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Household use of irritant and sprayed cleaning products and asthma endotypes. A Brief Report

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Author contributions

E.P.D.S and E.D. contributed to the analysis and interpretation of the data, and primary manuscript preparation. R.N., L.O. and V.S. were involved in the data interpretation and critical revision of the manuscript. R.N., J.Q., R.V. participated in the acquisition of the data and were involved in the data interpretation and critical revision of the manuscript. O.D. and N.L.M. developed the study hypotheses, participated in the acquisition of the data and contributed to data interpretation, primary manuscript preparation and critical revision of the manuscript. All authors approved the final version of the manuscript. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical Considerations & Disclosures

The study was conducted in accordance with the Declaration of Helsinki. Approvals were obtained from the relevant Ethics Committees and the Institutional Review Board Committees: INSERM, RBM ‘Recherche BioMédicale’ (n°RBM 91-005, 08/1991; and

n°RBM 01-11, 02/2002); CNIL ‘Commission Nationale de l’Informatique et des Libertés’ (n°109 427, 04/1990; and n°900 198, 10/2000); the Institutional Review Board Committees of Cochin Port-Royal Hospital and Necker-Enfants Malades Hospital, Paris, France (n°01-07-07, 09/2001; n°04-05-03, 11/2004; n°04-11-13, 11/2004; and n°04-11-18, 12/2004); and DGS ‘Direction Générale de la Santé’ (n°DGS 910 048, 07/1991; and n°DGS 2002/0106, 02/2002). Participants signed a written informed consent.

Data availability

Due to third party restrictions, EGEA data are not publicly available. Please see the following URL for more information: <https://cohorte-egea.fr/en/contact>. Interested researchers should contact egea.cohorte@inserm.fr with further questions regarding data access.

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To the Editor

Disinfectants and cleaning products are commonly used by workers, especially women, and are already known as an occupational risk factor of asthma (1,2). In the last two decades, evidence is growing on the harmful role of the weekly use of household cleaning products for respiratory health, especially irritants and those used in spray form (3–5). Their use could influence the incidence, clinical expression and control of asthma. Among the variety of ingredients contained in cleaning products, some are considered as irritants (e.g., bleach, acids) and/or sensitizers (e.g., perfumes) and may be associated with asthma through different mechanisms that remain poorly understood (6–9). Asthma is a complex, heterogeneous and variable over time disease. Two main types of asthma have been described : (i) the common “type-2-high” (T2) asthma, in which Th2 cells or innate lymphoid type 2 cells (ILC2s) are activated inducing mostly eosinophilic inflammation, partly Immunoglobulin E (IgE)-related (ii) a poorly understood “type-2-low” (non-T2) in which neutrophilic inflammation has been suggested (10). Beyond these two large groups, clustering approaches integrating a large number of clinical and biological characteristics of patients have been used to characterize various asthma endotypes (11). Considering asthma heterogeneity (10) could improve our understanding of the mechanisms involved in the effects of household cleaning products on asthma (3).

We aimed to evaluate the associations between household use of irritant and sprayed cleaning products with respiratory endotypes, based on cross-sectional data from the Epidemiological study on the Genetics and Environment of Asthma (EGEA).

The EGEA epidemiological study is a multicenter cohort initiated with 2,047 participants, aged from 7 to 70 years, followed since 1991 (12). Using data from the second survey

(EGEA2: 2003-2007, n=1,601 participants), five respiratory endotypes were previously identified by a cluster analysis considering demographic, clinical/functional and biological characteristics of participants (13). Among the five endotypes, two were identified in never-asthma participants (NA) based on the absence (NA1, reference group) or presence (NA2) of respiratory symptoms (wheezing, shortness of breath, nocturnal symptoms, chronic cough, phlegm, dyspnea). Compared to NA1, the NA2 endotype included participants with respiratory symptoms, treated by inhaled steroids, and with high blood neutrophil and eosinophil counts (possibly with undiagnosed asthma or another respiratory condition). Three endotypes were identified in participants with current asthma (CA): CA1, CA2, and CA3. In the CA1 endotype, participants had treated adult-onset asthma, poor lung function and highest blood neutrophil count and Fluorescent Oxidation Products (FLOPs) level, a biological marker of damages related to oxidative stress. In the CA2 endotype, participants had middle-age onset asthma, rhinitis and low IgE level. In the CA3 endotype, participants had inactive/mild untreated childhood-onset asthma, allergic sensitization and high IgE level. We assessed the household use of irritants (bleach, ammonia, acids and solvents) and sprays at EGEA2 by self-administered standardized questionnaire. The reference group was the same for all exposure variables and defined as a no weekly use of irritants and sprays(4). We studied the weekly use of irritants/sprays (reference, ≥ 1 day/week irritants/sprays), the frequency of use of irritants/sprays (reference, 1-3 days/week, 4-7 days/week) and the number of irritants/sprays used (reference, 1 product, ≥ 2 products).

