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Functional and biological characteristics of asthma in cleaning workers

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SUMMARY

Objectives: Cleaning workers have an increased risk of asthma but the underlying mechanisms are largely unknown. We studied functional and biological characteristics in asthmatic cleaners and compared these to healthy cleaners.

Methods: Forty-two cleaners with a history of asthma and/or recent respiratory symptoms and 53 symptom-free controls were identified. Fractional exhaled nitric oxide (FeNO) was measured and forced spirometry with reversibility testing was performed. Total IgE, pulmonary surfactant protein D and the 16 kDa Clara Cell secretory protein were measured in blood serum. Interleukins and other cytokines, growth factors, cys-leukotrienes and 8-isoprostane were measured in exhaled breath condensate. Information on occupational and domestic use of cleaning products was obtained in an interview. Associations between asthma status, specific 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 postbronchodilator FEV1, a higher prevalence of atopy (42% vs.

10%) and a 2.9 (CI 1.5–5.6) times higher level of total IgE. Asthma status was not associated with the other respiratory biomarkers. Most irritant products and sprays were more often used by asthmatic cleaners. The use of multiuse products, glass cleaners and polishes at work was associated with higher FeNO, particularly in controls.

Conclusions

Asthma in cleaning workers is characterised by non-reversible lung function decrement and increased total IgE. Oxidative stress, altered lung permeability and eosinophilic inflammation are unlikely to play an important underlying role, although the latter may be affected by certain irritant cleaning exposures.

INTRODUCTION

A growing body of epidemiologic research now suggests that cleaning workers are at increased risk of asthma and related respiratory symptoms.[1, 2, 3, 4 and 5] In Catalonia, Spain, cleaning-related exposures have been identified as one of the main causes of physician-diagnosed occupational asthma.[6] Among the cleaning-related exposures investigated, occupational use of products containing respiratory irritants such as hypochlorite bleach and ammonia have been associated with asthma and asthma-related conditions.[7, 8, 9 and 10] Domestic use of cleaning products, in particular those in spray form, has been also suggested as a risk factor for asthma.[11 and 12]

Despite the increasing epidemiological evidence supporting elevated risks of asthma among cleaners,[1 and 5] limited data are available to describe the physiologic characteristics of cleaning-related asthma or suggest underlying mechanisms by which cleaning-related exposures may impact respiratory health. It has been proposed that inhalation of compounds with respiratory irritant properties may induce bronchial epithelial damage and facilitate allergic sensitization by triggering a pro-inflammatory response, neurogenic inflammation, increased lung permeability, and remodelling of the airways epithelium.[13] Non-allergic-mediated bronchial inflammation has also been described; specifically, occupational and non-occupational exposures alike may lead to non-eosinophilic bronchial inflammation and the onset or aggravation of asthma through non-allergic pathways.[14] Specific sensitization to the individual components of cleaning product formulations may also play a role in the observed risk of asthma among cleaners.[15]

Such inflammatory processes may be detected by characterization of biomarkers of respiratory health. Cytokines and growth factors involved in the inflammatory response in asthma can be measured in exhaled breath condensate (EBC), a suitable non-invasive matrix for this purpose.[16] Eosinophilic inflammation can be evaluated using the fraction of exhaled nitric oxide (FeNO).[17] Finally, bronchial epithelium damage may alter lung permeability, and can be assessed by the blood serum levels of pulmonary proteins which move passively across the alveolar epithelial barrier into the peripheral blood stream when the lung epithelium permeability is compromised.[18]

We conducted this study to describe the functional and biological characteristics of asthma in cleaning workers and to compare a group of cleaners with asthma with a group of cleaning workers free of respiratory symptoms. These findings are based on analysis of the second stage of a multi-stage study of cleaning-related exposures and

asthma. In the first stage of the project, we evaluated risk factors for asthma and asthma-related symptoms among professional cleaning workers.[9] In this second stage, we assess the inflammatory profile, oxidative stress, sensitisation to aeroallergens, lung epithelium permeability, bronchial hyperresponsiveness and lung function in asthmatic and non-asthmatic cleaners identified in the first stage of the project. With this analysis, we provide a description of the physiological and functional characteristics of asthma in cleaning workers compared to a healthy population with similar sociodemographic characteristics and evaluate associations of domestic and occupational use of cleaning products with asthma and biomarkers of respiratory health.

