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ABSTRACT

Background: Bleach is widely used for household cleaning. Although it is recognized that occupational use of bleach may have adverse respiratory health effects, it is unknown whether common domestic use of bleach may be a risk factor for asthma.
Aim: To assess whether the domestic use of bleach for home cleaning is associated with asthma and other respiratory outcomes.
Methods: Questionnaire-based information on respiratory symptoms and cleaning habits and data from skin prick-tests, bronchial responsiveness challenge and white blood cells were analyzed in 607 women participating in the follow-up of the Epidemiological Study on the Genetics and Environment of Asthma (EGEA). Bleach use was evaluated in 3 categories (<1 day/week; 1–3 days/week; 4–7 days/week "frequent").
Results: Overall, 37% of the women reported using bleach weekly. Women using bleach frequently (11%) were more likely to have current asthma as compared to non-users (adjusted Odds-Ratio (aOR) = 1.7; 95% Confidence Interval (95%CI) 1.0–3.0). Among women with asthma, frequent use of bleach was significantly associated with higher blood neutrophil cell counts. Bleach use was significantly associated with non-allergic asthma (aOR 3.3; 95%CI 1.5–7.1), and more particularly with non-allergic adult-onset asthma (aOR 4.9; 95%CI 2.0–11.6). Consistently, among women without allergic sensitization, significant positive associations were found between use of bleach and bronchial hyperresponsiveness, asthma like-symptoms and chronic cough. No association was observed for allergic asthma.
Conclusions: Frequent use of bleach for home-cleaning is associated with non-allergic adult-onset asthma, elevated neutrophil counts and lower-airway symptoms in women.

1. Introduction

The need for more research on asthma risk factors that operate through non-allergic mechanisms has been highlighted, as it

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appears that a significant proportion of adult asthma cases is not attributable to atopic sensitization [1,2]. In particular, there is a growing interest for the role of low to moderate exposure to irritants in the development of non-allergic asthma [3–6]. Recent occupational studies demonstrate an increased risk of asthma in cleaners and health-care workers exposed to cleaning products, especially in women [4,7–13]. It has been found that professional cleaners in private homes (*vs.* industrial cleaners) reported more frequent asthma and adverse respiratory symptoms [14,15]. Specific exposures incriminated in these studies include the use of bleach, ammonia, quaternary ammonium compounds and sprays [8,9,12].

Although cleaning products are widely used at home, few studies have investigated the effects of their nonprofessional use in the general population. Recent studies have shown that domestic use of cleaning sprays is associated with an increased risk of asthma and wheeze among adults [16–18] and children [19]. Household cleaning products include sensitizers but also airway irritants such as bleach. Bleach is one of the most common products used all around the world for home cleaning [9,20]. Bleach is a sodium hypochlorite solution that has been used for more than 200 years. It was initially used for bleaching clothes, then found to have disinfectant properties [21]. Bleach might have protective effects against allergic diseases through inactivation of indoor allergens and pathogens [20,22]. Conversely, bleach may have adverse respiratory effects, either through acute high-level inhalation of chlorine or chloramine gas due to inappropriate mixture of bleach with other agents, or possibly through exposures to low-level of chlorine-derived irritants [20,23]. To the best of our knowledge, no study has investigated whether common domestic use of bleach is associated with allergic and non-allergic asthma. One population-based study has shown that adults using bleach for home-cleaning were less likely to be sensitized to indoor and outdoor allergens, but more likely to have respiratory symptoms [20].

The purpose of the present study was to investigate the relationship between domestic use of bleach for cleaning and asthma and respiratory outcomes in women from the epidemiological study of genetics and environment of asthma (EGEA). Because bleach may have a protective effect on allergic sensitization, and bleach use has been found to be associated with irritant-induced (non-allergic) asthma in occupational setting, we considered separately allergic and non-allergic asthma. Then, to investigate the relationships between bleach use and respiratory symptoms and bronchial-hyperresponsiveness, we stratified the analysis on allergic status.

