Original research

Association between occupational exposure to irritant agents and a distinct asthma endotype in adults

Miora Valérie Andrianjafimasy ,[1] Mickaël Febrissy,[2] Farid Zerimech,[3,4] Brigitte Dananché,[5] Hans Kromhout ,[6] Régis Matran,[3,4] Mohamed Nadif,[2] Dominique Oberson-Geneste,[7] Catherine Quinot,[1] Vivi Schlünssen,[8,9] Valérie Siroux,[10] Jan-Paul Zock,[11] Nicole Le Moual ,[1] Rachel Nadif,[1] Orianne Dumas [1]

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For numbered affiliations see end of article.

Correspondence to
Dr Orianne Dumas, Inserm, CESP, Équipe d'Épidémiologie respiratoire intégrative, 16 avenue Paul Vaillant Couturier, 94807 Villejuif, France; orianne.dumas@inserm.fr

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ABSTRACT

Aim The biological mechanisms of work-related asthma induced by irritants remain unclear. We investigated the associations between occupational exposure to irritants and respiratory endotypes previously identified among never asthmatics (NA) and current asthmatics (CA) integrating clinical characteristics and biomarkers related to oxidative stress and inflammation.

Methods We used cross-sectional data from 999 adults (mean 45 years old, 46% men) from the case-control and familial Epidemiological study on the Genetics and Environments of Asthma (EGEA) study. Five respiratory endotypes have been identified using a cluster-based approach: NA1 (n=463) asymptomatic, NA2 (n=169) with respiratory symptoms, CA1 (n=50) with active treated adult-onset asthma, poor lung function, high blood neutrophil counts and high fluorescent oxidation products level, CA2 (n=203) with mild middle-age asthma, rhinitis and low immunoglobulin E level, and CA3 (n=114) with inactive/mild untreated allergic childhood-onset asthma. Occupational exposure to irritants during the current or last held job was assessed by the updated occupational asthma-specific job-exposure matrix (levels of exposure: no/medium/high). Associations between irritants and each respiratory endotype (NA1 asymptomatic as reference) were studied using logistic regressions adjusted for age, sex and smoking status.

Results Prevalence of high occupational exposure to irritants was 7% in NA1, 6% in NA2, 16% in CA1, 7% in CA2 and 10% in CA3. High exposure to irritants was associated with CA1 (adjusted OR aOR, (95% CI) 2.7 (1.0 to 7.3)). Exposure to irritants was not significantly associated with other endotypes (aOR range: 0.8 to 1.5).

Conclusion Occupational exposure to irritants was associated with a distinct respiratory endotype suggesting oxidative stress and neutrophilic inflammation as potential associated biological mechanisms.

Key messages

What is already known about this subject?
- Epidemiological studies have suggested a role of repeated, chronic occupational exposure to low/moderate levels of irritant agents in causing asthma.
- Biological mechanisms by which exposure to irritant agents affect respiratory health remain unclear.

What are the new findings?
- High occupational exposure to irritants was associated with a respiratory endotype characterised by active treated adult-onset asthma, poor lung function, high blood neutrophil counts and high fluorescent oxidation products level, a biomarker of damages related to oxidative stress.
- No other endotype was associated with irritants.

How might this impact on policy or clinical practice in the foreseeable future?
- Results provide additional knowledge on the biological mechanisms of irritant-induced asthma, suggesting oxidative stress and neutrophilic inflammation as potential mechanisms.
- If replicated, these findings may help improving the recognition and management of irritant-induced work-related asthma.

INTRODUCTION

Asthma is a heterogeneous chronic inflammatory disease encompassing several phenotypes that may have various risk factors including occupational exposures.[1 2] More than 500 workplace sensitising or irritant agents have been identified as possible risk factors for asthma.[2 3] Work-related asthma is thus considered as a good model to study asthma in general.[4] Irritant-induced asthma remains poorly understood. Occupational asthma induced by irritants was first described as sudden onset of asthma after a single high peak of exposure to irritants.[5] In the last decade, several epidemiological studies have suggested a role of repeated, chronic exposure to low/moderate levels of irritant agents in causing asthma.[2 5 6] However, the biological mechanisms by which exposure to irritant agents affect respiratory health remain unclear.[3 5–7]