METHODS

Study design and population

We conducted a case-control study nested within a large cross-sectional study of asthma among cleaning company employees in Barcelona, Spain. The study design and methods of the questionnaire survey have been described previously.[9] 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. No measurements of lung function or any biomarker were conducted for the first stage of the project. Based on such questionnaires, we identified 70 prevalent 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 any lower tract respiratory symptom and without a history of asthma. A similar symptom-based definition of asthma has been used previously.[7] 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 fifty-three controls (44%) were finally enrolled in the study (Fig. 1). Eligible participants and non-participants did not differ in age, educational level, sex, smoking status and symptoms either among cases or controls. A higher prevalence of adult-onset asthma was found among non-participant cases compared to participants (Supplement Table 1).

[FIGURE 1]

The present study was approved by the ethics committee of Parc de Salut Mar, Barcelona, and the participants provided written informed consent.

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.[19] Data on the use of cleaning products in the previous year and the average number of hours per week of product use was obtained separately for domestic and occupational cleaning activities. The selected list of cleaning products was based on findings from previous studies.[7 and 9]

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 min after the administration of 400 μg salbutamol via metered dose inhaler, following standard recommendations.[20 and 21] FEV_1 and FVC were expressed as percentages of the age-, sex- and height-specific predicted values. All models were adjusted for cigarette pack-years.
All participants who were eligible for methacholine challenge testing were invited to a second clinic visit where a bronchial hyperresponsiveness (BHR) test was conducted following the ECRHS protocol.[19]

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/s and following international recommendations.[22] 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.[23] Treatment of samples has been described previously.[24 and 25] 8-Isoprostane was analysed 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 used 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 analysed using commercial kits (Biovendor Laboratorní medicína a.s., Modrice, Czech Republic).[24] 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 evaluated the levels of specific IgE against 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 to increase the statistical power. 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, while associations with (log-transformed) continuous outcomes were evaluated using multivariable linear regression. Associations with biomarkers were expressed as Geometric Mean Ratios, computed as the exponential of the beta coefficient obtained from multivariable linear regression models. 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 for each cleaning product analysed. All models were adjusted by domestic use of the studied cleaning product, occupational use of the studied cleaning product, age, 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 primary education or less (cases: 62%, controls: 70%). Most cases and controls were overweighted (60% and 64% with BMI $\geq$ 25, respectively). The score of asthma[26] among cases was on average 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 in previous studies.[9] Atopy and sensitisation to latex and dust mite was more prevalent among cases than controls (Table 1).

[TABLE 1]

Lung function testing

Forced spirometry tests of 28 (67%) cases and 44 (83%) controls met the ATS/ERS quality criteria (Table 2) and were, therefore, considered for analyses. 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. A higher proportion of cases as compared to controls presented a percentage of predicted FEV_1 below 85% both before and after the inhalation of bronchodilator. On the other hand, we found no differences in the proportion of cases and controls that showed a percentage of predicted FVC below 85%. 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]

Biological markers

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 serum IgE than controls after adjusting by sex, age and smoking status.

[TABLE 3]

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 depending on the cleaning product and whether the exposure occurred at home or at work. Cases reported a more frequent use of multi-use products compared to controls. The highest risk of asthma was observed among those who used multi-use products at both settings in the previous year (Supplement Table 2). Additionally, asthma was associated with occupational use of multi-use products in spray form (Table 4). Occupational use of soaps or detergents showed a statistically significant inverse association with asthma. In general, ORs appeared higher when evaluating domestic exposure compared to occupational exposure.

[TABLE 4]

Regarding the association between biomarkers and the use of cleaning products both at home and at work, the initial analysis strategy was stratifying for cases and controls showing highly imprecise results. Therefore, we conducted a cross-sectional analysis including both cases and controls adjusted for age, sex and smoking status. Occupational use of multi-use 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 FeNO. Occupational use of glass cleaners was also associated with higher levels of TNF-α. The use of hydrochloric acid and degreasers at work during the previous year was associated with increased IgE levels. Regarding exposures at home, 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 biomarkers concentrations in EBC are provided in the online supplement (Supplement Tables 3 and 4).