2. Material and methods

2.1. Study design and subjects

EGEA [24] is a case-control study combined with a family study of relatives of patients with asthma, with 2047 participants (7–70 years) recruited at baseline (asthma cases (n = 388), first-degree relatives and spouses (n = 1244), controls (n = 415)) [25]. In 2003–2007, participants were invited to a follow-up study (EGEA2, n = 1601), involving a medical examination following a standardized protocol, and standardized questionnaires (derived from the European Community Respiratory Health Survey questionnaire, which was developed using questions of the British Medical Research Council, European Coal and Steel Community, and American Thoracic Society), to diagnose asthma and evaluate respiratory and allergic symptoms, treatments and environmental exposures, including the household use of cleaning products over the last 12 months [16]. A biobank including blood samples has been established (BB-0033-00043). White blood cells counts and total serum IgE have been measured as described previously [26]. Lung function tests, including methacholine challenge, and skin prick tests (SPT) to 12 aeroallergens were performed. The study protocol was approved by local ethic committees (Necker Enfants-Malades Hospital, Paris) and written informed consent was obtained from all participants.

The present analysis included 607 women aged ≥18 years at EGEA2, after exclusion of women with asthma in remission (n = 45), or with missing values for domestic tasks (n = 48), respiratory symptoms (n = 5) or SPT (n = 76) (Fig. 1).

2.2. Methods

Participants were considered to have “ever asthma” if they were recruited as a case at EGEA1, or if they answered positively to one of the two questions: “have you ever had attacks of breathlessness at rest with wheezing?” or “have you ever had asthma attacks?” at EGEA1 or EGEA2 [27]. As proposed for the European Community Respiratory Health Survey (ECRHS) [28], subjects with “ever asthma” who, in addition, reported asthma attacks, asthma treatment and/or asthma-like symptoms (wheezing, nocturnal chest tightness, attack of breathlessness following activity, at rest or at night time) in the past 12 months at EGEA2, were considered to have “current asthma” [16]. Subjects with ever asthma but no current asthma at EGEA2 were excluded from the analysis (Fig. 1). The group of subjects with “never asthma” consisted of subjects who did not report asthma ever at EGEA1 and EGEA2. Adult-onset asthma was defined as an age at first asthma attack ≥16 years [16,28]. Atopy (SPT+) was defined by the presence of at least 1 positive SPT (mean wheal diameter ≥3 mm than the negative control) out of 12 aeroallergens [16]. Allergic and non-allergic asthma were defined as current asthma with and without atopy. Furthermore, allergic/inflammatory phenotypes have also been defined as previously described [26], taking into account: i) eosinophil counts, with a cut-off point of ≥250 eosinophils counts/mm^3 and ii) neutrophil counts, with a cut-off point of >5000 neutrophils counts/mm^3. An asthma symptom score was calculated, independently of asthma status, as the number of positive answers to 5 questions (wheeze with breathlessness, woken up with chest tightness, attack of shortness of breath at rest, attack of shortness of breath after exercise, woken up by an attack of shortness of breath in the last 12 months) [29]. Bronchial hyperresponsiveness (BHR) was defined as a decline in FEV_1 of ≥20% of its post-dilution value for a methacholine cumulative dose ≤ 1 mg. Participants were classified as exposed to bleach ‘weekly’ (1–3 or 4–7 days/week) or non-exposed (never, <1 day/week). Use of bleach 4–7 day/week was defined as ‘frequent’.

2.3. Statistical analysis

Associations between the frequency of bleach use and dichotomous outcomes including current asthma, BHR and respiratory symptoms were evaluated by logistic regression. Associations between the frequency of bleach use and 3-level outcomes (asthma status: allergic asthma and non-allergic asthma as compared to never-asthma and symptom score when considered as a categorical variable (0; 1; ≥2)), were evaluated by multinomial regression models. When considering the 6-level symptom score, the association with use of bleach was evaluated by negative binomial regression model, to control for over-dispersion.

Sensitivity analyses were performed, considering different definitions for asthma phenotypes. We first used a more specific definition of asthma, where only women with positive responses to asthma questions and BHR were defined as “asthmatics” (women reporting asthma but without BHR were excluded from this

