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Orianne Dumas, PhD, [1,2], Valérie Siroux, PhD, [3,4], Frédéric Luu, MSc, [1,2], Rachel Nadif, PhD, [1,2], Jan-Paul Zock, PhD, [5,6,7], Francine Kauffmann, MD, [1,2] and Nicole Le Moual, PhD, [1,2].

1. Inserm, Center for research in Epidemiology and Population Health (CESP), U1018, Respiratory and Environmental Epidemiology team, F-94807, Villejuif, France.

2. Univ Paris-Sud, UMRS 1018, F-94807, Villejuif, France.

3. Inserm U823, Centre de Recherche Albert Bonniot, La Tronche, France

4. Université Joseph Fourier, Grenoble, France

5. Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain.

6. Hospital del Mar Research Institute (IMIM), Barcelona, Spain.

7. CIBER Epidemiología y Salúd Publica (CIBERESP), Barcelona, Spain.

INSTITUTIONS AT WHICH THE WORK WAS PERFORMED:

1. Inserm, Center for research in Epidemiology and Population Health (CESP), U1018, Respiratory and Environmental Epidemiology team, F-94807, Villejuif, France.

2. Univ Paris-Sud, UMRS 1018, F-94807, Villejuif, France.

CONTACT INFORMATION:

Orianne Dumas

Respiratory and environmental Epidemiology, CESP/U 1018 Inserm

16, avenue Paul Vaillant Couturier

94807 Villejuif Cedex, France

Email: orianne.dumas@inserm.fr

Tel: +33 1 45 59 53 57 / Fax: +33 1 45 59 51 69

CONFLICT OF INTEREST STATEMENT

All the authors declare they have no conflict of interest.

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EGEA cooperative group:

Coordination: F Kauffmann; V Siroux (epidemiology) F Demenais (genetics); I Pin (clinical aspects); R Nadif (biology).
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Data and quality management: Inserm ex-U155 (Egea1): J Hochez; Inserm CESP/U 1018, Villejuif: N Le Moual, Inserm ex-U780: C Ravault; Inserm ex-U794: N Chateigner; Grenoble: J Ferran.

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ABSTRACT

Background: We aimed to assess the associations between occupational exposure to cleaning products, a gender-related exposure, and asthma characteristics, considering clinical, immunological and inflammatory aspects.

Methods: Analyses were conducted in 391 women (73 with adult-onset asthma) from the follow-up of the Epidemiological Study on the Genetics and Environment of Asthma (EGEA). Occupational exposure to cleaning/disinfecting products was estimated using the asthma-specific job-exposure-matrix (44 women exposed).

Results: Occupational exposures were associated with more symptomatic asthma (Odds Ratio (95% CI): 2.8(1.2–6.4)) and severe asthma (5.1(1.7–15.3)). An association was suggested for poorly controlled asthma (2.2(0.9–5.5)). Associations were observed for asthma without positive skin prick test (3.0(1.1–8.3)), with a low IgE level (2.8(1.2–6.2)), and with a low eosinophil count (3.2(1.5-7.1)).

Conclusions: Results strengthen the evidence of a deleterious role of cleaning products in asthma and are consistent with the hypothesis of non-allergic mechanisms in relation to workplace cleaning exposures.

KEY WORDS

Cleaning product; occupational exposure; occupational asthma; work-related asthma; asthma characteristics

INTRODUCTION

Occupational exposures may account for 10-15% of adult-onset asthma [Torén and Blanc 2009; Ghosh et al. 2013]. Among the numerous workplace substances associated with asthma, cleaning and disinfecting products have been identified as hazardous agents in several studies, as recently reviewed [Zock et al. 2010; Dumas et al. 2013]. Exposure to cleaning products is common both at the workplace and at home, and women remain more prone to this exposure than men [Rosenman et al. 2003; Pechter et al. 2005; Quirce and Barranco 2010; Liss et al. 2011; Arif and Delclos 2012; Le Moual et al. 2012]. Evidence is increasing that not only occupational, but also domestic cleaning exposures may increase the risk of asthma [Zock et al. 2007; Le Moual et al. 2012].

