Asthma and hand dermatitis in cleaning workers: characteristics and risk factors

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This thesis has been conducted at the Centre for Research in Environmental Epidemiology (CREAL) under the supervision of Dr. Jan-Paul Zock and tutored by Prof. Josep Maria Antó Boqué.

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In loving memory to my grand parents,

Manuel Vizcaya and Ascensión Fernández.

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Oxford, 2011. EPICOH congress.

2 ABSTRACT

ABSTRACT

Introduction

There is evidence that cleaning workers are at higher risk of asthma and hand dermatitis but the specific risk factors the mechanisms remain unknown to date.

Methods

A systematic review of the literature was performed. A two stage epidemiological study was designed to investigate the objectives. The first stage consisted of a cross-sectional survey of asthma and hand dermatitis symptoms among employees of cleaning companies. The second stage consisted of a case-control study of asthma biomarkers and lung function among current cleaning workers. The project evaluated the associations of asthma, biomarkers of immune response, inflammation, oxidative stress, eosinophilic inflammation and lung epithelium damage with cleaning related exposures.

Results

(i) Cleaning workers are at increased risk of asthma compared to other workers and the main risk factors are the use of irritant and multiuse cleaning products and working at hospitals, outdoor areas and private homes; (ii) Cleaning workers have a higher prevalence of hand dermatitis compared to other workers and the main risk factors are the use of irritant and perfumed cleaning products and working at outdoor areas, residential building common areas and schools; (iii) Risks factors for asthma and hand dermatitis are convergent; (iv) Asthmatic cleaning workers had similar biomarker levels of lung eosinophilia, inflammation and damage than non-asthmatics, but lower lung function and higher total and specific serum IgE levels.

Conclusions

Irritant-induced asthma plays an important role in cleaning-related asthma, but allergic sensitisation must be considered. Dermal exposure to irritant or allergenic cleaners may cause hand dermatitis and asthma. Prevention measures must be considered to reduce the burden of disease associated to cleaning-related exposures.

RESUMEN

Introducción

Hay evidencia de que los trabajadores de limpieza tienen un mayor riesgo de asma y dermatitis de manos, pero los factores de riesgo específicos y los mecanismos implicados son aún desconocidos.

Métodos

Se realizó una revisión sistemática de la literatura. Se diseñó un estudio epidemiológico de dos etapas para investigar los objetivos. La primera etapa consistió en un estudio transversal sobre síntomas de asma y de dermatitis de manos en una población de empleados en empresas de limpieza. La segunda etapa consistió en un estudio de casos y controles en el que se evaluaron biomarcadores de asma y función pulmonar en una población de trabajadores de limpieza. El proyecto evaluó las asociaciones de asma, biomarcadores de respuesta inmunológica, inflamación, eosinofilia e inflamación pulmonar, estrés oxidativo y daño en el epitelio pulmonar con exposiciones específicas relacionadas con la limpieza.

Resultados

(i) Los trabajadores de limpieza tienen mayor riesgo de asma que otros trabajadores y los principales factores de riesgo son el uso de productos irritantes y multiusos y trabajar en hospitales, áreas abiertas y casas particulares; (ii) Los trabajadores de limpieza tienen mayor prevalencia de dermatitis de manos que otros trabajadores y los principales factores de riesgo son el uso de productos irritantes y perfumados y trabajar en áreas abiertas, en comunidades o porterías y en escuelas; (iii) Los factores de riesgo para asma y dermatitis de manos son convergentes; (iv) Los limpiadores asmáticos tenían niveles similares de biomarcadores de eosinofilia e inflamación pulmonar, daño epitelial y estrés oxidativo que los no asmáticos pero peor función pulmonar y mayor nivel de IgE total y específica en suero.

Conclusiones

El asma inducido por irritantes juega un papel importante en el asma relacionado con la limpieza, pero la sensibilización alérgica también debe considerarse. La exposición dérmica a limpiadores irritantes o alergénicos puede causar asma y dermatitis de manos. Deben considerarse medidas de prevención para reducir la carga de enfermedad asociada a las exposiciones relacionadas con la limpieza.

RESUM

Introducció

Hi ha evidència de que els treballadors de la neteja tenen un major risc d'asma i dermatitis de mans, però els factors de risc específics i els mecanismes implicats són encara desconeguts.

Mètodes

Es va realitzar una revisió sistemàtica de la literatura. Es va disenyar un estudi epidemiològic en dues etapes per a investigar els objectius. La primera etapa va consistir en un estudi transversal sobre símptomes d'asma i de dermatitis de mans en una població d'empleats en empreses de neteja. La segona etapa va consistir en un estudi de casos i controls en el que es varen avaluar biomarcadors d'asma i funció pulmonar en una població de treballadors de la neteja. El projecte va avaluar les associacions d'asma, biomarcadors de resposta immunològica, inflamació, eosinofília i inflamació pulmonar, estrès oxidatiu i dany a l'epiteli pulmonar amb exposicions específiques relacionades amb la neteja.

Resultats

(i) Els treballadors de neteja tenen major risc d'asma que altres treballadors i els principals factors de risc són l'ús de productes irritants i multiús i treballar a hospitals, àrees obertes i cases particulars; (ii) Els treballadors de la neteja tenen major prevalença de dermatitis de mans que altres treballadors i els principals factors de risc son l'ús de productes irritants i perfumats i treballar a àrees obertes, comunitats i porteries i escoles; (iii) Els factors de risc per asma i dermatitis de mans són convergents; (iv) Els netejadors asmàtics tenien nivells semblants de biomarcadors d'eosinofília i inflamació pulmonar, dany epitelial i estrès oxidatiu als dels no asmàtics, però pitjor funció pulmonar i major nivell d'IgE total i específica en sèrum.

Conclusions

L'asma induït per irritants juga un paper important en l'asma relacionat amb la neteja, però la sensibilització al·lèrgica també s'ha de considerar. L'exposició dèrmica a netejadors irritants o al·lergènics pot causar asma i dermatitis de mans. S'han de considerar mesures preventives per a reduir la càrrega de malaltia associada a les exposicions relacionades amb la neteja.

3 PREFACE

This thesis represents a compilation of the scientific publications co-authored by the PhD candidate according to the procedures of the Biomedicine PhD program of the Department of Experimental and Health Sciences of University Pompeu Fabra. The book includes an abstract, a general introduction consistent of background, rationale and objectives, results (one review paper and three original articles), a global discussion and final conclusions.

The thesis is focused on the respiratory and dermal effects of cleaning-related exposures. The core of the results is based on data from the Epidemiological Study of Asthma in Cleaning Workers (EPIASLI-2). EPIASLI-2 was lead by Dr. Jan-Paul Zock and co-ordinated by the PhD candidate during four years including data gathering, management and analysis. Hints for future research in cleaning-related health are provided as well as the future involvement of the candidate in the topic.

4 ABREVIATIONS

BDC	Bronchodilator challenge
BHR	Bronchial hyperresponsiveness
BMI	Body mass index
CC16	16kDa Clara cell secretory protein
EBC	Exhaled breath condensate
EPIASLI	Epidemiological study of asthma and cleaning work
$FEF_{25\%-75\%}$	Forced expiratory flow between 25% and 75% of FVC
FeNO	Fraction of exhaled nitric oxide
FEV_1	Forced expiratory volume in the first second
FGF	Fibroblast growth factor
FVC	Forced vital capacity
GM	Geometric mean
GMR	Geometric mean ratio
IFN-γ	Interferon gamma
IgE	Immunoglobulin E
IL	Interleukin
Ip10	Interferon- γ-induced protein
OA	Occupational asthma
OR	Odds ratio
SP-D	Pulmonary surfactant protein-D
TNF-α	Tumour necrosis factor alpha
VEGF	Vascular endothelial growth factor
WEA	Work-exacerbated asthma
WRA	Work-related asthma

5 INTRODUCTION

5.1. Asthma

5.1.1. Definition

Asthma is a complex respiratory disorder defined by its clinical, physiological and pathological characteristics (1). The main clinical feature is a history of episodic attacks of shortness of breath, often during night, and wheeze. At the physiological level it is characterised by reversible airflow limitation, which is not always complete and may occur spontaneously or with adequate treatment. The dominant pathological characteristic is airways inflammation and remodelling of the epithelium (2). Several different cells and cellular elements play a role in the onset or aggravation of asthma, which has several genetic and environmental factors that lead to many different phenotypes of the disease (1).

5.1.2. The burden of asthma

Asthma is one of the most common chronic disorders in the world and its prevalence varies across the world (3). It is estimated that around 300 million people in the world currently suffer from asthma (4), and the global prevalence ranges from 1 to 18% across different countries (2) (figure 1). Among other chronic diseases, asthma has a large impact on public health; it has been estimated that asthma accounts for 15 million of disability-adjusted life years (DALYs) lost per year, representing 1% of all DALYs lost worldwide. Asthma, considered a preventable disease, accounts for 1 in every 250 deaths worldwide (4).

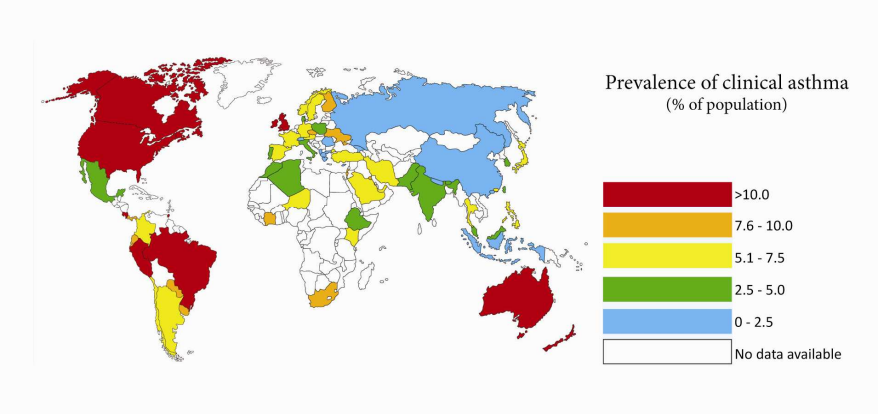

Figure 1. World map of the prevalence of clinical asthma . *(Adapted from Masoli, 2004)*

The number of asthmatic people has been increasing constantly in the last decades, mainly in developed countries (3;5;6) (figure 1). It has been hypothesized that the westernisation of countries is associated with increasing rates of asthma around the world with a parallel rise of atopy and other allergy-related disorders like eczema and rhinitis (4). Gene-environment interactions and epigenetics may be an alternative explanation, or at least complementary, for the increased rates of asthma (3). However, some authors suggest that the increase in asthma rates have reached a plateau (7). On the other hand, some authors suggest that the increasing rates in asthma may be apparent but not real and due to an increased awareness of asthma symptoms and/or an increased willingness of reporting them (8) and, perhaps, an increase in the recognition and diagnosis by physicians. In poorer countries, asthma incidence has increased as well, but at slower rates (9). A follow-up study conducted in Africa showed an increased prevalence of asthma, allergic rhinitis and atopic eczema among adolescents (10).

5.1.3. Classification of asthma

Diagnosis of asthma in the clinical practice is the simplification of a multi-phenotypic disorder into a single disease (11). The goal of the classification of asthma is to facilitate a better understanding of the disease characteristics and aetiology both for researchers and clinicians and thus to help its management. Asthma, as a complex disease, has different factors that define many distinguishable phenotypes (1;12;13). Two main broad categories of asthma, allergic and non-allergic, have been the most common classification both in research and in clinical practice. Although the association between asthma and atopy is well established, the links between these two conditions are not completely defined. In Europe the percentage of new-onset asthma in adults attributable to atopy represents a small proportion that varies across countries from 12 to 21% (14). Other classifications from the American and European guidelines have been proposed for asthma according to the severity of its clinical traits and, more recently, to the level of control of the disease manifestations with medication (1). Besides this, several other phenotypes may be considered based on the current knowledge of asthma characteristics like clinical and physiological traits other than severity or resistance to treatment, environmental triggers and inflammatory sub-phenotypes (11).

Table 1. Phenotypes of asthma

Classification	Description	Subcategories	References
Clinical or physiological phenotypes			
Severity-defined	Symptoms and lung function before treatment.	Intermittent, mild persistent, moderate persistent and severe persistent	(1)
Exacerbation-prone	Defined by the frequency and severity of asthma exacerbations		(15;16)
Chronic airflow restriction	Marked airflow restriction but moderate symptoms and exacerbations		(17;18)
Treatment-resistant	Level of asthma control with medication.	Controlled, partly controlled and uncontrolled	(1)
Defined by age at onset	Cut point age must be defined arbitrarily a priori (12 or 16 years old are generally used)	Early/childhood-onset (first attack: <16y) and late/adult-onset (first attack: >16y)	(19;20)
Environmental triggers			
Environmental allergens	Allergic sensitisation as a cause for the development of asthma	Allergic and non-allergic	(14;21;22)
Aspirin or NSAID drugs	Induced by aspirin or other NSAIDs. Usually affects leukotrienes synthesis pathways.		(23;24)
Occupational allergens or irritants	Asthma due to causes present in the workplace.	Occupational asthma, work aggravated asthma and RADS	(25-28)
Menses	Pre-menstruation asthma. Probably due to the pro-inflammatory properties of hormones.		(29)
Exercise	Asthma triggered by cold-air or in response to exercise		(30)
Inflammatory phenotypes			
Eosinophilic	Increased count of eosinophils in the airways		(13;31;32)
Neutrophilic	Increased count of neutrophils in the airways		(12;13;33)
Pauci-granulocitic	Normal levels of eosinophils and neutrophils in the airways		(13;33)

Table 1 summarises the main phenotypes associated with each of the three former categories with examples and relevant publications. A special consideration must be given to the point that all this phenotypes are dynamic and that there is multiple overlap (figure 2).

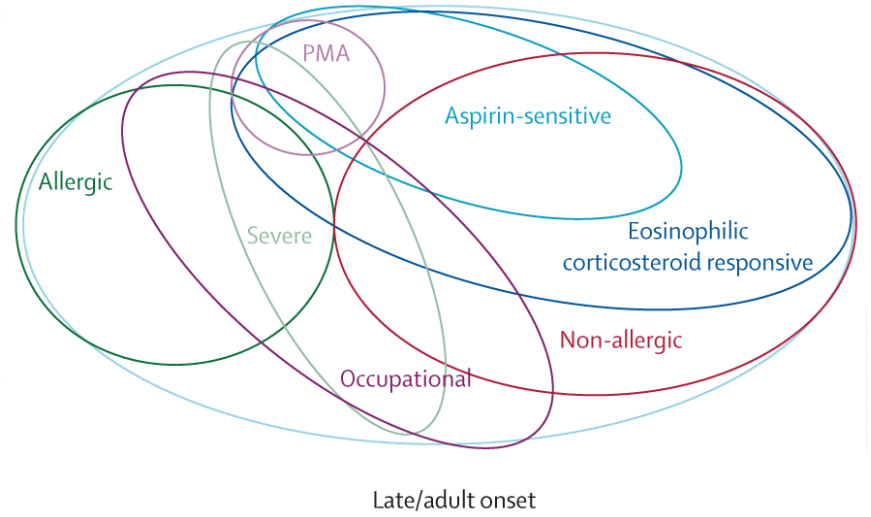

Figure 2. Venn diagram approach to the identification of phenotypes of adult-onset asthma. *(Adapted from Wenzel, 2006)*

5.2. Work-related asthma

5.2.1. Definitions and burden of disease

For a disease that was described many centuries ago (34), defining work-related asthma (WRA) has met several difficulties. WRA is a generic term that encompasses both occupational asthma (OA) and work-exacerbated asthma (WEA) (35). In the American Thoracic Society guidelines, OA is defined as asthma caused by exposures present during work, with a cause-specific relationship between workplace exposure and asthma. WEA is defined as the aggravation of pre-existing or coincident asthma

due to work-specific causes (36). Similarly, authors of a critical review of the definitions and types of OA stated that the definition of OA should be limited to those conditions in which asthma is caused by occupation (37) and differentiated from WEA. There are two recognised subtypes of OA: 1) immunological occupational asthma, and 2) Irritant-induced asthma (36;37).

WRA is one of the most common occupational respiratory diseases worldwide (26;38-40). Epidemiological studies indicate that a range of 7-51% of all asthma cases may be attributable to occupational exposures, with a median population-attributable risk (PAR%) of 17% (41). The 2002 American Thoracic Society statement on the contribution of occupational exposures to asthma suggest that the median PAR% is 15% (42). In European countries, more recent evidence set the population-attributable risk (PAR%) of adult asthma to occupational exposures between 10 and 25%, equivalent to a new-onset occupational asthma of 250-300 cases per million people per year (25).

There are two common variants of WRA that should be differentiated: asthma-like disorder and eosinophilic bronchitis. The former is characterised by asthma symptoms that may occur in naïve subjects without previous exposure to asthmogens and that are associated with systemic symptoms. The latter is characterised by chronic cough and sputum eosinophilia in the absence of variable airflow limitation (28;43).

5.2.2. Socio-economic and clinical implications

Although, both OA and WEA represent a common entity, the socioeconomic and clinical implications differ considerably (28). Reducing workplace exposure to respiratory irritants, controlling exposure to

relevant environmental allergens and irritants such as tobacco smoke and optimizing asthma therapy often allow workers with WEA to continue working in the same job (28;36). These options can be managed at lower costs than the cost of completely removing a subject with OA from the workplace, which is the recommended preventive measure in this case (28). Despite these secondary preventive measures, around 70% of workers with OA who ceased their offending occupational exposures still experience asthma symptoms and retain non-specific bronchial hyperresponsiveness during years, (36) suggesting the importance of reducing the burden of disease rather than improving management. As suggested by Paggiaro et al., the determinants of this unfavourable prognosis are: long duration of the exposure before the onset of asthma, long duration of symptoms before diagnosis, baseline airway obstruction, dual response after specific challenge testing and the persistence of markers of airway inflammation in bronchoalveolar lavage fluid and bronchial biopsy (44). Furthermore, other occupational respiratory disorders related to asthma, such as chronic bronchitis, may also persist after exposure cessation (45). Although the decrease in pharmaceutical expenses and asthma severity, exposure cessation leads to socioeconomic consequences for the offended worker such as loss of work-derived income and/or professional downgrading (46). The socioeconomic impact of WEA has been less studied, but the outcomes appear similar to those of OA (47;48), and thus deserves a special attention different of non-occupational asthma, since the consequences differ.

5.2.3. Occupational asthma

Occupational asthma (OA) is defined as a disease characterized by variable airflow limitation and/or airway hyper-responsiveness due to

causes and conditions attributable to a particular occupational environment and not stimuli encountered outside the workplace (49). To date, more than 350 substances have been recognized as a cause of OA or chronic bronchitis by the US National Institute of Health (50). There is general agreement that OA can be divided into two different types according to the implicated mechanisms: immunological and non-immunological OA. The latter is generally characterised by the absence of a latency period (27;28). However, It is known that asthma may be induced after repetitive moderate-to-high irritant exposures or after a single massive exposure to irritants (RADS or acute irritant induced-asthma) (36;51;52). Immunological IgE-mediated, appears after a period necessary for the sensitisation to the causal agent, and may be IgE-mediated (for high molecular weight (HMW) and some low molecular weight (LMW) agents) or non-IgE-mediated (for most LMW agents) (27). There are several cellular and molecular events associated with the pathophysiology of OA. The inflammation process is similar in both IgE dependent and IgE independent immunological OA (figure 3). In IgE dependent OA, there is an increase in the number of activated eosinophils, lymphocytes and mast cells in response to the antigen presence in the airways, as a consequence of a CD4 type 2 immunologic response that leads to the production of specific IgE antibodies by interleukin (IL)-4/IL-13–stimulated B cells (28). In IgE independent OA, a mixed CD4/CD8 type 2/type 1 immunologic response may play a role. The mechanisms of non-immunological or irritant-induced asthma are not well understood yet. It has been suggested that alarm signals after lung epithelium damage may activate in turn a cellular inflammatory response that leads to asthma (28). In all cases, thickening of the reticular basal membrane is considered a histopathologic feature of OA (28).

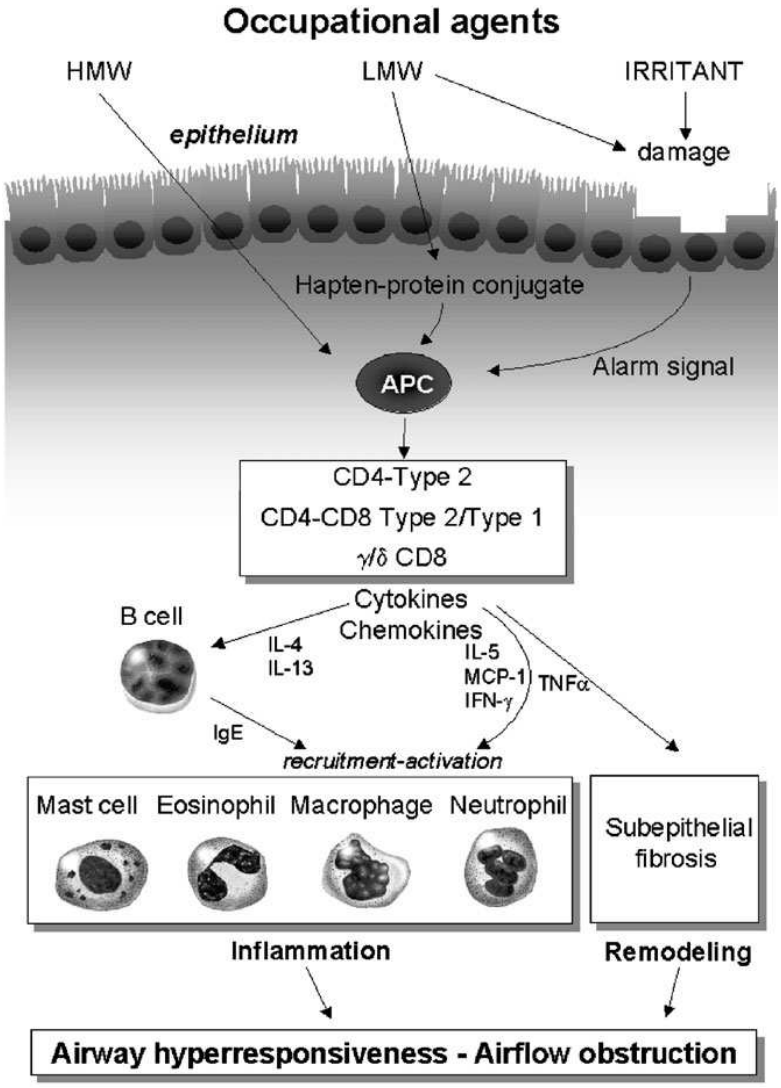

Figure 3. Possible mechanisms in OA. *(Adapted form Mapp et al. 2005 AJRCCM)*

5.2.3.1. Immunological occupational asthma

Usually OA involves a specific IgE-mediated mechanism. In this case, OA is similar to asthma unrelated to work (27;28;53). As mentioned above, there are several occupational agents that have been identified as asthmogens, particularly HMW agents (eg, wheat flour and other plant

animal or enzymatic proteins) which induce asthma through sensitisation and posterior production of specific IgE antibodies. Similarly, some LMW agents may induce asthma through IgE-dependent mechanisms (eg, chlorinated platinum salts, trimellitic anhydride and other acids anhydride) (54;55). In this case, LMW agents act as haptens and need to conjugate with autologous or heterologous proteins to produce an IgE-mediated response.

Many LMW agents cause asthma that has the clinical and physiological characteristics of atopic asthma, but without consistent detectable levels of specific IgE antibodies or upregulation of IgE receptors (27;56). The most paradigmatic case is diisocyanates which are the main cause of occupational asthma according to several surveillance programs around the world (38;40). Some studies have shown a similar IgE-mediated response in asthmatics due to HMW agents and asthmatics due to diisocyanates (57). In some cases a mixed Th1/Th2 response is triggered by the exposure to diisocyanates, what is compatible with the absence of atopy and high levels of eosinophils in the airways (58), but still an immunologic response.

The airway inflammation process is similar in IgE-mediated and non IgE-mediated responses. In both cases, eosinophilia is associated with an increased number of $CD4^+$ T cells, increased expression of IL-2 receptor and production of several proinflammatory cytokines and chemokines such as tumour necrosis factor α, Interferon-γ, monocyte chemoattractant protein 1 and several IL, mainly IL-2 and IL-5 (27;28). Release of inflammatory mediators such as cys-leukotrienes may also be involved in immunological OA response (27;59).

5.2.3.2. Irritant-induced occupational asthma

Irritant-induced asthma is an area of uncertainty as it is probably the less known part of asthma. Although some efforts have been made in the improvement of management and prevention strategies of acute irritant induced asthma, diagnosis, mechanisms, and prognosis are not well understood up to date (60). It has been suggested that an inflammatory response may be the consequence of damage in the lung epithelium (27), but the target for the injury has not been clearly identified yet (61). The consequences that arise from a denuded bronchial epithelium are multiple: exposure of nerve endings leading to neurogenic inflammation; loss of relaxing epithelial factors; release of inflammatory mediators such as leukotrienes B_4 and C_4 and proinflammatory cytokines; secretion of growth factors for epithelial and endothelial vascular cells, fibroblasts and smooth muscle cells; and, finally, matrix degradation (27). Animal models also showed functional and pathological changes in the airways resulting from oxidative stress (62), and lung neutrophilia as a consequence of the exposure to chlorine gas (63). In line with this result, case series of irritant-induced asthma in three asthmatic patients showed that eosinophilic inflammation is unlikely to play a key role in the mechanisms of nonimmunological OA (52).

To date few studies have dealt with the differentiation between acute and non-acute irritant-induced asthma (the latter also known as not-so-sudden irritant-induced asthma) (64). Most of the authors consider irritant-induced asthma as a consequence of acute and often accidental exposure to a high concentration of irritant inhalants (28). It is generally considered a subtype of occupational asthma and was first described as reactive airways dysfunction syndrome (RADS) in 1985 by Brooks and co-

workers (65). Later, Tarlo and Broder named it irritant-induced asthma and included the possibility of multiple exposure incidents as the cause of initiation of asthma (66). In 2000, Quirce and co-workers reported 3 cases of irritant-induced asthma that could not be strictly diagnosed as RADS because in none of them the onset of asthma symptoms was associated with a single and brief exposure to high concentrations of irritants (52). Nowadays, there is evidence that workfers with recurrent exposure to moderate levels of irritants, like cleaning and healthcare workers, during a long period have a larger risk of asthma (25;67-69).

5.2.4. Work-exacerbated asthma

Work-exacerbated asthma (WEA) has been somewhat overlooked compared to the tremendous efforts to improve the understanding and management of OA (70). Recently, a statement of the American Thoracic Society (ATS) on WEA has been published attempting to inform research and public health agendas and to give a consensus approach to the management and understanding of this particular case of work-related asthma (71). According to this statement, WEA represents between 13 to 58% of all working adults with asthma with a median prevalence of 21%. Previously, another ATS statement on OA noted that there may be much greater morbidity and productivity loss associated with exacerbations of pre-existing asthma due to workplace exposures" than from asthma caused by work (42). Objective tests to assess and/or confirm WEA are not usual. PEF variability at work and away from work is a common and useful tool to confirm OA. A study on 34 subjects with WRA demonstrated that PEF variability was not useful to differentiate OA and WEA. However, subjects with WEA showed high variability of PEF at work and away from work (72).