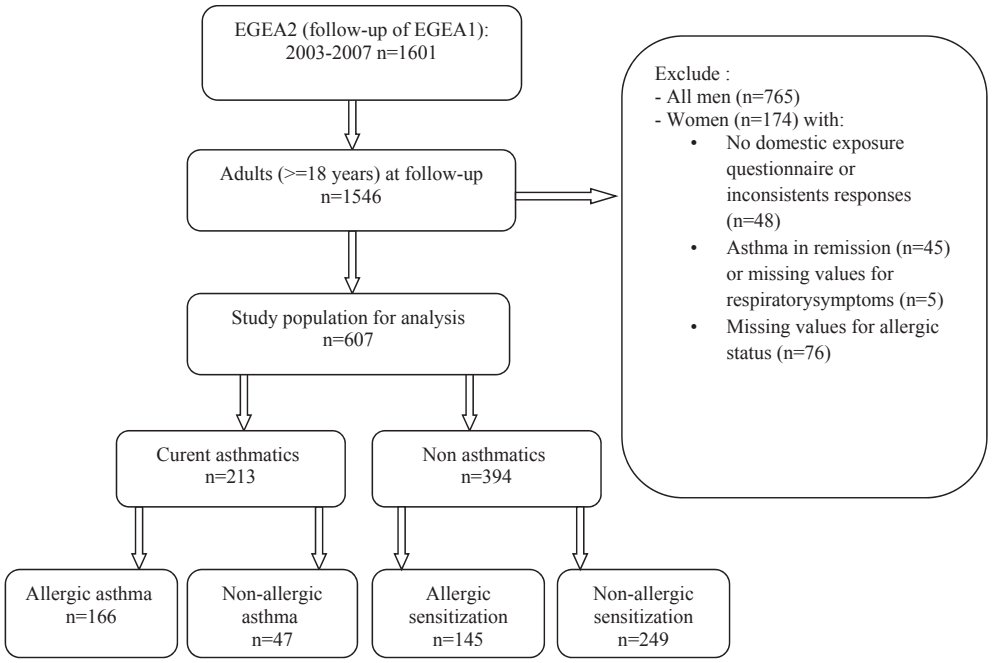

Fig. 1. Flow chart for the selected population. Fig. 1 represents the selection of population included for the present analyzes. As compared to women not included in the present analysis, women included were older ($p < 0.001$) and did more cleaning tasks ($p = 0.004$). There was no difference in use of bleach, smoking status, body mass index, and allergic status between the two groups.

analysis). Secondly, we considered separately 'adult-onset asthma' and 'childhood-onset asthma'.

All analyses were adjusted for age, smoking (never, ex-, current), body mass index (BMI; $\leq$25 kg/m^2) and occupational exposure to asthmagens. More detailed methods are presented in the Supplementary Material.

3. Results

Of the 607 women included in the present analysis (Fig. 1), 213 had current asthma, and among them 166 had allergic asthma. The mean age was 44 years, 10% were obese (BMI$\geq$30 kg/m^2), 20% were current smoker and 53% had a university degree (Table 1). Overall, 77% of the women reported cleaning their homes weekly and 37% using bleach weekly. Women with allergic asthma were younger than those without asthma, whereas women with non-allergic asthma were older ($p < 0.0001$). As expected, women with non-allergic asthma were more likely to have adult-onset asthma as compared to women with allergic asthma (Supplementary Material Table E1). Women with non-allergic asthma used bleach more frequently compared to women with allergic asthma and women without asthma ($p = 0.003$), whereas no difference was observed regarding occupational exposures, or frequency of home-cleaning. Education level (a proxy for socioeconomic status) was associated with bleach use, but was not associated with asthma. A parental history of asthma was more frequently reported by women with allergic asthma, but parental asthma was not associated with bleach use.

3.1. Bleach and asthma

No significant association was observed between the use of bleach and current asthma in univariate model (odds-ratio (OR [95%CI]) for bleach use 1–3 day/week: 0.92 [0.63–1.37] and 4–7 day/week; 1.39 [0.82–2.36]). When adjusted for age, the association between frequent (4–7 days/week) use of bleach and current asthma was borderline significant (adjusted Odds-ratio, aOR = 1.70 [0.98–2.95]; p = 0.06). This association was not further modified after additional adjustment for smoking habits, BMI and exposure to asthmagens.

3.2. Bleach and allergic and non-allergic asthma

Frequent use of bleach was significantly associated with non-allergic asthma (aOR = 3.30 [1.53–7.13]) (Table 2). The analysis stratified by age showed an increased risk of asthma associated with frequent use of bleach in both age groups (Odds-ratios all greater than 2), although the association was not significant in older women (Table 2). No association was observed with allergic asthma. The sensitivity analysis using asthma associated with BHR showed similar patterns of associations (Table 2). When considering adult-onset asthma, the association between frequent domestic use of bleach and non-allergic asthma further increased (aOR = 4.86 [2.04–11.58]). Frequent use of bleach remained significantly associated with non-allergic asthma after further adjustment for domestic use of cleaning sprays (aOR = 3.17 [1.44–7.00]) and after exclusion of women with lifetime occupational exposure to cleaning agents (aOR = 3.15 [1.43–6.95]).