One of the biological mechanisms that could underlie irritant-induced asthma is oxidative stress that reflects the imbalance between reactive oxygen species (ROS) and antioxidant defenses in favour of the former.[2 8 9] Neutrophilic inflammation[2 3] has also been suggested. However, few studies have examined the role of these pathways in irritant-induced asthma, especially in human.[7 10]

Asthma heterogeneity has classically been approached by investigating different phenotypes, defined as a set of observable clinical characteristics.[11] Endotypes, that is, disease subtypes characterised by a distinct functional or pathobiological mechanism[12] would allow to better understand the biological mechanisms associated with irritant-induced asthma.[11] In the Epidemiological study on the Genetics and Environments of Asthma (EGEA), we recently identified five respiratory endotypes using cluster analysis jointly integrating asthma clinical characteristics and biomarkers related to oxidative stress and inflammation.[13] In particular, we identified among asthmatics an endotype characterised by poor lung function, respiratory symptoms, high level of fluorescent oxidation products (FlOPs, a biomarker of damages related to oxidative stress) and high blood neutrophil counts. We hypothesised occupational exposure to irritants may be associated to this specific endotype.

The updated occupational asthma-specific job exposure matrix (OAsJEM),[14] of the former asthma-specific job exposure matrix,[15] has recently been published with improved assessment of occupational exposure, specifically for irritant agents. Taking advantage of these novel exposure data and the identification of respiratory endotypes in EGEA, we investigated the associations between occupational exposure to irritants and respiratory endotypes.

METHODS

The EGEA study

EGEA is a French cohort started in 1990s with two follow-ups over 20 years. The first EGEA survey (EGEA1) included cases with asthma recruited in five chest clinics, their first-degree relatives and population-based controls (n=2047). A first follow-up of the participants was completed in 2003–2007 (EGEA2), including 1602 subjects with complete examination, almost exclusively adults (98%). At each survey, participants answered a standardised questionnaire on asthma, occupational history and environmental exposures. The protocol and participants' characteristics have been described previously,[16] and details are provided in online supplemental file 1. The EGEA collection was certified ISO 9001 (2006–2018) and is referenced in the Biobank network.[17] Ethical approval was obtained from the relevant institutional review board committees (Cochin Port-Royal Hospital and Necker-Enfants Malades Hospital, Paris). Participants signed a written informed consent.

At EGEA2, participants with 'ever asthma' were those recruited as cases at EGEA1, or family members or controls who answered positively to one of two standardised questions. Among participants with ever asthma, current asthma was defined by respiratory symptoms, asthma attacks or treatment in the past 12 months (see online supplemental file 1).

Selection of the study population

The present cross-sectional study was based on data collected at the first follow-up (EGEA2). Participants less than 16 years old (n=31), those with ever asthma but without current asthma (n=125), or with missing data for any of the clinical and biological characteristics used to define endotypes (n=378) were excluded from the analyses. We also excluded participants who had never worked (n=60) or with missing data for occupational history (n=4). Finally, because our analysis focused on exposure to irritants, we excluded participants exposed only to occupational sensitizers in the current or last held job (n=5, all only exposed to high molecular weight agents). In total, 999 participants were selected (online supplemental figure E1).

Occupational exposure to irritant agents

Complete occupational history was collected at EGEA2 with information on job, industry and tasks. Jobs were coded according to the International Standard Classification of Occupation 1988 by an experienced coder. Occupational exposures to 30 agents at risk for asthma classified in seven groups were estimated using the OAsJEM (http://oasjem.vjf.inserm.fr/index-en.htm).[14] To improve the exposure estimate, the OAsJEM assessment was completed by an expert reassessment step for selected job codes defined a priori and regrouping jobs with heterogeneous tasks and/or industries. If the job description provided sufficient information, two experts (BD, DOG) reevaluated exposure levels case by case, independently of each other and blinded of asthma status. In case of disagreement between the experts, the final decision was taken by consensus (BD, DO-G, CQ, NLM).