The main cause of WEA is irritant exposure. Exposure to cleaning bleach, glutaraldehyde/ortho-phtaldehyde, chloramines, ethylene oxide and formalin/formaldehyde was associated with increased odds of WEA among healthcare workers from Texas and WEA increased in a dose-dependent manner for exposure in the longest job to disinfectants/sterilants (73). Tarlo and colleagues published a comparison of OA and WEA among 609 workers' claim compensation in Ontario, Canada (100% of records in 4 years). Among WEA cases 67% were exposed to irritants (eg, paints, solvents, acids, ammonia, second-hand smoke) and 40% to accidental acute exposures (74). According to an analysis of the of the European Community Respiratory Health Survey, occupation contributes to approximately one in seven cases of severe exacerbation of asthma in a working population (75). In this study, the occupations with the highest risk of WEA compared to white-collar workers were nurses, bakers and drivers. Regarding exposures, biological dusts, gas and fumes were strongly associated with WEA (75). It is unclear to which extent the exposure to cleaning agents contributes to WEA (76).

In summary, there is a need for further efforts to reduce the substantial socio-economic and health impact of WEA. Research to identify risk factors; to understand natural history and to investigate mechanisms of WEA should improve diagnostic, treatment and preventive strategies.

5.3. Hand dermatitis

5.3.1. Definition and burden of hand dermatitis

Hand dermatitis or hand eczema (both terms are interchangeable) is a common dermatological disorder that often becomes chronic (77;78). Diagnosis of hand dermatitis may be misleading due to its wide

aetiological and clinical heterogeneity and the concurrence of symptoms with other morbidities (79). Pustular psoriasis, lichen planus and porphyria cutanea are examples of similar cutaneous disorders (78), thus it is needed to do a differential diagnosis to address hand dermatitis in the clinical practice. The point prevalence in westernised countries is between 3 and 4% and the lifetime prevalence is around 15% being significantly higher among women than among men (80). Incidence rate of hand eczema in a Danish twin's cohort was 8.8 per 1000 person-years, with higher incidence among women, although differences were non-significant (81). One of main risk factors among this cohort besides genetic factors was wet work, including the use of gloves. In a 2003 report from the UK, 39000 people were suffering from skin disorders caused by their work and the estimations suggest that 4300 new cases diagnosed each year with approximately 237000 lost work days per year (82). Interestingly, the healthcare sector had a special relevance in this figures (83).

5.3.2. Risk factors for hand dermatitis

Differences in hand dermatitis risks between sexes are generally explained by different environmental exposures (84) and by the increased prevalence of atopic dermatitis among women (80;85) rather than different susceptibility. The effect of age on dermatitis is different among women and men. Among the former, there is an inverse association between age and dermatitis, whereas among the latter, the effect modification is not so evident (86;87). Socioeconomic factors may also influence the onset and prognosis of hand dermatitis (80). A large Norwegian survey showed that individuals with lower education, lower

income and those men who lived alone had higher prevalence of hand dermatitis (88).

Besides the mentioned demographic and socio-economic risk factors, the most important host determinant for hand dermatitis is atopy (89;90). A Danish study including 1438 adolescents found that hand eczema was significantly associated with atopic dermatitis as well as inhalant allergy (89). Meding and colleagues found that atopic dermatitis was only a risk factor in subjects aged below 30 years (91). Therefore, the effect of atopic dermatitis seemed to be less important with increasing age. It is important to mention that the worst prognosis of hand eczema is when a combination of allergic and irritant dermatitis is present (92). As in any other health disorder strongly related to allergy and atopy, genetic factors and gene-environment interactions also play an important role in the development of hand dermatitis (90;93).

Occupational hand eczema accounts for more than 90% of the observed occupational skin disease, thus being one of the most common occupational disorders (94). It may occur after the exposure to several known offenders which may be very specific like nickel (95) or cephalosporines (96), or very unspecific like wet work (80;94;97). Similarly to asthma, cleaners, hairdressers and healthcare workers have an increased risk of hand eczema compared to other workers (94;98;99). This is probably due to the recurrent exposure to irritants and to wet work, the latter being one of the main causes of non-allergic occupational hand dermatitis (86). Other studies found controversial results regarding wet work and hand eczema (100). Nevertheless, the results of this study suggest that younger women are more exposed to wet work than older

women and, moreover, they found an association between hand eczema and the use of protective gloves. This research group found that high-risk occupations for hand eczema were often exposed to wet work and irritants (101). The consequence for workers with occupational hand dermatitis is often quitting their job (102) or, in the best case scenario, healthcare consumption and sickness absence (84).

5.3.3. Relationships with asthma

There is a recent interest in investigating the links between lung and skin occupational diseases (103). Several exposures act as risk factors for both asthma and dermatitis, thus increasing the probability of having both diseases concurrently. Atopic dermatitis per se, has been described as a major risk factor for the development of asthma among children, what is known as "the atopic march" (104). An ecological approach to the environmental factors associated with asthma and eczema during childhood showed that both diseases were positively associated with GNP, trans fatty acids intake, paracetamol sales, and women smoking, and inversely associated with food of plant origin, pollen, immunisations, tuberculosis notifications, air pollution, and men smoking. The magnitude of these associations was small, but consistent in direction between both conditions (105). However, other authors reported that several risk factors have differential effects on infant wheeze and atopic dermatitis, suggesting a different aetiology (106).

Apart from the concurrent inhalant and dermal exposures leading to skin and lung diseases, chronic beryllium disease may occur through dermal exposure and sensitisation, as suggested by studies on animals (107). Sensitisation to isocyanates through the skin may occur even in the

presence of protective barriers (103) eventually leading to non-IgE mediated asthma. There is a vast body of evidence of the relationship between asthma and isocyanates, what has lead to the development of preventive measures such as diminishing the irritant properties of products containing di- and poly- isocyanates (108). Despite the reduced respiratory exposure, dermal exposure may occur and lead to sensitisation (103). After sensitisation, the respiratory exposure to very low levels of isocyanates (even below regulatory and detectable levels) may lead to asthma (109). Several studies in animals and humans have demonstrated that dermal sensitisation may lead to asthma development (109). Factors typically present in the cleaning workforce such as frequent use of soaps and cleaners, wet work, physical trauma, heat and low humidity and the use of gloves may impair the skin natural barrier and facilitate allergen entry leading to sensitization and asthma (110). A recent study based on a cleaning workforce showed that cleaning workers are both at increased risk of asthma and skin disorders (111;112).

5.4. Cleaning work and adverse health effects

5.4.1. Cleaning products and the cleaning sector

Cleaning products are chemical compounds used to maintain the hygienic and aesthetic conditions of surfaces and objects (76;113). These products have become essential in modern life and are used in almost every workplace and home. To achieve supplying this demand, the cleaning products manufacturer industry has developed a wide range of products with a high degree of task-specificity both for general public and for professional cleaners (114). The main components of cleaning products are disinfectants, detergents and tensioactives (eg, Linear Alkylbenzene Sulfonates), alkaline agents (eg, sodium hydroxide, ammonia), acids (eg,

hydrochloric acid), complexing agents (water softeners), solvents, corrosion inhibitors (eg, monoethanolamine), film formers and polishes (eg, acryl polymers, polyethylene), preservatives (eg, benzalkonium chloride, isothiazolinones, formaldehyde), and perfumes or scents (eg, limonene, pinene) (115).

The cleaning services industry covers an important economic activity in westernised countries accounting for more than seven billion pounds turnover in the 2010 in the UK (116). In 1995 there were 12,402 companies offering cleaning services in Spain, employing more than 230,000 workers and with an annual turnover of 2,504 million Euros (117). In Catalonia, a highly industrialised region in the north-west of Spain, more recent data is available (118). In 2008, 3,841 companies offering cleaning services employed 97,455 workers and had an annual turnover of 1,806 million Euros. According to this Catalan government survey, around 80% of the workers were women. The range of cleaning activities developed by such industry is very wide and comprises very specific tasks (eg, cleaning of silos, sewage system or construction debris) and more general maintenance duties (eg, cleaning private homes or offices). Besides cleaning tasks, many cleaning companies offer other services including janitoring, catering and private security.

The adverse effects of exposure to the chemical components of cleaning products have been studied by the scientific and the industrial communities (115;119-125). The main health outcomes associated with cleaning products include dermal and respiratory effects of cleaning products. It is known that some cleaning products may act as irritants, sensitizers or both at the same time (76). New-onset asthma may be

caused by sensitisation due to the exposure to cleaning products and it can be IgE-mediated or non IgE-mediated. Accidental exposure to a high concentration of irritant cleaning products or persistent exposure to moderate levels, may also lead to irritant-induced asthma. Worsening of pre-existing asthma or triggering of other asthma-like respiratory disorders may also develop as a consequence of exposure to cleaning products. Besides cleaning workers, several other occupations involved in cleaning tasks have been identified as high-risk occupations for asthma, including nurses and other healthcare workers (113). Dermal effects such as irritant contact dermatitis on hands and wrists are common among cleaning workers (126;127). It may be a consequence of wet work and the use of irritant and degreasing cleaning products (128-130). In addition, cleaning products contain chemicals that may act also as contact allergens (131;132) causing allergic sensitisation and dermatitis.

5.4.2. Work-related asthma among cleaning workers

In the last decade, several epidemiological and surveillance studies have shown an increased risk of asthma among cleaning workers (124;133;134). Epidemiological evidence of this increased risk is consistent across countries and populations. Back in 1994, a community-based case-control study conducted in Singapore showed an increased risk of asthma in cleaning workers (135) (CITA Ng 1994). However, the first large cohort study that showed an increased risk of asthma symptoms among cleaning workers was the European community Respiratory Health Study (ECRHS). Kogevinas and colleagues published in 1999 a comparison between several occupations at high risk of asthma and clerical workers in a population-based sample from 12 countries. Cleaners presented a two-fold risk of prevalent asthma symptoms and/or medication for asthma as well as a two-fold risk of bronchial hyperresponsiveness (136). In the

follow-up of the ECRHS cohort, new-onset asthma incidence in adults was higher among cleaners compared to other occupations (25). Interestingly, an analysis of the of the ECRHS-II showed a higher incidence of adult asthma among those participants using sprayed or aerosolized cleaning products at home (137). A special interest on the topic arose in Spain, and a population-based study was conducted to study the risk of asthma among domestic cleaning women. The results of this study showed that those employed in domestic cleaning had higher risk of asthma (69). Further analysis in these cleaning workers showed an increased risk of asthma and/or chronic bronchitis associated with the use of hypochlorite bleach and ammonia during domestic cleaning work (138).

Other occupations that involve the use of cleaning products as part of their daily duties, like nurses and other related healthcare workers, showed a higher risk of asthma. Among European nurses, those using bleach and/or ammonia and those using any products in spray form presented a two-fold risk of new-onset asthma compared to a referent population of administrative workers (139). A large cross-sectional study among healthcare workers in Texas showed an increased risk of physician-diagnosed asthma after entry into health profession among those healthcare workers who performed cleaning-related tasks as part of their daily duties (68).

Several registry-based studies highlighted the importance of cleaning-related exposures and cleaning work as an important aetiological factor for asthma. In Catalonia, Spain, a voluntary surveillance system for occupational respiratory diseases was implemented (38). The results showed that a half of all reported respiratory diseases diagnosed were

occupational asthma and a 9% of the cases were attributed to occupational exposures to cleaning products. Interestingly, another 13% of the reported respiratory diseases were diagnosed as acute inhalations of which 22% were due to cleaning tasks. One of the main conclusions was that the compulsory scheme for reporting occupational respiratory diseases was underreporting in Catalonia. In the US, an analysis of the data from the Sentinel Event Notification System for Occupational Risks (SENSOR) from four states showed that cleaning workers and those other workers from the educational services involved in cleaning tasks were one of the most reported occupation for new-onset occupational asthma as well as work-aggravated asthma (140). Cleaning products were also among the causal agents. Similar studies in Canada yielded similar results regarding cleaning work and asthma (141), whereas in developing countries, cleaning agents are the main cause of occupational asthma (26).

In summary, many studies have tried to disentangle the specific risk factors for asthma and asthma symptoms among cleaning workers yielding heterogeneous results. It appears that exposure to irritant products such as hypochlorite bleach and ammonia play a key role both in the development and aggravation of the disease. The exposure to cleaning products is a function of both the product formulation and the application form (76). It is known, that the use of cleaning products in spray or aerosolised form, likely facilitates the inhalation of its chemical components, increases the risk of asthma (137). Nevertheless, there are several aspects that have not been covered properly, such as the biological and clinical profile of asthmatic cleaners, the underlying mechanisms and the causality of the effect.

5.4.3. Cleaning work and hand dermatitis

As mentioned above, cleaning workers are exposed to a wide variety of irritants and wet work tasks as well as dusty environments (101), and these conditions favour the occurrence of hand eczema. Irritant contact dermatitis is the most common subtype of dermatitis and, in the case of pre-existing allergic dermatitis, irritant exposures may worsen the disease or facilitate the onset (84). Cleaning products contain chemicals that may act as sensitizers and/or as irritants (131;132) including the surfactant anionic surfactant sodium lauryl sulphate, which is responsible of many cases of occupational hand dermatitis due to cleaning-related exposures (142;143). A synergistic effect of contact allergens and irritants has been described (92;144;145), highlighting the importance of combined exposures as is the case of cleaning products.

There is evidence of an increased risk of skin disorders, especially hand dermatitis, among cleaning workers. Lynde and colleagues found that cleaning workers had higher prevalence of skin symptoms compared to other building workers (146) and, furthermore, those cleaners with less training presented a higher prevalence compared to better trained cleaners. Cleaning and kitchen workers from hospitals presented also higher prevalence of hand dermatitis (127;147;148). Other healthcare workers involved in wet work presented also a high prevalence of hand contact dermatitis either with an allergic or irritant nature (149).

6 RATIONALE

There is extensive evidence that cleaning-related exposures are associated with asthma-like and dermal disorders. However, only few and small workforce based studies have been conducted in cleaning workers. Identifying the specific risk factors and the patho-physiological and clinical characteristics of the associated disorders is crucial to establish new prevention measures that reduce the burden of respiratory disease among cleaning workers. The inclusion of the clinical and biological characterisation of the cleaning-related respiratory disorders will help to improve the acknowledgement among the physicians community of the problem in the daily routine at their practice. Moreover, it will help to identify the specific mechanisms that lead to cleaning-related respiratory disorders and thus to help in the diagnosis and treatment of such disorders. Beyond their professional use, cleaning products are widely used as household chemicals. The results of the thesis, although difficult to be extrapolated directly to the general population, should be considered in order to create new prevention policies for reduction of the adverse effects of domestic and indoor exposures to cleaning agents.

7 OBJECTIVES

7.1. Overall objective

The overall aim of the thesis is to characterise the risk factors and the clinical, functional and biological characteristics of cleaning-related asthma-like and dermal disorders in a workforce-based study. There are four specific objectives.

7.2. Specific objectives

- To update the state of the art of the topic on cleaning-related exposures and asthma.
- To evaluate the prevalence of asthma-like symptoms and the associated risk factors among employees of cleaning companies.
- To evaluate the occupational and non-occupational use of cleaning products and their associations with asthma and respiratory symptoms among cleaning workers.
- To assess the clinical, functional and biological characteristics of asthma in cleaning workers.
- To evaluate the prevalence of hand eczema and related symptoms and the associated risk factors among employees of cleaning companies.

8 METHODS AND RESULTS

8.1. The EPIASLI-2 project

EPIASLI-2 was designed after the extensive evidence of an increased risk of asthma among cleaning workers and the large experience of the CREAL occupational research team in the topic of cleaning and asthma (25;35;69;115;136-138;150-153). The specific methods and results of the study are described in each paper, as well as the discussion of the main findings. However, it may be useful to include a brief overview of the project in order to give a framework for the present thesis. As mentioned in the introduction, only a few and small workforce-based studies on asthma and cleaning work have been published. EPIASLI-2 tried to fill this gap and to give, for the first time, an approach to the patho-physiological characteristics of asthma related to cleaning exposures.

The workforce-based perspective of EPIASLI-2, which gives a selected group less biased and with a large range of exposures was choose to give an approach to the possible mechanistic pathways that lead to asthma among cleaners. The project was divided into two stages: a cross-sectional study and a nested case-control study. In the first stage, we included 37 companies covering a wide range of activities and number of employees. Designated companies' representatives (usually a human resources manager) acted as mediators between their employees and us, given that the current legislation on personal data protection (154) made impossible to contact directly the workers or to obtain registers of the companies' employees. Companies' representatives obtained self-administered questionnaires from 917 employees including validated questions on

asthma history, respiratory and dermatologic symptoms and demographic characteristics.

Based on their responses to the cross-sectional survey, a selection of 42 cases with asthma or asthma symptoms and 53 controls with no lower tract airways symptoms underwent a thorough clinic visit to evaluate their physiological, functional and inflammatory status. Twenty cases were also enrolled in a 15-days panel study to evaluate the short-term effects of cleaning exposures. Besides the workforce-based epidemiological study, fourteen cleaning workers diagnosed with occupational asthma in a pulmonary department of Vall d'Hebron hospital (Barcelona, Spain) underwent the clinic visit and provided the same information and samples.

8.2. First paper

Update on asthma and cleaners

Jan-Paul Zock, David Vizcaya, Nicole Le Moual

Curr Opin Allergy Clin Immunol 2010;10 (2):114-20.

UPDATE ON ASTHMA AND CLEANERS

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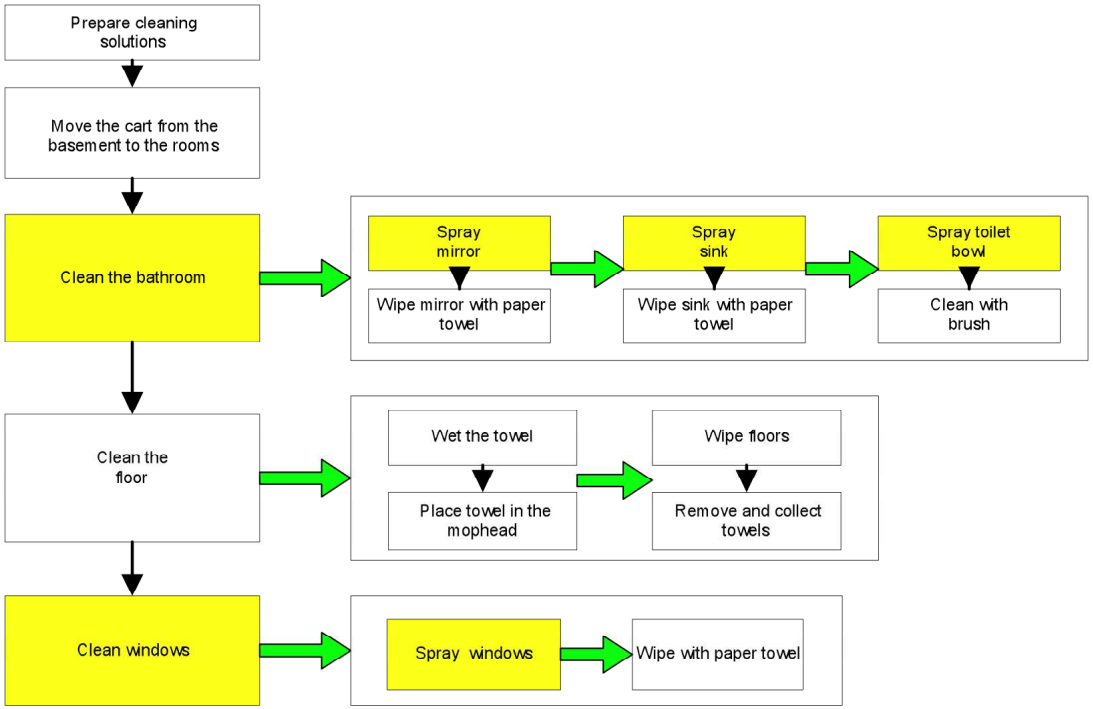
Table 1: Summary of main findings on the relation between cleaning exposures and respiratory health from recent papers describing original studies

Type and design of study	Study population	Main findings	Ref.
Multi-centre population-based longitudinal study	General population samples from Europe, USA and Australia; including 358 cleaners, 291 nurses and 3501 homemakers. Years 1990–2003.	- Incidence of asthma 2.2 per 1000 person-years - Increased risk for new-onset asthma among: · cleaning workers · those with occupational exposure to cleaning products · nurses, particularly those who use ammonia, bleach and/or cleaning sprays · homemakers who use sprays	(25;137;139;153)
Surveillance programme; voluntary notification of work-related respiratory diseases	174 newly diagnosed cases of occupational asthma from Catalonia, Spain. Year 2002.	- Incidence of occupational asthma 77 cases per million - In 15% of the cases causal agents were cleaning products - Incidence of acute inhalations 20 cases per million - Cleaning was the most frequently reported occupation (26%)	(38)
Data linkage of compensation claims and physician billing data	12,554 new-onset asthma cases among 782,908 with claims in Alberta, Canada. Years 1995–2004.	- Incidence rate of new-onset asthma 1.6% - Increased risk related to cleaning agents in men but not in women.	(141)
Surveillance SENSOR	265 educational service workers with work-related asthma from four USA states. Years 1993–2000.	- Cleaning workers accounted for 12% of the cases of work-related asthma - Cleaning products were causal agents for 20% of all cases - Most commonly reported were formaldehyde, graffiti remover, bleach, carpet cleaners and ammonia solution	(140)
Workforce-based cross-sectional study	566 non-domestic cleaners and 587 other building workers from Ontario, Canada.	- Cleaning women had higher risk of work-related respiratory symptoms - Main risk factors for work-related symptoms among male cleaners were waxing and wax stripping of floors, spot cleaning of carpets, oiling of furniture, cleaning tiles and cleaning grout	(112;146)

Workforce-based cross-sectional study	175 cleaning and disinfecting workers in the French food industry and 70 non-exposed.	Risk of irritative symptoms increased with exposure (either intensity or duration).	(159)
Workforce-based cross-sectional study	341 non-domestic cleaners employed in cleaning service companies from Brazil	- Chlorine bleach was the most common agent related to respiratory symptoms. - Risk of work-related asthma or rhinitis increased with exposure duration	(158)
Workforce-based; panel study	43 Spanish domestic cleaners with asthma and/or chronic bronchitis	Lower respiratory tract symptoms were more common on working days, and independently associated with diluted bleach, degreasing sprays and air refreshing sprays - 30% had occupational asthma according to analysis of repeated peak flow measurements	(150)
Workforce-based; panel study	25 homemakers with and 19 without asthma from USA	- Among asthmatic women, respiratory symptoms were more common after cleaning work - No effects were apparent in non-asthmatic women	(157)
Workforce-based; cross-sectional study.	2738 Health care professionals (448 nurses) from Texas, USA	- Increased risk of new-onset asthma and respiratory symptoms associated with exposure to cleaning agents used for instruments and surfaces - Highest risks found among nurses	(67;68)

Figure 1: Process flow diagram of the tasks performed for patient room cleaning. The shaded boxes indicate cleaning tasks/steps with higher potential for inhalation exposure. Reproduced from (122).



NOTE: PREVIOUSLY PUBLISHED. Bello A, Quinn MM, Perry MJ, Milton DK. Characterization of occupational exposures to cleaning products used for common cleaning tasks--a pilot study of hospital cleaners. Environ Health 2009; 8:11.

**** Papers of special interest in this review***

(137) Zock JP, Plana E, Jarvis D, *et al.* The use of household cleaning sprays and adult asthma: an international longitudinal study. Am J Respir Crit Care Med 2007; 176:735–741.

* This study identified domestic use of cleaning sprays to be associated with new-onset asthma.

(141) Cherry N, Beach J, Burstyn I, *et al.* Data linkage to estimate the extent and distribution of occupational disease: new onset adult asthma in Alberta, Canada. Am J Ind Med 2009; 52:831–840.

* This study linked data from compensation claims and physician billing data. An increased risk of new-onset occupational asthma related to cleaning agents in men was reported.

(122) Bello A, Quinn MM, Perry MJ, Milton DK. Characterization of occupational exposures to cleaning products used for common cleaning tasks--a pilot study of hospital cleaners. Environ Health 2009; 8:11.

* This paper describes an integrated approach to characterise exposures to cleaning products, with an application in hospital cleaners.

8.3. Second paper

A workforce-based study of occupational exposures and asthma symptoms in cleaning workers

David Vizcaya, Maria C Mirabelli, Josep-Maria Antó, Ramon Orriols, Felip Burgos, Lourdes Arjona, Jan-Paul Zock

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Vizcaya D, Mirabelli MC, Anto JM, Orriols R, Burgos F, Arjona L, et al. A workforce-based study of occupational exposures and asthma symptoms in cleaning workers. Occup Environ Med. 2011 Dec;68 (12):914-919.

A workforce-based study on occupational exposures and asthma symptoms in cleaning workers

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KEYWORDS: Asthma, cleaners, irritants. **WORD COUNT:** 3398

'WHAT THIS PAPER ADDS' BOX

- Cleaning workers are at increased risk of asthma but the underlying responsible exposures are unknown.
- Cleaning workers are widely exposed to different irritant cleaning products.
- The use of irritant cleaning products is associated with respiratory symptoms.
- Control measures to reduce or avoid exposure to irritant cleaning products may help reduce the burden of respiratory disorders in cleaning workers.

8.4. Third paper

Occupational risk factors for hand dermatitis among professional cleaners in Spain

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Contact Dermatitis. Provisionally accepted.

Occupational risk factors for hand dermatitis among professional cleaners in Spain

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manuscript was drafted and revised by M. Mirabelli. All authors contributed to the interpretation of the data, reviewed and revised the manuscript for intellectual content, and approved the final manuscript.

Summary

Background. Dermatitis is an important health outcome for workers whose jobs put them in contact with skin allergens, irritants, or sensitizing agents.

Objectives. We conducted analysis of data from the Epidemiological Study on the Risk of Asthma in Cleaning Workers 2 (EPIASLI2) study to assess worksites and cleaning products as risk factors for hand dermatitis among professional cleaning workers.

Materials/Methods. We distributed 4,993 questionnaires to employees of 37 cleaning companies and used data from 818 (16%) respondents who provided information about skin symptoms and cleaning-related exposures. We assessed associations between the frequencies of worksite and cleaning product exposures and a symptom-based definition of hand dermatitis among current cleaning workers (n=693) and a comparison population (n=125).

Results. Hand dermatitis was reported by 28% of current cleaning workers, versus 18% of the comparison population, and was associated with cleaning outdoor areas and schools, and the use of hydrochloric acid (prevalence ratio [PR]: 1.92, 95% confidence interval [CI]: 1.22, 3.02) and dust mop products (PR: 1.75, 95% CI: 1.11, 2.75).