In the French Epidemiological study on the Genetics and Environment of Asthma, occupational exposure to cleaning products was associated with severe asthma at the baseline survey (EGEA1, 1991-1995) [Le Moual et al. 2005]. Further analyses conducted on the more detailed phenotypic and exposure data at follow-up (EGEA2, 2003-2007) suggest an adverse effect of specific cleaning products in asthma among women, both for occupational (decalcifiers, sprays and ammonia among women hospital workers) [Dumas et al. 2012] and domestic (the use of sprays) exposures [Le Moual et al. 2012]. Despite the increasing evidence of a causal role of cleaning products in asthma, the question whether cleaning products may be associated with asthma-like respiratory disorders rather than “true” asthma remains discussed [Vizcaya et al. 2011]. Additional association studies relying on refined asthma characteristics, for instance accounting for the disease severity or control, are warranted.

The need to better characterize the asthma phenotypes associated with cleaning activities has been underlined [Zock et al. 2010; Vizcaya et al. 2013]. While the nature of the relationship between asthma and atopy remains a matter of debate [Douwes et al. 2011; Pekkanen et al. 2012], there is a general agreement that occupational asthma may be induced through immunologic or non immunologic mechanisms [Maestrelli et al. 2009; Malo and Chan-Yeung 2009], related to different

types of occupational exposures (allergens or irritants). Cleaning products are sometimes classified as low molecular weight agents, with a sensitizing potential [Maestrelli et al. 2009; Malo and Chan-Yeung 2009]. However, most cleaning products are hypothesized to induce asthma through irritant-induced mechanisms [Zock et al. 2010; Vizcaya et al. 2011; Lillienberg et al. 2013], which remain largely unknown [Maestrelli et al. 2009]. In this context, focusing on asthma characteristics, considering allergy or inflammatory markers (skin prick test (SPT) response, total immunoglobulin E (IgE) level, blood eosinophil and neutrophil counts) among subjects with asthma, may provide novel insights on the underlying mechanisms involved in the association between asthma and occupational exposure.

Taking advantage of the detailed asthma characterization of the EGEA2 participants, we aimed to assess the associations between occupational exposure to cleaning products and asthma characteristics, including clinical, immunological and inflammatory aspects.

MATERIAL AND METHODS

Population

The EGEA baseline study (1991 – 1995) included asthma cases recruited in chest clinics, their first degree relatives and population based controls (2047 participants) [Kauffmann et al. 1997]. The current analysis used the data from the follow-up (EGEA2, 2003 – 2007), where 92% of the initial population answered a brief postal questionnaire. More detailed information was recorded for 1601 subjects (77% of the initial population and 58 new family members not examined at baseline). The follow-up included a medical examination, including lung function tests, SPT to 12 aeroallergens and assessment of total serum IgE and white blood cell counts from blood samples in a centralized laboratory. The study protocol was approved by the institutional ethics committee (baseline study: Cochin Port-Royal Hospital, Paris; follow-up: Necker-Enfants Malades Hospital, Paris), and all participants gave written informed consent.

The selection of the study population is presented in figure 1. Briefly, a total of 669 adult women had complete data for all the variables of interest. After selecting only women with current adult onset asthma or without asthma, and with occupational exposure to cleaning products or never exposed (reference group defined below), the study population consisted in 391 women, including 73 women with current adult onset asthma.

Asthma characteristics

Subjects with asthma were cases recruited at baseline [Kauffmann et al. 1997], as well as family members or controls who answered positively to one of the two standardized questions: "have you ever had attacks of breathlessness at rest with wheezing?" or "have you ever had asthma attacks?". Among them, those reporting an age at the first asthma attack > 16 years were classified as having adult-onset asthma. Current asthma was defined as ever asthma and report of asthma attacks, respiratory symptoms or asthma treatment in the last 12 months [Cazzoletti et al. 2007; Siroux et al. 2009]. Several asthma characteristics were defined as previously in EGEA [Le Moual et al. 2012], based on standardized definitions or international guidelines.