In the present study, we considered exposures to 19 agents known or suspected to cause asthma through irritant mechanisms, including chronic low-to-moderate level of exposures. Within this large group of irritant agents, two partly overlapping subgroups were further identified: highly reactive chemicals (eight agents) and biocides (five agents). In addition, we grouped three specific agents in a subgroup 'cleaning products / disinfectants' (online supplemental table E1). Among the 19 irritant agents, nine agents were also classified as low molecular weight (LMW) sensitizers, because for these nine agents both mechanisms have been suggested[14] (online supplemental table E1).

The OAsJEM classified exposures to each irritant agent into three classes: 'high' for high probability of exposure and moderate-to-high intensity, 'medium' for low-to-moderate probability or low intensity of exposure, and 'no' for unlikely to be exposed. When analysing groups of agents, the maximum exposure level among all agents in the group was considered. In all analyses, the reference group included participants classified as 'non-exposed' to all of the 30 agents of the OAsJEM.

Definition of respiratory endotypes

Five respiratory endotypes were previously identified by cluster analysis[13] and are described in table 1: 2 among never asthmatics (NA) and 3 among current asthmatics (CA), after taking into account a total of 23 variables for NA and 28 variables for CA. Cluster analysis jointly considered personal (age, sex, smoking status and body mass index (BMI)), clinical/functional (age of asthma onset, respiratory symptoms, asthma treatments, dyspnoea, skin prick tests positivity for at least one of 12 aeroallergens, current rhinitis, ever eczema, asthma attacks, hospital or emergency admission, forced expiratory volume in 1 s and forced vital capacity), and biological (neutrophil and eosinophil counts, total immunoglobulin E (IgE) and level of FlOPs) characteristics. More details on variables and cluster analysis used to define respiratory endotypes are provided in online supplemental file 1. A detailed description of all characteristics included in the cluster analysis is shown in online supplemental table E2.

Table 1 Description of the five respiratory endotypes

Name	Description	n (%)
Among non-asthmatics		
NA1	Asymptomatic: absence of symptoms	463 (46.3)
NA2	Respiratory symptoms and dyspnoea, use of inhaled corticosteroids, high neutrophil and eosinophil counts	169 (16.9)
Among current asthmatics		
CA1	Active treated (active asthma and use of asthma treatments), adult-onset asthma, poor lung function, respiratory symptoms, highest FlOPs level and neutrophil count	50 (5.0)
CA2	Rhinitis and low IgE level	203 (20.3)
CA3	Childhood-onset asthma, allergic sensitisation and highest IgE level	114 (11.4)

FlOPs: fluorescents oxidation products, a biomarker of damages related to oxidative stress.
.CA, current asthmatics; IgE, immunoglobulin E; NA, never asthmatics.

Statistical analyses

χ^2 tests and Fisher exact tests were used to study the association between occupational exposure to irritant agents and each endotype in univariate models. Logistic regression models using generalised estimated equation were performed to take into account familial dependence, and adjusted for age (continuous), sex and smoking status (non-smokers, ex and current smokers). In the main analyses, irritant agents were estimated by OAsJEM completed by the expert reassessment step. As clinical characteristics integrated in the definition of endotypes have been defined in the last 12 months and three endotypes have been defined among CA, exposures of interest were evaluated for the current or last held jobs. In a secondary analysis, we investigated the association between lifetime occupational exposure (instead of current exposure) to irritants and respiratory endotypes. In all models, the endotype of asymptomatic NA1 was used as reference group for the outcome and 'no exposure' to any OAsJEM agent was used as reference group for occupational exposure.

Three sensitivity analyses were carried out. First, we studied association between irritant agents estimated by OAsJEM only that is, without the expert reassessment step. Second, due to the partial overlap between the subgroups of irritants and LMW agents, we studied the associations between occupational exposures to LMW agents and endotypes. Third, the main analysis does not adjust for BMI as obesity has been described as an asthma comorbidity and asthma in obese patients may correspond to a specific asthma endotype.[18] However, as high BMI has also been described as a risk factor for asthma,[18] BMI was added to the other confounders in a sensitivity analysis.

Statistical analyses were performed using SAS statistical software (V.9.4; SAS Institut). A p value of <0.05 was considered statistically significant.