Conclusions. Professional cleaning workers may not be sufficiently protected from cutaneous disease at work. Future research should further investigate the roles of multiple product exposures and personal protective equipment.

Key words: cleaning; dermatitis; epidemiology; occupational diseases; occupational exposure

Introduction

Professional cleaning workers keep homes, hospitals, hotels, office buildings, restaurants, schools, shopping areas, sidewalks, and other public and private spaces clean. The cleaning activities they perform range from light tasks, such as dusting, sweeping, and vacuuming, to specialized activities that require hazardous cleaning solutions, heavy equipment, and job training (115;169).

Men and women in the cleaning industry routinely come into contact with a wide range of hazards potentially responsible for causing occupational skin diseases. Professional cleaning workers clean and sanitize surfaces that put their skin in contact with biological, chemical, and physical hazards. The process of cleaning and disinfecting also exposes workers to a range of cleaning products that varies widely according to the cleaning tasks and locations. While some cleaning agents seem to be simple and relatively safe (e.g., soap and water, vinegar), many contain preservatives, solvents, fragrances, and other compounds with well-known irritating or sensitizing properties (131). In addition, cleaning may involve “wet work” that may impair the epidermal barrier, allowing for skin irritation and sensitivity (126;128). To reduce the risk of exposure to both the substances being cleaned and the cleaning products themselves, workers may use gloves or other personal protective equipment that protect the skin from hazardous exposures, but that may also exacerbate skin allergies or irritate the skin.

Previous research provides evidence of an elevated prevalence of hand dermatitis among cleaning workers in hospitals (147;170) and school buildings (146). We conducted the present study to assess a wide range of worksites, cleaning activities, and cleaning products as risk factors for hand dermatitis

among men and women employed in the cleaning industry in the province of Barcelona, Spain.

Materials and Methods

Study population and data collection

Epidemiological Study on the Risk of Asthma in Cleaning Workers 2 (EPIASLI2) was a two-stage epidemiologic study conducted to assess associations between cleaning work, including specific worksites and exposures to cleaning products, and dermatologic and respiratory health symptoms (171). The study methods have been described previously (171). Summarized briefly, between February and December 2008, 4 993 self-administered, paper-and-pencil-style questionnaires were distributed to employees of 37 cleaning companies operating in the province of Barcelona, Spain. Nine hundred and fifty questionnaires were returned by mail; of those, 132 (14%) were excluded because they were incomplete or lacked responses to key questionnaire items and the remaining 818 respondents constituted our final study population for analyses of the cross-sectional survey data. Following the cross-sectional survey, 95 participants were recruited into a nested case-control study designed to further assess associations between cleaning work and respiratory disease (172). Data for the sub-study were collected when participants completed a clinical exam and an interviewer-administered questionnaire. For 70 of the 95 participants (74%), the clinic exam included an in-person skin health evaluation, therefore our final study population includes additional data collection for a subset of 70. The study was approved by the ethics committee of the Instituto Municipal de Asistencia Sanitaria (IMAS) and the analytic plan for this analysis was also approved by the Institutional Review Board of the Wake Forest School of Medicine.

Occupational exposures

Participants were categorized as working as cleaners at the time of their participation using the questions “have you ever worked as a cleaner?”, “what position do you currently hold in your company?”, and responses to a series of questions about cleaning worksites, activities, and products used at work. As in previous analyses of EPIASLI2 data (171), respondents who indicated that they currently work as cleaners and those with positive responses to any of the questions about cleaning worksites, activities, and products in the last month were categorized as “current” cleaning workers (n=693). Those who indicated that they had worked, but do not currently work as a cleaner were categorized as “former” cleaning workers (n=57). The remaining respondents were those who had never worked as cleaners (n=68); this population includes office workers and other employees not performing cleaning jobs. In this analysis, former cleaning workers and those who had never worked as cleaners comprise the comparison population.

Respondents with positive answers to the series of questions about worksites (e.g., hospitals, private homes, schools), activities (e.g., window cleaning), and products (e.g., ammonia, bleach, glass cleaner) used in the last 12 months were then asked to estimate the frequency of their work at these sites, performing these activities, or using these products, respectively, during the last month. Glove use was accessed using a single questionnaire item: “how often did you use rubber gloves during the last 12 months?” Whether the respondent cleaned his/her own home was assessed with the question “do you do cleaning tasks in your home?” Missing responses to these questions were re-assigned as negative responses – that is, not using the specific cleaning product, use of rubber gloves less than once per week, and not cleaning one’s own home.

Dermatitis and eczema

Participants reported whether they had a history of eczema or other skin allergy by responding to the following question: “have you ever had eczema or other skin allergies?” The questionnaire also included a series of questions developed by Coenraads et al. (173) and Smit et al. (174) to assess the 12 month prevalence of symptoms of hand dermatitis or eczema (hereafter referred to as “hand dermatitis”). The symptoms of hand dermatitis included the following: (a) red and swollen hands or fingers, (b) red hands or fingers and fissures, (c) vesicles on the hands or between the fingers, (d) scaling hands or fingers with fissures, and (e) itching hands or fingers with fissures. Symptoms were then classified using the methods described in Smit et al.; that is, participants were classified as having hand dermatitis if they indicated that they had at least one of the symptoms in the last 12 months and that the symptom(s) lasted more than 3 weeks or occurred more than once (174).

For 70 participants who completed the in-person clinic exam portion of the study, questionnaire items included in the survey at the clinic exam were identical to those included in the cross-sectional study described above. The clinic exam also included an in-person assessment by an occupational medicine physician with specialized training in dermatology and evaluation of de-identified photographs of the hands, wrists, and forearms by a dermatologist with expertise in contact dermatitis. The in-person assessment was based upon a visual evaluation of the hands, wrists, and forearms and conversation with the participant at the time of the exam. Evaluation of de-identified photographs occurred after photographs of the fronts and backs of participants hands were taken at the time of the exam. Photographs were taken with a Sony Cyber-shot® digital camera (model: DSC-W55), from a distance of 50 cm, and the images were stored digitally and reviewed later.

Each of the 70 participants was classified as positive or negative for hand dermatitis independently by the two clinicians. For cases in which the two assessments generated discrepant results, the in-person and photographic assessments were re-evaluated together to reach a final classification.

Statistical analysis

We estimated associations between each cleaning-related risk factor and hand dermatitis using Poisson regression models, specified with a log link and robust error variance estimation (175;176). Cleaning-related risk factors included employment as a current cleaner, worksite, cleaning activities, and products used at work. Results for current cleaning were generated using a single model estimating the prevalence of hand dermatitis among current cleaning workers (n=693) compared to the prevalence of hand dermatitis among former and never cleaning workers (i.e., the comparison population, n=125). Results for each worksite were generated using two models. First, we used a model estimating the prevalence of hand dermatitis among current cleaning workers who have and have not cleaned at the specific type of worksite in the last 12 months compared to the prevalence of hand dermatitis in the comparison population. In order for the estimates generated for the effect of cleaning at the specific worksite within the last 12 months to include the full study population and to retain the ability to directly contrast the estimates across worksites, the population that reported not cleaning the specific type of worksite in the last 12 months is included in each model and the results are presented. Effect estimates presented for the population not cleaning the specific worksite within the last 12 months may be interpreted as the effect of currently cleaning, but not cleaning at the specific worksite; the primary outcome of interest generated using these models is the prevalence of hand dermatitis among current cleaning workers who reported cleaning the specific

worksite in the last 12 months relative to the prevalence of hand dermatitis in the comparison population. Second, we used a model estimating the prevalence of hand dermatitis with increasing frequency of work at the specific type of worksite in the population of current cleaning workers who reported such work within the last 12 months compared to the prevalence of hand dermatitis in the comparison population. Results for analyses of work activities and use of cleaning products were generated using similar models. All models were adjusted for age, country of birth (Spain versus other), sex, history of eczema or other skin allergy, cleaning one's own home, and frequency of glove use at work (<1 day/week, 1-3 days/week, 4+ days/week). Associations are presented as prevalence ratios (PRs) with 95% confidence intervals (CIs). All analyses were performed using SAS version 9.1 (SAS Institute, Inc.).

In a second set of analyses, we used data collected at the time of the clinic exam (n=70) to compare the classifications of hand dermatitis based on participants' responses to survey items about hand dermatitis with the classification based on the dermatologic assessment. We considered the dermatologic assessment as the gold standard and calculated the sensitivity, specificity, positive predictive value, and negative predictive value of the questionnaire-based classification of hand dermatitis.

Results

Characteristics of the 818 study participants are shown in Table 1. Overall, the population of current cleaning workers was slightly older (median age: 45 years) than the comparison population (median age: 40 years), and included larger proportions of women (84% versus 74%) and individuals who clean their own homes (95% versus 83%). The percentage of current cleaning workers with current asthma was slightly higher (11% versus 7%) and the percentages

of respondents with a history of eczema or other skin allergy were similar in the two populations (29% versus 30%).

Of the individual skin symptoms included in our questionnaire, the most prevalent symptoms reported were red hands or fingers with fissures (20%) among current cleaning workers and scaling hands or fingers with fissures (9%) in the comparison population; thirty-six percent (n=248) of the current cleaning workers and 22% (n=27) of the comparison population reported one or more of the symptoms (Table 2). Overall, 28% of current cleaning workers and 18% of the comparison population (former cleaners: 14%; never cleaners: 21%) met our definition for hand dermatitis and the prevalence among current cleaning workers was elevated compared to the comparison population (PR: 1.60, 95% CI: 1.03, 2.47) (Table 3). Like all our models, this estimate was generated using a model adjusted for potential confounders selected *a priori*, as well as for cleaning one's own home (PR: 1.14, 95% CI: 0.56, 2.32) and the frequency of using rubber gloves at work (1-3 days/week versus <1 day/week: PR: 1.12, 95% CI: 0.78, 1.61; 4-7 days/week versus <1 day/week: PR: 0.98, 95% CI: 0.74, 1.30) (data not shown).

Current cleaning workers cleaning outdoor areas (PR: 1.85, 95% CI: 1.16, 2.96), residential building common areas (PR: 1.77, 95% CI: 1.11, 2.84), and schools (PR: 1.84, 95% CI: 1.15, 2.93), and those who reported cleaning up at a construction or renovation site (PR: 1.87, 95% CI: 1.18, 2.95) each reported significantly higher prevalences of hand dermatitis compared to the comparison group (Table 3). For respondents working in residential building common areas in the last 12 months, we observed a monotonic increase in the prevalence of hand dermatitis from 24% among those who reported cleaning in a residential building common area <1 day per week to 38% among those

working 4+ days per week. A similar increase was observed among respondents working in schools in the last 12 months, where the prevalence of hand dermatitis increased from 22% to 43%.

Among current cleaning workers using specific cleaning products, the highest prevalences of hand dermatitis were observed among those who reported moderately frequent (1-3 days per week) use of hydrochloric acid (prevalence: 40%, PR: 1.73, 95% CI: 1.00, 2.99) and dust mop products (prevalence: 36%, PR: 2.12, 95% CI: 1.22, 3.71) (Table 4). Relative to the comparison group, elevated PRs were also observed among current cleaning workers who reported frequent (4+ days per week) use of products, including ammonia (PR: 2.22, 95% CI: 1.26, 3.91), bleach (PR: 2.02, 95% CI: 1.20, 3.39), multi-use cleaning products (PR: 2.24, 95% CI: 1.31, 3.83), and perfumed products (PR: 1.96, 95% CI: 1.18, 3.26). The use of degreasing agents was associated with hand dermatitis, regardless of how frequently it was used (<1 day per week: PR: 1.79, 95% CI: 1.04, 3.05; 1-3 days per week: PR: 1.85, 95% CI: 1.08, 3.14; 4+ days per week: PR: 1.77, 95% CI: 1.04, 3.02). When we assessed the role of using multiple products, we found a monotonic increase in the prevalence of hand dermatitis with increasing numbers of different cleaning products (Table 5).

When we compared the our survey-based definition of hand dermatitis to classifications based upon dermatologic assessments in the sub-sample of 70, we found that using the questionnaire-based definition, 49% of the sample was classified as having hand dermatitis, compared to 24% when the definition was based on a dermatologic exam. Using the dermatologic exam classification as the gold standard, analysis of our questionnaire-based definition generated a

sensitivity of 0.82, a specificity of 0.62, a positive predictive value of 0.41, and a negative predictive value of 0.92.

Discussion

In these data, we identified groups of professional cleaning workers at elevated risk of hand dermatitis. Our results extend previous findings from epidemiologic research into skin symptoms in cleaning workers (146;147;170) by reporting elevated risk among users of products known to affect the respiratory tract and skin (115;130;133), providing evidence of increased risk with increasing frequency of use, and generating increasing adjusted risk estimates for workers performing a variety of tasks or using multiple products.

In addition to occupational risk factors, individual susceptibility factors such as atopy also play a role in the prevalence of hand dermatitis. In our data, hand dermatitis was reported among 39% more respondents with than without a self-reported history of eczema or other skin allergy. Although our data collection was not designed to distinguish allergic from irritant dermatitis, the cleaning-related exposures we identify here should be considered risk factors for both. Indeed, the adjusted PR generated for current cleaning overall was similar to those generated when the data were stratified by self-reported history of eczema or other skin allergy (history: PR: 1.61; no history: PR: 1.57). These estimates and stratified estimates for particular worksites and cleaning products (not shown) do not provide sufficient evidence of effect modification by atopic status; improved information about atopy and a larger sample size would have allowed us to more thoroughly explore this potential effect modification. Nonetheless, any interventions aimed at reducing these exposures will likely reduce the burden of hand dermatitis among atopic and non-atopic individuals.

The validity statistics of our symptom-based definition of hand dermatitis compared to the dermatologic evaluation are similar to those published previously (177;178) and suggest that outcome misclassification may affect our results. In particular, our definition may overestimate the prevalence of current hand dermatitis in this population. This is unsurprising, given that our survey-based definition assessed 12-month prevalence, whereas the in-person dermatologic assessment was based on symptoms visible at the time of the exam. Indeed, some participants described improvement of their symptoms at the time of the physical examination. Still, these data provide strong evidence of the importance of hand dermatitis symptoms among cleaning workers. That over 41% of the respondents who indicated that they had hand dermatitis in the last 12 months had their symptoms observed by our study team suggests a high incidence of hand dermatitis or a long duration of the condition in this population.

Our findings should be interpreted with particular attention to the low survey response rate in the EPIASLI2 study. Limitations of our study design and response rate as well as a comparison of demographic characteristics of study participants and non-responders in two cleaning companies have been described elsewhere (171). If participation in our study was associated with symptom status differently among current and non-current cleaners, then our results may be affected by a response bias. A comparison of demographic characteristics at two cleaning companies by responder status did not reveal major differences between the two populations with respect to the characteristics evaluated (171). Because of laws protecting personally identifying information in Spain (154), our study did not include any additional data collection from non-responders and we are not able to draw further

conclusions about differences between responders and non-responders (171). The prevalence of hand dermatitis reported by participants in our study is within the range of those reported among cleaners (126;146;179) and general population-based samples (80;180), suggesting that despite the low response rate, the external validity of our data is not markedly compromised. In fact, enrollment of 818 participants into a research study focused on the health of workers in large and diverse industry in which investigator and other public health personnel have limited workplace access is a noteworthy strength of our study.

Our findings may also be affected by the healthy worker survivor effect. If individuals who are susceptible to hand dermatitis or who have a history of hand dermatitis left their cleaning jobs, then the workplace-based recruitment in the EPIASLI2 study may have excluded individuals with cleaning-related dermatitis. If symptomatic individuals reduced the frequency of their use of specific cleaning products, then our analysis may have incorrectly attributed their symptoms to a category of less frequent use. Similarly, if symptomatic individuals moved into administrative jobs, then our analysis incorrectly attributes their cleaning-related symptoms to the comparison population. If our study were affected in this way by the healthy worker effect, then our results may underestimate the actual burden of professional cleaning on skin health.

Symptoms of hand dermatitis may have long-term consequences for employment, economics, and quality of life (181-184). Our findings indicate potential opportunities for reducing hand dermatitis among professional cleaning workers; namely, the feasibility of performing cleaning work using fewer cleaning products and less hazardous products should be evaluated.

Other aspects of cleaning work that may affect the risk of hand dermatitis include cleaning techniques, product mixtures and dilutions, methods used to mix and dilute products, and safety training. Improved information about the types of gloves used, hours of use, and number of glove changes would provide valuable information about the role of gloves in protecting workers during specific activities and from individual products and product mixtures.

In conclusion, our findings support the hypothesis that cleaning work is a risk factor for hand dermatitis and that professional cleaning workers may not be sufficiently protected from dermal hazards at work. Occupational medicine and dermatology specialists, and others who provide healthcare to professional cleaners, should be aware of the health risks of performing cleaning work and handling specific cleaning products and the possibility that symptoms of cutaneous disease are underreported and underdiagnosed in this population. These results justify further evaluation of primary prevention methods to reduce cleaning workers' contact with dermal hazards.

Table 1. Demographic characteristics and the prevalence of hand dermatitis among current cleaning workers and members of the comparison population

	Total Population	Comparison Population		Current Cleaning Workers	
	No. (%)	No. (%)	No. (%) with Hand Dermatitis	No. (%)	No. (%) with Hand Dermatitis
Total	818 (100)	125	22 (18)	693	191 (28)
Demographic Characteristics					
Age, in years					
Mean ± SD	45 ± 10		42 ± 11		45 ± 10
Median	45		40		45
Minimum-Maximum	18-65		22-61		18-65
Country of birth					
Spain	608 (74)	107 (86)	19 (18)	501 (72)	151 (30)
Other	210 (26)	18 (14)	3 (7)	192 (28)	40 (21)
Sex					
Female	673 (82)	92 (74)	17 (18)	581 (84)	168 (29)
Male	145 (17)	33 (26)	5 (15)	112 (16)	23 (21)
Cleaning					
Cleans own home					
No	53 (6)	21 (17)	2 (10)	32 (5)	5 (16)
Yes	765 (94)	104 (83)	20 (19)	661 (95)	186 (28)
Rubber glove use in the last 12 months?					
<1 day/week	266 (33)	101 (81)	17 (17)	165 (24)	45 (27)
1-3 days/week	108 (13)	4 (3)	2 (50)	104 (15)	31 (30)
4+ days/week	444 (54)	20 (16)	3 (15)	424 (61)	115 (27)
Health History					
Current asthma symptoms[1]					
No	736 (90)	116 (93)	19 (16)	620 (89)	160 (26)
Yes	82 (10)	9 (7)	3 (33)	73 (11)	31 (42)
History of eczema or other skin allergy					
No	579 (71)	88 (70)	9 (10)	491 (71)	76 (15)
Yes	239 (29)	37 (30)	13 (35)	202 (29)	115 (57)

[1] As defined in Vizcaya et al. (9): positive response to at least one of the following questions: "Have you been woken by an attack of shortness of breath at any time in the last 12 months?", "Have you had an attack of asthma in the last 12 months?", "Are you currently taking any medicines including inhalers, aerosols or tablets for asthma?"

Table 2. Skin symptoms in the last 12 months, as reported by current cleaning workers and members of the comparison population, and criteria used to define hand dermatitis

	Total Population (N=818)	Comparison Population (N=125)	Current Cleaning Workers (N=693)
	No. (%)	No. (%)	No. (%)
Symptoms			
Red hands or fingers and fissures	146 (18)	10 (8)	136 (20)
Scaling hands or fingers, with fissures	136 (17)	11 (9)	125 (18)
Red, swollen hands or fingers	124 (15)	10 (8)	114 (16)
Itching hands or fingers, with fissures	102 (12)	8 (6)	94 (14)
Vesicles on hands or between fingers	43 (5)	5 (4)	38 (5)
Criteria			
≥1 symptom	275 (34)	27 (22)	248 (36)
≥1 symptom that lasted >3 weeks or occurred >once[1]	213 (26)	22 (18)	191 (28)
≥2 symptoms that lasted >3 weeks or occurred >once	95 (12)	6 (5)	89 (13)

[1] Definition of hand dermatitis used in this analysis

Table 3. Associations of cleaning worksite and major work activities with hand dermatitis

	No.	No. (%) with Hand Dermatitis	PR (95% CI)[1]	No.	No. (%) with Hand Dermatitis	PR (95% CI)[1]	No.	No. (%) with Hand Dermatitis	PR (95% CI)[1]	No.	No. (%) with Hand Dermatitis	PR (95% CI)[1]
Comparison population	125	22 (18)	1.00									
Current cleaning workers	693	191 (28)	1.60 (1.03, 2.47)									
Worksite:	**Hospitals**			**Kitchens**			**Laboratories**			**Outdoor Areas**		
In the last 12 months												
No[2]	515	135 (26)	1.59 (1.03, 2.47)	532	146 (27)	1.61 (1.04, 2.50)	572	157 (27)	1.61 (1.04, 2.49)	525	137 (26)	1.51 (0.97, 2.36)
Yes	178	56 (31)	1.62 (1.00, 2.62)	161	45 (28)	1.54 (0.94, 2.53)	121	34 (28)	1.53 (0.91, 2.57)	168	54 (32)	1.85 (1.16, 2.96)
Frequency in the last month[3]												
<1 day/week	58	15 (26)	1.04 (0.51, 2.13)	88	24 (27)	1.33 (0.68, 2.61)	54	17 (31)	1.72 (0.85, 3.48)	56	20 (36)	1.97 (1.07, 3.64)
1-3 days/week	15	6 (40)	1.70 (0.61, 4.73)	32	10 (31)	1.29 (0.53, 3.11)	15	4 (27)	1.32 (0.40, 4.31)	33	15 (45)	2.20 (1.20, 4.05)
4+ days/week	105	35 (33)	1.19 (0.63, 2.26)	41	11 (27)	1.25 (0.56, 2.77)	52	13 (25)	1.26 (0.57, 2.78)	79	19 (24)	1.52 (0.80, 2.86)
Worksite:	**Other Healthcare Settings**			**Private Homes**			**Residential Building Common Areas**			**Schools**		
In the last 12 months												
No	612	164 (27)	1.59 (1.03, 2.46)	480	130 (27)	1.59 (1.03, 2.45)	499	131 (26)	1.53 (0.98, 2.37)	537	138 (26)	1.53 (0.98, 2.38)
Yes	81	27 (33)	1.64 (0.97, 2.78)	213	61 (29)	1.64 (1.01, 2.66)	194	60 (31)	1.77 (1.11, 2.84)	156	53 (34)	1.84 (1.15, 2.93)
Frequency in the last month												
<1 day/week	41	13 (32)	1.60 (0.75, 3.40)	79	16 (20)	1.22 (0.62, 2.41)	66	16 (24)	1.63 (0.87, 3.05)	64	14 (22)	1.28 (0.64, 2.56)
1-3 days/week	10	4 (40)	1.66 (0.55, 4.97)	78	32 (41)	2.40 (1.30, 4.45)	62	19 (31)	1.74 (0.89, 3.37)	9	3 (33)	2.48 (0.98, 6.29)
4+ days/week	30	10 (33)	1.50 (0.72, 3.11)	56	13 (23)	1.29 (0.61, 2.73)	66	25 (38)	2.08 (1.17, 3.67)	83	36 (43)	2.05 (1.14, 3.69)
Work Activities:	**Construction/renovation Clean-up**			**Floor Cleaning**			**Street/sidewalk Clean-up**			**Window Cleaning**		
In the last 12 months												
No	533	134 (25)	1.50 (0.96, 2.34)	602	166 (28)	1.60 (1.03, 2.48)	631	173 (27)	1.62 (1.05, 2.50)	440	122 (28)	1.65 (1.06, 2.57)
Yes	160	57 (36)	1.87 (1.18, 2.95)	91	25 (27)	1.58 (0.91, 2.75)	62	18 (29)	1.44 (0.80, 2.58)	253	69 (27)	1.50 (0.94, 2.40)
Frequency in the last month												
<1 day/week	92	32 (35)	1.54 (0.88, 2.69)	50	17 (34)	1.53 (0.73, 3.21)	34	9 (26)	1.21 (0.49, 2.95)	67	17 (25)	1.50 (0.82, 2.75)
1+ days/week	68	25 (37)	1.76 (0.98, 3.13)	41	8 (20)	0.86 (0.39, 1.89)	28	9 (32)	1.30 (0.53, 3.18)	186	52 (28)	1.75 (0.99, 3.08)

[1] Adjusted for age, country of birth, sex, history of eczema or other skin allergy, cleaning one's own home, and frequency of rubber glove use. [2] Current cleaning workers who did not work at the worksite or perform the work activity in the last 12 months are included in each model. Effect estimates presented for the population not cleaning the specific worksite within the last 12 months may be interpreted as the effect of currently cleaning, but not cleaning at the specific worksite. The primary outcome of interest generated using these models is the prevalence of hand dermatitis among current cleaning workers who reported cleaning the specific worksite in the last 12 months relative to the prevalence of hand dermatitis in the comparison population. [3] Frequency in the last month among respondents who reported working at the worksite or performing the work activity in the last 12 month

Table 4. Associations of cleaning product use in the last 12 months and frequency of use in the last month with hand dermatitis

