voor de kooklessen en de gezellige uurtjes die die lessen met zich meebrengen. Door je verhalen heb ik veel geleerd over onze familie en over Indonesië. We willen graag nog meer lessen volgen!

Frouk, lieve 'tant', wat fijn dat je je zo af en toe over je nichtje ontfermt en dat je zo met me meeleeft. Dank voor alle gezellige etentjes bij jou en Johan thuis, vol goede gesprekken. Hopelijk volgen er nog vele meer!

Lieve papa, hoewel het pas in het afgelopen jaar vorm heeft gekregen, heb ik de liefde voor het onderwijs van jou 'geërfd'. Hoe jij het beste uit je leerlingen weet te halen is voor mij een groot voorbeeld. Heel veel dank dat je altijd voor me klaarstaat (al moet je ervoor naar Tokio rijden) en ook altijd laat weten hoe trots je op me bent, wat ik ook doe. En natuurlijk voor je hulp bij alle technische zaken in mijn leven:-).

Lieve Fried, heel erg bedankt voor al je warmte en je grote interesse. De gesprekken over het leven en de 'papieren bal' vind ik heel waardevol en ik zie uit naar de volgende ronde.

Lieve Wip, jij weet het al, maar ik wil op deze plek graag nog weer eens laten weten dat ik ongelooflijk blij met jou ben. Je optimisme en je humor hebben me op de been gehouden als ik het even niet meer zag zitten de afgelopen maanden. Door je doortastendheid en hulp bij het redigeren van mijn boekje is het me gelukt om de deadlines (bijna allemaal) te halen. Wat heerlijk dat er straks even niets meer hoeft en dat we straks op vakantie kunnen zonder artikelen 'tussen ons in'. En wat leuk dat mijn familie, sinds ik jou ken, meteen ook is uitgebreid met hele fijne mensen: Jannie en Gert, dank voor jullie enorme interesse en voor de gezellige etentjes en uitjes. Jet, Maud, Kaya en Vigo: wat gezellig om samen aan tafel te 'smullen' van de door Kaya en Vigo -in eigen keuken- gebakken (hete!) eitjes en gezonde groentes en daarnaast te genieten van wat Maud ons voor lekkers voorschotelt!

Lieve mama, mijn proefschrift is aan jou opgedragen. Ik weet zeker dat je er nu bij bent en dat je ook heel erg geniet. Je lieve glimlach staat in mijn geheugen gegrift en al het moois dat je me meegegeven hebt, blijft bestaan. Ik ben enorm trots jouw dochter te mogen zijn.

Curriculum Vitae

Jiska Annette Patiwael werd geboren op 30 september 1977 te Nieuwegein. In 1995 behaalde zij haar gymnasium diploma aan het Dr. F. H. de Bruyne Lyceum te Utrecht. In datzelfde jaar startte zij met de studie geneeskunde aan de Katholieke Universiteit Leuven in België. De geneeskunde opleiding werd in het jaar daarop vervolgd aan de Universiteit Leiden, waar in 2003 het artsexamen werd behaald. In de jaren erna was zij werkzaam als ANIOS op de poli allergologie van het Erasmus MC te Rotterdam en bij de Allergie Praktijk Arnhem. In februari 2006 begon zij aan haar promotieonderzoek onder leiding van prof. dr. R. Gerth van Wijk op de afdeling inwendige geneeskunde, sector allergologie, Erasmus MC te Rotterdam. Sinds maart 2011 is zij werkzaam als arts-docent aan de masteropleiding geneeskunde van het VUmc te Amsterdam.

Portfolio

Courses

Classical methods for Data-analysis (NIHES), 2008	5.7 ECTS

Conferences

Dutch Society for Allergology (NVvA) Congress 2010, oral presentation	1 ECTS
European Academy of Allergy and Clinical Immunology (EAACI) Congress 2009, poster presentation	1 ECTS
European Academy of Allergy and Clinical Immunology (EAACI) Congress 2008, oral presentation	1 ECTS
Dutch Society for Allergology (NVvA) Congress 2007, poster presentation	1 ECTS
World congress on Work-Related & Environmental Allergy (WOREAL) 2007, oral presentation	1 ECTS
European Academy of Allergy and Clinical Immunology (EAACI) Congress 2006	1 ECTS

Teaching activities

Teaching medical students, VUmc Amsterdam, 2011	20 ECTS