3.3. Bleach, BHR and respiratory symptoms

Among women without allergic sensitization, weekly use of bleach was associated with BHR (aOR = 2.09 [1.04–4.20]) and a significant trend was observed between the frequency of bleach use and BHR (p for trend = 0.04) (Supplementary Material Fig. E1) after adjustment for age and smoking habits. A positive significant association between frequent bleach use and symptom score was observed in women without allergic sensitization (ratio of the mean score: 1.69 [1.17–2.45]) but not in allergic women (1.21 [0.84–1.73]). Significant associations were also observed between frequent bleach use and chronic cough (aOR = 6.02 [2.04–17.75]), and symptom score considered as a categorical variable (aOR = 3.66

Table 1
Population characteristics according to asthma and allergic status of 607 women participating in the EGEA study.

	Total	Never asthma	Current Asthma		P value
	N = 607	N = 394	SPT- N = 47	SPT+ N = 166	
Age, mean (SD)	44.1 (15.7)	46.4 (15.5)	49.1 (14.7)	37.0 (14.4)	<0.001
BMI, kg/m^2 (%)					0.08
<20	14.6	12.7	8.5	21.1	
[20–25]	55.5	58.1	55.3	49.4	
[25–30]	19.9	20.6	21.3	18.1	
≥30	10.0	8.6	14.9	11.4	
Smoking status (%)					0.70
Never smoker	54.8	55.7	57.5	51.8	
Ex-smoker	24.9	24.7	27.7	24.7	
Current smoker	20.3	19.6	14.9	23.5	
Education level (%)					0.69
Primary	20.8	20.8	27.7	18.8	
Secondary	26.2	25.4	25.5	26.2	
University	53.0	53.8	46.8	52.	
Eosinophilia[a],≥250cells/mm^3 (%)	22.2	13.4	27.7	41.2	<0.001
Neutrophilia[a],≥5000cells/mm^3 (%)	22.2	19.6	27.7	26.7	0.12
Total IgE, ≥100 UI/ml (%)	35.1	25.1	19.1	63.4	<0.001
FEV1, <80%predicted (%)	7.3	3.6	6.4	16.3	<0.001
BHR, PD_{20}≤1mg (n = 421) (%)	30.9	16.4	56.3	60.6	<0.001
Chronic phlegm (%)	5.1	3.9	13.0	5.6	0.03
Chronic cough (%)	8.0	6.7	21.4	7.6	0.004
Symptom score ≥2 (%)	33.0	12.4	72.3	70.5	<0.001
Occupational exposure (%)					
Asthma JEM[b]					0.64
Non exposed	79.2	79.5	73.0	77.7	
Exposed to non asthmagens	6.8	5.8	6.4	9.0	
Exposed to asthmagens	14.0	14.7	10.6	13.3	
Exposed to cleaning agents (JEM[b] or job)	5.3	4.6	4.3	7.2	
Home Cleaning (%)					
<1 day/week	23.0	23.4	17.0	23.5	0.36
1–3 days/week	52.2	51.8	46.8	54.8	
4–7 days/week	24.8	24.8	36.2	21.7	
Bleach use at home (%)					
<1 day/week	62.5	62.8	54.3	63.9	0.003
1–3 days/week	26.6	27.5	17.4	27.1	
4–7 days/week	10.9	9.7	28.3	9.0	

[a] The cut-off points for eosinophil and neutrophil counts correspond to the 75th percentiles in the EGEA adult sample [26].
[b] JEM: Asthma-specific Job Exposure Matrix (http://asthmajem.vjf.inserm.fr/), evaluate occupational exposures to 22 agents: 18 known asthmagens (at high risk for asthma) and 4 work environments with exposure to irritants, or with low level of exposure to chemicals or allergens and classified a priori "non asthmagenic" agents at the set-up of the JEM BHR: Bronchial hyperresponsiveness SPT: skin prick tests to 12 common aeroallergens.