The traits characterizing the clinical expression of asthma were asthma control, symptoms and severity. Asthma severity was assessed following the 2002-2006 Global Initiative for Asthma (GINA) guidelines [De Marco et al. 2006], by combining data on the clinical features of the patients and the asthma treatment level. Women with current adult-onset asthma were classified as 'severe persistent' or 'not severe' (intermittent, mild and moderate), and compared to women without asthma. Asthma control was assessed based on the GINA 2006-2010 guidelines [Cazzoletti et al. 2007; Siroux et al. 2009], and combined diurnal and nocturnal respiratory symptoms, asthma attacks, lung function, hospitalization for asthma and use of reliever medication. Women with current adult-onset asthma were classified as poorly controlled (i.e. uncontrolled or partly controlled) or controlled, and compared to women without asthma. Five asthma symptoms over the past 12

months have previously been proposed [Pekkanen et al. 2005; Sunyer et al. 2007] to define an asthma symptom score. In the current study, the same list of symptoms was used to classify women with asthma into two groups more (≥2 symptoms) or less (0-1 symptom) symptomatic [Le Moual et al. 2012]. Both groups were compared to women without asthma.

Allergic and inflammatory characteristics were also studied. SPT were performed for 12 aeroallergens (cat, *Dermatophagoides pteronyssinus*, *Blattela germanica*, olive, birch, *Parieteria judaica*, timothy grass, *Cupressus*, ragweed pollen, *Aspergillus*, *Cladosporium herbarum*, *Alternaria tenuis*). SPT to each allergen was positive for a mean wheal diameter > 3 mm than the negative control. Blood Inflammatory patterns based on eosinophil and neutrophil counts were defined as previously in EGEA, with cut-off points corresponding to the 75th percentile in the EGEA adult population [Nadif et al. 2009]. Subjects with asthma were classified according to SPT response (SPT+, at least one positive test *vs.* SPT-, no positive test), total IgE level (<100 *vs.* ≥100 IU/ml), eosinophil count (<250 *vs.* ≥250 cells./mm^3) and neutrophil count (<5000 *vs.* ≥5000 cells./mm^3), and compared to subjects without asthma.

Occupational exposure to cleaning products

At EGEA2, a complete occupational history was recorded by questionnaire with information regarding position, industry and job task. A 4-digit code according to the International Standard Classification of Occupation 1988 (ISCO-88) was assigned by an experienced coder [Dumas et al. 2011]. The asthma-specific job-exposure-matrix (JEM) provides an evaluation (yes/no) of exposure to a list of 18 agents/work environments at high risk for asthma and 4 agents/work environments potentially at risk for respiratory health [Kennedy et al. 2000] (see supplementary table E1 for complete list of agents / work environments). The application of the JEM is completed by an occupational expert re-evaluation step, designed to improve exposure assessment [Kennedy et al. 2000; Dumas et al. 2012]. In the current study, the asthma JEM was used to estimate exposure to

industrial cleaning/disinfecting products (1 of the 18 agents at high risk for asthma). Lifetime occupational exposure to cleaning products (i.e., exposure to cleaning products in at least one job since the first reported job) was studied. Exposed women were mainly personal care workers [Dumas et al. 2012]. The reference category corresponded to 347 women never exposed to any of the remaining 21 agents of the JEM, at risk for asthma or respiratory health.

Statistical analyses

The analyses were conducted in 391 women with current adult-onset asthma or without asthma. First, the associations between occupational exposure to cleaning products and current adult-onset asthma were evaluated in women using logistic regressions. Then, women with adult-onset asthma were classified according to the studied characteristics and were compared to women without asthma. Allergy and inflammatory patterns were also studied as parameters defining asthma characteristics, as we aim to better understand the underlying mechanisms in the relationship between occupational exposure to cleaning products and adult-onset asthma (non allergic or allergic mechanisms). Associations between occupational exposure to cleaning products and asthma characteristics were evaluated by multinomial regressions (seven outcome variables for asthma characteristics, as described in Figure2, with women without asthma as the reference category in all the models). All analyses were adjusted for age and smoking status. Because of the associations previously observed between domestic use of cleaning sprays and asthma [Zock et al. 2007; Le Moual et al. 2012], and because of potential relationship between workplace and domestic habits, analyses were also adjusted for domestic use of sprays. Further adjustment for body mass index or menopausal status did not modify the results (not shown).