	No.	No. (%) with Hand Dermatitis	PR (95% CI)[1]	No.	No. (%) with Hand Dermatitis	PR (95% CI)[1]	No.	No. (%) with Hand Dermatitis	PR (95% CI)[1]	No.	No. (%) with Hand Dermatitis	PR (95% CI)[1]
Comparison Population	125	22 (18)	1.00									
Cleaning Product:	**Air Fresheners**			**Ammonia**			**Bleach**			**Degreasing Agents**		
Used in the last 12 months												
No[2]	351	98 (28)	1.65 (1.06, 2.56)	406	110 (27)	1.62 (1.05, 2.51)	160	38 (24)	1.53 (0.97, 2.42)	240	61 (25)	1.59 (1.02, 2.49)
Yes	342	93 (27)	1.52 (0.96, 2.41)	287	81 (28)	1.55 (0.97, 2.49)	533	153 (29)	1.66 (1.04, 2.66)	453	130 (29)	1.61 (1.02, 2.54)
Frequency of use in the last month[3]												
<1 day/week	68	16 (24)	1.28 (0.68, 2.41)	107	23 (21)	1.26 (0.68, 2.35)	77	17 (22)	1.51 (0.82, 2.78)	110	29 (26)	1.79 (1.04, 3.05)
1-3 days/week	74	18 (26)	1.28 (0.67, 2.46)	64	19 (30)	2.03 (1.09, 3.80)	89	25 (28)	1.69 (0.96, 2.99)	135	44 (33)	1.85 (1.08, 3.14)
4+ days/week	200	58 (29)	1.44 (0.84, 2.46)	116	39 (34)	2.22 (1.26, 3.91)	367	111 (30)	2.02 (1.20, 3.39)	208	57 (27)	1.77 (1.04, 3.02)
Cleaning Product:	**Dust Mop Products**			**Glass Cleaners**			**Hydrochloric Acid**			**Multi-use Products**		
Used in the last 12 months												
No	347	86 (25)	1.49 (0.95, 2.33)	274	77 (28)	1.68 (1.09, 2.61)	389	83 (21)	1.41 (0.90, 2.21)	258	66 (26)	1.60 (1.03, 2.49)
Yes	346	105 (30)	1.75 (1.11, 2.75)	419	114 (27)	1.50 (0.94, 2.38)	304	108 (36)	1.92 (1.22, 3.02)	435	125 (29)	1.60 (1.00, 2.55)
Frequency of use in the last month												
<1 day/week	73	15 (21)	1.46 (0.78, 2.74)	64	16 (25)	1.67 (0.90, 3.09)	120	38 (32)	1.59 (0.92, 2.75)	66	13 (20)	1.56 (0.78, 3.11)
1-3 days/week	74	27 (36)	2.12 (1.22, 3.71)	107	28 (26)	1.49 (0.83, 2.70)	87	35 (40)	1.73 (1.00, 2.99)	89	21 (24)	1.53 (0.86, 2.73)
4+ days/week	199	63 (32)	1.93 (1.16, 3.19)	248	70 (28)	1.75 (1.04, 2.97)	97	35 (36)	1.54 (0.87, 2.73)	280	91 (33)	2.24 (1.31, 3.83)
Cleaning Product:	**Perfumed Products (e.g., pine)**			**Polishes or Waxes**			**Rug or Carpet Cleaners**			**Solvents**		
Used in the last 12 months												
No	310	77 (25)	1.54 (0.98, 2.40)	504	137 (27)	1.56 (1.00, 2.42)	576	160 (28)	1.61 (1.04, 2.50)	553	155 (28)	1.62 (1.05, 2.52)
Yes	383	114 (30)	1.67 (1.06, 2.64)	189	54 (29)	1.71 (1.06, 2.75)	117	31 (26)	1.51 (0.90, 2.54)	140	36 (26)	1.51 (0.92, 2.49)
Frequency of use in the last month												
<1 day/week	58	12 (21)	1.48 (0.77, 2.85)	236	53 (22)	1.85 (1.01, 3.40)	52	17 (33)	1.52 (0.78, 2.97)	77	24 (31)	1.55 (0.85, 2.80)
1-3 days/week	71	19 (27)	1.60 (0.88, 2.92)	37	10 (27)	1.81 (0.83, 3.94)	27	3 (11)	0.56 (0.19, 1.63)	20	6 (30)	1.43 (0.58, 3.49)
4+ days/week	254	83 (33)	1.96 (1.18, 3.26)	74	21 (28)	1.69 (0.91, 3.15)	38	11 (29)	1.06 (0.49, 2.31)	43	6 (14)	0.78 (0.34, 1.81)

[1] Adjusted for age, country of birth, sex, history of eczema or other skin allergy, cleaning one's own home, and frequency of rubber glove use [2] Current cleaning workers who did not work at the worksite or perform the work activity in the last 12 months are included in each model. Effect estimates presented for the population not cleaning the specific worksite within the last 12 months may be interpreted as the effect of currently cleaning, but not cleaning at the specific worksite. The primary outcome of interest generated using these models is the prevalence of hand dermatitis among current cleaning workers who reported cleaning the specific worksite in the last 12 months relative to the prevalence of hand dermatitis in the comparison population. [3] Frequency in the last month among respondents who reported working at the worksite or performing the work activity in the last 12 month

Table 5. Associations of the numbers of different types of worksites and different cleaning products used in the last 12 months with hand dermatitis

	No.	No. (%) with Hand Dermatitis	PR (95% CI)[1]
Comparison Population	125	22 (18)	1.00
Number of worksite types			
0	159	31 (19)	1.38 (0.85, 2.25)
1-2	327	97 (30)	1.69 (1.06, 2.69)
3+	207	63 (30)	1.80 (1.11, 2.93)
Number of different cleaning products			
0	86	20 (23)	1.62 (0.97, 2.72)
1-3	95	23 (24)	1.41 (0.81, 2.45)
4-6	225	58 (26)	1.50 (0.91, 2.48)
7+	287	90 (31)	1.70 (1.04, 2.75)

[1] Adjusted for age, country of birth, sex, history of eczema or other skin allergy, cleaning one's own home, and frequency of rubber glove use

8.5. Fourth paper

Functional and biological characteristics of asthma in cleaning workers

David Vizcaya, Ramon Orriols, Maria C. Mirabelli, Josep Maria Antó, Esther Barreiro, Felip Burgos, Lourdes Arjona, Federico Gomez, Jan-Paul Zock

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Functional and biological characteristics of asthma in cleaning workers

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ABSTRACT

Objectives: Cleaning workers have an increased risk of asthma but the underlying mechanisms are largely unknown. We aimed to characterise the functional and biological profile of asthma in cleaning workers.

Methods: We selected forty-two cleaning workers with persistent asthma or asthma symptoms and 53 respiratory symptom-free controls. Fractional exhaled nitric oxide (FeNO) was measured and forced spirometry with reversibility testing was performed. Total IgE, pulmonary surfactant protein D and the 16kDa Clara Cell protein were measured in blood serum. Interleukins, growth factors, cys-leukotrienes and 8-isoprostane were measured in exhaled breath condensate. Participants provided details about occupational and domestic use of cleaning products. Associations between asthma symptoms, functional and biological characteristics and the use of cleaning products were evaluated using multivariable linear and logistic regression analyses.

Results: Asthma was associated with an 8% (95% confidence interval (CI) 1-15%) lower post-bronchodilator FEV_1 and was not associated with FeNO (Mean Ratio 1.1; CI 0.8-1.3) or any other respiratory biomarkers. Asthmatics had on average 3-times higher levels of total IgE than controls. The use of multiuse products, glass cleaners and polishes was associated with higher FeNO.

Conclusions: Asthma in cleaning workers is characterised by obstructive lung function impairment and increased total IgE. Oxidative stress and eosinophilic inflammation are unlikely to play an important underlying role. Certain cleaning exposures may induce airways inflammation.

'WHAT THIS PAPER ADDS' BOX

- Cleaning workers are at increased risk of asthma but the underlying mechanisms and biological characteristics are unknown.
- Asthma in cleaning workers may be characterised by low lung function and non-eosinophilic inflammation, suggestive of an irritant-induced mechanism.
- Further research is needed to confirm the role of irritant-induced asthma among cleaning workers

INTRODUCTION

There is extensive epidemiological evidence that cleaning workers are at increased risk of asthma and related respiratory symptoms (25;69;133;134;136). Occupational use of irritant cleaning products, including hypochlorite bleach and ammonia, has been associated with asthma (138;139;171). Moreover, cleaning-related exposures are one of the main causes of occupational asthma diagnosed by clinicians in Catalonia, Spain (38). Beyond the occupational use, domestic exposure to cleaning products, in particular those in spray form, has been also suggested as a risk factor for asthma (137).

Despite the extensive epidemiological evidence of increased risks of asthma in cleaners, the physiological characteristics and the underlying mechanisms remain unknown. Inhalation of irritants, yielding bronchial epithelial damage, may result in several events: a pro-inflammatory response, a neurogenic inflammation due to exposed nerve endings and finally an increased lung permeability and remodelling of the airways epithelium, facilitating allergic sensitisation (27). Non-eosinophilic

inflammation has been associated with occupational and non-occupational exposures that lead to the onset or aggravation of asthma through non-allergic pathways (33). However, specific sensitization to cleaning chemicals may play an additional role (76). Several cytokines and growth factors are involved in the inflammatory response in asthma and can be measured in exhaled breath condensate (EBC), a suitable non-invasive matrix for this purpose (185). The fraction of exhaled nitric oxide (FeNO) is widely used as a marker of eosinophilic inflammation (186). Pulmonary proteins move passively across the alveolar epithelial barrier into the peripheral blood stream when the lung epithelium permeability is compromised (187).

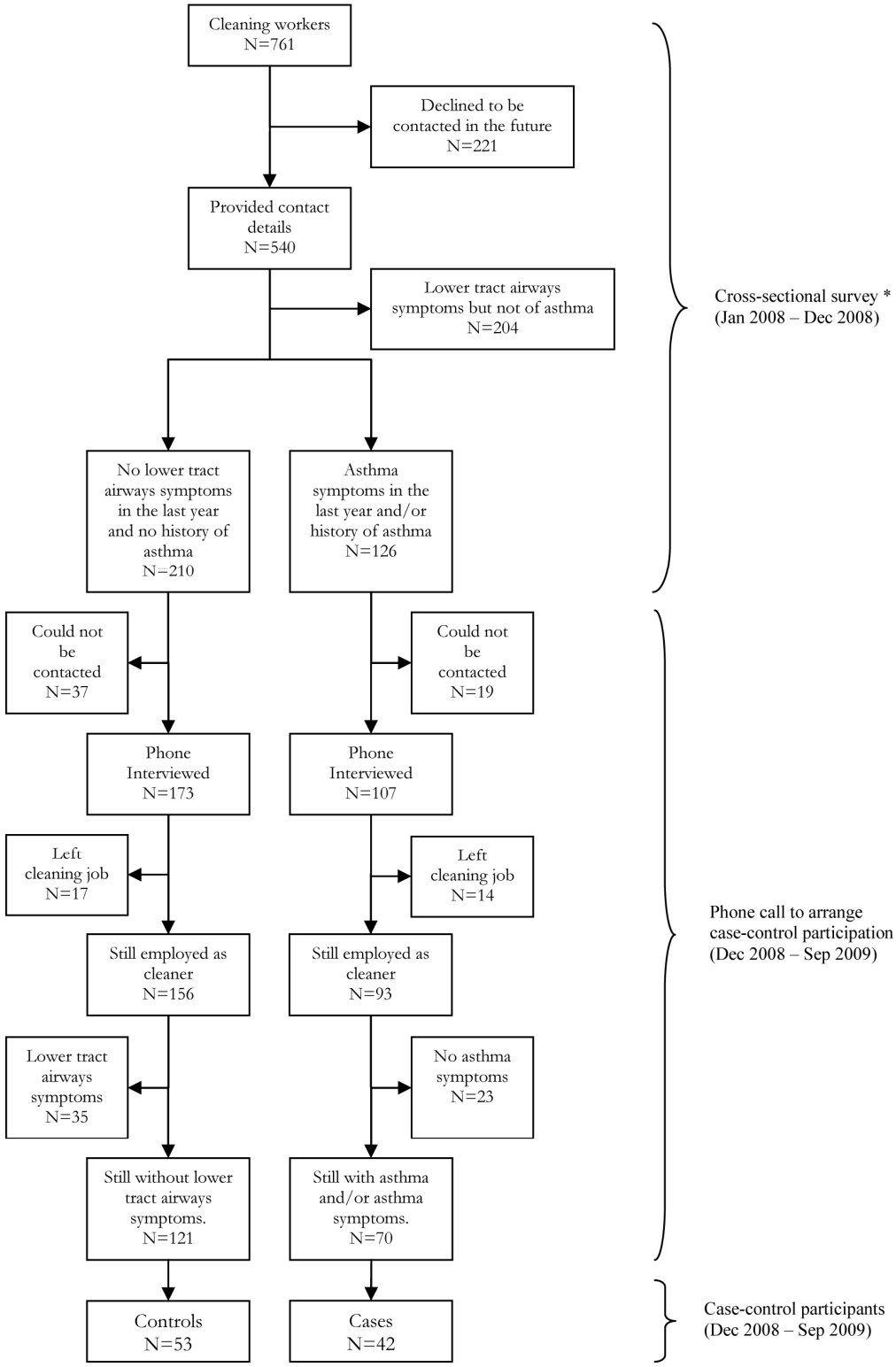
The overall aim of this study was to evaluate the functional and biological characteristics of asthma in cleaning workers. This study is framed within a larger project on asthma and cleaning-related exposures. In a previous stage, we evaluated risk factors for asthma symptoms among cleaning companies' employees (171). In this second stage, we assessed the inflammatory profile, oxidative stress, sensitisation to aeroallergens, lung epithelium permeability, bronchial hyperresponsiveness and lung function in asthmatic and non-asthmatic cleaners. We also evaluated the associations of domestic and occupational use of cleaning products with asthma and with specific respiratory biomarkers.

METHODS

Study design and population

An asthma prevalent case-control study was nested within a large cross-sectional study among cleaning companies' employees in Barcelona, Spain. The study design and methods of the questionnaire survey have

been described previously (171). Briefly, in 2008 we obtained self-administered questionnaires including information on respiratory symptoms and asthma from 761 cleaning workers currently employed at 37 cleaning companies in Barcelona. We identified 70 cases with asthma symptoms (wheeze, chest tightness, breathlessness at rest, breathlessness after exercise and nocturnal breathlessness attack) in the last year and/or with a history of asthma and 121 controls without lower tract respiratory symptoms and without a history of asthma. Between December 2008 and September 2009, selected cases and controls were interviewed by telephone. Those who were still employed as cleaning workers and who still met the case and control inclusion criteria were invited to participate in a detailed clinic visit. Forty-two cases (60%) and 53 controls (44%) were finally enrolled in the study (Figure 1). Eligible participants and non-participants did not differ in age, educational level, sex, smoking status and symptoms either in cases or controls (Supplement table 1). The present study was approved by the ethics committee of Parc de Salut Mar, Barcelona. Participants provided written informed consent.



* [8]. *Vizcaya et al., 2011.*

Face-to-face interview

Information on respiratory symptoms, job history, domestic and occupational cleaning-related exposures, smoking habits and demographic characteristics was obtained during a computer-assisted face-to-face interview. Respiratory health questions were taken from the Spanish version of the European Community Respiratory Health Survey questionnaire (165). Data on domestic and occupational use of cleaning products in the previous year and the average number of hours of product use per week was obtained. Questions on cleaning products were based on findings from a previous study (171).

Lung function testing

Forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC) and forced expiratory flow between 25% and 75% of FVC ($FEF_{25\%-75\%}$) were measured with an EasyOne portable spirometer (ndd Medical Technologies, Zürich, Switzerland) before and 15 minutes after the administration of 400 µg salbutamol via metered dose inhaler, following standard recommendations (188;189). FEV_1 and FVC are expressed as percentages of the age-, sex- and height-specific predicted values (190).

All participants who were eligible for methacholine challenge testing were invited to a second clinic visit for bronchial hyperresponsiveness (BHR) testing in Hospital del Mar (Barcelona, Spain) (165).

Fraction of exhaled nitric oxide (FeNO)

FeNO was measured using an electrochemical portable device (NIOX-MINO; Aerocrine, Solna, Sweden) with a constant airflow rate of 50

mL/sec and following international recommendations (191). Levels were expressed as parts per billion (ppb).

Determination of biological markers in exhaled breath condensate (EBC)

EBC was collected using an EcoScreen® condenser (Jaeger GmbH, Würzburg, Germany) following ATS/ERS Task Force recommendations (192). Treatment of samples has been described previously (193;194). 8-Isoprostane was analyzed using an enzyme-linked immunosorbent assay (ELISA; Cayman Chemical, Ann Arbor, MI, USA). BD Cytometric Bead Array (CBA; BD Biosciences, Erembodegem, Belgium) and the BD FACSCalibur Flow Cytometer (Becton Dickinson, San Jose, CA, USA), a particle-based immunoassay, were used to measure the following 10 cytokines and 2 growth factors: vascular endothelial growth factor (VEGF), basic fibroblast growth factor (FGF), tumour necrosis factor (TNF), interleukin (IL) 2, IL-4, IL-5, IL-8, IL-10, IL-12, IL-13, interferon-gamma (IFN-γ), and IFN-γ–induced protein 10 (Ip10). We assumed the manufacturer recommendations of the corresponding lower limit of detection for each biomarker.

Determination of biological markers in blood serum

Blood serum samples were collected by venipuncture. CC16 and SP-D were analyzed using commercial kits (Biovendor Laboratorní medicína a.s., Modrice, Czech Republic) (193). The concentration of total IgE, and specific IgE against Dust mite (*Dermatophagoides pteronyssinus*) and latex in serum was determined using Chemoluminescent immunoanalysis (IMMULITE 2000. Siemens). We assessed qualitatively the levels of specific IgE to common aeroallergens using the Phadiatop test

(Pharmacia ImmunoCAP; Pharmacia, Uppsala, Sweden) as a proxy for atopy.

Data analysis

Levels of all cytokines and growth factors measured in EBC were dichotomised as detectable or non-detectable. Analysis was conducted if more than 5% of cases and controls were detectable. The distributions of the concentration of all biomarkers followed a log-normal shape. The associations between asthma and dichotomous outcomes were evaluated using multivariable logistic regression analyses, while associations with (log-transformed) continuous outcomes were evaluated using multivariable linear regression analyses. All models were adjusted for age, sex and smoking status (never, former and current smoker). The association between asthma and the use of cleaning products was evaluated with multivariable logistic regression models. All models were adjusted for age, concurrent use of the same cleaning product at home and work, sex and smoking status (never, former and current smoker). Statistical analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Cases and controls were both predominantly women (Table 1). Cases were on average six years younger than controls and more likely to smoke. A relatively high proportion of both groups was born outside Spain (30%) and reported educational attainment of level of primary education or less (cases: 62%, controls: 70%). The majority of cases and controls were overweight (60% and 64% with BMI≥25, respectively). The score of asthma (167) among cases was 2.2, 24% of them reported

having had asthma confirmed by a physician, and 17% had their first asthma attack after the age of 16. Nineteen cases (45%) presented current asthma as defined previously (171). Atopy and sensitisation to latex and dust mite was more prevalent among cases than controls (table 1).

Table 1. Demographic and respiratory health characteristics of the studied population.

	Controls n=53	Cases n=42
Female	47 (89%)	39 (93%)
Age, mean ± SD	48 ± 8	42 ± 10
Smoking		
Never smoker	30 (57%)	14 (33%)
Former smoker	15 (28%)	7 (17%)
Packs-year, mean ± SD	5 ± 6	28 ± 31
Current smoker	8 (15%)	21 (50%)
Packs-year, mean ± SD	15 ± 8	29 ± 24
Country of birth		
Spain	37 (70%)	30 (71%)
Other	16 (30%)	12 (29%)
Educational level		
Less than primary school	7 (13%)	5 (12%)
Primary school	30 (57%)	21 (50%)
Secondary school or higher	16 (30%)	16 (38%)
Body Mass Index (kg/m^2)		
< 20	2 (4%)	1 (2%)
20 to 24.9	17 (32%)	16 (38%)
25 to 29.9	25 (47%)	12 (29%)
≥ 30	9 (17%)	13 (31%)
Years employed as a cleaning worker, mean ± SD	11.6 ± 8.0	12.0 ± 8.2
Doctor diagnosed asthma	-	10 (24%)
Adult onset asthma	-	7 (17%)
Current asthma ‡	-	19 (45%)
Asthma score, mean (SD)	-	2,2 (1,4)
Chronic cough	-	16 (38%)
Chronic phlegm	-	10 (24%)
Upper respiratory tract symptoms	19 (36%)	27 (64%)
Atopy †	5 (10%)	17 (42%)
Sensitisation to latex *	1 (2%)	3 (7%)
Sensitisation to *D. pteronyssinus* *	2 (4%)	13 (31%)

n (%) unless otherwise indicated

‡ Wheeze with breathlessness and/or attack of asthma in the last year and/or currently taking medication for asthma

† Phadiatop test positive. [specific IgE]>0.35 kU/L at least for 1 of 10 common aeroallergens.

* Concentration of specific IgE in blood serum higher than 0.35 kU/L

Lung function testing

Forced spirometry tests of 27 (69%) cases and 45 (85%) controls met the ATS/ERS quality criteria (Table 2). Measurements of FEV_1, the FEV_1/FVC ratio and $FEF_{25\%-75\%}$ were significantly lower in cases than in controls. No significant differences in FVC were observed. Reversibility of bronchial obstruction was similar in cases and controls both as a percentage of change and as a difference of FEV_1 or FVC before and after the inhalation of bronchodilator. A subgroup of 11 cases underwent methacholine challenge testing and showed higher prevalence of BHR compared to 11 controls.

Table 2. Functional characteristics of cases and controls

	Controls (n=45)	Cases (n=27)	Adj. mean difference (95%CI) †
Prebronchodilator, mean (SD)			
FEV_1 (Predicted %)	99.3 (13.0)	92.6 (11.4)	-6.8 (-14.0 to 0.3)
FVC (Predicted %)	96.8 (12.7)	97.5 (12.9)	-1.2 (-9.2 to 7.0)
$FEF_{25-75\%}$ (L/s)	2.9 (0.9)	2.4 (0.9)	-0.5 (-1.0 to -0.1)
FEV_1/FVC	0.82 (0.04)	0.77 (0.07)	-0.04 (-0.07 to -0.01)
Postbronchodilator, mean (SD) ‡			
FEV_1 (Predicted %)	100.7 (12.2)	94.2 (10.3)	-7.8 (-14.9 to -0.7)
FVC (Predicted %)	96.0 (12.6)	97.7 (12.9)	-1.2 (-9.6 to 7.2)
$FEF_{25-75\%}$ (L/s)	2.9 (1.2)	2.2 (1.5)	-1.0 (-2.3 to 0.3)
FEV_1/FVC	0.83 (0.05)	0.78 (0.07)	-0.05 (-0.09 to -0.02)
FEV_1/FVC<0.7, n (%)	0 (0)	3 (12)	
FVC postBD - FVC preBD (mL), mean (SD)	-25.2 (17.6)	5.6 (20.5)	9.8 (-127 to 146)
FEV_1 postBD - FEV_1 preBD (mL), mean (SD)	36.2 (12.6)	62.8 (14.7)	1.5 (-83 to 86)
FVC postBD / FVC preBD (%), mean (SD)	99.1 (5.2)	100.4 (6.0)	1.1 (-3.0 to 5.1)
FEV_1 postBD / FEV_1 preBD (%), mean (SD)	101.4 (4.6)	102.7 (5.7)	0.2 (-2.9 to 3.3)
Bronchodilator challenge test cutpoints, n (%)			
C: 10% change in FEV_1 or FVC	2 (5)	4 (16)	
D: 150 ml change in FEV_1 or FVC	8 (18)	6 (24)	
Bronchial hyperresponsiveness (PD_{20}<1mg), n (%) **	0 (0)	6 (55)	
Bronchial hyperresponsiveness (PD_{20}<2mg), n (%) **	3 (27)	9 (82)	

** Methacholine challenge test. N=11 controls and 11 cases.

† Coefficient and 95%CI from linear regression models adjusted for age, height, sex, and packs-year smoked.

‡ Spirometry 15 minutes after the inhalation of 400mg of salbutamol: n (controls, cases) = 44, 25.

Molecular analysis

Levels of FeNO, SP-D and CC16 were similar in both groups (Table 3). Cases and controls did not differ in the percentage of detectable levels of ILs and growth factors. Cys-leukotrienes and 8-isoprostane were detectable in almost all the analysed samples of EBC and no differences between cases and controls were found in the average level of both markers. Cases had significantly higher levels of total IgE than controls regardless of differences in sex, age and smoking status.

Table 3. Biological characteristics of cases and controls

		Controls (n=51)	Cases (n=41)	
		GM	GM	GM Ratio* (95%CI)
FeNO (ppb)		19.9	17.9	1.1 (0.8 - 1.3)
Serum total [IgE] (IU/mL)		14.9	39.7	2.9 (1.5 - 5.6)
Serum [SP-D] (ng/mL)		39.2	31.2	0.8 (0.5 - 1.1)
Serum [CC16] (ng/mL)		6.8	5.9	0.9 (0.8 - 1.2)
Exhaled breath condensate (pg/mL)				
[8-isoprostane]		1.9	1.7	1.2 (0.7 - 1.8)
[Cys-leukotrienes]		55.5	52.0	1.6 (0.7 - 3.9)
Exhaled breath condensate	**Lower limit of detection (pg/mL)**	**% detectable**	**% detectable**	**OR* (95%CI)**
FGF	3.4	35%	41%	0.6 (0.2 - 1.7)
IL-13	0.6	20%	32%	1.2 (0.4 - 3.8)
TNF-α	0.7	18%	29%	1.3 (0.4 - 4.1)
IFN-γ	1.8	10%	5%	0.3 (0.0 - 2.1)
VEGF	4.5	6%	5%	0.8 (0.1 - 6.6)
IL-4	1.4	4%	5%	n.a.
IL-8	1.2	4%	5%	n.a.
Ip10	0.5	2%	2%	n.a.
IL-5	1.1	2%	5%	n.a.
IL-10	0.1	2%	5%	n.a.
IL-12	0.6	2%	5%	n.a.
IL-2	11.2	0%	2%	n.a.

* Exponential of the coefficient from linear regression models of the log-transformed variable adjusted for age, sex and smoking status.

FeNO: Fraction of exhaled nitric oxide. SP-D: Surfactant Protein D. CC16: 16kDa Clara Cell Protein. EBC: Exhaled Breath Condensate. FGF: basic Fibroblast Growth Factor. VEGF: Vascular Endothelial Growth Factor. TNF-α: Tumour Necrosis Factor alpha. IFN-γ: Interferon gamma. Ip10: IFN-γ–induced protein. IL: Interleukin.

GM: geometric mean. n.a.: not analysed (<5% of detectables)

Domestic and occupational use of cleaning products and asthma

Cases and controls reported frequent domestic and occupational use of hypochlorite bleach, soaps or detergents and degreaser (Table 4). The association with asthma symptoms varied between cleaning products and whether the exposure occurred at home or at work. Cases reported a more frequent use of multi-use products with a positive dose-response relationship in terms of hours-per-week of use compared to controls and the higher risk was observed among those who used multiuse products at both settings in the previous year (Supplement table 2). Asthma was associated with occupational use of multiuse sprays (table 4). Occupational use of soaps or detergents showed a statistically significant inverse association with asthma with a clear dose-response relationship (Data not shown). In general, ORs appeared higher when evaluating domestic exposure.

Table 4. Occupational and domestic use of cleaning products in the previous year and asthma.