[1.50–8.95], symptom score ≥2) (Fig. 2). Significant trends were also observed for chest tightness at night and shortness of breath after exercise (Supplementary Material Fig. E1). In contrast, among women with allergic sensitization no association was observed between the use of bleach and respiratory outcomes neither in univariate model (Fig. E2) nor after adjustment (Fig. E3).

3.4. Asthma-related outcomes in women with asthma

Among women with current asthma (Table 3), the frequency of women with a "high neutrophil" cell-count profile increased from 21% to 30% and 46% in women using bleach less than 1 day per week, 1–3 days per week and 4–7 days per week, respectively (p for trend = 0.006). No dose-response association was observed between bleach use and asthma control, asthma symptom score and eosinophilia.

4. Discussion

Our study is the first to show that the use of bleach for domestic cleaning is associated with non-allergic asthma in women. Among women without allergic sensitization, significant positive associations were observed between bleach use and bronchial hyperresponsiveness, asthma-like symptoms and chronic cough. Furthermore, among women with asthma, frequent use of bleach was associated with an elevated neutrophil cell count. In contrast, no association was observed between bleach use and allergic asthma.

Our findings are consistent with work-related asthma studies showing that professional use of bleach is associated with asthma and respiratory symptoms [3,8,9,30,31] and with studies showing that occupational exposure to cleaning products is associated with non-allergic asthma but not with allergic asthma [11,32,33]. In a recent panel study [30], the professional use of bleach was associated with lower respiratory tract symptoms among participants without atopy, with OR of similar magnitude (3.2 [1.4 to 7.5]). Our finding of an association between domestic use of bleach and non-allergic asthma remained significant after exclusion of women with occupational exposure, and adds to previous results from EGEA on occupational cleaning [11]. In contrast studies considering domestic use of cleaning sprays showed odds-ratios of similar magnitude for allergic and non-allergic asthma [16,17]. While domestic sprays contain perfumes that may have sensitizing effects, bleach and most industrial cleaning products are thought to have adverse respiratory effects through irritant-induced mechanisms. Noteworthy, in our study, the association between use of bleach and non-allergic asthma remained significant after exclusion of women with occupational exposure to cleaning agents and after further adjustment for domestic use of sprays. Our findings of an increased risk of asthma-like symptoms, BHR, and chronic cough

Table 2
Associations between use of bleach and current asthma, allergic asthma and non-allergic asthma.

Frequency of bleach use	Adjusted odds-ratio (95% CI)		
	Never-asthma	Current asthma SPT−	Current asthma SPT+
	n = 394	n = 47	n = 166
Never or <1 day/week	1.00 (ref)		
1–3 days/week		0.67 (0.29–1.56)	1.27 (0.81–0.99)
4–7 days/week		**3.30 (1.53–7.13)**	1.19 (0.61–2.33)
Stratified analysis[a]			
	In women aged < 50 years		
	n = 206	n = 25	n = 131
Never or <1 day/week	1.00 (ref)		
1–3 days/week		0.15 (0.02–1.17)	1.12 (0.65–1.92)
4–7 days/week		**4.02 (1.47–10.96)**	1.49 (0.66–3.39)
	In women aged ≥ 50 years		
	n = 188	n = 21	n = 35
Never or <1 day/week	1.00 (ref)		
1–3 days/week		1.28 (0.46–3.55)	1.54 (0.71–3.33)
4–7 days/week		2.00 (0.57–7.01)	0.82 (0.22–3.02)
Sensitivity analyses			
	Asthma + BHR		
	n = 394	n = 18	n = 66
Never or <1 day/week	1.00 (ref)		
1–3 days/week		0.91 (0.28–3.03)	1.06 (0.52–2.16)
4–7 days/week		2.89 (0.83–10.05)[¥]	0.63 (0.17–2.29)
	Adult-onset asthma		
	n = 394	n = 31	n = 49
Never or <1 day/week	1.00 (ref)		
1–3 days/week		0.99 (0.38–2.54)	1.06 (0.55–2.06)
4–7 days/week		**4.86 (2.04–11.58)**	1.39 (0.67–3.39)
	Childhood-onset asthma		
	n = 394	n = 14	n = 111
Never or <1 day/week	1.00 (ref)		
1–3 days/week		0.47 (0.10–2.20)	1.47 (0.87–2.50)
4–7 days/week		2.06 (0.56–7.97)	1.40 (0.61–3.23)