RESULTS

The women included in the analyses were aged 48 years on average (respectively 47 and 50 years in women without asthma and with current adult-onset asthma). Clear different pattern were observed between women without asthma and women with current adult-onset asthma for lung function tests, skin prick tests and blood eosinophil count (table 1). Women with asthma also had a higher IgE level than women without asthma, and the association reached significance (p=0.05) after adjusting for age. Among women with current adult-onset asthma, 32.3% had severe persistent asthma, 60.6% had poorly controlled asthma, and 63.9% had ≥2 asthma symptoms.

A total of 39.9% of the women were current or ex-smokers, and respectively 26.3% and 18.4% used 1 and ≥2 types of domestic cleaning sprays weekly. Occupational exposure to cleaning products was not associated with domestic use of cleaning sprays or smoking habits. Lifetime occupational exposure to cleaning products was observed in 44 women, of which 12 were currently exposed.

A higher risk of current adult-onset asthma was observed for lifetime occupational exposure to cleaning products, with an odds-ratio (OR) of 2.01 (95% confidence interval: 0.99-4.06, p=0.05). The association was more pronounced and significant (2.16 (1.03-4.54), p=0.04) after adjusting for age, smoking status, and domestic use of cleaning sprays. Higher ORs were observed for the association between current occupational exposure and current adult-onset asthma: 2.33 (0.84-6.44), (unadjusted OR) and 2.47 (0.87-6.99) (adjusted OR), though the associations did not reach significance (p=0.10 and p=0.08 respectively).

In all but one asthma subcategories, ORs greater than one (ranging from 1.19 to 5.10) were observed for the association with lifetime occupational exposure to cleaning products. Severe persistent asthma was markedly associated with exposure to cleaning products, with and adjusted OR of 5.10 (1.70 – 15.3). An intermediate, non significant OR was observed for mild to moderate asthma (1.49 (0.58 – 3.82)). A similar trend was observed for the relationship between occupational exposure to cleaning products and poor asthma control, as well as with asthma symptoms. ORs greater than 2 were observed for poorly-controlled asthma (2.19 (0.87-5.49)) and for asthma with a ≥2 symptoms (2.84 (1.25-6.42)).

Regarding allergic and inflammatory characteristics, elevated and significant ORs were observed for the association between exposure to cleaning products and asthma with SPT- (3.04 (1.12-8.30)) and with a low IgE level (2.75 (1.23-6.16)). Lower and non significant ORs were observed for asthma with SPT+ (1.63 (0.58 – 4.55)) and with a high IgE level (1.43 (0.40 – 5.16)). Workplace exposure to cleaning products was markedly associated with asthma with low eosinophil count (3.23 (1.46-7.13)), while an OR below the unity was observed for asthma with a high eosinophil count (0.87 (0.19 – 3.88)). Both asthma with low neutrophil count and asthma with high neutrophil count were positively associated with asthma, with ORs of similar magnitude (respectively 2.30 (1.04-5.09) and 2.14 (0.57-7.94)), though only the association with asthma with low neutrophil count reached significance.

DISCUSSION

In women, marked associations were observed between occupational exposure to cleaning products and asthma characteristics. Exposure to cleaning products was associated with severe forms of asthma. Associations were observed for asthma with a low IgE level and without positive SPT, as well as with asthma with a low eosinophil count.

The EGEA detailed and standardized questionnaire and the medical examination allowed a good phenotypic characterization of the participants. Such precise information is rarely available in large studies. Precise data were recorded regarding occupational history, and exposure was evaluated by a JEM, limiting recall bias [De Vocht et al. 2005]. The asthma-specific JEM is frequently used in the literature (http://cesp.vjf.inserm.fr/asthmajem/index.htm). Its application included an occupational hygiene expert re-evaluation step to reduce misclassification [Kennedy et al. 2000], and previous analyses have suggested that the highly specific exposure assessment provided by the JEM is a strength to detect of associations with asthma [Dumas et al. 2012]. Lifetime occupational exposure was studied rather than current exposure. Indeed, occupational asthma may appear without a

latency period (acute irritant induced asthma), but occurs in most cases after a latency period of a few month to several years after first exposure [Maestrelli et al. 2009; Descatha et al. 2007]. Studying lifetime exposure also aimed at reducing the healthy worker survivor effect bias [Le Moual et al. 2008]. Analyses were adjusted for smoking habits and domestic use of cleaning sprays to address potential confounding.