RESULTS

Characteristics of the study population

Table 2 shows the personal and clinical characteristics of the 999 participants and according to respiratory endotypes. The mean age of all participants was 45 years, 54% were women, 22% were current smokers and 11% were obese. Among endotypes in NA, participants in NA1 (n=463) had an average age of 47

Table 2 Description of personal, clinical and biological characteristics of the study population at Epidemiological study on the Genetics and Environments of Asthma (EGEA2) (N=999) according to respiratory endotypes

		Never asthmatics (n=632)		Current asthmatics (n=367)		
	All participants N=999	NA1 n=463	NA2 n=169	CA1 n=50	CA2 n=203	CA3 n=114
Age, years	44.8±15.8	47.0±14.8	48.5±16.0	53.2±15.5	41.9±15.1	32.4±13.2
Sex, women	542 (54.3)	255 (55.1)	105 (62.1)	26 (52.0)	113 (55.7)	43 (37.7)
Smoking status						
Non-smokers	487 (48.8)	235 (50.8)	76 (45.0)	24 (48.0)	88 (43.4)	64 (56.1)
Ex-smokers	290 (29.0)	148 (32.0)	42 (24.8)	20 (40.0)	68 (33.5)	12 (10.5)
Current smokers	222 (22.2)	80 (17.3)	51 (30.2)	6 (12.0)	47 (23.1)	38 (33.3)
Body mass index, kg/m^2†						
<20	95 (9.5)	43 (9.3)	9 (5.3)	1 (2.00)	25 (12.3)	17 (14.9)
20–25	501 (50.2)	243 (52.5)	77 (45.6)	21 (42.0)	89 (43.8)	71 (62.3)
25–30	295 (29.5)	135 (29.2)	59 (34.9)	15 (30.0)	67 (33.0)	19 (16.7)
≥30	108 (10.8)	42 (9.1)	24 (14.2)	13 (26.0)	22 (10.8)	7 (6.1)
Age of asthma onset†						
≥16 years	133 (36.2)	–	–	31 (62.0)	77 (37.9)	25 (21.9)
Asthma symptom score*, median (min–max)	1 (0–5)	0 (0–4)	1 (0–4)	4 (1–5)	2 (0–5)	1 (0–5)
Chronic cough	81 (8.1)	1 (0.2)	31 (18.3)	21 (42.0)	24 (11.8)	4 (3.5)
Chronic phlegm	70 (7.0)	0	27 (16.0)	16 (32.0)	22 (10.8)	5 (4.4)
FEV_1 % predicted	102±18.5	108±16.1	104±17.7	76.2±21.7	97.2±17.3	97.0±15.6
Total IgE, IU/mL, GM (Q1–Q3)	67.5 (23.2–195)	40.3 (15.8–101)	50.6 (16.1–135)	144 (65.4–372)	125 (46–279)	203 (95.2–536)
Eosinophil counts, cells/mm^3	198±163	155±108	177±138	301±320	255±181	253±187
Neutrophil counts, cells/mm^3	4012±1410	3915±1278	4177±1487	4986±1651	4130±1584	3522±1074
FlOPs level, RFU/mL, GM (Q1–Q3)	94.2 (80.7–107)	94.5 (81.8–109)	97.3 (82.6–111)	106 (92.1–118)	91.7 (79.3–105)	88.9 (77.6–99.2)

Data are presented as n (%) or mean±SD unless otherwise stated. Q1: 1st quartile; Q3: 3rd quartile.
A biomarker of damages related to oxidative stress.
*Five-level of asthma symptom score based on the number of respiratory symptoms during the past 12 months,[40] not included in the cluster analysis.
†Included as continuous variables in the cluster analysis.
CA, current asthmatics; FEV1, forced expiratory volume in one second; FlOPs, fluorescent oxidation products; GM, geometric mean; IgE, immunoglobulin E; NA, never asthmatics.