	Occupational use in the last year			Domestic use in the last year		
	Controls (n=53)	Cases (n=42)		Controls (n=53)	Cases (n=42)	
	n (%)	n (%)	OR* (95%CI)	n (%)	n (%)	OR** (95%CI)
Ammonia	10 (19)	12 (29)	2.7 (0.9 - 8.2)	14 (26)	13 (31)	1.1 (0.4 - 3.2)
Bleach	47 (89)	39 (93)	1.1 (0.1 - 11)	41 (77)	37 (90)	4.0 (0.8 - 21)
Degreasers	26 (49)	25 (59)	1.2 (0.5 - 3.0)	33 (62)	31 (76)	1.5 (0.5 - 4.6)
Drain products	3 (6)	1 (2)	0.2 (0.0 - 2.9)	5 (9)	6 (15)	1.3 (0.3 - 6.0)
Dust mop products	18 (34)	19 (45)	1.9 (0.7 - 5.2)	8 (15)	8 (20)	0.8 (0.2 - 3.1)
Glass cleaners	19 (36)	17 (40)	1.0 (0.3 - 2.7)	28 (53)	31 (76)	3.3 (1.1 - 9.9)
Hydrochloric acid	4 (8)	5 (12)	1.5 (0.3 - 7.7)	6 (11)	4 (10)	0.6 (0.1 - 3.0)
Limescale removers	23 (43)	20 (48)	0.2 (0.1 - 0.7)	17 (32)	25 (61)	3.8 (0.8 - 19)
Multiuse products	12 (23)	15 (33)	2.3 (0.7 - 7.0)	21 (40)	27 (66)	2.1 (0.8 - 5.8)
Polishes and waxes	7 (13)	6 (14)	1.1 (0.2 - 5.2)	3 (6)	7 (17)	3.9 (0.8 - 19)
Soaps or detergents	37 (70)	21 (50)	0.2 (0.1 - 0.7)	34 (64)	28 (68)	1.5 (0.5 - 4.5)
Stain removers	5 (9)	4 (9)	0.8 (0.1 - 4.1)	5 (9)	11 (27)	2.7 (0.7 - 9.8)
Spray or aerosolised form						
Multiuse products	5 (9)	7 (17)	4.1 (1.0 - 18)	n.a.	n.a.	n.a.
Degreasers	8 (15)	9 (21)	1.1 (0.4 - 3.1)	n.a.	n.a.	n.a.
Dust mop products	16 (30)	17 (40)	1.5 (0.6 - 3.9)	n.a.	n.a.	n.a.
Limescale removers	4 (8)	4 (10)	1.5 (0.5 - 5.0)	n.a.	n.a.	n.a.
Glass cleaners	16 (31)	14 (33)	1.2 (0.3 - 5.9)	n.a.	n.a.	n.a.
Num different sprays						
0	22 (42)	14 (33)	1	n.a.	n.a.	n.a.
1-2	22 (42)	17 (40)	0.8 (0.3 - 2.4)	n.a.	n.a.	n.a.
3-5	9 (17)	11 (26)	2.1 (0.6 - 7.4)	n.a.	n.a.	n.a.

* Association between asthma and occupational use of cleaning products using logistic regression models adjusted for age, domestic use of the product, sex and smoking habit. Reference category for each model: no occupational use of the product ever in the last year

** Association between asthma and domestic use of cleaning products using logistic regression models adjusted for age, occupational use of the product, sex and smoking habit. Reference category for each model: no domestic use of the product ever in the last year

n.a.: information not available

Occupational use of multiuse products during the previous year, adjusted for domestic use of the same product, was associated with increased levels of FeNO, serum IgE and FGF in EBC among cases and controls regardless of their symptomatic status (table 5). Cleaning workers who used glass cleaners and polishes or waxes at work showed higher levels

of TNF-α in EBC and FeNO which, in addition, was also increased among those subjects using glass cleaners at work. IgE was also increased among cleaners who reported the use of hydrochloric acid and degreasers at work during the previous year. Domestic use of ammonia during the previous year was associated with higher levels of 8-isoprostane in EBC and the use of hydrochloric acid with higher levels of TNF-α. Geometric means of the concentrations are provided in the online supplement (Supplement tables 3 and 4). Evaluation of these associations stratified for cases and controls showed heterogeneous results.

Table 5. Associations between occupational and domestic use of cleaning products and biomarker levels among all cases and controls.

	Continuous variables						Categorical variables (detectable vs. non-detectable)			
	FeNO	CC16	SP-D	IgE	8-isoprostane	Cys-leukotrienes	FGF	TNF-α	IL-13	IFN-γ
	GMR* (95%CI)	GMR* (95%CI)	GMR* (95%CI)	GMR* (95%CI)	GMR* (95%CI)	GMR* (95%CI)	OR** (95%CI)	OR** (95%CI)	OR** (95%CI)	OR** (95%CI)
Ammonia										
Occupational	0.9 (0.7 - 1.1)	1.0 (0.8 - 1.3)	1.0 (0.7 - 1.5)	1.4 (0.7 - 3.0)	0.9 (0.5 - 1.4)	1.2 (0.5 - 3.1)	0.7 (0.2 - 2.3)	1.4 (0.4 - 4.8)	0.7 (0.2 - 2.6)	0.9 (0.1 - 6.6)
Domestic	1.1 (0.8 - 1.4)	0.9 (0.7 - 1.2)	1.0 (0.7 - 1.5)	0.6 (0.3 - 1.2)	**1.7 (1.1 - 2.7)**	0.4 (0.2 - 1.1)	1.4 (0.5 - 4.0)	1.5 (0.5 - 5.1)	2.5 (0.8 - 8.6)	1.6 (0.2 - 12)
Bleach										
Occupational	1.2 (0.8 - 1.9)	1.4 (0.9 - 2.2)	1.6 (0.7 - 3.5)	2.2 (0.5 - 9.3)	0.8 (0.3 - 1.9)	1.2 (0.2 - 7.5)	n.a.	n.a.	n.a.	n.a.
Domestic	0.9 (0.7 - 1.3)	0.9 (0.6 - 1.2)	0.9 (0.5 - 1.5)	1.0 (0.4 - 2.6)	0.8 (0.4 - 1.6)	0.9 (0.3 - 2.9)	n.a.	n.a.	n.a.	n.a.
Degreasers										
Occupational	1.1 (0.9 - 1.4)	0.9 (0.7 - 1.1)	0.8 (0.6 - 1.2)	**1.8 (1.0 - 3.3)**	0.5 (0.3 - 0.7)	0.7 (0.3 - 1.6)	0.8 (0.3 - 2.1)	0.6 (0.2 - 1.6)	0.7 (0.2 - 1.9)	0.2 (0.0 - 1.7)
Domestic	1.1 (0.9 - 1.4)	1.0 (0.8 - 1.2)	1.1 (0.7 - 1.6)	0.9 (0.4 - 1.7)	0.7 (0.5 - 1.1)	0.8 (0.3 - 2.0)	1.1 (0.4 - 3.3)	1.7 (0.5 - 6.4)	1.1 (0.3 - 3.8)	0.3 (0.0 - 2.1)
Dust mop products										
Occupational	1.0 (0.8 - 1.2)	0.9 (0.8 - 1.2)	1.0 (0.7 - 1.5)	1.8 (0.9 - 3.4)	0.9 (0.6 - 1.4)	1.5 (0.6 - 3.3)	1.1 (0.4 - 2.9)	1.8 (0.6 - 5.3)	0.7 (0.2 - 2.1)	3.2 (0.5 - 20.7)
Domestic	1.1 (0.8 - 1.4)	1.0 (0.8 - 1.4)	0.8 (0.5 - 1.2)	1.0 (0.4 - 2.5)	1.5 (0.8 - 2.6)	0.6 (0.2 - 1.8)	0.8 (0.2 - 2.9)	0.6 (0.1 - 2.9)	0.5 (0.1 - 2.8)	0.5 (0.0 - 6.2)
Glass cleaners										
Occupational	**1.3 (1.1 - 1.7)**	0.9 (0.7 - 1.1)	1.0 (0.7 - 1.5)	1.4 (0.7 - 2.7)	1.1 (0.7 - 1.7)	1.7 (0.7 - 4.2)	1.4 (0.5 - 3.9)	**3.1 (1.0 - 9.8)**	1.2 (0.4 - 3.8)	1.0 (0.2 - 5.8)
Domestic	0.9 (0.7 - 1.1)	1.0 (0.8 - 1.3)	0.9 (0.6 - 1.2)	1.3 (0.6 - 2.5)	0.9 (0.6 - 1.5)	0.6 (0.2 - 1.4)	1.3 (0.5 - 3.5)	1.7 (0.5 - 5.9)	1.4 (0.4 - 4.3)	0.7 (0.1 - 4.0)
Hydrochloric acid										
Occupational	1.2 (0.9 - 1.7)	0.9 (0.6 - 1.2)	1.0 (0.5 - 1.7)	**3.5 (1.2 - 9.8)**	1.0 (0.5 - 2.1)	1.1 (0.3 - 4.0)	0.8 (0.2 - 3.9)	0.4 (0.1 - 3.1)	0.4 (0.1 - 2.4)	0.8 (0.1 - 11)
Domestic	0.7 (0.5 - 1.0)	0.8 (0.6 - 1.2)	1.1 (0.6 - 2.0)	0.8 (0.3 - 2.1)	0.9 (0.4 - 1.9)	0.5 (0.1 - 1.6)	2.0 (0.5 - 8.8)	**7.3 (1.4 - 39)**	4.0 (0.8 - 20)	2.6 (0.2 – 33)
Limescale removers										
Occupational	1.1 (0.9 - 1.4)	1.0 (0.8 - 1.3)	0.8 (0.6 - 1.2)	1.6 (0.8 - 3.0)	0.7 (0.4 - 1.1)	1.8 (0.8 - 4.2)	1.0 (0.4 - 2.6)	0.3 (0.1 - 1.1)	0.2 (0.1 - 0.8)	0.1 (0.0 - 1.5)
Domestic	1.0 (0.8 - 1.3)	0.9 (0.7 - 1.1)	1.2 (0.8 - 1.7)	1.1 (0.6 - 2.2)	1.1 (0.7 - 1.7)	1.1 (0.5 - 2.6)	1.1 (0.4 - 2.9)	3.0 (0.9 - 9.9)	1.8 (0.6 - 5.9)	2.0 (0.3 – 14)

Multiuse products										
Occupational	**1.4 (1.1 - 1.7)**	1.0 (0.8 - 1.2)	0.9 (0.6 - 1.4)	**2.1 (1.0 - 4.2)**	1.3 (0.8 - 2.1)	1.9 (0.8 - 4.9)	**2.9 (1.0 - 8.7)**	2.5 (0.8 - 7.7)	1.1 (0.4 - 3.4)	3.1 (0.5 – 17)
Domestic	1.0 (0.8 - 1.2)	1.0 (0.8 - 1.3)	1.0 (0.7 - 1.5)	1.0 (0.5 - 2.0)	1.0 (0.6 - 1.5)	1.0 (0.4 - 2.2)	1.0 (0.4 - 2.8)	0.9 (0.3 - 2.6)	1.0 (0.3 - 2.9)	2.5 (0.4 - 18)
Polishes and waxes										
Occupational	**1.6 (1.2 - 2.1)**	1.2 (0.8 - 1.6)	1.4 (0.8 - 2.4)	1.5 (0.6 - 4.3)	1.4 (0.7 - 2.7)	1.0 (0.3 - 4.0)	0.7 (0.2 - 3.2)	1.6 (0.4 - 7.6)	1.8 (0.4 - 8.1)	1.0 (0.1 - 101)
Domestic	1.0 (0.7 - 1.3)	0.8 (0.6 - 1.2)	1.2 (0.7 - 2.2)	0.7 (0.2 - 2.0)	1.5 (0.7 - 3.1)	1.2 (0.3 - 4.9)	1.1 (0.2 - 5.3)	1.3 (0.2 - 7.2)	2.0 (0.4 - 10)	2.9 (0.2 - 54)
Soaps or detergents										
Occupational	0.9 (0.8 - 1.1)	1.0 (0.8 - 1.3)	0.8 (0.6 - 1.2)	0.6 (0.3 - 1.1)	0.8 (0.5 - 1.2)	0.7 (0.3 - 1.7)	1.1 (0.4 - 2.7)	0.7 (0.2 - 1.9)	0.6 (0.2 - 1.6)	0.2 (0.0 - 1.5)
Domestic	1.2 (0.9 - 1.4)	1.0 (0.8 - 1.3)	1.2 (0.8 - 1.7)	0.9 (0.4 - 1.7)	1.3 (0.8 - 2.0)	0.9 (0.4 - 2.1)	1.3 (0.5 - 3.7)	0.6 (0.2 - 1.8)	0.9 (0.3 - 2.6)	0.2 (0.0 - 1.2)

* Geometric means ratio and 95% confidence intervals from multivariable linear regression models of the log-transformed variables including all cases and controls. Independent variables included in the models: domestic use of cleaning product, occupational use of cleaning product, age, sex and smoking habit. ** Odds ratio and 95% confidence intervals from multivariable logistic regression models including all cases and controls. Independent variables included in the models: domestic use of cleaning product, occupational use of cleaning product, age, sex and smoking habit. n.a.: not analysed.

FeNO: Fraction of exhaled NO. SP-D: Serum surfactant Protein D. CC16: Serum 16kDa Clara Cell Protein. EBC: Exhaled Breath Condensate. FGF: EBC basic Fibroblast Growth Factor. VEGF: EBC Vascular Endothelial Growth Factor. TNF-α: EBC Tumour Necrosis Factor alpha. IFN-γ: EBC Interferon gamma. Ip10: EBC IFN-γ–induced protein. IL: EBC Interleukin.

DISCUSSION

This study suggests that cleaning workers with asthma are characterised by lower spirometric indices indicative of non-reversible airways obstruction and non-eosinophilic inflammation. We found no differences in levels of biomarkers oxidative stress or remodelling of the airways between asthmatics and non-asthmatics. Asthmatic cleaners are more often atopic and show higher serum total IgE levels than healthy cleaners.

This is the first study that evaluated thoroughly the biological characteristics of asthma in cleaning workers. The lower values of post-bronchodilator FEV_1, $FEF_{25\%-75\%}$ and the ratio FEV_1/FVC of cases compared to controls suggest a functional phenotype with airflow limitation. The reversibility of bronchial obstruction, which is one of the main characteristics of asthma (1;195), was not different between cases and controls. Nevertheless, it has been previously reported that non-eosinophilic asthmatics with low FEV_1, are less commonly bronchodilator test positive compared to eosinophilic asthmatics (32). Furthermore, thickening of the reticular basal membrane is considered a histopathologic feature of occupational asthma, and may be an alternative explanation for the non-reversibility of airways obstruction (28). Cases also showed a higher prevalence of bronchial hyperresponsiveness, which was measured in a subsample of 11 cases and 11 controls. No differences in age, lung function, sex and smoking habit were found between eligible participants and non-participants of methacholine challenge testing.

Cases and controls showed, on average, very similar levels of FeNO, and the lack of association was not affected by adjustment for age, sex and smoking status. Additional adjustment for other determinants such as

atopy and body mass index yielded very similar results, suggesting that these factors were not confounding the relationship between asthma and FeNO. In addition, when limiting the analysis to cases with active asthma as defined previously (171), or to individuals with adult-onset asthma, the results did not change. Thus, this lack of difference in FeNO suggests that eosinophilic inflammation does not play a predominant role in asthma in cleaning workers. According to the literature (33;52), the non-eosinophilic phenotype is characteristic of irritant-induced asthma, which has been proposed as the main mechanistic hypothesis for cleaning-related asthma and asthma-like disorders.

The increased levels of IgE observed among cases compared to controls and the increased proportion of Phadiatop test positives may be related to lung damage due to the inhalation of irritants, which facilitates an immunological response to sensitizers (27;33). In addition, a previous study showed an association between atopic sensitisation and the exposure to non-allergenic disinfectants (196). Alternatively, some cleaning products contain sensitizers, which may explain the increased levels of IgE (76). In a previous study we found no association of atopy and asthma and/or chronic bronchitis in domestic cleaning workers, but higher total serum IgE level (138). It is important to highlight that phadiatop test is a method that assesses the levels of specific IgE levels for ten common aeroallergens, and may have a component of false positives (197). On the other hand, an international study with a case-case design found that asthmatic cleaners had less atopy than asthmatic office workers (151). Cases and controls showed similar levels of 8-isoprostane in EBC, which is in line with our results of FeNO (198). Cys-leukotrienes, growth factors and cytokines levels were also similar in cases and controls. The replication of the analyses restricted to cases with either adult-onset asthma or current asthma did not show any further association. Irritant-induced asthma is usually less severe in

terms of uncontrolled disease than immunological asthma, and may be an alternative explanation for the lack of associations between respiratory biomarkers and asthma among cleaning workers in our study (11).

We evaluated both occupational and domestic exposure to cleaning products, and their association with asthma symptoms and respiratory biomarkers. Occupational and domestic use of multiuse products appeared as a consistent risk factor. This observation was strengthened by a dose-dependent association when evaluating the duration of use (data not shown). In addition, multiuse products' use in spray form, likely facilitates inhalatory exposure (137), was strongly associated with asthma. Multiuse product is a generic term that refers to complex formulae for cleaning products based on non-ionic tensioactives, often Linear Alkylbenzene Sulfonate, which have been previously described as an occupational asthmogen (119). We also found indications that the use of irritants, including ammonia (138;139;171), hypochlorite bleach (138;139), polishes or waxes (112), glass cleaners and dust mop products was associated with asthma.

The relationships between the use of specific products and biomarkers were heterogeneous but, interestingly, occupational use of multiuse products was associated with increased levels of FeNO, total IgE and FGF. This is suggestive of an inflammatory profile more related to immunological asthma (27;33). We assessed the associations of biomarkers and products without avoiding any possible mechanistic pathway, thus we did not adjust for case-control status. We initially performed a separate analysis for cases and controls, although it was limited by statistical power (Supplement tables 5 and 6). Nevertheless, the associations between multi-use products and FeNO, total IgE and FGF

pointed in the same direction for cases and controls, suggesting a sub-clinical effect independent of asthma.

A particular strength of this study was the detailed assessment of functional and biological characteristics of asthma. We evaluated biomarkers indicative of a variety of patho-physiological processes including inflammation, oxidative stress, airways damage and affected permeability. Additional strengths included a confirmation of the case or control status in an intermediate step between the initial questionnaire and the clinic visit. The inclusion and exclusion criteria were largely based on reported respiratory symptoms, which typically show a considerable variability over time when repeatedly assessed. This is related to the intermittent nature of the underlying respiratory condition (true variation) as well as to measurement error (199). Misclassification of asthma status was reduced by following the conservative approach in which both cases and controls met the inclusion criteria for case or control status twice, approximately one year apart. Thus, our final study population included cases with persistent asthma symptoms and controls without temporary symptoms.

There are a number of potential limitations that need to be considered. First, the study population was relatively small. This affected the statistical power for detecting small differences between cases and controls and limited the assertiveness of the conclusions. This is due in part to the workforce-based and cross-sectional-nested nature of the study, what made difficult approaching participants due to an already limited population and a very restrictive Spanish legislation on personal data protection (154;171). However, our approach provided us a less biased study population, with a wide range of occupational exposures. In our opinion, the large amount of biological and questionnaire data

obtained and the reduced misclassification of asthma compensate the low sample size. Furthermore, our results are consistent with previous findings (133;134). Second, several cleaning products have strong odours that may have been overreported by asthmatic cases and potentially lead to a bias of our results away from the null (200). However, the differences in risks for domestic and professional use of some odorous products (e.g., ammonia) suggest that overreporting was unlikely to have introduced a major bias. Finally, we controlled potential confounding by adjustment for age, sex and smoking status in all analyses. Current smoking was strongly related to asthma in our study, and rather than being a strong risk factor for asthma this was likely driven by the selection criteria for controls excluding those with chronic bronchitis symptoms. As a result, although not included in the inclusion criteria, cases had more chronic bronchitis symptoms than controls. Therefore the association between current smoking and asthma was determined by cases with chronic bronchitis symptoms. Indeed, when excluding cases with chronic bronchitis symptoms, the association between current smoking and case/control status attenuated. When the main analyses were repeated without adjustment for smoking status, or when excluding current and former smokers, no major differences in associations could be found. Thus, in spite of a potential overadjustment for smoking, this is unlikely to have had a major influence on our findings.

In conclusion, this work contributes to disentangling the physiological characteristics of the respiratory disorders associated to cleaning-related exposures. Our results suggest that a non-reversible bronchial obstruction component is present in asthmatic cleaners and that eosinophilic inflammation and oxidative stress are unlikely to play a key role in the increased risk of asthma symptoms. Our findings about

occupational and domestic exposure to cleaning products highlight the importance both for general public health and occupational safety. Further studies on the mechanisms of asthma in individuals exposed to cleaning agents are recommended.

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SUPPLEMENT

Supplement table 1. Demographic characteristics and symptoms at the first study of eligible participants and non-participants

	Eligible controls (n=121)			Eligible cases (n=70)		
	Non-participants n=69	Participants n=52	p-value	Non-participants n=28	Participants n=42	p-value
Female	58 (84%)	46 (88%)	0.49	26 (93%)	39 (93%)	1.00
Age, mean ± SD	47 ± 9	47 ± 8	0.76	45 ± 10	42 ± 10	0.14
Smoking						
Never smoker	45 (67%)	37 (71%)	0.47	15 (54%)	16 (39%)	0.17
Former smoker	9 (13%)	9 (17%)		0 (0%)	4 (10%)	
Current smoker	13 (19%)	6 (11%)		13 (46%)	21 (51%)	
Country of birth						
Spain	51 (77%)	34 (68%)	0.26	22 (85%)	29 (71%)	0.19
Other	15 (23%)	16 (32%)		4 (15%)	12 (29%)	
Educational level						
Less than primary school	14 (20%)	5 (10%)	0.12	4 (14%)	5 (12%)	0.48
Primary school	46 (67%)	33 (63%)		21 (75%)	27 (66%)	
Secondary school or higher	9 (13%)	13 (25%)		3 (11%)	9 (22%)	
Doctor diagnosed asthma	n.a.	n.a.		14 (52%)	14 (34%)	
Adult onset asthma	n.a.	n.a.		11 (39%)	7 (17%)	0.03
Current asthma ‡	n.a.	n.a.		20 (48%)	22 (52%)	0.57
Asthma score, mean (SD)	n.a.	n.a.		2.5 ± 1.5	2.2 ± 1.3	0.40
Upper respiratory tract symptoms	15 (22%)	17 (33%)	0.18	21 (75%)	32 (76%)	0.91

Supplement table 2. Setting of use of cleaning products during the last year and association with case/control status.

	Controls (n=52)	Cases (n=41)	
	n (%)	n (%)	OR * (95%CI)
Ammonia			
Neither at home or work	32 (61)	23 (55)	1
Either at home or work	20 (38)	19 (45)	1.8 (0.7 - 4.6)
Only at work	6 (11)	6 (14)	2.3 (0.6 - 9.7)
Only at home	10 (19)	7 (17)	1.0 (0.3 - 3.5)
At work and home	4 (8)	6 (14)	3.2 (0.7 - 15.1)
Degreasers			
Neither at home or work	10 (19)	5 (12)	1
Either at home or work	42 (81)	36 (88)	0.7 (0.2 - 2.7)
Only at work	10 (19)	5 (12)	0.3 (0.1 - 2.1)
Only at home	16 (31)	11 (27)	0.6 (0.1 - 2.9)
At work and home	16 (30)	20 (49)	1.1 (0.3 - 4.9)
Dust mop products			
Neither at home or work	31 (60)	21 (51)	1
Either at home or work	21 (40)	20 (49)	1.6 (0.6 - 4.1)
Only at work	13 (24)	12 (29)	1.8 (0.6 - 5.2)
Only at home	3 (6)	1 (2)	- -
At work and home	5 (9)	7 (17)	1.6 (0.4 - 6.8)
Glass cleaners			
Neither at home or work	21 (40)	8 (19)	1
Either at home or work	31 (60)	33 (80)	2.3 (0.8 - 6.6)
Only at work	4 (8)	2 (5)	- -
Only at home	12 (23)	16 (39)	2.4 (0.7 - 8.9)
At work and home	15 (28)	15 (37)	3.2 (0.9 - 11.3)
Hydrochloric acid			
Neither at home or work	43 (83)	33 (80)	1
Either at home or work	9 (17)	8 (19)	1.0 (0.3 - 3.4)
Only at work	3 (6)	4 (10)	1.9 (0.3 - 11.9)
Only at home	5 (9)	3 (7)	0.7 (0.1 - 4.0)
At work and home	1 (2)	1 (2)	- -
Limescale removers			
Neither at home or work	23 (44)	11 (27)	1
Either at home or work	29 (55)	30 (73)	2.4 (0.8 - 6.9)
Only at work	12 (23)	5 (12)	0.8 (0.2 - 3.8)
Only at home	6 (11)	10 (24)	3.5 (0.8 - 15.0)
At work and home	11 (21)	15 (37)	3.5 (1.0 - 13)
Multiuse products			
Neither at home or work	28 (54)	10 (24)	1
Either at home or work	24 (46)	31 (76)	2.7 (1.0 - 7.3)
Only at work	4 (8)	4 (10)	1.8 (0.3 - 11.1)
Only at home	12 (23)	16 (39)	2.0 (0.6 - 6.4)
At work and home	8 (15)	11 (27)	5.0 (1.3 - 19.0)

Soaps or detergents			
Neither at home or work	10 (19)	6 (15)	1
Either at home or work	42 (81)	35 (85)	0.9 (0.2 - 3.2)
Only at work	9 (17)	7 (17)	0.6 (0.1 - 3.3)
Only at home	6 (11)	14 (34)	3.5 (0.7 - 17.6)
At work and home	27 (52)	14 (34)	0.5 (0.1 - 2.0)
Stain removers			
Neither at home or work	43 (83)	26 (63)	1
Either at home or work	9 (17)	15 (37)	2.1 (0.7 - 6.1)
Only at work	4 (8)	4 (10)	1.1 (0.2 - 7.0)
Only at home	4 (8)	11 (27)	3.3 (0.8 - 13.2)
At work and home	1 (2)	0 (0)	- -

* Logistic regression models adjusted for age, sex and smoking status

Supplement table 3. Occupational use of cleaning products in the last year and biomarkers levels

	Continuous variables						Categorical variables			
	FeNO	CC16	SP-D	IgE	8-isoprostane	Cys-leukotrienes	FGF	TNF-α	IL-13	IFN-γ
	GM	GM	GM	GM	GM	GM	n (%)	n (%)	n (%)	n (%)
Ammonia										
No exposure	19.1	6.3	35.1	23.2	2	53.3	28 (41)	15 (22)	18 (26)	5 (7)
Exposure	18.6	6.6	37.1	26.8	2.1	56	7 (32)	6 (27)	5 (23)	2 (9)
Bleach										
No exposure	22.9	5.4	31.9	15.7	3	49	n.a.	n.a.	n.a.	n.a.
Exposure	18.6	6.5	35.9	25	1.9	54.4	n.a.	n.a.	n.a.	n.a.
Degreasers										
No exposure	18.6	6.7	39.3	16	2.9	69.7	16 (37)	11 (26)	11 (26)	4 (9)
Exposure	19.3	6.1	32.4	34.7	1.5	43.4	19 (40)	10 (21)	12 (25)	3 (6)
Dust mop products										
No exposure	19.3	6.5	35.9	19.3	2.1	46.8	21 (38)	11 (20)	16 (29)	3 (5)
Exposure	18.6	6.3	35	34.3	2	66.5	14 (39)	10 (28)	7 (19)	4 (11)
Glass cleaners										
No exposure	17.2	6.5	36.3	20.2	2	48.4	20 (34)	9 (15)	13 (22)	4 (7)
Exposure	22.7	6.3	34.3	31.7	2	64.5	15 (45)	12 (36)	10 (30)	3 (9)
Hydrochloric acid										
No exposure	18.7	6.5	35.8	21.3	2	55	31 (38)	19 (23)	21 (26)	6 (7)
Exposure	22	5.4	33.5	69.8	2.1	46.3	4 (44)	2 (22)	2 (22)	1 (11)
Limescale removers										
No exposure	18.7	6.4	37.7	19.6	2.4	38.8	19 (39)	14 (29)	17 (35)	6 (12)
Exposure	19.4	6.4	33	30.9	1.6	82.9	16 (38)	7 (17)	6 (14)	1 (2)
Multiuse products										
No exposure	17.5	6.3	36.1	19.2	1.9	45.2	21 (32)	12 (18)	16 (25)	3 (5)
Exposure	23.6	6.6	34.1	42.9	2.3	88.6	14 (54)	9 (35)	7 (27)	4 (15)
Polishes and waxes										
No exposure	17.8	6.3	33.8	22.5	1.9	54.3	31 (40)	17 (22)	18 (23)	5 (6)

Exposure	28	7.2	49.5	36.5	3.2	52.2	4 (31)	4 (31)	5 (38)	2 (15)
Soaps or detergents										
No exposure	20.4	6.2	40	31.4	2.3	72.4	12 (34)	9 (26)	10 (29)	4 (11)
Exposure	18.1	6.5	32.8	20	1.8	44.6	23 (41)	12 (21)	13 (23)	3 (5)

GM: Geometric mean. N.a.: not analysed. FeNO: Fraction of exhaled NO. SP-D: Sserum surfactant Protein D. CC16: Serum 16kDa Clara Cell Protein. EBC: Exhaled Breath Condensate. FGF: EBC basic Fibroblast Growth Factor. VEGF: EBC Vascular Endothelial Growth Factor. TNF-α: EBC Tumour Necrosis Factor alpha. IFN-γ: EBC Interferon gamma. Ip10: EBC IFN-γ–induced protein. IL: EBC Interleukin.