Crude and adjusted associations for potential confounders (age, gender, smoking status (14) and occupational exposure to asthmagens (4), as previously performed) between weekly use of irritants and sprays and respiratory endotypes were estimated by polytomous logistic regressions. We conducted a sensitivity analysis by assessing associations in women only, as

a previous study showed that men do not frequently use household cleaning products at EGEA2 (15). Analyses were performed using SAS v9.4 (SAS Institute, Cary NC).

Analyses were carried on 1,039 adult participants for whom data were available on respiratory endotypes and household cleaning products at EGEA2. Participants were 44 years old on average, 54% were women and 22% were current smokers. Respiratory endotypes were described in details in Table 1, 46% were in NA1, 17% in NA2, 5% in CA1, 20% in CA2 and 12% in CA3. Only 16% (*versus* 55% of women) and 27% (*versus* 57% of women) of men reported a weekly use of irritants or sprays, respectively.

After adjusting for potential confounders, we found that an almost daily use (4-7 days/week) of irritants (10%) increased the risk of CA2. For sprays, an almost daily use (13%) was associated with an increased risk of CA2 and the use of at least two sprays (16%) with an increased risk of both CA1 and CA2 (Table 2).

When analyses were restricted to women, after adjusting for potential confounders, we observed more marked associations of an almost daily use of irritants (15%) with CA2 (OR=2.80[1.34-5.85]), as well as of an almost daily use of sprays (19%) with NA2 (OR=1.95[0.99-3.87]) and CA2 (OR=2.22[1.14-4.33]) and of the weekly use of at least two sprays (26%) with CA1 (OR=3.29[1.15-9.41]) and CA2 (OR=2.18[1.20-3.96]).

Our results showed that a high frequency and number of irritants and sprays used at home was associated with two asthma endotypes. Indeed, an almost daily use of irritants was positively associated with an endotype characterized by middle-age onset asthma, rhinitis and low IgE level (CA2) and a high frequency and number of sprays weekly used was positively

associated with CA2 and an asthma endotype characterized by treated adult-onset asthma, poor lung function, high blood neutrophil count and FLOPs level (CA1). We found more marked results in women regarding an almost daily use of irritants and a high use of sprays. We hypothesized that it is due to the fact that cleaning habits differ between men and women, e.g., men are less involved in household tasks and use less frequently cleaning products than women (15). For this reason, we could not do formal interaction tests.

Our study, the first to evaluate associations of the household use of irritant and sprayed cleaning products with asthma endotypes, strengthened results of other studies showing adverse effects of the household use of these products on asthma (3). In a previous study on EGEA data, occupational exposure to irritants was associated with CA1 (neutrophilic inflammation and oxidative stress) (14). In the current study, we did not evidence a statistically significant association of a high use of irritants at home with CA1, despite ORs > 1.70. The small number of participants in CA1, as well as differences at home and at work in exposure assessment methods and in the types and level of irritant exposure may partly explain this result. We observed a positive association of an almost daily use of irritants with CA2, consisting of participants with rhinitis and low IgE level, consistent with a role of non IgE-related mechanisms in the association between irritants and asthma. Regarding sprays, we observed that a high use was associated with CA1 and CA2. Sprayed products might contain several ingredients that can be both respiratory sensitizers and irritants (3). Based on our results, sprays are likely to affect asthma by mechanisms involving a neutrophilic inflammation and oxidative stress but not an IgE-related mechanism. No association was observed with CA3 after adjustment for potential confounders, which could be explained by the characteristics of this endotype which included 63% of men with inactive/mild untreated childhood-onset asthma and high IgE level. Overall, our results (both

for irritants and sprays) are consistent with the evidence of mostly non-IgE related mechanisms in the association between cleaning products and asthma, as suggested by epidemiological studies on occupational exposure (6).

The main strength of the current study is the use of data from the EGEA cohort in which asthma endotypes were identified using a wide range of sociodemographic, clinical/functional and biological data collected, allowing us to comprehensively account for asthma heterogeneity (13). Moreover, two endotypes were defined in never-asthma participants, whether they have or not respiratory symptoms, which enabled us to compare each endotype to a reference group less prone to misclassification errors. The main limitation of our study is the small number of participants per endotype which induced a lack of statistical power for some analyses. Finally, household exposure to cleaning products was only evaluated by questionnaire, relying on participant declaration, which could lead to potential differential and non-differential misclassification biases (3). Moreover, this evaluation method does not allow us to access any information on the composition of the products studied, especially those classified as sensitizers/irritants. Therefore, it is difficult to make specific hypotheses on the underlying mechanisms by which cleaning products might affect respiratory health without having access to these data.