Odds-ratio (aOR) are adjusted for age, body mass index, smoking status, occupational exposure to asthmagens. *p = 0.06.
BHR: Bronchial hyperresponsiveness; Asthma + BHR: a more specific definition of asthma where only women with both asthma and BHR were defined as "asthmatics" (women with asthma but no BHR were excluded from this analysis).
Bold figures shows OR 95%CI that are significant (with p < 0.05).
[a] aOR are adjusted for age and smoking status, too few subjects per group for a full adjusted model. For the analysis of adult-onset-asthma, women with asthma onset before the age of 16 years were excluded. For childhood-onset asthma, women with asthma onset after age 16 years were excluded. [¥]p = 0.09.

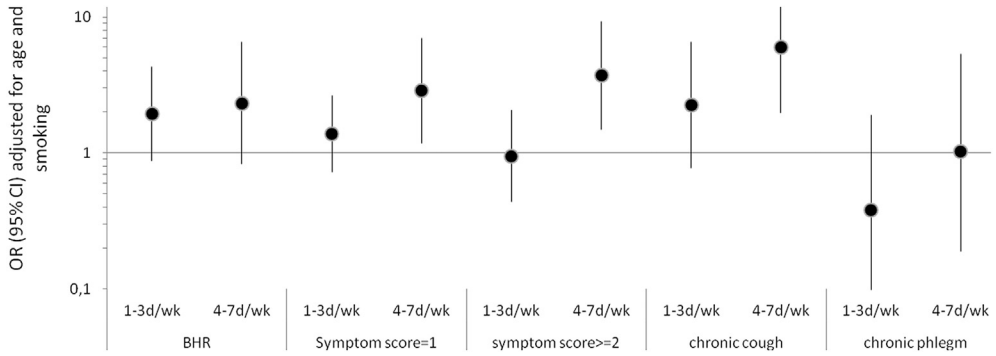

Fig. 2. Association between use of bleach and BHR, asthma symptom scores, chronic cough and chronic phlegm in women without allergic sensitization. Fig. 2 represents Odds-Ratios (OR) and 95% Confidence Intervals for the associations between bleach use and BHR, asthma symptom score, chronic cough and chronic phlegm, in 295 women without allergic sensitization (178 using bleach <1day per week; 79 using bleach 1–3 days/week and 38 using bleach 4–7 days/week). ORs are adjusted for age and smoking (too few subjects per group for a full adjusted model). Adjusted-model p for trends were: p = 0.04 for BHR; p = 0.02 for symptom score = 1; p = 0.01 for symptom score≥2; p = 0.001 for chronic cough, and p = 0.8 for chronic phlegm. Reference category consisted of participants that use bleach never or less than once a week.

are consistent with previous studies [20,22,23]. In the only other study on the association between nonprofessional use of bleach and respiratory symptoms, significant associations were observed between bleach and asthma like symptoms and chronic cough, but no clear association was found for asthma [20]. However, the outcome considered in that study was 'asthma ever in life', and the authors did not differentiate allergic and non-allergic asthma. In children, another cross-sectional study showed that children living in a house regularly cleaned with bleach were less likely to be sensitized to indoor allergens and to have asthma, but more likely to have recurrent bronchitis [22]. There are a few reports suggesting that exposure to chlorine bleach may increase BHR [9,23]. Our results are also consistent with studies of environmental exposure to chlorine. Although different mechanisms might be

Table 3
Associations between bleach use and asthma-related outcomes in women with current asthma.

	Frequency of use of bleach (days/week)in women with current asthma				
	<1 day/wk n = 131	1–3 days/wk n = 53	4–7 days/wk n = 28	p value	p for trend
Eosinophilia[a], ≥250 cells/mm^3, n (%)	53 (40.5)	17 (32.7)	11 (39.3)	0.61	0.62
Neutrophilia[a,b], ≥5000 cells/mm^3, n (%)	28 (21.4)	16 (30.2)	13 (46.4)	**0.02**	**0.006**
Severe asthma, n (%)	34 (26.6)	16 (32.0)	9 (33.3)	0.65	0.38
Poorly controlled asthma, n (%)	67 (51.9)	36 (72.0)	12 (46.2)	**0.03**	0.58
Symptom score ≥2, n (%)	90 (68.7)	37 (69.8)	23 (82.1)	0.36	0.22

Bold figures shows significant p value.
[a] The cut-off points for eosinophil and neutrophil counts correspond to the 75th percentiles in the EGEA adult sample [20].
[b] The adjusted odds-ratio for the association between bleach use and neutrophil cell counts >5000 cells/mm^3 were aOR 1.57; 95%CI 0.72–3.43 for bleach use 1–3 days/week; and aOR 2.76; 95%CI 1.10–6.89 for bleach use 4–7 days/week.

involved, chlorinated swimming pool attendance has been shown to have adverse respiratory effects in swimmers and swimming-pool workers, even in those who do not enter the water [23,34,35].