Supplement table 4. Domestic use of cleaning products in the last year and biomarkers levels

	Continuous variables						Categorical variables			
	FeNO	CC16	SP-D	IgE	8-isoprostane	Cys-leukotrienes	FGF	TNF-α	IL-13	IFN-γ
	GM	GM	GM	GM	GM	GM	n (%)	n (%)	n (%)	n (%)
Ammonia										
No exposure	19.2	6.6	35.4	27.8	1.8	63.4	25 (39)	14 (22)	15 (23)	5 (8)
Exposure	18.6	6.0	35.9	17.0	2.7	33.7	10 (38)	7 (27)	8 (31)	2 (8)
Bleach										
No exposure	21.2	6.7	41.4	27.4	3.1	57.1	n.a.	n.a.	n.a.	n.a.
Exposure	18.4	6.4	34.4	23.0	1.9	54.1	n.a.	n.a.	n.a.	n.a.
Degreasers										
No exposure	19.5	6.7	36.3	23.5	2.9	68.9	10 (34)	5 (17)	7 (24)	4 (14)
Exposure	18.5	6.3	35.2	23.9	1.7	49.4	25 (42)	16 (27)	16 (27)	3 (5)
Dust mop products										
No exposure	19.0	6.5	37.0	22.2	1.9	57.9	30 (40)	18 (24)	21 (28)	6 (8)
Exposure	18.3	6.3	29.8	32.3	2.6	38.8	5 (33)	3 (20)	2 (13)	1 (7)
Glass cleaners										
No exposure	19.3	6.4	39.6	17.8	2.3	65.3	11 (33)	5 (15)	7 (21)	3 (9)
Exposure	18.6	6.4	33.3	28.4	1.9	48.9	24 (43)	16 (29)	16 (29)	4 (7)
Hydrochloric acid										
No exposure	19.6	6.6	35.3	24.9	2.1	59.9	30 (38)	16 (20)	19 (24)	6 (8)
Exposure	13.8	5.0	37.7	16.1	1.9	29.9	5 (50)	5 (50)	4 (40)	1 (10)
Limescale removers										
No exposure	19.0	6.7	35.4	21.0	2.3	50.0	17 (36)	8 (17)	11 (23)	4 (9)
Exposure	18.7	6.1	35.8	27.6	1.8	60.2	18 (43)	13 (31)	12 (29)	3 (7)
Multiuse products										
No exposure	19.2	6.4	36.3	20.6	2.1	54.1	14 (33)	9 (21)	10 (23)	2 (5)
Exposure	18.5	6.5	34.8	27.5	2.0	54.9	21 (46)	12 (26)	13 (28)	5 (11)
Polishes and waxes										

No exposure	18.7	6.5	34.7	24.6	2.0	54.7	31 (39)	18 (22)	19 (24)	6 (8)
Exposure	20.6	5.9	43.0	17.9	2.8	53.3	4 (44)	3 (33)	4 (44)	1 (11)
Soaps or detergents										
No exposure	18.4	6.4	34.3	28.5	2.1	57.9	11 (35)	9 (29)	9 (29)	5 (16)
Exposure	19.1	6.5	36.2	21.6	2.1	52.7	24 (41)	12 (21)	14 (24)	2 (3)

GM: Geometric mean. N.a.: not analysed. FeNO: Fraction of exhaled NO. SP-D: Sserum surfactant Protein D. CC16: Serum 16kDa Clara Cell Protein. EBC: Exhaled Breath Condensate. FGF: EBC basic Fibroblast Growth Factor. VEGF: EBC Vascular Endothelial Growth Factor. TNF-α: EBC Tumour Necrosis Factor alpha. IFN-γ: EBC Interferon gamma. Ip10: EBC IFN-γ–induced protein. IL: EBC Interleukin

Supplement table 5. Associations between occupational and domestic use of cleaning products and biomarker levels among cases

	Continuous variables						Categorical variables (detectable vs. non-detectable)		
	FeNO	CC16	SP-D	IgE	8-isoprostane	Cys-leukotrienes	FGF	TNF-α	IL-13
	GMR* (95%CI)	GMR* (95%CI)	GMR* (95%CI)	GMR* (95%CI)	GMR* (95%CI)	GMR* (95%CI)	OR** (95%CI)	OR** (95%CI)	OR** (95%CI)
Ammonia									
Occupational	0.8 (0.5 - 1.2)	1.2 (0.8 - 1.8)	1.2 (0.5 - 2.8)	0.9 (0.3 - 2.9)	1.4 (0.6 - 3.3)	1.3 (0.2 - 7.2)	0.5 (0.1 - 2.8)	1.0 (0.2 - 5.0)	0.4 (0.1 - 2.5)
Domestic	1.0 (0.7 - 1.5)	0.9 (0.6 - 1.4)	1.1 (0.5 - 2.5)	0.7 (0.2 - 2.2)	1.7 (0.8 - 3.9)	0.3 (0.1 - 2.0)	2.5 (0.5 - 12)	1.9 (0.4 - 9.5)	4.4 (0.8 - 25)
Bleach									
Occupational	0.8 (0.2 - 3.6)	1.7 (0.3 - 8.6)	0.2 (0.0 - 6.6)	n.a.	0.2 (0.0 - 5.3)	n.a.	n.a.	n.a.	n.a.
Domestic	0.7 (0.4 - 1.3)	1.4 (0.7 - 2.6)	1.3 (0.4 - 5.0)	0.3 (0.0 - 1.8)	1.4 (0.3 - 5.7)	0.7 (0.0 - 13)	n.a.	n.a.	n.a.
Degreasers									
Occupational	1.0 (0.7 - 1.4)	0.8 (0.6 - 1.2)	1.0 (0.5 - 2.0)	1.1 (0.4 - 2.9)	**0.3 (0.1 - 0.5)**	1.1 (0.2 - 5.7)	0.7 (0.2 - 2.6)	0.3 (0.1 - 1.5)	0.9 (0.2 - 3.8)
Domestic	1.1 (0.7 - 1.7)	1.1 (0.7 - 1.7)	1.0 (0.4 - 2.5)	0.8 (0.2 - 2.7)	0.8 (0.4 - 1.6)	0.6 (0.1 - 5.5)	1.7 (0.3 - 9.6)	8.5 (0.5 - 145)	4.5 (0.5 - 45)
Dust mop products									
Occupational	0.9 (0.6 - 1.3)	1.0 (0.6 - 1.4)	1.0 (0.4 - 2.4)	2.3 (0.7 - 7.5)	0.8 (0.3 - 2.0)	2.1 (0.4 - 11)	1.7 (0.4 - 8.0)	1.0 (0.2 - 4.9)	0.3 (0.1 - 1.6)
Domestic	1.2 (0.7 - 1.8)	1.2 (0.8 - 1.9)	0.9 (0.3 - 2.2)	0.4 (0.1 - 1.4)	1.8 (0.7 - 5.0)	0.9 (0.1 - 10.3)	1.2 (0.2 - 6.8)	0.6 (0.1 - 4.1)	1.1 (0.1 - 8.2)
Glass cleaners									
Occupational	1.3 (0.9 - 2.0)	0.9 (0.6 - 1.4)	0.9 (0.4 - 2.1)	1.8 (0.5 - 5.8)	0.8 (0.3 - 2.0)	2.3 (0.4 - 13)	1.1 (0.2 - 5.7)	2.4 (0.4 - 13)	0.6 (0.1 - 3.2)
Domestic	0.8 (0.6 - 1.3)	0.9 (0.6 - 1.4)	0.6 (0.3 - 1.5)	1.2 (0.3 - 4.0)	1.8 (0.7 - 4.8)	0.5 (0.1 - 3.4)	3.5 (0.5 - 22)	1.3 (0.2 - 8.9)	1.6 (0.3 - 11)
Hydrochloric acid									
Occupational	1.5 (0.9 - 2.6)	1.1 (0.7 - 1.9)	1.7 (0.6 - 5.2)	2.5 (0.5 - 12)	1.5 (0.4 - 4.8)	5.0 (0.4 - 69)	0.7 (0.1 - 9.9)	n.a.	0.3 (0.0 - 5.4)
Domestic	1.0 (0.6 - 1.8)	0.7 (0.4 - 1.2)	1.1 (0.3 - 3.6)	1.8 (0.3 - 9.7)	0.8 (0.2 - 3.5)	0.7 (0.1 - 9.4)	n.a.	n.a.	n.a.
Limescale removers									
Occupational	1.2 (0.8 - 1.7)	1.0 (0.7 - 1.4)	0.9 (0.4 - 1.9)	1.8 (0.6 - 5.1)	0.5 (0.2 - 1.1)	2.8 (0.6 - 14)	0.9 (0.2 - 3.7)	0.4 (0.1 - 2.0)	0.4 (0.1 - 1.8)
Domestic	1.0 (0.7 - 1.4)	0.9 (0.6 - 1.4)	1.1 (0.5 - 2.5)	0.8 (0.3 - 2.6)	1.2 (0.5 - 2.8)	1.0 (0.2 - 5.6)	3.6 (0.7 - 17)	6.3 (0.9 - 46)	1.8 (0.4 - 8.8)
Multiuse products									
Occupational	1.3 (0.9 - 1.9)	1.1 (0.8 - 1.7)	0.9 (0.4 - 1.9)	2.6 (0.9 - 7.5)	1.8 (0.8 - 3.8)	2.1 (0.4 - 11)	1.5 (0.4 - 6.2)	1.1 (0.2 - 5.1)	0.3 (0.1 - 1.8)
Domestic	1.0 (0.7 - 1.4)	1.0 (0.7 - 1.5)	0.9 (0.4 - 2.0)	1.5 (0.5 - 4.0)	1.7 (0.8 - 3.7)	1.1 (0.2 - 5.5)	2.2 (0.5 - 9.5)	1.0 (0.2 - 4.8)	1.5 (0.3 - 6.9)
Polishes and waxes									

Occupational	1.3 (0.7 - 2.3)	1.0 (0.6 - 1.9)	1.6 (0.5 - 5.1)	1.1 (0.2 - 6.3)	1.8 (0.5 - 5.8)	1.5 (0.1 - 20)	1.7 (0.1 - 26)	2.5 (0.2 - 38)	5.9 (0.4 - 99)
Domestic	1.0 (0.6 - 1.8)	1.1 (0.6 - 2.0)	1.6 (0.5 - 5.2)	0.5 (0.1 - 2.8)	1.7 (0.5 - 5.3)	1.4 (0.1 - 14.5)	0.3 (0.0 - 3.7)	0.4 (0.0 - 4.6)	0.5 (0.0 - 7.3)
Soaps or detergents									
Occupational	1.0 (0.7 - 1.4)	1.0 (0.7 - 1.5)	0.8 (0.4 - 1.7)	0.9 (0.3 - 2.6)	0.9 (0.4 - 1.9)	1.5 (0.3 - 8.7)	1.5 (0.4 - 6.2)	0.8 (0.2 - 3.6)	0.6 (0.1 - 2.5)
Domestic	1.1 (0.7 - 1.6)	1.2 (0.8 - 1.8)	1.2 (0.5 - 2.8)	0.7 (0.2 - 2.5)	1.9 (0.8 - 4.4)	1.2 (0.2 - 7.1)	3.4 (0.6 - 18)	1.5 (0.3 - 8.5)	2.6 (0.4 - 16)

* Geometric means ratio and 95% confidence intervals from multivariable linear regression models of the log-transformed variables including all cases and controls. Independent variables included in the models: domestic use of cleaning product, occupational use of cleaning product, age, sex and smoking habit. ** Odds ratio and 95% confidence intervals from multivariable logistic regression models including all cases and controls. Independent variables included in the models: use of cleaning product at home, use of cleaning product at work, age, sex and smoking habit. n.a.: not analysed. FeNO: Fraction of exhaled NO. SP-D: Sserum surfactant Protein D. CC16: Serum 16kDa Clara Cell Protein. EBC: Exhaled Breath Condensate. FGF: EBC basic Fibroblast Growth Factor. VEGF: EBC Vascular Endothelial Growth Factor. TNF-α: EBC Tumour Necrosis Factor alpha. IFN-γ: EBC Interferon gamma. Ip10: EBC IFN-γ–induced protein. IL: EBC Interleukin.

Supplement table 6. Associations between occupational and domestic use of cleaning products and biomarker levels among controls

	Continuous variables						Categorical variables (detectable vs. non-detectable)		
	FeNO	CC16	SP-D	IgE	8-isoprostane	Cys-leukotrienes	FGF	TNF-α	IL-13
	GMR* (95%CI)	GMR* (95%CI)	GMR* (95%CI)	GMR* (95%CI)	GMR* (95%CI)	GMR* (95%CI)	OR** (95%CI)	OR** (95%CI)	OR** (95%CI)
Ammonia									
Occupational	1.0 (0.7 - 1.4)	0.9 (0.6 - 1.2)	0.9 (0.5 - 1.4)	1.4 (0.5 - 3.6)	**0.5 (0.3 - 0.9)**	0.9 (0.3 - 2.8)	1.1 (0.2 - 7.4)	1.6 (0.2 - 15)	1.0 (0.1 - 8.4)
Domestic	1.1 (0.8 - 1.5)	0.9 (0.7 - 1.2)	0.9 (0.6 - 1.5)	0.5 (0.2 - 1.2)	1.5 (0.9 - 2.6)	0.4 (0.1 - 1.4)	0.7 (0.1 - 3.8)	1.6 (0.2 - 13)	1.5 (0.2 - 10.4)
Bleach									
Occupational	1.2 (0.8 - 2.0)	1.4 (0.8 - 2.2)	1.9 (1.0 - 3.8)	1.4 (0.3 - 5.7)	1.0 (0.4 - 2.4)	1.3 (0.2 - 8.0)	n.a.	n.a.	n.a.
Domestic	1.0 (0.7 - 1.5)	0.7 (0.5 - 1.1)	0.8 (0.5 - 1.4)	1.1 (0.3 - 3.6)	0.6 (0.3 - 1.2)	0.7 (0.2 - 2.6)	n.a.	n.a.	n.a.
Degreasers									
Occupational	1.2 (0.9 - 1.6)	1.0 (0.7 - 1.3)	0.7 (0.5 - 1.1)	3.0 (1.5 - 6.1)	0.7 (0.4 - 1.2)	0.4 (0.2 - 1.1)	0.8 (0.2 - 3.2)	0.4 (0.1 - 2.3)	0.3 (0.0 - 1.7)
Domestic	1.1 (0.8 - 1.4)	1.0 (0.7 - 1.3)	1.1 (0.7 - 1.6)	0.7 (0.3 - 1.6)	0.6 (0.4 - 1.1)	0.9 (0.3 - 2.5)	0.8 (0.2 - 3.8)	0.5 (0.1 - 3.8)	0.2 (0.0 - 1.8)
Dust mop products									
Occupational	1.0 (0.8 - 1.4)	0.9 (0.7 - 1.2)	1.0 (0.7 - 1.5)	1.5 (0.7 - 3.4)	0.8 (0.5 - 1.4)	0.9 (0.4 - 2.4)	0.6 (0.1 - 2.8)	1.6 (0.2 - 9.7)	0.8 (0.1 - 5.4)
Domestic	0.9 (0.6 - 1.4)	0.8 (0.5 - 1.2)	0.6 (0.3 - 1.1)	2.5 (0.8 - 8.0)	1.1 (0.5 - 2.3)	0.3 (0.1 - 1.4)	0.1 (0.0 - 3.4)	0.2 (0.0 - 5.2)	
Glass cleaners									
Occupational	**1.3 (1.0 - 1.8)**	0.8 (0.6 - 1.1)	1.0 (0.6 - 1.5)	1.0 (0.4 - 2.5)	1.5 (0.8 - 2.6)	1.5 (0.5 - 4.6)	2.8 (0.5 - 17)	1.4 (0.2 - 9.9)	2.4 (0.3 - 16)
Domestic	0.9 (0.7 - 1.2)	1.1 (0.8 - 1.5)	1.1 (0.7 - 1.6)	1.0 (0.4 - 2.3)	0.6 (0.4 - 1.1)	0.5 (0.2 - 1.3)	1.2 (0.2 - 6.5)	5.9 (0.5 - 63)	1.1 (0.2 - 6.8)
Hydrochloric acid									
Occupational	0.8 (0.5 - 1.3)	0.6 (0.4 - 1.1)	**0.4 (0.2 - 0.9)**	2.8 (0.6 - 12)	0.5 (0.2 - 1.2)	0.3 (0.1 - 1.3)	0.4 (0.0 - 5.8)	0.1 (0.0 - 5.2)	0.2 (0.0 - 6.8)
Domestic	0.6 (0.4 - 0.9)	0.9 (0.6 - 1.5)	1.0 (0.6 - 1.9)	0.5 (0.2 - 1.8)	0.9 (0.4 - 2.0)	0.3 (0.1 - 1.2)	0.1 (0.0 - 1.6)	1.1 (0.1 - 20)	0.9 (0.1 - 12)
Limescale removers									
Occupational	1.0 (0.7 - 1.3)	1.1 (0.8 - 1.5)	0.7 (0.5 - 1.1)	1.5 (0.6 - 3.4)	1.0 (0.6 - 1.7)	1.1 (0.4 - 3.1)	2.2 (0.4 - 11)	0.4 (0.0 - 3.1)	0.1 (0.0 - 1.5)
Domestic	1.0 (0.8 - 1.4)	0.9 (0.6 - 1.2)	1.4 (1.0 - 2.2)	0.8 (0.3 - 1.9)	0.9 (0.5 - 1.6)	0.9 (0.3 - 2.5)	0.4 (0.1 - 2.3)	1.4 (0.2 - 9.5)	1.7 (0.3 - 12)
Multiuse products									
Occupational	**1.5 (1.1 - 2.1)**	0.9 (0.6 - 1.2)	1.1 (0.7 - 1.8)	1.3 (0.5 - 3.7)	0.8 (0.5 - 1.6)	1.8 (0.5 - 6.5)	**58.3 (2.3 - 1451)**	10.1 (0.7 - 151)	14.1 (0.9 - 235)
Domestic	0.9 (0.7 - 1.2)	1.1 (0.8 - 1.5)	1.2 (0.8 - 1.8)	0.6 (0.3 - 1.4)	**0.6 (0.4 - 1.0)**	0.8 (0.3 - 2.3)	0.3 (0.0 - 2.8)	0.5 (0.1 - 4.1)	0.4 (0.1 - 3.4)
Polishes and waxes									
Occupational	**1.8 (1.2 - 2.7)**	1.0 (0.7 - 1.6)	1.0 (0.5 - 2.0)	1.7 (0.4 - 6.5)	1.1 (0.5 - 2.3)	0.4 (0.1 - 2.1)	1.1 (0.1 - 13)	2.4 (0.2 – 29)	2.2 (0.2 - 26)
Domestic	1.0 (0.6 - 1.9)	**0.5 (0.3 - 0.9)**	0.8 (0.4 - 1.8)	0.7 (0.1 - 3.7)	0.5 (0.2 - 1.9)	0.4 (0.0 - 2.9)	n.a.	8.3 (0.3 - 208)	4.6 (0.2 - 93)
Soaps or detergents									

Occupational	0.8 (0.6 - 1.2)	1.1 (0.8 - 1.5)	0.8 (0.5 - 1.2)	0.8 (0.3 - 2.0)	1.1 (0.6 - 2.2)	0.5 (0.2 - 1.5)	0.3 (0.0 - 2.5)	0.5 (0.1 - 5.2)	1.2 (0.1 - 10)
Domestic	1.2 (0.9 - 1.7)	0.8 (0.6 - 1.2)	1.2 (0.7 - 1.9)	0.6 (0.2 - 1.5)	0.8 (0.4 - 1.6)	0.8 (0.3 - 2.4)	3.3 (0.4 - 27)	0.4 (0.0 - 3.6)	0.3 (0.0 - 2.6)

* Geometric means ratio and 95% confidence intervals from multivariable linear regression models of the log-transformed variables including all cases and controls. Independent variables included in the models: domestic use of cleaning product, occupational use of cleaning product, age, sex and smoking habit. ** Odds ratio and 95% confidence intervals from multivariable logistic regression models including all cases and controls. Independent variables included in the models: domestic use of cleaning product , occupational use of cleaning product, age, sex and smoking habit. n.a.: not analysed. FeNO: Fraction of exhaled NO. SP-D: Sserum surfactant Protein D. CC16: Serum 16kDa Clara Cell Protein. EBC: Exhaled Breath Condensate. FGF: EBC basic Fibroblast Growth Factor. VEGF: EBC Vascular Endothelial Growth Factor. TNF-α: EBC Tumour Necrosis Factor alpha. IFN-γ: EBC Interferon gamma. Ip10: EBC IFN-γ–induced protein. IL: EBC Interleukin.

9 DISCUSSION

This section is meant to comprise a global discussion of the results presented in this thesis. Rather than repetitive, it is complementary to the discussion paragraphs of the four papers and the aim was to provide a broader and more integrated interpretation of the entire study project.

9.1. What added EPIASLI-2 to the current knowledge?

EPIASLI-2 was set up as the first epidemiological study meant to fill some of the gaps present in the current literature regarding the associations between asthma and dermatitis and cleaning-related exposures. The main objective of the project was to characterize the biological, functional and clinical profile of asthma in cleaning workers. Besides, EPIASLI-2 was also designed to evaluate cleaning-related risk factors for asthma and for hand dermatitis.

We first conducted a cross-sectional study among cleaning companies' employees in order to study the prevalence of asthma symptoms across job positions and the associated risk factors related to cleaning work. Our results confirmed the increased risk of asthma among cleaning workers compared to other employees of the same companies. Moreover, we found that the prevalence of adverse respiratory effects was consistently higher among former cleaning workers who are still employed in the cleaning sector than in current or never cleaners. This is suggestive of a possible healthy worker survivor effect, inherent to every industry-based study, and thus a possible underestimation of the relative risk for current cleaners. In this survey, we also evaluated the dermal effects associated with cleaning work. We confirmed that cleaning work is a high risk

occupation for hand dermatitis. To evaluate the specific exposures associated with both asthma and dermatitis, we included questions on the use of certain cleaning products. Since this was a self-reported survey, we evaluated the association of generic cleaning products with both health outcomes rather than doing specific assessment of the chemical constituents. Interestingly, we found that several cleaning products, including hydrochloric acid, ammonia and multiuse products, were a risk factor for both hand dermatitis and asthma symptoms.

In the second stage of EPIASLI-2, we conducted a thorough respiratory and immunological evaluation of the functional and biological characteristics of cleaning workers with and without asthma symptoms. The complete biological profile evaluated included markers of eosinophilic inflammation (FeNO), bronchial inflammation (IL-2, 4, 5, 8, 10, 12 & 13, IFN-γ, TNF-α,IP-10 and cys-leukotrienes), airways remodelling (FGF and VEGF) and oxidative stress (8-Isoprostane) measured in EBC; we also evaluated serum levels of lung epithelium damage biomarkers (SP-D and CC16) and IgE (quantification of total IgE and specific IgE against latex and dust mites, and categorisation of the presence or absence of specific IgE against ten different aeroallergens using the Phadiatop® test). We also performed a cross-sectional analysis of the association between respiratory biomarkers and the use of specific cleaning products.

Cleaning exposures are increasingly being recognised as an etiologic factor for asthma by the clinical community. This is confirmed by the large number of surveillance and case series studies published in the last few years (38;51;140;201). Among the scientific community, the

evidence for cleaner's asthma is increasingly accepted, although the responsible risk factors and the mechanisms by which respiratory symptoms and molecular events are triggered remain to be explored in depth.

Our results point in the same direction as previous studies and provide a framework for risk factors among cleaning professionals as well as an in-depth description of the main patho-physiological characteristics. As discussed in the second and fourth papers, irritant-induced asthma seems to play a key role. This is suggested by the associations found between asthma symptoms and the use of irritant cleaning products and impaired lung function, as well as by the lack of association between asthma symptoms and FeNO, suggesting that eosinophilic inflammation does not play a predominant role (33). However, the increased levels of total and specific IgE in cases with asthma symptoms compared to controls indicated that immunological asthma may play an important role as well.

9.1.1. Prevalence of asthma symptoms and cleaning exposures

The evaluation of the relationships between asthma and hand dermatitis with cleaning products and workplaces comprised an important part of the thesis. According to the hypotheses based on current knowledge, the use of cleaning products at work appeared to be a clear risk factor for asthma and hand dermatitis symptoms. In addition, and interestingly, I found that the association between asthma and domestic use of cleaning products was apparently stronger than for occupational use. This may be related to the different level of skills and training required for performing domestic and occupational tasks (160) rather than differences in the composition of domestic and professional cleaning agents. In fact, in

previous population-based studies on Spanish cleaning workers, domestic cleaning work was associated with respiratory symptoms, whereas industrial cleaning work was not a strong risk factor (69;152). On the other hand, in several other countries, industrial cleaning workers showed a higher risk of asthma (112;158;164). As expected, hospital cleaning workers have a special relevance in the observed higher prevalence of asthma symptoms. In previous studies across different countries, a consistent increased prevalence of asthma symptoms among healthcare workers was reported, and especially among those using cleaning agents in their daily routine (68;139). The high demand of cleaning standards and the use of strong disinfectants as well as the exposure to other asthmogens indirectly related to cleaning tasks (eg, latex) may be a plausible explanation for this increased risk.

Cleaners with asthma symptoms employed in cleaning companies used more irritant cleaning agents (hydrochloric acid, ammonia and hypochlorite bleach) than their healthy co-workers. This association, that may or may not be causal, has been previously reported and suggests that irritant exposures play an important role in the underlying causes of the increased prevalence and incidence of asthma among cleaners. Besides irritant agents, the use of multiuse products was consistently associated with prevalent asthma symptoms.