Table 3 Associations between current occupational exposure to any irritant agents and respiratory endotypes (N=999)

	Occupational exposure to any irritant agents				
	No exposure	Medium	P§	High	P§
NA2 versus NA1					
n*	455 (122 vs 333)	132 (36 vs 96)		44 (11 vs 33)	
$_{crude}$OR (95% CI)	1	1.03 (0.66 to 1.60)	0.92	0.91 (0.46 to 1.81)	0.80
†$_{adjusted}$OR (95% CI)	1	0.98 (0.61 to 1.56)	0.93	0.93 (0.46 to 1.89)	0.85
CA1 versus NA1					
n*	367 (34 vs 333)	104 (8 vs 96)		41 (8 vs 33)	
$_{crude}$OR (95% CI)	1	0.78 (0.35 to 1.72)	0.62	**2.53 (1.02 to 6.27)**	**0.05**
†$_{adjusted}$OR (95% CI)	1	0.77 (0.34 to 1.74)	0.52	**2.70 (1.00 to 7.33)**	**0.05**
CA2 versus NA1					
n*	483 (150 vs 333)	134 (38 vs 96)		48 (15 vs 33)	
$_{crude}$OR (95% CI)	1	0.85 (0.56 to 1.30)	0.55	1.02 (0.51 to 1.98)	0.98
†$_{adjusted}$OR (95% CI)	1	0.87 (0.56 to 1.34)	0.52	1.04 (0.52 to 2.10)	0.91
CA3 versus NA1					
n*	408 (75 vs 333)	124 (28 vs 96)		44 (11 vs 33)	
$_{crude}$OR (95% CI)	1	1.28 (0.78 to 2.12)	0.30	1.49 (0.72 to 3.07)	0.29
†$_{adjusted}$OR (95% CI)	1	1.19 (0.69 to 2.07)	0.53	1.28 (0.56 to 2.90)	0.56

Significant results in bold.
OR for the association between occupational exposure and each endotype (never asthmatics (NA2), current asthmatics (CA1), CA2 or CA3 vs NA1).
*n total (n in NA2, CA1, CA2 or CA3 vs n in NA1).
†Adjusted for age, sex and smoking status; §for the univariate model ($_{crude}$OR), p values correspond to p values of χ^2 test or Fisher exact test.

years, 55% were women. In NA2 (n=169), 65% were women, 30% were current smokers and 35% were overweight. Among endotypes in CA, participants in CA1 (n=50) had an average age of 53 years, 12% were current smokers, 30% were overweight and 26% were obese. In CA2 (n=203), 33% were ex-smokers, and 33% were overweight. Participants in CA3 (n=114) were younger with an average age of 32 years, 62% were men and 33% were current smokers.

Occupational exposure to irritant agents in each respiratory endotype is described in online supplemental table E3. Among all participants, 72% had no exposure to irritants, 21% had medium exposure and 8% had high exposure. Regarding subgroups of irritants 4% of all participants had high exposure to highly reactive chemicals or biocides and 3% had high exposure to cleaning and disinfecting products. CA1 had the highest percentage of participants with high exposure to any irritant agents as well as each subgroup of irritants. The job titles of the eight participants in the CA1 endotype with high occupational exposure to irritants are described in online supplemental table E4. After the expert reassessment step, the number of participants classified with high or medium exposure slightly decreased while the number of participants classified as unexposed slightly increased (online supplemental table E5).

Associations between occupational exposure to any irritant agents and respiratory endotypes

We observed a positive and significant association between high exposure to irritant agents and CA1 (vs NA1, adjusted OR (aOR) (95% CI) =2.70 (1.00 to 7.33), table 3). No significant association was observed between medium exposure to irritants and CA1. We did not observe any significant association between any irritant agents and the other endotypes. Similar results were observed with exposure to irritants estimated without the expert reassessment step aOR (95% CI) =2.79 (1.19 to 6.56) for CA1 versus NA1, (online supplemental table E6).

When we further adjusted for BMI, results remained similar with ORs>2.5 for the association between irritants and CA1 (online supplemental table E7). We did not observe a significant association between lifetime occupational exposure to irritants and CA1 nor the other endotypes (table 4).

Associations between occupational exposure to subgroups of irritants and CA1 endotype

Despite the small sample size, we observed an association between high exposure to biocides and CA1 aOR (95% CI)=3.13 (1.00 to 9.83), (online supplemental table E8). Despite ORs higher

Table 4 Associations between lifetime occupational exposure to any irritant agents and respiratory endotypes respiratory endotypes