Among women with asthma, we did not find any significant association between bleach use and asthma severity, control, eosinophilia and symptom score. Frequent bleach users were more likely to have elevated blood neutrophils, which is consistent with the view that neutrophilic inflammation in asthma might be related to exposure to environmental irritants [4,23,36]. A study among asthmatic patients showed that bleach inhalation challenge may induce an increase of neutrophils in sputum [31]. Douwes et al. have proposed that a major proportion of asthma is based on neutrophilic airway inflammation possibly triggered by non-allergic environmental exposure, although exposure to cleaning products was not namely suggested [2]. Our results are based on blood neutrophil counts and the cut-off point to define "high levels" corresponded to the 75th percentiles of the EGEA adult sample [26]. Although blood levels are likely to provide different information as compared to local (such as BAL or sputum) inflammatory markers, a previous analysis in EGEA has demonstrated that inflammatory "patterns" defined using blood eosinophil and neutrophil counts were associated with different phenotypic characteristics of asthma [26]. Unfortunately, these analyses could not be run separately in subjects with allergic/non-allergic asthma, due to limited sample size.

One of the strength of the EGEA study relates to the fine characterization of asthma phenotypes and the use of standardized questionnaires including detailed questions both on domestic and occupational use of cleaning products. Because our hypothesis, based on findings on occupational-asthma, was that bleach use might be associated with irritant-induced asthma (as opposed to sensitizer-induced asthma), we initially performed a multinomial logistic regression to separate allergic and non-allergic asthma phenotypes. Furthermore, as proposed by Pekkannen [37], to ensure that the observed association between bleach use and non-allergic asthma was not related to a protective effect of bleach on allergic sensitization, we performed a supplementary analysis to assess the association between bleach use and current asthma after stratification on atopy. A similar significant association between bleach use and asthma observed in women without allergic sensitization but no association was found in those with allergic sensitization (results not shown). While the inflammatory process associated with exposure to irritant is likely to occur in allergic subjects as well as in non-allergic subjects, bleach might have some protective effect in allergic subjects through possible inactivation of allergens [22]. It might be speculated also that allergic subjects are more likely to have developed asthma earlier in their life, and that bleach exposure might not further increase the risk of asthma in these subjects. This hypothesis is consistent with the lower prevalence of adult-onset asthma in women with allergic asthma. Another strength is the specificity of our results with significant associations observed for adult-onset asthma. Bleach use remained significantly associated with non-allergic asthma in younger women (<50 year-old), limiting possible misclassification with COPD. In addition our study is the first study to show an association between domestic bleach use and BHR, which is an objective outcome associated with airway inflammation. Our study has some limitations. As in most epidemiological studies, the definition of asthma was based on a standardized questionnaire. The question on self-reported asthma is considered to have a high specificity when compared to a clinical diagnosis of asthma, but low sensitivity [38]. The analysis considering asthma symptom score, which partly addresses the issue of low sensitivity and possible undiagnosed asthma, or a more specific definition of asthma (self-reported asthma associated with BHR) showed consistent findings, indicating that our results are not driven by the asthma definition used. Another limitation of our study is the relatively low number of cases with non-allergic asthma. However, our findings are supported by additional results in non-allergic subjects, showing that bleach use was positively associated with BHR and the asthma symptom score, which totalized a large number of subjects. Alike the single other study on domestic use of bleach and respiratory health [20], we could not assess the temporal relationship between the use of bleach and asthma onset due to the cross-sectional design of our data. However, as previously described [16] frequency of home-cleaning (regardless of the specific products used) was not associated with asthma. Furthermore, the percentage of women using bleach frequently varied according to their allergic status (above 25% in women with non-allergic asthma, but only 9% in women with allergic asthma). It is therefore unlikely that the relationship observed between bleach use and non-allergic asthma might be due to reverse causation (i.e. women with asthma would use bleach more frequently due to their having asthma). The fact that the association was strengthened when considering adult-onset asthma only, and that exposure to bleach is recognized as a risk factor for occupational asthma [7,11] further reduce the likelihood of reverse causation. Conversely, a potential bias related to a "healthy user effect" might be present if women experiencing respiratory symptoms when using bleach reduce their use of bleach, as previously suggested in EGEA for the use of sprays [16]. Therefore, the relationship between the use of bleach and asthma (either allergic or non-allergic asthma) might be underestimated.