In conclusion, an almost daily use of irritants was associated with one asthma endotype, whereas a high use of sprays at home was associated with the same asthma endotype and another one, providing further evidence of the harmful role of the use of these products for asthma. Our results suggest the existence of overlapping non-IgE related mechanisms in the effects of cleaning products on asthma. Therefore, further studies are needed to assess the

associations of the composition of cleaning products used at home with asthma endotypes in order to identify the compounds at risk and better understand the mechanisms involved.

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Table 1. Description of the study population according to respiratory endotypes

	Never-asthma n = 655			Current asthma n = 384	
	NA1 n = 483	NA2 n = 172	CA1 n = 51	CA2 n = 210	CA3 n = 123
Gender, n (%)					
Men	223 (46.2)	64 (37.2)	23 (45.1)	94 (44.8)	78 (63.4)
Women	260 (53.8)	108 (62.8)	28 (54.9)	116 (55.2)	45 (36.6)
Age (years), mean ± sd	46.4 ± 15.3	48.0 ± 16.3	53.5 ± 15.5	40.6 ± 15.3	31.1 ± 12.7
Smoking status, n (%)					
Never smoker	245 (50.7)	75 (44.1)	24 (47.1)	94 (44.8)	69 (56.1)
Ex-smoker	152 (31.5)	43 (25.3)	21 (41.2)	69 (32.9)	13 (10.6)
Current smoker	86 (17.8)	52 (30.6)	6 (11.7)	47 (22.3)	41 (33.3)
BMI (Body Mass Index- kg/m²), n (%)					
<25	297 (61.5)	90 (52.3)	23 (45.1)	121 (57.6)	99 (80.5)
≥25	186 (38.5)	82 (47.7)	28 (54.9)	89 (42.4)	24 (19.5)
Educational level, n (%)					
< high school diploma	245 (50.7)	99 (57.6)	38 (74.5)	93 (44.5)	57 (46.7)
≥ high school diploma	238 (49.3)	73 (42.4)	13 (25.5)	116 (55.5)	65 (53.3)
Occupational exposure, n (%)					
Not exposed	345 (71.4)	130 (75.6)	35 (68.6)	165 (79.3)	85 (69.1)
Exposed to non asthmagens	69 (14.3)	23 (13.4)	8 (15.7)	21 (10.1)	20 (16.3)
Exposed to asthmagens	69 (14.3)	19 (11.0)	8 (15.7)	22 (10.6)	18 (14.6)
Asthma symptom score, median (min-max)	0 (0-4)	1 (0-4)	3 (1-5)	2 (0-5)	1 (0-5)
Chronic cough, n (%)	1 (0.2)	32 (18.6)	20 (39.2)	24 (11.4)	4 (3.2)
Chronic phlegm, n (%)	0	28 (16.3)	16 (31.3)	21 (10.0)	5 (4.1)
FEV₁ % predicted	101 ± 14.6	98 ± 16.2	71 ± 19.8	92 ± 16.5	93 ± 14.4
Total IgE, IU/mL, GM (Q1-Q3)	37.8 (16-105)	59.7 (15-135)	149 (56-372)	138 (48-303)	193 (91-531)
Eosinophil counts, cells/mm³	155 ± 107	179 ± 139	297 ± 319	253 ± 179	249 ± 160
Neutrophil counts, cells/mm³	3911 ± 1272	4155 ± 1464	4972 ± 1640	4169 ± 1580	3531 ± 1084

FIOPs level, RFU/mL, GM (Q1-Q3)	93.3 (81.3-107.1)	97.7 (83.2-109.6)	107.1 (93.3-117.5)	91.2 (77.6-104.7)	87.1 (75.8-97.7)
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NA1: never-asthma participants without respiratory symptoms (n=483);

NA2: never-asthma participants with respiratory symptoms, treated by inhaled steroids, with high blood neutrophil and eosinophil counts (n=172);

CA1: current asthma participants with treated adult-onset asthma, poor lung function, highest blood neutrophil count and FIOPs level (n=51);

CA2: current asthma participants with middle-age onset asthma, rhinitis and low IgE level (n=210);

CA3: current asthma participants with inactive/mild untreated childhood-onset asthma, allergic sensitization and high IgE level (n=123).