9.1.2. Hand dermatitis and cleaning exposures

The association between hand dermatitis and cleaning work is well established. Our findings provide evidence that the use of certain cleaning products and working in certain places may be responsible for this increased risk of skin symptoms. Knowing the responsible agents

may help to identify the population at a higher risk of suffering skin disorders among the cleaning workforce. Cleaning work often implies environmental exposures that may lead to dermatitis. Dusty environments, wet work, poor ventilation and extreme temperatures may cause or facilitate the onset and aggravation of skin disorders.

Protective devices such as gloves may be helpful to reduce the exposure to cleaning agents potentially harmful to the skin. However, an improper use of such devices may induce or aggravate hand skin symptoms as a consequence of impaired transpiration resulting in wet exposure.

9.1.3. Patho-physiological characteristics of asthma in cleaning workers

The increased asthma risk among cleaning workers who use hypochlorite bleach, ammonia and hydrochloric acid in their daily duties, suggests that irritant-induced asthma plays a key role. This was supported by the biological and functional profile of asthmatic cleaners. The low levels of FeNO observed among cleaning workers with asthma symptoms suggests that eosinophilic inflammation does not play a predominant role, which is a characteristic of irritant-induced asthma (33;52). The lower values of post-bronchodilator FEV_1 and FEV_1/FVC observed in asthmatic cleaning workers confirms the presence of an irreversible obstruction, probably related to the thickening of the bronchial epithelium, characteristic of OA (28).

The increased levels of IgE among asthmatic cleaning workers compared to healthy cleaners suggest that immunological mechanisms may be also related to asthma and/or asthma symptoms. As mentioned in the introduction, there are several pathways through which exposure to

cleaning agents may lead to allergic sensitization. First, several cleaning agents contain volatile chemicals that, after inhalation exposure, may act as sensitizers (pinene, d-limonene, formaldehyde and benzalkonium chloride among others) (76). Second, dermal exposure to sensitizers may induce allergic response and sensitization (103;109). Finally, it is known that exposure to irritant inhalants may damage the lung epithelium facilitating sensitization to common aeroallergens (27). The plausibility of an immunological mechanism is also supported by the increased risk of asthma symptoms among cleaners who use multiuse products. This type of generic product is meant to be useful for a variety of cleaning tasks, usually related to the cleaning of hard surfaces and stains. The formula differs considerably between brands, but is generally based on non-ionic tensioactives, usually Linear Alkylbenzene Sulfonates, which have known asthmogenic properties (119) through allergic mechanisms. According to the results of the fourth paper, the use of multiuse products was also associated with increased levels of FeNO, total IgE in serum and FGF in EBC, supporting that exposure to cleaning agents may be related to asthma mediated by allergic mechanisms as well.

9.1.4. Methodological issues related to the workforce-based design

As mentioned above, EPIASLI-2 was conceived as a workforce-based study. This choice had strengths and limitations that will be discussed further in this section. Since it is a professional duty, cleaners are exposed to cleaning agents several hours per day and perform very specialised tasks as well as more general and less skilled cleaning activities. Therefore, the range and number of different exposures related to cleaning tasks considered is expected to be higher among professional cleaners than among the general population. In addition, it also might provide a less biased control population since it is expected to

find a great homogeneity among employees of the same company in the same job position.

On the other hand, it was impossible to conduct a follow-up among non-responders. Spanish legislation on personal data protection is very restrictive, and it reaches its highest level of stringency in regards to corporate information such as personal data of employees, even under the circumstances of willingness of the companies to collaborate. For this reason, the only option to reach the employees of the participant companies was through the companies itself, and only those employees who responded to the survey provided some personal contact information.

During the process of recruiting cleaning companies for participation in the study, I contacted more than 1,000 via post mail, had face-to-face meetings with many of them and contacted two associations of cleaning employers both at regional and national level. However, most of the contacted cleaning companies declined to participate or did not respond to the invitation. Although this was very disappointing since the beginning, it has not been a real problem for properly addressing the aims of EPIASLI-2, since having a sample of representative companies was out of the scope of this project and the internal validity of the study was not affected. Nevertheless, increasing the number of participant companies would have been beneficial for obtaining a larger population of workers.

The workforce-based design has been one of the main challenges of EPIASLI-2 because of the above mentioned difficulties. Nevertheless, it

has been beneficial with regards to the originality of the project and the consideration of a better defined study population. Future workforce-based studies in Spain should be considered. In my opinion, unions and a particular Spanish type of organisation in charge of occupational health (*Mutuas*) could be better intermediates between researchers and the workforce, that is, the study participants. The provision of sufficient information to the companies and the integration of the companies into the study could be helpful. Providing reports both to companies and workers in a reasonable time after publication in the scientific media could be considered to be an essential part of the research.

9.2. Strengths

The main strength of this project is the thorough evaluation of cleaning exposures on the one hand and biological characteristics on the other. This study is unprecedented in the understanding of the patho-physiological characteristics of asthma in cleaning workers. In this regard, we have provided a basis for forthcoming projects on mechanisms of cleaning-related asthma. It is also evident that the research group in which I have developed this work was the first that followed the trail of a relationship between asthma and cleaning products and have followed studying this relation during the last decade. The association of asthma and cleaning-related exposures is more widely accepted nowadays by clinicians and public health researchers.

EPIASLI-2 is one of the first large workforce-based studies in cleaning workers conducted in Europe. This type of design has been useful to obtain a population with a wide range of different exposures related to cleaning tasks. Professional cleaning workers have a better knowledge of

the products they use, thus reducing the chances for misclassification of the exposures. Moreover, this type of design provided us a more homogeneous, and thus less biased, population, since it is expected to have similar non-occupational related exposures among workers of the same cleaning companies and with the same job positions. This has likely helped to reduce residual confounding in the estimated risks.

9.3. Limitations

I have discussed previously one of the main limitations of the study: the impracticality of a follow-up of non-responders in the first stage of the project (cross-sectional survey) due to the restrictive Spanish legislation on personal data protection. This impairment during the recruitment of the participants who comprised the study population may have led to a selection bias, but as discussed in the second paper, it is improbable to have occurred. Nevertheless, it affected the number of asthmatic cases and controls available for the second stage of the project (case-control study) limiting thus, the statistical power of the analyses conducted and the assertiveness of the conclusions included in the fourth paper. Other biases that may have affected the results and the conclusions of the present work have been discussed in each of the papers. Briefly, a recall bias may have occurred, since asthmatic subjects seem to be more prone to recall strong odours. However, the lack of association of asthma symptoms with cleaning products with strong scents (eg, solvents) suggests that this bias, if present, have not affected the results. Potential selection bias in the case-control study was assessed comparing participants and non-participants characteristics. We found no differences between groups for age, sex, educational level, birth country or, in the cases group, for the score of asthma symptoms.

9.4. What remains to be explored after EPIASLI2? Moving forward in cleaning-related health

Although a new wave of interest in the health hazards associated with cleaning exposure has arisen in the last few years, there are still gaps in the understanding of asthma and dermatitis among cleaners. In the following paragraphs, I will discuss the main issues related to cleaning- and health that needs further research and attention from the stakeholders.

9.4.1. Exposure assessment

Exposure to cleaning products is very complex since the formulae of commercial and industrial products are sufficient for compliance with legislation in terms of disclosure of harmful products, but often not transparent and detailed enough for quantitative and qualitative evaluation of specific chemicals. Many of the available cleaning products contain mixtures of chemical ingredients in different proportions according to their purpose. Even plain cleaning agents, like ammonia or hydrochloric acid, contain other chemicals agents that may be harmful (eg, buffers). The form of application (diluted, undiluted, sprayed or aerosolised, with a mop, cloth or scouring pad, etc.) may be relevant too for the respiratory and dermal exposure to cleaning products. Bello and co-workers quantified the exposure to airborne agents due to cleaning tasks in a pilot simulation study (123). They found some of the chemicals concentrations to approach the occupational exposure limits, suggesting the importance of conducting further research in this area. Similarly, other studies in cleaning workers showed that levels of exposure to certain airborne agents like chlorine or ammonia may exceed occupational exposure limits (138). However, to date there are no large

exposure assessment studies that have characterised the complexity of cleaning-related exposures. Further research on the exposure to cleaning agents is highly recommended to help quantify the actual risks among workers and general population who use them.

9.4.2. Risk assessment and causality relations

Risk assessment is a powerful science that joins multidisciplinary knowledge to achieve actual risks associated with exposures and outcomes that help policy-makers to take actions to reduce the burden of disease. Cleaning related exposure has been studied for many years but, besides systematic review articles, only a few integrated publications have dealt with the association between asthma and cleaning products. These publications may have been affected by conflicts of interest, since they were performed by the cleaning product manufacturer industry in order to comply with Federal US and European Union demands on safety and health.

Causality is a pending point in cleaning-related asthma. Only a few longitudinal studies on asthma have evaluated cleaning exposures and, usually, only work-related exposures (25). There is a need of more longitudinal studies both at the general population and at the industry level to evaluate the cause-effect relation between cleaning-related exposures and asthma.

9.4.3. Mechanisms of asthma in cleaning workers

Due to the complex chemical nature of cleaning agents that include allergic sensitizers and irritants, understanding the mechanisms that lead to asthma is challenging and deserves a particular attention. According to recent studies, it appears that both immunological and irritant-induced

asthma may play a role, with an apparent predominant role of the latter. As mentioned in the introduction, irritant-induced asthma mechanisms comprise a field of uncertainty but the current findings on non-eosinophilic bronchial inflammation associated with the use of cleaning products suggest that non-immunological mechanisms may play a crucial role in the development of asthma. However, irritant exposures may compromise the permeability properties of the lung epithelium and thus facilitate the sensitisation to aeroallergens, most of them common in dusty and poor ventilated areas, as are the work conditions in many cleaning jobs and tasks. Moreover, several ingredients of cleaning agents may also act as sensitizers. Dermatitis mechanisms associated with cleaning work are better understood. Contact sensitization through the skin is also common among cleaning workers, but in this case irritant hazards play an important role in the onset of the disease. Analogous with the case of asthma, sensitization may be also facilitated by the removal of the protective physical properties of the skin.

In summary, the mechanisms and thus the pathophysiological characteristics of asthma among cleaning workers need further research.

9.4.4. The future work in EPIASLI-2

The papers included in this thesis represent the core results of EPIASLI-2. However, there are still two major objectives that I will analyse and publish on a short-term basis. Other remaining more detailed objectives can be evaluated by prospective students to prepare theses for bachelor or master's degrees.

We conducted a panel study among 21 of the asthmatic cases. A 15-day diary of symptoms and exposures was obtained as well as three measurements per day of peak expiratory flow (PEF) rate and FEV_1. I have started the analysis of these data in collaboration with David Gimeno from the University of Texas at San Antonio.

During the realisation of the case-control study we invited 14 cleaning workers previously diagnosed with occupational asthma by a chest physician from Hospital Vall d'Hebron to participate in the study. These asthmatic patients provided the same information and samples and followed the same protocol as the rest of participants of the case-control study (paper 4) identified through the cross-sectional survey. A case series article will follow the analysis of the available data both from EPIASLI-2 and the clinical history at the Hospital.

Besides this, I am coordinating the preparation of a series of informative reports that will be sent to the participant companies and workers whose address was provided within their contact details. The companies' reports will be unified to keep confidentiality of the workers from smaller companies. All workers who participated in the case-control study will receive an additional report with their own results of the measurements of biomarkers levels and lung function.

9.5. Recommendations

9.5.1. To the cleaning companies and employees

All the cleaning companies that participated in EPIASLI-2 had already implemented an internal occupational safety programme, which would be the first recommendation to keep work conditions as healthy and safe

as possible. Nevertheless, the efforts in these programmes are usually focused on musculoskeletal disorders, dermatitis and work accidents (spills, falls from the same or different level, etc.). Given the high prevalence of respiratory symptoms among cleaning workers, it is important to include in their programmes the monitoring of respiratory health effects of cleaning work. The recommendations of the international guidelines for occupational asthma differ when it is caused or aggravated by work exposures. However, it is always advisable, and most effective, to prevent by reducing or eliminating asthma triggers, monitoring suspected asthma cases and reduce existing morbidity with confirmed cases (35). Hand dermatitis has also a great impact among cleaning workers. Both companies and cleaners should be aware what the main known risk factors are. Training and the proper use of the available protective equipment should be considered prior to the performance of cleaning tasks.

Although at this stage the level of evidence may not be sufficient to implement health policies for asthma and dermatitis, companies and workers should be aware of the potential risk associated with the exposure to certain cleaning products and apply the precautionary principle whenever possible.

9.5.2. To the stakeholders and policy-makers

After more than fifteen years of research in the topic of asthma and cleaning work, a vast body of evidence is available to the policy-makers. The introduction of preventive strategies to reduce the burden of respiratory and skin disease among workers exposed to cleaning agents is highly desirable. Nevertheless, there is a need to study more thoroughly several key aspects of cleaning-related asthma in order to

understand how the disease is triggered in order to be more accurate in the treatment and prevention of the disease.

10 CONCLUSIONS

- There is a vast body of evidence that cleaning workers and other individuals exposed to cleaning products either at home or at work are at higher risk of asthma.

However, further research in exposure assessment, the cause-effect relationships and the pathophysiological characteristics of asthma and cleaning exposures is required.

- Cleaning workers have a higher prevalence of hand dermatitis.

Hand dermatitis symptoms were reported by 28% of current cleaning workers, versus 18% of former and never cleaning workers.

- Hand dermatitis was strongly associated with the use of irritant cleaning products and working at schools or outdoor areas among cleaning workers.

Hydrochloric acid, ammonia bleach and dust mop products were the main cleaning agents associated with hand dermatitis.

- Cleaning workers have a higher prevalence of asthma symptoms.

Current and former cleaning workers present a higher prevalence of asthma symptoms and current compared to other employees of the same companies who never performed professional cleaning tasks.

- Cleaners who are working at hospitals form a large workforce and present a high risk of asthma symptoms.

Cleaners working at private homes, kitchens, outdoors and other healthcare settings different of hospitals also have a greater risk of asthma symptoms compared to never cleaners.

- Cleaners who use irritant products have a higher risk of asthma symptoms

The use of hydrochloric acid, ammonia and bleach among others is associated with asthma symptoms in cleaning workers.

- The use of multiuse cleaning products is associated with asthma symptoms and lung inflammation biomarkers.

Multiuse cleaning products contain chemical agents that have been previously reported as asthmogens.

- Asthmatic cleaning workers are characterised by non-eosinophilic inflammation, low lung function and increased levels of total IgE in serum.

This is consistent with previous publications mentioned in the introduction.

11 REFERENCES

(1) Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald M, et al. Global strategy for asthma management and prevention: GINA executive summary. Eur Respir J 2008 Jan;31(1):143-78.

(2) Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA). Date last updated, 2010. Available from: http://www.ginasthma.org/. 2010.

(3) Subbarao P, Mandhane PJ, Sears MR. Asthma: epidemiology, etiology and risk factors. CMAJ 2009 Oct 27;181(9):E181-E190.

(4) Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy 2004 May;59(5):469-78.

(5) Brogger J, Bakke P, Eide GE, Johansen B, Andersen A, Gulsvik A. Long-term changes in adult asthma prevalence. Eur Respir J 2003 Mar;21(3):468-72.

(6) Sunyer J, Anto JM, Tobias A, Burney P. Generational increase of self-reported first attack of asthma in fifteen industrialized countries. European Community Respiratory Health Study (ECRHS). Eur Respir J 1999 Oct;14(4):885-91.

(7) Eder W, Ege MJ, von ME. The asthma epidemic. N Engl J Med 2006 Nov 23;355(21):2226-35.

(8) Barraclough R, Devereux G, Hendrick DJ, Stenton SC. Apparent but not real increase in asthma prevalence during the 1990s. Eur Respir J 2002 Oct;20(4):826-33.

(9) Asher MI, Montefort S, Bjorksten B, Lai CK, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet 2006 Aug 26;368(9537):733-43.

(10) Zar HJ, Ehrlich RI, Workman L, Weinberg EG. The changing prevalence of asthma, allergic rhinitis and atopic eczema in African adolescents from 1995 to 2002. Pediatr Allergy Immunol 2007 Nov;18(7):560-5.

(11) Wenzel SE. Asthma: defining of the persistent adult phenotypes. Lancet 2006 Aug 26;368(9537):804-13.

(12) Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. Am J Respir Crit Care Med 2010 Feb 15;181(4):315-23.

(13) Porsbjerg C, Lund TK, Pedersen L, Backer V. Inflammatory subtypes in asthma are related to airway hyperresponsiveness to mannitol and exhaled NO. J Asthma 2009 Aug;46(6):606-12.

(14) Anto JM, Sunyer J, Basagana X, Garcia-Esteban R, Cerveri I, De MR, et al. Risk factors of new-onset asthma in adults: a population-based international cohort study. Allergy 2010 Aug;65(8):1021-30.

(15) Ayres JG, Jyothish D, Ninan T. Brittle asthma. Paediatr Respir Rev 2004 Mar;5(1):40-4.

(16) Barnes PJ, Woolcock AJ. Difficult asthma. Eur Respir J 1998 Nov;12(5):1209-18.

(17) Covar RA, Spahn JD, Murphy JR, Szefler SJ. Progression of asthma measured by lung function in the childhood asthma management program. Am J Respir Crit Care Med 2004 Aug 1;170(3):234-41.

(18) Yoshikawa T, Kanazawa H. Phenotypic differences between asymptomatic airway hyperresponsiveness and remission of asthma. Respir Med 2011 Jan;105(1):24-30.

(19) ten BA, Zwinderman AH, Sterk PJ, Rabe KF, Bel EH. Factors associated with persistent airflow limitation in severe asthma. Am J Respir Crit Care Med 2001 Sep 1;164(5):744-8.

(20) Bush A, Menzies-Gow A. Phenotypic differences between pediatric and adult asthma. Proc Am Thorac Soc 2009 Dec;6(8):712-9.

(21) Sheffield PE, Weinberger KR, Kinney PL. Climate change, aeroallergens, and pediatric allergic disease. Mt Sinai J Med 2011 Jan;78(1):78-84.

(22) Kim HY, DeKruyff RH, Umetsu DT. The many paths to asthma: phenotype shaped by innate and adaptive immunity. Nat Immunol 2010 Jul;11(7):577-84.

(23) Lee JH, Haselkorn T, Borish L, Rasouliyan L, Chipps BE, Wenzel SE. Risk factors associated with persistent airflow limitation in severe or difficult-to-treat asthma: insights from the TENOR study. Chest 2007 Dec;132(6):1882-9.

(24) Farooque SP, Lee TH. Aspirin-sensitive respiratory disease. Annu Rev Physiol 2009;71:465-87.

(25) Kogevinas M, Zock JP, Jarvis D, Kromhout H, Lillienberg L, Plana E, et al. Exposure to substances in the workplace and new-onset asthma: an international prospective population-based study (ECRHS-II). Lancet 2007 Jul 28;370(9584):336-41.

(26) Jeebhay MF, Quirce S. Occupational asthma in the developing and industrialised world: a review. Int J Tuberc Lung Dis 2007 Feb;11(2):122-33.

(27) Maestrelli P, Boschetto P, Fabbri LM, Mapp CE. Mechanisms of occupational asthma. J Allergy Clin Immunol 2009 Mar;123(3):531-42.

(28) Mapp CE, Boschetto P, Maestrelli P, Fabbri LM. Occupational asthma. Am J Respir Crit Care Med 2005 Aug 1;172(3):280-305.

(29) Martinez-Moragon E, Plaza V, Serrano J, Picado C, Galdiz JB, Lopez-Vina A, et al. Near-fatal asthma related to menstruation. J Allergy Clin Immunol 2004 Feb;113(2):242-4.

(30) Carlsen KH, Anderson SD, Bjermer L, Bonini S, Brusasco V, Canonica W, et al. Exercise-induced asthma, respiratory and allergic disorders in elite athletes: epidemiology, mechanisms and diagnosis: part I of the report from the Joint Task Force of the European Respiratory Society (ERS) and the European Academy of Allergy and Clinical Immunology (EAACI) in cooperation with GA2LEN. Allergy 2008 Apr;63(4):387-403.

(31) Venge P. The eosinophil and airway remodelling in asthma. Clin Respir J 2010 May;4 Suppl 1:15-9.

(32) Wenzel SE, Schwartz LB, Langmack EL, Halliday JL, Trudeau JB, Gibbs RL, et al. Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. Am J Respir Crit Care Med 1999 Sep;160(3):1001-8.

(33) Douwes J, Gibson P, Pekkanen J, Pearce N. Non-eosinophilic asthma: importance and possible mechanisms. Thorax 2002 Jul;57(7):643-8.

(34) Bernardino Ramazzini. Tratado de las enfermedades de los artesanos. 1999 ed. Madrid: Instituto Nacional de medicina y salud en el trabajo; 1713.

(35) Guidelines for assessing and managing asthma risk at work, school, and recreation. Am J Respir Crit Care Med 2004 Apr 1;169(7):873-81.

(36) Vandenplas O, Toren K, Blanc PD. Health and socioeconomic impact of work-related asthma. Eur Respir J 2003 Oct;22(4):689-97.

(37) Vandenplas O, Malo JL. Definitions and types of work-related asthma: a nosological approach. Eur Respir J 2003 Apr;21(4):706-12.

(38) Orriols R, Costa R, Albanell M, Alberti C, Castejon J, Monso E, et al. Reported occupational respiratory diseases in Catalonia. Occup Environ Med 2006 Apr;63(4):255-60.

(39) Orriols R, Isidro I, Abu-Shams K, Costa R, Boldu J, Rego G, et al. Reported occupational respiratory diseases in three Spanish regions. Am J Ind Med 2010 Sep;53(9):922-30.

(40) McDonald JC, Chen Y, Zekveld C, Cherry NM. Incidence by occupation and industry of acute work related respiratory diseases in the UK, 1992-2001. Occup Environ Med 2005 Dec;62(12):836-42.

(41) Toren K, Blanc PD. Asthma caused by occupational exposures is common - A systematic analysis of estimates of the population-attributable fraction. BMC Pulm Med 2009;9(1):7.

(42) Balmes J, Becklake M, Blanc P, Henneberger P, Kreiss K, Mapp C, et al. American Thoracic Society Statement: Occupational contribution to the burden of airway disease. Am J Respir Crit Care Med 2003 Mar 1;167(5):787-97.

(43) Gibson PG, Fujimura M, Niimi A. Eosinophilic bronchitis: clinical manifestations and implications for treatment. Thorax 2002 Feb;57(2):178-82.

(44) Paggiaro PL, Vagaggini B, Bacci E, Bancalari L, Carrara M, Di FA, et al. Prognosis of occupational asthma. Eur Respir J 1994 Apr;7(4):761-7.

(45) Hedlund U, Jarvholm B, Lundback B. Persistence of respiratory symptoms in ex-underground iron ore miners. Occup Med (Lond) 2006 Sep;56(6):380-5.

(46) Moscato G, Dellabianca A, Perfetti L, Brame B, Galdi E, Niniano R, et al. Occupational asthma: a longitudinal study on the clinical and socioeconomic outcome after diagnosis. Chest 1999 Jan;115(1):249-56.

(47) Larbanois A, Jamart J, Delwiche JP, Vandenplas O. Socioeconomic outcome of subjects experiencing asthma symptoms at work. Eur Respir J 2002 Jun;19(6):1107-13.

(48) Vandenplas O, Henneberger PK. Socioeconomic outcomes in work-exacerbated asthma. Curr Opin Allergy Clin Immunol 2007 Jun;7(3):236-41.

(49) Chan-Yeung M, Malo JL, Tarlo SM, Bernstein L, Gautrin D, Mapp C, et al. Proceedings of the first Jack Pepys Occupational Asthma Symposium. Am J Respir Crit Care Med 2003 Feb 1;167(3):450-71.

(50) Haz-Map: Occupational exposure to hazardous agents. http://hazmap.nlm.nih.gov/. 2011.

(51) Sastre J, Madero MF, Fernandez-Nieto M, Sastre B, del P, V, Potro MG, et al. Airway response to chlorine inhalation (bleach) among cleaning workers with and without bronchial hyperresponsiveness. Am J Ind Med 2011 Apr;54(4):293-9.

(52) Quirce S, Gala G, Perez-Camo I, Sanchez-Fernandez C, Pacheco A, Losada E. Irritant-induced asthma: clinical and functional aspects. J Asthma 2000 May;37(3):267-74.

(53) Malo JL. Future advances in work-related asthma and the impact on occupational health. Occup Med (Lond) 2005 Dec;55(8):606-11.

(54) Zeiss CR. Advances in acid anhydride induced occupational asthma. Curr Opin Allergy Clin Immunol 2002 Apr;2(2):89-92.

(55) Biagini RE, Bernstein IL, Gallagher JS, Moorman WJ, Brooks S, Gann PH. The diversity of reaginic immune responses to platinum and palladium metallic salts. J Allergy Clin Immunol 1985 Dec;76(6):794-802.

(56) Jones MG, Floyd A, Nouri-Aria KT, Jacobson MR, Durham SR, Taylor AN, et al. Is occupational asthma to diisocyanates a non-IgE-mediated disease? J Allergy Clin Immunol 2006 Mar;117(3):663-9.

(57) Malo JL, L'Archeveque J, Lummus Z, Bernstein D. Changes in specific IgE and IgG and monocyte chemoattractant protein-1 in workers with occupational asthma caused by diisocyanates and removed from exposure. J Allergy Clin Immunol 2006 Aug;118(2):530-3.

(58) Del Prete GF, De CM, D'Elios MM, Maestrelli P, Ricci M, Fabbri L, et al. Allergen exposure induces the activation of allergen-specific Th2 cells in the airway mucosa of patients with allergic respiratory disorders. Eur J Immunol 1993 Jul;23(7):1445-9.

(59) Eum SY, Maghni K, Hamid Q, Campbell H, Eidelman DH, Martin JG. Involvement of the cysteinyl-leukotrienes in allergen-induced airway eosinophilia and hyperresponsiveness in the mouse. Am J Respir Cell Mol Biol 2003 Jan;28(1):25-32.

(60) Bardana EJ, Jr. Reactive airways dysfunction syndrome (RADS): guidelines for diagnosis and treatment and insight into likely prognosis. Ann Allergy Asthma Immunol 1999 Dec;83(6 Pt 2):583-6.

(61) Gautrin D, Boulet LP, Boutet M, Dugas M, Bherer L, L'Archeveque J, et al. Is reactive airways dysfunction syndrome a variant of occupational asthma? J Allergy Clin Immunol 1994 Jan;93(1 Pt 1):12-22.

(62) Martin JG, Campbell HR, Iijima H, Gautrin D, Malo JL, Eidelman DH, et al. Chlorine-induced injury to the airways in mice. Am J Respir Crit Care Med 2003 Sep 1;168(5):568-74.

(63) Tian X, Tao H, Brisolara J, Chen J, Rando RJ, Hoyle GW. Acute lung injury induced by chlorine inhalation in C57BL/6 and FVB/N mice. Inhal Toxicol 2008 Jul;20(9):783-93.