Besides the well described reactive airway dysfunction syndrome (RADS) following an acute massive exposure to irritants (such as after accidental mixing of bleach), which may develop into persistent asthma [23,39,40], it is increasingly recognized that occupational asthma might develop after repeated or prolonged exposure to low/moderate levels of irritants at work, possibly via oxidative stress and direct injury to the bronchial mucosa [3–5,23,32,41]. The main component of household bleach is

sodium hypochlorite [9]. We did not have details on how bleach was used in the home, but Sartre et al. have shown that subjects using bleach either by spraying or by pouring the bleach over the surface may be exposed to potentially irritant concentrations of chlorine [31]. Chlorine-derived products are strong oxidants and could cause disruptions of epithelial tight junctions, which could then facilitate the penetration of allergens and migration of inflammatory cells across the epithelial barrier [42,43]. In a murine model, chlorine exposure induced an oxidative injury associated with a predominantly neutrophilic airway inflammation [44]. Although the mechanisms for asthma onset following long-term occupational exposure to irritants remain unclear [4,5], one might speculate that similar mechanisms may occur in the case of frequent domestic exposure to chlorine-derived products [23]. The fraction of exhaled nitric oxide (FeNO), which is commonly considered as a noninvasive indirect marker of airway inflammation, was found to be elevated in atopic subjects when exposed to the relevant allergen [45], and was found to be associated with eosinophilic asthma and with allergy in EGEA [46]. Interestingly, cleaning products in spray form (potentially sensitizer properties due to perfumes) were associated with an increase in FeNO level, whereas no association was observed with domestic exposure to bleach [28]. Overall, these results suggest non-allergic mechanisms involving neutrophilic inflammation related to exposure to irritants.

Our findings show that domestic use of bleach for cleaning is associated with non-allergic asthma in women. In women without allergic sensitization, positive trends were observed between the frequency of bleach use and bronchial responsiveness, respiratory symptoms and chronic cough. As pointed before, cleaning-related asthma is preventable [13]. Although longitudinal studies are required to conclude on a causal relationship, these findings point toward an effect of domestic use of bleach for cleaning in the development of lower airway inflammation and occurrence of respiratory symptoms. In the general population, it has been shown that women were at increased risk of developing non-allergic asthma as compared to men [47] but the reasons for such a difference have not been identified. In the present study the proportion of men reporting frequent use of bleach for household cleaning was relatively small (2% vs. 11% in women). It has been proposed that domestic exposure to cleaning products may partly explain gender difference in asthma control [7,16]. The relatively high frequency of bleach use for home-cleaning by women all around the world, together with the strong association between bleach use and non-allergic asthma found in our study, emphasize the need for (re)-considering the use of bleach for cleaning as a potential concern for public health. From a clinical point of view, our results suggest considering exposure to bleach for cleaning in women presenting with non-allergic asthma.

Author's contributions

B Matulonga, M Rava, B Leynaert and N Le Moual were involved in the conception, hypotheses delineation, and design of the analysis strategy of the study.

V Siroux, I Pin, A Bernard, R Nadif and N Le Moual participated in the acquisition of the data.

B Matulonga, M Rava, V Siroux, A Bernard, O Dumas, I Pin, JP Zock, R Nadif, B Leynaert and N Le Moual participated in the data analysis and interpretation of the data.

B Matulonga, B Leynaert and N Le Moual wrote the manuscript.

B Matulonga, M Rava, V Siroux, A Bernard, O Dumas, I Pin, JP Zock, R Nadif, B Leynaert and N Le Moual reviewed the manuscript, revised it critically before its submission and approved the final version.

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Competing interest

The authors have no conflict of interest to declare.

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Appendix A. Supplementary data

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