However, our results should be interpreted with caution because of relatively low numbers for some categories of asthma characteristics, which also prevented to conduct further analyses of the effect of specific cleaning products. In addition, this analysis included only women as too few men were exposed to cleaning products at the workplace to be studied [Dumas et al. 2012].

Pronounced associations (ORs > 2) were observed between severe and more symptomatic asthma and workplace exposure to cleaning products, and a suggestive association was observed for poorly controlled asthma. A similar pattern was observed for domestic use of cleaning sprays in EGEA2 [Le Moual et al. 2012]. Severe asthma can be considered as a very specific definition of asthma. The consistency of the results between the different measures of asthma clinical expression and between domestic and workplace exposures, strengthen the evidence of a deleterious effect of cleaning products in asthma. In terms of public health implications, while domestic exposure is much more frequent in the general population, exposure levels are probably higher at the workplace, and hence, both are likely to contribute substantially to the burden of the disease.

Although only subjects with adult-onset asthma were included in the analyses, the observed associations may reflect both occupational asthma and work-exacerbated asthma. Previous studies have observed associations between exposure to cleaning products and worsening of respiratory/asthma symptoms at work [Medina-Ramón et al. 2006; Arif and Delclos 2012], as well as with new onset asthma [Kogevinas et al. 2007; Zock et al. 2007], and both are important public health issues [Torén and Blanc 2009; Henneberger et al. 2011]. Cleaning products are often irritants. The role of irritant exposures, even at low to moderate doses, has been emphasized in work-

exacerbated asthma [Henneberger et al. 2011], and is increasingly suggested in occupational asthma [Labrecque 2012].

Different markers were used to evaluate the allergic component of asthma. Workplace exposure to cleaning products was significantly associated with asthma without positive SPT and with a low total IgE level in women. Modest and non significant associations were observed for asthma with positive SPT or with a high IgE level. Consistent results have been observed in European [Zock et al. 2002; Lillienberg et al. 2013] and Taiwanese [Wang et al. 2010] populations. Though low numbers preclude strong conclusions, these findings are consistent with the hypothesis of the existence of non allergic mechanisms for occupational cleaning products. Conversely, for domestic exposure to sprays in EGEA2, more similar ORs were observed in subjects with asthma with SPT+ and with SPT-, and a significant association with IgE-dependent asthma was observed [Le Moual et al. 2012]. However, cleaning products used at home and at the workplace may differ. Domestic sprays contain perfumes, which may have sensitizing properties. In occupational context, associations with asthma have been reported for a larger scope of products, and the role of irritant exposures has been emphasized [Zock et al. 2010; Vizcaya et al. 2011; Dumas et al. 2012]. In the current study, exposed workers are likely to use several cleaning products, including bleach, ammonia, sprays, etc. [Dumas et al. 2012]. Concurrent exposure to latex is also possible, but no significant association was observed between latex and asthma in EGEA2 [Dumas et al. 2012]. In the current study, the absence of association with characteristics of allergic asthma might be partly due to a healthy worker hire effect [Dumas et al. 2011], but subjects with asthma in childhood were excluded to limit this phenomenon.

Literature regarding inflammatory cells in asthma related to cleaning products is scarce. We observed that workplace exposure to cleaning products was markedly associated with asthma with low eosinophil count. Associations of similar magnitude were observed for asthma with low and high neutrophil count. Consistent results were previously observed, both for eosinophilic and neutrophilic patterns, in relation to domestic use of sprays in EGEA2 [Le Moual et al. 2012]. In studies of inflammatory cells in sputum of workers with occupational asthma due to low molecular weight

agents in general (including some cleaning or disinfecting products), non-eosinophilic asthma predominated [Anees et al. 2002], and eosinophilia was lower than in workers with occupational asthma caused by high molecular weight agents [Talini et al. 2011]. In a study of asthma-related biological characteristics in cleaning workers, eosinophilic inflammation (evaluated using the fraction of exhaled nitric oxide) did not appear to play a major role [Vizcaya et al. 2013]. Overall, these results are in line with our findings regarding eosinophils. The role of neutrophilic inflammation in asthma is less well-known, but could be related to irritant exposures [Wenzel 2006]. In addition, non allergic mechanisms have been suggested for neutrophilic asthma [Nadif et al. 2009]. Larger studies, with precise phenotypic characterization, are needed to further understand asthma related to cleaning products.