[TABLE 5]

DISCUSSION

This study suggests that cleaning workers with asthma or asthma symptoms are characterised by non-reversible airway obstruction and non-eosinophilic inflammation. Airway obstruction is indicated by the results of basal spirometry and bronchodilator challenge testing; non-eosinophilic inflammation is indicated by the results of FeNO testing. We found no differences between cases and controls in levels of biomarkers of oxidative stress or remodelling of the airways. Asthmatic cleaners are more often atopic and show higher serum total IgE levels than asymptomatic 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 was not different between cases and controls. It has been previously reported that non-

eosinophilic asthmatics with low FEV_1, are less commonly bronchodilator test positive compared to eosinophilic asthmatics.[27] Thickening of the reticular basal membrane, considered a histopathologic feature of occupational asthma, may be an alternative explanation for the non-reversibility of airways obstruction.[28] However, the non-reversibility obstruction of the airways may be due to the presence of other related diseases such as chronic obstructive pulmonary disease (COPD) among symptomatic cases. We evaluated the proportion of cases and controls with FEV_1/FVC lower than 0.70, a diagnostic criterion for COPD accepted by the international respiratory societies,[29] and found that only three out of 42 cases met this criteria. Therefore, although it cannot be excluded that cases have other diseases than asthma, our results are not incompatible with known asthma phenotypes. Cases also showed a higher prevalence of unspecific bronchial hyperresponsiveness, which was measured in a subsample of 11 cases and 11 controls using the metacholine challenge test. No differences in age, basal 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, even after adjusting for age, sex and smoking status. Additional adjustment for other known 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 our population. Limiting the analysis to cases with current asthma, or to individuals with adult-onset asthma, did not change the results. This lack of difference in FeNO suggests that eosinophilic inflammation does not play a predominant role in asthma in cleaning workers. This result is compatible with previous studies reporting that the non-eosinophilic asthma phenotype is characteristic of irritant-induced asthma, which has been proposed as the main mechanistic hypothesis for cleaning-related asthma and asthma-like disorders.[14 and 30] 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.[13 and 14] In addition, a previous study showed an association between atopic sensitisation and the exposure to non-allergenic disinfectants.[31] Alternatively, some cleaning products contain sensitizers, which may explain the increased levels of IgE.[15] In a previous study we found no association between atopy and asthma and/or chronic bronchitis in domestic cleaning workers, but higher total serum IgE level.[7] 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.[32] On the other hand, an international study with a case–case design found that asthmatic cleaners had less atopy than asthmatic office workers.[33] In addition to the above mentioned causes for increased IgE and atopy, it is important to take into account that a pre-existing immunological asthma may be aggravated after the exposure to irritants at work.[34]

Up to date there are no reference values for the studied EBC biomarkers. For this reason, rather than descriptive we performed a classic case-control analysis to evaluate the association of these biomarkers and cleaning-related asthma. Cases and controls showed similar levels of 8-isoprostane in EBC, which according to the literature is in line with our results of FeNO.[35] 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. It has been suggested that irritant-induced asthma is usually less severe in terms of control of the 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.[36]

We evaluated both occupational and domestic exposure to cleaning products, and its association with asthma symptoms and respiratory biomarkers. Occupational and domestic use of multi-use products appeared as a consistent risk factor. In addition, multi-use products' use in spray form, likely facilitates inhalatory exposure,[11] was strongly associated with asthma. Multi-use product is a generic term that refers to complex formulae for cleaning products containing chemicals such as benzenesulfonic acid and aliphatic alcohols. We also found indications that the use of irritants including ammonia and hypochlorite bleach,[7, 8 and 9] polishes or waxes,[37] glass cleaners, and dust mop products was associated with asthma.