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Table 2. Associations between weekly use of irritants and sprays and respiratory endotypes

	Weekly use of irritants*	Weekly use of sprays*	Weekly use of irritants					Weekly use of sprays				
			All	Frequency of use		Number of irritants used		All	Frequency of use		Number of sprays used	
			n (%)	n (%)	≥1 d/week	1-3 d/week	4-7 d/week	1/week	≥2/week	≥1 d/week	1-3 d/week	4-7 d/week
NA1 (reference) ORs	142 (37)	177 (42)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
NA2 Crude ORs [95% IC]	58 (43)	73 (49)	1.31 [0.88-1.95]	1.32 [0.85-2.04]	1.28 [0.66-2.51]	1.33 [0.87-2.04]	1.22 [0.58-2.55]	1.32 [0.91-1.92]	1.17 [0.77-1.78]	1.74 [1.01-2.99]	1.30 [0.85-1.98]	1.37 [0.80-2.36]
Adjusted ORs [95% IC]			1.13 [0.72-1.77]	1.11 [0.68-1.79]	1.20 [0.59-2.45]	1.14 [0.71-1.83]	1.07 [0.49-2.32]	1.17 [0.78-1.75]	1.06 [0.68-1.66]	1.46 [0.82-2.59]	1.22 [0.78-1.89]	1.11 [0.62-1.97]
CA1 Crude ORs [95% IC]	18 (44)	21 (48)	1.36 [0.71-2.61]	1.20 [0.58-2.51]	1.84 [0.70-4.84]	1.23 [0.60-2.53]	1.85 [0.65-5.24]	1.27 [0.68-2.37]	1.08 [0.53-2.21]	1.79 [0.76-4.24]	0.80 [0.36-1.78]	2.30 [1.08-4.90]
Adjusted ORs [95% IC]			1.22 [0.58-2.56]	1.07 [0.47-2.43]	1.70 [0.60-4.85]	1.08 [0.49-2.42]	1.81 [0.59-5.51]	1.37 [0.70-2.68]	1.19 [0.56-2.54]	1.85 [0.74-4.59]	0.88 [0.38-2.03]	2.58 [1.12-5.92]
CA2 Crude ORs [95% IC]	68 (40)	81 (44)	1.15 [0.79-1.66]	1.03 [0.68-1.56]	1.51 [0.84-2.69]	1.12 [0.75-1.68]	1.24 [0.64-2.41]	1.10 [0.77-1.56]	0.89 [0.60-1.34]	1.65 [1.00-2.72]	0.79 [0.52-1.21]	1.76 [1.10-2.79]
Adjusted ORs [95% IC]			1.26 [0.83-1.91]	1.09 [0.69-1.73]	1.89 [1.00-3.55]	1.25 [0.80-1.95]	1.31 [0.65-2.63]	1.08 [0.74-1.56]	0.86 [0.57-1.32]	1.71 [1.01-2.89]	0.80 [0.52-1.24]	1.73 [1.05-2.85]
CA3 Crude ORs [95% IC]	20 (20)	37 (32)	0.45 [0.26-0.76]	0.53 [0.30-0.93]	0.18 [0.04-0.77]	0.39 [0.21-0.72]	0.65 [0.26-1.64]	0.66 [0.43-1.02]	0.71 [0.44-1.15]	0.53 [0.24-1.16]	0.58 [0.34-0.97]	0.85 [0.45-1.58]
Adjusted ORs [95% IC]			0.66 [0.36-1.20]	0.81 [0.43-1.51]	0.25 [0.05-1.12]	0.64 [0.33-1.25]	0.73 [0.27-1.96]	0.73 [0.45-1.17]	0.76 [0.46-1.28]	0.60 [0.26-1.39]	0.59 [0.34-1.03]	1.08 [0.54-2.15]

Crude and adjusted Odds Ratios (ORs) for age, gender, smoking status and occupational exposure of associations of weekly use of irritants and sprays with respiratory endotypes, estimated by polytomous logistic regression models. Results presented in bold are statistically significant.

*Participants with a weekly use of irritants/sprays were compared to those without a weekly use of both irritants and sprays (NA1, n=247; NA2, n=77; CA1, n=23; CA2, n=103; CA3, n=78).

NA1: never-asthma participants without respiratory symptoms (n=483, reference group);

NA2: never-asthma participants with respiratory symptoms, treated by inhaled steroids, with high blood neutrophil and eosinophil counts (n=172);
CA1: current asthma participants with treated adult-onset asthma, poor lung function, highest blood neutrophil count and FOPs level (n=51);
CA2: current asthma participants with middle-age onset asthma, rhinitis and low IgE level (n=210);
CA3: current asthma participants with inactive/mild untreated childhood-onset asthma, allergic sensitization and high IgE level (n=123).

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