In conclusion, results from the EGEA study support the adverse effects of exposure to cleaning products in women asthma. We observed that cleaning products were related to severe forms of asthma. Allergic and non-allergic mechanisms may be involved, and the current study is consistent with the hypothesis of the existence of non-allergic mechanisms in relation to workplace cleaning exposures.

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FIGURES

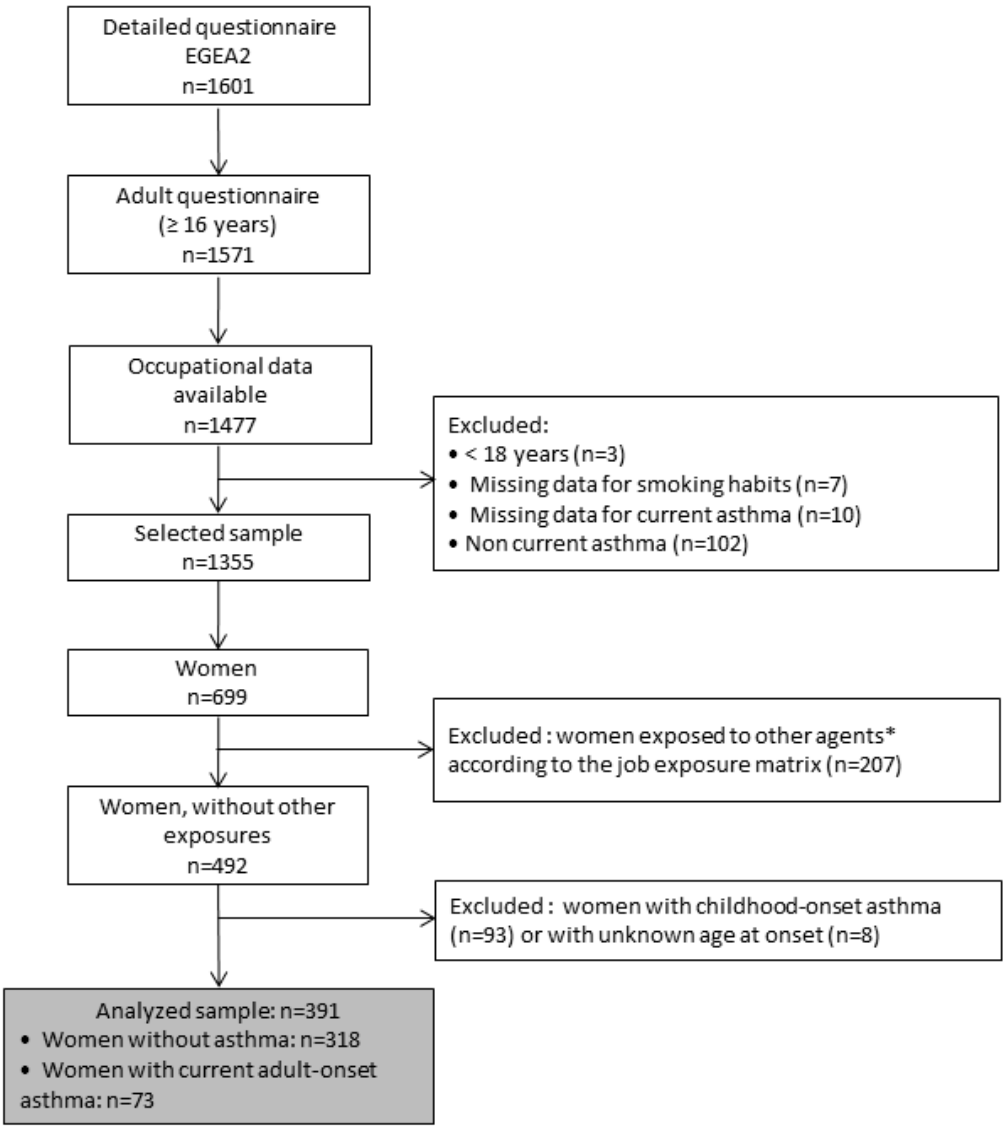

Figure 1. Selection of the study population.