The cross-sectional association between the use of specific products and biomarkers were heterogeneous but, interestingly, occupational use of multi-use products was associated with increased levels of FeNO, total IgE and FGF. This is suggestive of an inflammatory profile more related to immunological asthma.[13 and 14] 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 pathophysiological 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.[38] Thus, potential 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. As a result, our final study population included cases with persistent asthma and/or asthma symptoms and controls without temporary respiratory 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 cross-sectional-nested and workforce-based 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 that made impossible to access any workers' personal data from the companies.[39] However, our industry-based 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 from a highly inaccessible population and the reduced misclassification of asthma compensate the low sample

size. Furthermore, our results are consistent with previous reports on asthma and cleaning workers.[1 and 5] 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.[40] However, the differences in the risks for domestic and professional use of some odorous products (e.g., ammonia) suggest that overreporting was unlikely to have introduced a major bias. Third, in our study population, adult-onset asthma cases may be underrepresented as compared to the previous study[9] (Supplement Table 1). Underrepresented diagnosed asthma cases may have led our results to an underestimation of the true differences in biological and functional markers between cases and controls. 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 (chronic cough and chronic phlegm). These symptoms were not part of the inclusion or exclusion criteria for cases and, as a result cases had more chronic bronchitis symptoms than controls. Therefore, the association between current smoking and asthma was determined by the 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 the 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 cleaners with asthma and/or asthma symptoms 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 are complementary to those published previously in this study population[9 and 41] and 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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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest.

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TABLES AND FIGURES

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%)

	Controls *n* = 53	**Cases *n* = 42**
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 [a]	–	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[b]	5 (10%)	17 (42%)
Sensitisation to latex[c]	1 (2%)	3 (7%)
Sensitisation to *D. pteronyssinus* [c]	2 (4%)	13 (31%)

n (%) unless otherwise indicated.
A Wheeze with breathlessness and/or attack of asthma in the last year and/or currently taking medication for asthma.
B Phadiatop test positive. [specific IgE]-->0.35 kU/L at least for 1 of 10 common aeroallergens.
C Concentration of specific IgE in blood serum higher than 0.35 kU/L.

Table 2. Functional characteristics of cases and controls.

	Controls (*n* = 44)	**Cases (*n* = 28)**	**Adj. Coeff. (95%CI) [b]**
Prebronchodilator			
FEV_1/FVC (%)	81.5 (4.4)	76.7 (6.5)	−4.4 (−7.4 to −1.5)
FVC (% Predicted), mean (SD)	96.7 (12.9)	97.8 (12.7)	3.2 (−3.7–10.1)
FEV_1 (% Predicted), mean (SD)	99.3 (13.1)	92.8 (11.2)	−6.8 (−14.0 to 0.3)
FVC (% Predicted) < 85, *n* (%)	10 (21)	7 (22)	0.5 (0.1–2.2)
FEV_1 (% Predicted) < 85, *n* (%)	5 (11)	9 (28)	1.5 (0.3–6.5)

	Controls (*n* = 44)	**Cases (*n* = 28)**	**Adj. Coeff. (95%CI)** [b]
$FEF_{25–75\%}$ (L/s)	2.9 (0.9)	2.4 (0.9)	−0.5 (−1.0 to −0.1)
Postbronchodilator[c]			
FEV_1/FVC (%)	83.4 (4.9)	77.9 (7.1)	−5.2 (−8.8 to −1.6)
FVC (% Predicted), mean (SD)	95.5 (12.7)	97.3 (13.2)	−1.2 (−9.6 to 7.2)
FEV_1 (% Predicted), mean (SD)	100.2 (12.4)	93.7 (10.7)	−7.8 (−14.9 to −0.7)
FVC (% Predicted) < 85, *n* (%)	11 (23)	9 (28)	1.4 (0.4–4.5)
FEV_1 (% Predicted) < 85, *n* (%)	4 (8)	8 (25)	2.0 (0.4–9.3)
$FEF_{25–75\%}$ (L/s)	2.9 (1.2)	2.2 (1.5)	−1.0 (−2.3 to 0.3)
FEV_1/FVC < 0.7, *n* (%)	0 (0)	3 (11)	–
FVC postBD - FVC preBD (mL), mean (SD)	−25.2 (17.6)	5.6 (20.5)	9.8 (−127–146)
FEV_1 postBD - FEV_1 preBD (mL), mean (SD)	36.2 (12.6)	62.8 (14.7)	1.5 (−83–86)
FVC postBD/FVC preBD (%), mean (SD)	99.1 (5.2)	100.4 (6.0)	1.1 (−3.0–5.1)
FEV_1 postBD/FEV_1 preBD (%), mean (SD)	101.4 (4.6)	102.7 (5.7)	0.2 (−2.9–3.3)
Bronchodilator challenge test cutpoints, *n* (%)			
C: 10% change in FEV_1 or FVC	2 (5)	3 (11)	2.7 (0.5–14.1)
D: 150 ml change in FEV_1 or FVC	8 (19)	6 (24)	1.2 (0.3–4.2)
Bronchial hyperesponsiveness (PD20 < 1 mg), *n* (%) [a]	0 (0)	6 (55)	–
Bronchial hyperesponsiveness (PD20 <2 mg), *n* (%) [a]	3 (27)	9 (82)	8.2 (0.7–97)