(64) Brooks SM, Hammad Y, Richards I, Giovinco-Barbas J, Jenkins K. The spectrum of irritant-induced asthma: sudden and not-so-sudden onset and the role of allergy. Chest 1998 Jan;113(1):42-9.

(65) Brooks SM, Weiss MA, Bernstein IL. Reactive airways dysfunction syndrome (RADS). Persistent asthma syndrome after high level irritant exposures. Chest 1985 Sep;88(3):376-84.

(66) Tarlo SM, Broder I. Irritant-induced occupational asthma. Chest 1989 Aug;96(2):297-300.

(67) Arif AA, Delclos GL, Serra C. Occupational exposures and asthma among nursing professionals. Occup Environ Med 2009 Apr;66(4):274-8.

(68) Delclos GL, Gimeno D, Arif AA, Burau KD, Carson A, Lusk C, et al. Occupational risk factors and asthma among health care professionals. Am J Respir Crit Care Med 2007 Apr 1;175(7):667-75.

(69) Medina-Ramon M, Zock JP, Kogevinas M, Sunyer J, Anto JM. Asthma symptoms in women employed in domestic cleaning: a community based study. Thorax 2003 Nov;58(11):950-4.

(70) Lemiere C. Occupational and work-exacerbated asthma: similarities and differences. Expert Rev Respir Med 2007 Aug;1(1):43-9.

(71) Henneberger PK, Redlich CA, Callahan DB, Harber P, Lemiere C, Martin J, et al. An Official American Thoracic Society Statement: Work-Exacerbated Asthma. Am J Respir Crit Care Med 2011 Aug 1;184(3):368-78.

(72) Chiry S, Cartier A, Malo JL, Tarlo SM, Lemiere C. Comparison of peak expiratory flow variability between workers with work-exacerbated asthma and occupational asthma. Chest 2007 Aug;132(2):483-8.

(73) Arif AA, Delclos GL. Association between cleaning-related chemicals and work-related asthma and asthma symptoms among healthcare professionals. Occup Environ Med 2011 May 20.

(74) Tarlo SM, Liss G, Corey P, Broder I. A workers' compensation claim population for occupational asthma. Comparison of subgroups. Chest 1995 Mar;107(3):634-41.

(75) Henneberger PK, Mirabelli MC, Kogevinas M, Anto JM, Plana E, Dahlman-Hoglund A, et al. The occupational contribution to severe exacerbation of asthma. Eur Respir J 2010 Oct;36(4):743-50.

(76) Quirce S, Barranco P. Cleaning agents and asthma. J Investig Allergol Clin Immunol 2010;20(7):542-50.

(77) Perry AD, Trafeli JP. Hand dermatitis: review of etiology, diagnosis, and treatment. J Am Board Fam Med 2009 May;22(3):325-30.

(78) Lynde C, Guenther L, Diepgen TL, Sasseville D, Poulin Y, Gulliver W, et al. Canadian hand dermatitis management guidelines. J Cutan Med Surg 2010 Nov;14(6):267-84.

(79) Molin S, Diepgen TL, Ruzicka T, Prinz JC. Diagnosing chronic hand eczema by an algorithm: a tool for classification in clinical practice. Clin Exp Dermatol 2011 Aug;36(6):595-601.

(80) Thyssen JP, Johansen JD, Linneberg A, Menne T. The epidemiology of hand eczema in the general population--prevalence and main findings. Contact Dermatitis 2010 Feb;62(2):75-87.

(81) Lerbaek A, Kyvik KO, Ravn H, Menne T, Agner T. Incidence of hand eczema in a population-based twin cohort: genetic and environmental risk factors. Br J Dermatol 2007 Sep;157(3):552-7.

(82) Jones J, Huxtable C, Hodgson J. Self-Reported Work-Related Illness in 2001/02; Results From a Household Survey. SW10102 London: Health and Safety Executive 2003.

(83) Walsh L, Turner S, Lines S, Hussey L, Chen Y, Agius R. The incidence of work-related illness in the UK health and social work sector: The Health and Occupation Reporting network 2002-2003. Occup Med (Lond) 2005 Jun;55(4):262-7.

(84) Meding B. Differences between the sexes with regard to work-related skin disease. Contact Dermatitis 2000 Aug;43(2):65-71.

(85) Schultz LF, Diepgen T, Svensson A. The occurrence of atopic dermatitis in north Europe: an international questionnaire study. J Am Acad Dermatol 1996 May;34(5 Pt 1):760-4.

(86) Meding B, Liden C, Berglind N. Self-diagnosed dermatitis in adults. Results from a population survey in Stockholm. Contact Dermatitis 2001 Dec;45(6):341-5.

(87) Dalgard F, Svensson A, Holm JO, Sundby J. Self-reported skin morbidity in Oslo. Associations with sociodemographic factors among adults in a cross-sectional study. Br J Dermatol 2004 Aug;151(2):452-7.

(88) Dalgard F, Svensson A, Holm JO, Sundby J. Self-reported skin morbidity in Oslo. Associations with sociodemographic factors among adults in a cross-sectional study. Br J Dermatol 2004 Aug;151(2):452-7.

(89) Mortz CG, Lauritsen JM, Bindslev-Jensen C, Andersen KE. Prevalence of atopic dermatitis, asthma, allergic rhinitis, and hand and contact dermatitis in adolescents. The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis. Br J Dermatol 2001 Mar;144(3):523-32.

(90) Bryld LE, Hindsberger C, Kyvik KO, Agner T, Menne T. Risk factors influencing the development of hand eczema in a population-based twin sample. Br J Dermatol 2003 Dec;149(6):1214-20.

(91) Meding B, Jarvholm B. Incidence of hand eczema-a population-based retrospective study. J Invest Dermatol 2004 Apr;122(4):873-7.

(92) Lantinga H, Nater JP, Coenraads PJ. Prevalence, incidence and course of eczema on the hands and forearms in a sample of the general population. Contact Dermatitis 1984 Mar;10(3):135-9.

(93) Bryld LE, Agner T, Kyvik KO, Brondsted L, Hindsberger C, Menne T. Hand eczema in twins: a questionnaire investigation. Br J Dermatol 2000 Feb;142(2):298-305.

(94) Lan CC, Tu HP, Lee CH, Wu CS, Ko YC, Yu HS, et al. Hand dermatitis among university hospital nursing staff with or without atopic eczema: assessment of risk factors. Contact Dermatitis 2011 Feb;64(2):73-9.

(95) Jensen P, Thyssen JP, Johansen JD, Skare L, Menne T, Liden C. Occupational hand eczema caused by nickel and evaluated by quantitative exposure assessment. Contact Dermatitis 2011 Jan;64(1):32-6.

(96) Antunes J, Silva R, Pacheco D, Travassos R, Filipe P. Occupational contact allergy to cephalosporins. Dermatol Online J 2011;17(5):13.

(97) Skoet R, Olsen J, Mathiesen B, Iversen L, Johansen JD, Agner T. A survey of occupational hand eczema in Denmark. Contact Dermatitis 2004 Oct;51(4):159-66.

(98) Meding B, Swanbeck G. Occupational hand eczema in an industrial city. Contact Dermatitis 1990 Jan;22(1):13-23.

(99) Lind ML, Albin M, Brisman J, Kronholm DK, Lillienberg L, Mikoczy Z, et al. Incidence of hand eczema in female Swedish hairdressers. Occup Environ Med 2007 Mar;64(3):191-5.

(100) Anveden I, Wrangsjo K, Jarvholm B, Meding B. Self-reported skin exposure -- a population-based study. Contact Dermatitis 2006 May;54(5):272-7.

(101) Anveden B, I, Alderling M, Jarvholm B, Liden C, Meding B. Occupational skin exposure to water: a population-based study. Br J Dermatol 2009 Mar;160(3):616-21.

(102) Lysdal SH, Sosted H, Andersen KE, Johansen JD. Hand eczema in hairdressers: a Danish register-based study of the prevalence of hand eczema and its career consequences. Contact Dermatitis 2011 Jun 21.

(103) Redlich CA, Herrick CA. Lung/skin connections in occupational lung disease. Curr Opin Allergy Clin Immunol 2008 Apr;8(2):115-9.

(104) Spergel JM. Epidemiology of atopic dermatitis and atopic march in children. Immunol Allergy Clin North Am 2010 Aug;30(3):269-80.

(105) Asher MI, Stewart AW, Mallol J, Montefort S, Lai CK, Ait-Khaled N, et al. Which population level environmental factors are associated with asthma, rhinoconjunctivitis and eczema? Review of the ecological analyses of ISAAC Phase One. Respir Res 2010;11:8.

(106) Linneberg A, Simonsen JB, Petersen J, Stensballe LG, Benn CS. Differential effects of risk factors on infant wheeze and atopic dermatitis emphasize a different etiology. J Allergy Clin Immunol 2006 Jan;117(1):184-9.

(107) Tinkle SS, Antonini JM, Rich BA, Roberts JR, Salmen R, DePree K, et al. Skin as a route of exposure and sensitization in chronic beryllium disease. Environ Health Perspect 2003 Jul;111(9):1202-8.

(108) Bello D, Herrick CA, Smith TJ, Woskie SR, Streicher RP, Cullen MR, et al. Skin exposure to isocyanates: reasons for concern. Environ Health Perspect 2007 Mar;115(3):328-35.

(109) Redlich CA. Skin exposure and asthma: is there a connection? Proc Am Thorac Soc 2010 May;7(2):134-7.

(110) Smith Pease CK, White IR, Basketter DA. Skin as a route of exposure to protein allergens. Clin Exp Dermatol 2002 Jun;27(4):296-300.

(111) Lynde CB, Obadia M, Liss GM, Ribeiro M, Holness DL, Tarlo SM. Cutaneous and respiratory symptoms among professional cleaners. Occup Med (Lond) 2009 Jun;59(4):249-54.

(112) Obadia M, Liss GM, Lou W, Purdham J, Tarlo SM. Relationships between asthma and work exposures among non-domestic cleaners in Ontario. Am J Ind Med 2009 Sep;52(9):716-23.

(113) Rosenman KD, Reilly MJ, Schill DP, Valiante D, Flattery J, Harrison R, et al. Cleaning products and work-related asthma. J Occup Environ Med 2003 May;45(5):556-63.

(114) International Association for Soaps, Detergents and Maintenance Products . 2011. 9-8-2011.

(115) Zock JP. World at work: cleaners. Occup Environ Med 2005 Aug;62(8):581-4.

(116) UK National Statistics Publication Hub. 2011.

(117) Instituto Nacional de Estadística (National Statistics Institute). España. 2011. 22-8-2011.

(118) Institut d'Estadística de Catalunya (Statistical Institute of Catalonia). Catalonia, Spain. 2011. 22-8-2011.

(119) Stenton SC, Dennis JH, Walters EH, Hendrick DJ. Asthmagenic properties of a newly developed detergent ingredient: sodium iso-nonanoyl oxybenzene sulphonate. Br J Ind Med 1990 Jun;47(6):405-10.

(120) Nomura T, Kimura S, Hata S, Kanzaki T, Tanaka H. The synthetic surfactants AS and LAS interrupt pregnancy in mice. Life Sci 1980 Jan 7;26(1):49-54.

(121) Dunagan SC, Dodson RE, Rudel RA, Brody JG. Toxics Use Reduction in the Home: Lessons Learned from Household Exposure Studies. J Clean Prod 2011 Mar 1;19(5):438-44.

(122) Bello A, Quinn MM, Perry MJ, Milton DK. Characterization of occupational exposures to cleaning products used for common cleaning tasks--a pilot study of hospital cleaners. Environ Health 2009;8:11.

(123) Bello A, Quinn MM, Perry MJ, Milton DK. Quantitative assessment of airborne exposures generated during common cleaning tasks: a pilot study. Environ Health 2010;9:76.

(124) Charles LE, Loomis D, Demissie Z. Occupational hazards experienced by cleaning workers and janitors: A review of the epidemiologic literature. Work 2009;34(1):105-16.

(125) Human and Environmental Risk Assessment on ingredients of household cleaning products. HERA initiative. 2011. 22-8-2011.

(126) Nielsen J. The occurrence and course of skin symptoms on the hands among female cleaners. Contact Dermatitis 1996 Apr;34(4):284-91.

(127) Nilsson E, Mikaelsson B, Andersson S. Atopy, occupation and domestic work as risk factors for hand eczema in hospital workers. Contact Dermatitis 1985 Oct;13(4):216-23.

(128) Jungbauer FH, Van Der Harst JJ, Schuttelaar ML, Groothoff JW, Coenraads PJ. Characteristics of wet work in the cleaning industry. Contact Dermatitis 2004 Sep;51(3):131-4.

(129) Nielsen JE. Skin symptoms on the hands of female house-cleaning personnel. Ugeskr Laeger 1998 Jun 1;160(23):3393-7.

(130) English JS. Current concepts of irritant contact dermatitis. Occup Environ Med 2004 Aug;61(8):722-6, 674.

(131) Magnano M, Silvani S, Vincenzi C, Nino M, Tosti A. Contact allergens and irritants in household washing and cleaning products. Contact Dermatitis 2009 Dec;61(6):337-41.

(132) Flyvholm MA. Contact allergens in registered cleaning agents for industrial and household use. Br J Ind Med 1993 Nov;50(11):1043-50.

(133) Jaakkola JJ, Jaakkola MS. Professional cleaning and asthma. Curr Opin Allergy Clin Immunol 2006 Apr;6(2):85-90.

(134) Zock JP, Vizcaya D, Le Moual N. Update on asthma and cleaners. Curr Opin Allergy Clin Immunol 2010 Apr;10(2):114-20.

(135) Ng TP, Hong CY, Goh LG, Wong ML, Koh KT, Ling SL. Risks of asthma associated with occupations in a community-based case-control study. Am J Ind Med 1994 May;25(5):709-18.

(136) Kogevinas M, Anto JM, Sunyer J, Tobias A, Kromhout H, Burney P. Occupational asthma in Europe and other industrialised areas: a population-based study. European Community Respiratory Health Survey Study Group. Lancet 1999 May 22;353(9166):1750-4.

(137) Zock JP, Plana E, Jarvis D, Anto JM, Kromhout H, Kennedy SM, et al. The use of household cleaning sprays and adult asthma: an international longitudinal study. Am J Respir Crit Care Med 2007 Oct 15;176(8):735-41.

(138) Medina-Ramon M, Zock JP, Kogevinas M, Sunyer J, Torralba Y, Borrell A, et al. Asthma, chronic bronchitis, and exposure to irritant agents in occupational domestic cleaning: a nested case-control study. Occup Environ Med 2005 Sep;62(9):598-606.

(139) Mirabelli MC, Zock JP, Plana E, Anto JM, Benke G, Blanc PD, et al. Occupational risk factors for asthma among nurses and related healthcare professionals in an international study. Occup Environ Med 2007 Jul;64(7):474-9.

(140) Mazurek JM, Filios M, Willis R, Rosenman KD, Reilly MJ, McGreevy K, et al. Work-related asthma in the educational services industry: California, Massachusetts, Michigan, and New Jersey, 1993-2000. Am J Ind Med 2008 Jan;51(1):47-59.

(141) Cherry N, Beach J, Burstyn I, Fan X, Guo N, Kapur N. Data linkage to estimate the extent and distribution of occupational disease: new onset adult asthma in Alberta, Canada. Am J Ind Med 2009 Nov;52(11):831-40.

(142) Effendy I, Maibach HI. Surfactants and experimental irritant contact dermatitis. Contact Dermatitis 1995 Oct;33(4):217-25.

(143) Agner T, Johansen JD, Overgaard L, Volund A, Basketter D, Menne T. Combined effects of irritants and allergens. Synergistic effects of nickel and sodium lauryl sulfate in nickel- sensitized individuals. Contact Dermatitis 2002 Jul;47(1):21-6.

(144) McLelland J, Shuster S, Matthews JN. 'Irritants' increase the response to an allergen in allergic contact dermatitis. Arch Dermatol 1991 Jul;127(7):1016-9.

(145) Pedersen LK, Johansen JD, Held E, Agner T. Augmentation of skin response by exposure to a combination of allergens and irritants - a review. Contact Dermatitis 2004 May;50(5):265-73.

(146) Lynde CB, Obadia M, Liss GM, Ribeiro M, Holness DL, Tarlo SM. Cutaneous and respiratory symptoms among professional cleaners. Occup Med (Lond) 2009 Jun;59(4):249-54.

(147) Gawkrodger DJ, Lloyd MH, Hunter JA. Occupational skin disease in hospital cleaning and kitchen workers. Contact Dermatitis 1986 Sep;15(3):132-5.

(148) Nilsson E. Contact sensitivity and urticaria in "wet" work. Contact Dermatitis 1985 Nov;13(5):321-8.

(149) Nettis E, Colanardi MC, Soccio AL, Ferrannini A, Tursi A. Occupational irritant and allergic contact dermatitis among healthcare workers. Contact Dermatitis 2002 Feb;46(2):101-7.

(150) Medina-Ramon M, Zock JP, Kogevinas M, Sunyer J, Basagana X, Schwartz J, et al. Short-term respiratory effects of cleaning exposures in female domestic cleaners. Eur Respir J 2006 Jun;27(6):1196-203.

(151) Zock JP, Kogevinas M, Sunyer J, Jarvis D, Toren K, Anto JM. Asthma characteristics in cleaning workers, workers in other risk jobs and office workers. Eur Respir J 2002 Sep;20(3):679-85.

(152) Zock JP, Kogevinas M, Sunyer J, Almar E, Muniozguren N, Payo F, et al. Asthma risk, cleaning activities and use of specific cleaning products among Spanish indoor cleaners. Scand J Work Environ Health 2001 Feb;27(1):76-81.

(153) Zock JP, Plana E, Anto JM, Benke G, Blanc PD, Carosso A, et al. Domestic use of hypochlorite bleach, atopic sensitization, and respiratory symptoms in adults. J Allergy Clin Immunol 2009 Oct;124(4):731-8.

(154) Ley Orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal. B O E 1999;14-12-1999(298):43088-99.

(155) Tarlo SM, Malo JL. An official ATS proceedings: asthma in the workplace: the Third Jack Pepys Workshop on Asthma in the Workplace: answered and unanswered questions. Proc Am Thorac Soc 2009 Aug 1;6(4):339-49.

(156) Malo JL, Chan-Yeung M. Agents causing occupational asthma. J Allergy Clin Immunol 2009 Mar;123(3):545-50.

(157) Bernstein JA, Brandt D, Rezvani M, Abbott C, Levin L. Evaluation of cleaning activities on respiratory symptoms in asthmatic female homemakers. Ann Allergy Asthma Immunol 2009 Jan;102(1):41-6.

(158) de Fatima ME, Algranti E, Medina Coeli ME, Antonio BM. Rhinitis and asthma symptoms in non-domestic cleaners from the Sao Paulo metropolitan area, Brazil. Occup Environ Med 2007 Jul;64(7):446-53.

(159) Massin N, Hecht G, Ambroise D, Hery M, Toamain JP, Hubert G, et al. Respiratory symptoms and bronchial responsiveness among cleaning and disinfecting workers in the food industry. Occup Environ Med 2007 Feb;64(2):75-81.

(160) Arif AA, Hughes PC, Delclos GL. Occupational exposures among domestic and industrial professional cleaners. Occup Med (Lond) 2008 Jul 14.

(161) Singer BC, Destaillats H, Hodgson AT, Nazaroff WW. Cleaning products and air fresheners: emissions and resulting concentrations of glycol ethers and terpenoids. Indoor Air 2006 Jun;16(3):179-91.

(162) Arif AA, Delclos GL, Whitehead LW, Tortolero SR, Lee ES. Occupational exposures associated with work-related asthma and work-related wheezing among U.S. workers. Am J Ind Med 2003 Oct;44(4):368-76.

(163) Kogevinas M, Anto JM, Soriano JB, Tobias A, Burney P. The risk of asthma attributable to occupational exposures. A population-based study in Spain. Spanish Group of the European Asthma Study. Am J Respir Crit Care Med 1996 Jul;154(1):137-43.

(164) Karjalainen A, Martikainen R, Karjalainen J, Klaukka T, Kurppa K. Excess incidence of asthma among Finnish cleaners employed in different industries. Eur Respir J 2002 Jan;19(1):90-5.

(165) Burney PG, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. Eur Respir J 1994 May;7(5):954-60.

(166) Font-Ribera L, Kogevinas M, Zock JP, Nieuwenhuijsen MJ, Heederik D, Villanueva CM. Swimming pool attendance and risk of asthma and allergic symptoms in children. Eur Respir J 2009 Dec;34(6):1304-10.

(167) Sunyer J, Pekkanen J, Garcia-Esteban R, Svanes C, Kunzli N, Janson C, et al. Asthma score: predictive ability and risk factors. Allergy 2007 Feb;62(2):142-8.

(168) Casset A, de Blay F. Health effects of domestic volatile organic compounds. Rev Mal Respir 2008 Apr;25(4):475-85.

(169) U S Department of Labor. Bureau of Labor Statistics U.S.Department of Labor: Occupational Outlook Handbook, 2010-11 Edition, *Building Cleaning Workers*. 2011.

(170) Hansen KS. Occupational dermatoses in hospital cleaning women. Contact Dermatitis 1983 Sep;9(5):343-51.

(171) Vizcaya D, Mirabelli MC, Anto JM, Orriols R, Burgos F, Arjona L, et al. A workforce-based study of occupational exposures and asthma symptoms in cleaning workers. Occup Environ Med. Published online 2011 May 10. doi:10.1136/oem.2010.063271

(172) Vizcaya D, Arjona L, Orriols MR, Barreiro E, Perez M, Burgos F, et al. Characteristics of asthma in cleaning workers: A case-control study. Annual Congress of the European Respiratory Society Meeting Barcelona, Spain Eur Resp J 2010;36:457s.

(173) Coenraads PJ, Nater JP, van der Lende R. Prevalence of eczema and other dermatoses of the hands and arms in the Netherlands. Association with age and occupation. Clin Exp Dermatol 1983 Sep;8(5):495-503.

(174) Smit HA, Coenraads PJ, Lavrijsen AP, Nater JP. Evaluation of a self-administered questionnaire on hand dermatitis. Contact Dermatitis 1992 Jan;26(1):11-6.

(175) Behrens T, Taeger D, Wellmann J, Keil U. Different methods to calculate effect estimates in cross-sectional studies. A comparison between prevalence odds ratio and prevalence ratio. Methods Inf Med 2004;43(5):505-9.

(176) Thompson ML, Myers JE, Kriebel D. Prevalence odds ratio or prevalence ratio in the analysis of cross sectional data: what is to be done? Occup Environ Med 1998 Apr;55(4):272-7.

(177) Vermeulen R, Kromhout H, Bruynzeel DP, de Boer EM. Ascertainment of hand dermatitis using a symptom-based questionnaire; applicability in an industrial population. Contact Dermatitis 2000 Apr;42(4):202-6.

(178) van Wendel de JB, Vermeulen R, Heederik D, van GK, Kromhout H. Evaluation of two self-administered questionnaires to ascertain dermatitis among metal workers and its relation with exposure to metal working fluids. Contact Dermatitis 2007 Jul;57(1):14-20.

(179) Singgih SI, Lantinga H, Nater JP, Woest TE, Kruyt-Gaspersz JA. Occupational hand dermatoses in hospital cleaning personnel. Contact Dermatitis 1986 Jan;14(1):14-9.

(180) Diepgen TL, Coenraads PJ. The epidemiology of occupational contact dermatitis. Int Arch Occup Environ Health 1999 Nov;72(8):496-506.

(181) Meding B, Swanbeck G. Consequences of having hand eczema. Contact Dermatitis 1990 Jul;23(1):6-14.

(182) Meding B, Wrangsjo K, Jarvholm B. Fifteen-year follow-up of hand eczema: persistence and consequences. Br J Dermatol 2005 May;152(5):975-80.

(183) Malkonen T, Alanko K, Jolanki R, Luukkonen R, Aalto-Korte K, Lauerma A, et al. Long-term follow-up study of occupational hand eczema. Br J Dermatol 2010 Nov;163(5):999-1006.

(184) Cvetkovski RS, Zachariae R, Jensen H, Olsen J, Johansen JD, Agner T. Prognosis of occupational hand eczema: a follow-up study. Arch Dermatol 2006 Mar;142(3):305-11.

(185) Corradi M, Gergelova P, Mutti A. Use of exhaled breath condensate to investigate occupational lung diseases. Curr Opin Allergy Clin Immunol 2010 Apr;10(2):93-8.

(186) Stewart L, Katial R. Exhaled nitric oxide. Immunol Allergy Clin North Am 2007 Nov;27(4):571-86.

(187) Broeckaert F, Bernard A. Clara cell secretory protein (CC16): characteristics and perspectives as lung peripheral biomarker. Clin Exp Allergy 2000 Apr;30(4):469-75.

(188) Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J 2005 Aug;26(2):319-38.

(189) Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J 2005 Nov;26(5):948-68.

(190) Roca J, Burgos F, Sunyer J, Saez M, Chinn S, Anto JM, et al. References values for forced spirometry. Group of the European Community Respiratory Health Survey. Eur Respir J 1998 Jun;11(6):1354-62.

(191) ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. Am J Respir Crit Care Med 2005 Apr 15;171(8):912-30.

(192) Horvath I, Hunt J, Barnes PJ, Alving K, Antczak A, Baraldi E, et al. Exhaled breath condensate: methodological recommendations and unresolved questions. Eur Respir J 2005 Sep;26(3):523-48.

(193) Font-Ribera L, Kogevinas M, Zock JP, Gomez FP, Barreiro E, Nieuwenhuijsen MJ, et al. Short-term changes in respiratory biomarkers after swimming in a chlorinated pool. Environ Health Perspect 2010 Nov;118(11):1538-44.

(194) Rodriguez-Trigo G, Zock JP, Pozo-Rodriguez F, Gomez FP, Monyarch G, Bouso L, et al. Health changes in fishermen 2 years after clean-up of the Prestige oil spill. Ann Intern Med 2010 Oct 19;153(8):489-98.

(195) Pellegrino R, Rodarte JR, Brusasco V. Assessing the reversibility of airway obstruction. Chest 1998 Dec;114(6):1607-12.

(196) Preller L, Doekes G, Heederik D, Vermeulen R, Vogelzang PF, Boleij JS. Disinfectant use as a risk factor for atopic sensitization and symptoms consistent with asthma: an epidemiological study. Eur Respir J 1996 Jul;9(7):1407-13.

(197) Vidal C, Gude F, Boquete O, Fernandez-Merino MC, Meijide LM, Rey J, et al. Evaluation of the phadiatop test in the diagnosis of allergic sensitization in a general adult population. J Investig Allergol Clin Immunol 2005;15(2):124-30.

(198) Montuschi P, Corradi M, Ciabattoni G, Nightingale J, Kharitonov SA, Barnes PJ. Increased 8-isoprostane, a marker of oxidative stress, in exhaled condensate of asthma patients. Am J Respir Crit Care Med 1999 Jul;160(1):216-20.