* Women unexposed to cleaning products according to the job exposure matrix, but exposed to other agents potentially hazardous for asthma or respiratory health, including high and low molecular weight agents, mixed environment, and irritants. See supplementary table E1 for the detailed list of agents / work environments and http://cesp.vjf.inserm.fr/asthmajem/ for more information.

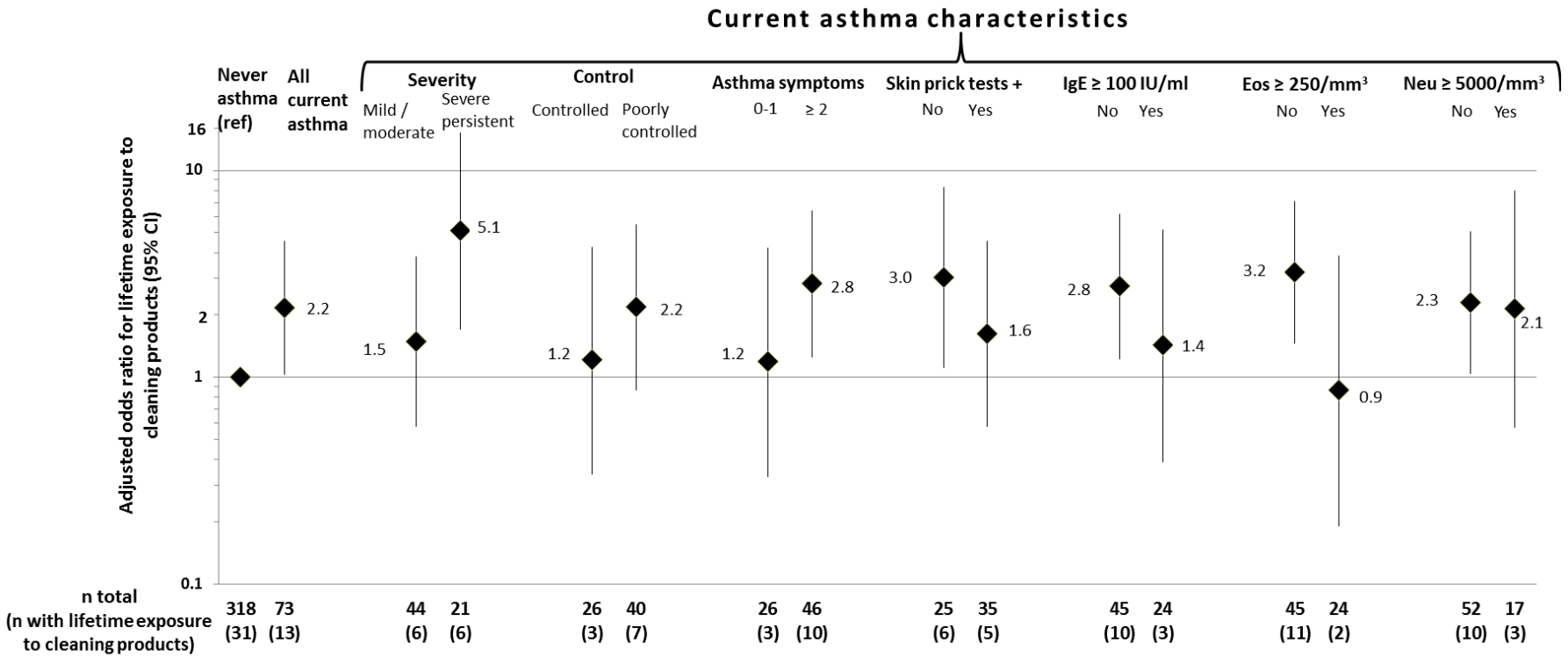

Figure 2. Associations of lifetime occupational exposure to cleaning products with current adult-onset asthma characteristics.

Odds ratios (95% confidence intervals), expressed with "never asthma" as reference, as previously in the study of domestic use of cleaning sprays. Odds ratios were estimated using separate multinomial logistic regression models, with asthma characteristics as outcomes, and occupational exposure as predictor. Analyses were adjusted for age, smoking habits and domestic exposure to cleaning sprays.