A Metacholine challenge test. *N* = 11 controls and 11 cases.
B Coefficient and 95%CI from linear regression models adjusted for age, height, sex, and packs-year smoked.
C Spirometry 15 min after the inhalation of 400 mg of salbutamol: *n* (controls, cases) = 44, 26.

Table 3. Biological characteristics of cases and controls.

	Controls (*n* = 51)	**Cases (*n* = 41)**	**GM ratio[a] (95%CI)**
	GM	**GM**	
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.

FeNO: Fraction of exhaled nitric oxide. SP-D: Surfactant Protein D. CC16: 16 kDa 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).
A Exponential of the coefficient from linear regression models of the log-transformed variable adjusted for age, sex and smoking status.

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)**	**OR[a] (95%CI)**	**Controls (*n* = 53)**	**Cases (*n* = 42)**	**OR[b] (95%CI)**
	***n* (%)**	***n* (%)**		***n* (%)**	***n* (%)**	
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)
Multi-use 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 aerosol form						
Multi-use 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.

	Occupational use in the last year			Domestic use in the last year		
	Controls (*n* = 53)	Cases (*n* = 42)	OR[a] (95%CI)	Controls (*n* = 53)	Cases (*n* = 42)	OR[b] (95%CI)
	n (%)	*n* (%)		*n* (%)	*n* (%)	
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.

n.a.: information not available.

A Odd ratios for asthma and occupational use of cleaning products from 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. One different model for each product.

B 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. One different model for each product.

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[a] (95% CI)	**GMR[a] (95% CI)**	**GMR[a] (95% CI)**	**GMR[a] (95% CI)**	**GMR[a] (95%CI)**	**GMR[a] (95%CI)**	**OR[b] (95% CI)**	**OR[b] (95% CI)**	**OR[b] (95% CI)**	**OR[b] (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 (0.2–12.5)
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)

	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[a] (95% CI)	GMR[a] (95% CI)	GMR[a] (95% CI)	GMR[a] (95% CI)	GMR[a] (95%CI)	GMR[a] (95%CI)	OR[b] (95% CI)	OR[b] (95% CI)	OR[b] (95% CI)	OR[b] (95% CI)
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 (0.1–10.9)
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 (1.4–39.1)**	4.0 (0.8–20.3)	2.6 (0.2–33.4)
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 (0.3–14.0)
Multi-use 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 (0.5–17.4)
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 (0.4–17.6)
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 (0.1–10.8)

	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[a] (95% CI)	**GMR[a] (95% CI)**	**GMR[a] (95% CI)**	**GMR[a] (95% CI)**	**GMR[a] (95%CI)**	**GMR[a] (95%CI)**	**OR[b] (95% CI)**	**OR[b] (95% CI)**	**OR[b] (95% CI)**	**OR[b] (95% CI)**
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 (0.4–10.5)	2.9 (0.2–54.5)
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)

n.a.: not analysed. FeNO: Fraction of exhaled NO. SP-D: Serum surfactant Protein D. CC16: Serum 16 kDa 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. Bold indicates statistically significant association at the 95% confidence level.

A 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.

B 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.