	Lifetime occupational exposure to any irritant agents		
	No exposure	Medium exposure	High exposure
NA2 versus NA1			
n†	303 (83 vs 220)	177 (50 vs 127)	151 (36 vs 115)
$_{crude}$OR (95% CI)	1	1.04 (0.70 to 1.56)	0.83 (0.53 to 1.30)
$_{adjusted}$OR (95% CI)*	1	1.09 (0.71 to 1.67)	0.84 (0.52 to 1.35)
CA1 versus NA1			
n†	240 (20 vs 220)	141 (14 vs 127)	131 (16 vs 115)
$_{crude}$OR (95% CI)	1	1.23 (0.61 to 2.46)	1.54 (0.76 to 3.12)
$_{adjusted}$OR (95% CI)*	1	1.28 (0.65 to 2.53)	1.37 (0.60 to 3.14)
CA2 versus NA1			
n†	324 (104 vs 220)	186 (59 vs 127)	155 (40 vs 115)
$_{crude}$OR (95% CI)	1	0.97 (0.67 to 1.41)	0.73 (0.48 to 1.12)
$_{adjusted}$OR (95% CI)*	1	0.92 (0.62 to 1.35)	0.77 (0.49 to 1.21)
CA3 versus NA1			
n†	276 (56 vs 220)	166 (39 vs 127)	134 (19 vs 115)
$_{crude}$OR (95% CI)	1	1.19 (0.76 to 1.86)	0.62 (0.36 to 1.09)
$_{adjusted}$OR (95% CI)*	1	1.04 (0.62 to 1.72)	0.69 (0.36 to 1.33)

OR: OR for the association between occupational exposure and each endotype (never asthmatics (NA2), current asthmatics CA1), CA2 or CA3 vs NA1).
*Adjusted for age, sex and smoking status.
†n total (n in NA2, CA1, CA2 or CA3 vs n in NA1).

than 2, there was no significant association between occupational exposure to highly reactive chemicals and cleaning products/disinfectants and CA1. Similar results were observed for subgroups of irritants estimated without the expert reassessment step. No significant association was observed between occupational exposure to LMW agents and CA1 (data not shown).

DISCUSSION

The present study investigated the associations between occupational exposure to irritant agents and respiratory endotypes identified by a cluster analysis among NA and among CA separately. We observed a significant association between current high exposure to irritant agents and an endotype predominantly characterised by adult-onset asthma, poor lung function, respiratory symptoms, high blood FlOP level and high neutrophil counts.

In our study, most of the asthmatics were recruited in chest clinics as asthma cases, with careful procedures set up to include true asthmatics, and others were mostly recruited as first-degree relatives of asthmatic cases, leading to the recruitment of participants with a wide range of asthma severity and control. The availability of key biomarkers related both to asthma and to inflammatory or oxidative stress pathways allowed identifying specific respiratory endotypes.[13] The characteristics included in the cluster analysis reflect as comprehensively as possible the participants' demographic, clinical and biological characteristics. We excluded variables missing for many participants such as the measurement of the exhaled fraction of nitric oxide (FeNO) which could have been useful to define the clusters. The EGEA study provides a relatively large sample of individuals with detailed characteristics on endotype (n=999). However, analyses by endotype resulted in smaller groups of individuals, in particular for the main endotype of interest (CA1, n=50), which is a limitation. Thus, although our findings are consistent with our a priori hypothesis of an association between occupational exposure to irritants and endotype CA1, they should be interpreted with caution and need to be confirmed in other studies. We used the recently updated OAsJEM[14] to improve exposure assessment. Indeed, the number of estimated agents has increased, ranging from 22 agents estimated by the previous asthma-specific JEM[15] to 30 agents at risk for asthma by the new OAsJEM. These 30 agents have been classified in large groups distinguishing sensitizers from irritants which is of interest for studying their associations with distinct respiratory endotypes. We investigated the association between several subgroups of irritants (biocides, highly reactive chemicals and cleaning products/disinfectants) and the endotype CA1. Despite the significant association for high exposure to any irritants, we did not observe significant association with specific subgroups. The analyses of subgroups of irritants were limited by the small sample size and should therefore be interpreted with caution. Nonetheless, they were consistent with those for the large group of irritants with ORs of the same order of magnitude (all >2.0). These subgroups of irritants were associated with asthma in previous studies. Indeed, associations between occupational exposure to pesticides,[19 20] classified in the biocides group in our study, and to cleaning products/disinfectants[10 21 22] and asthma have been reported. Beside irritant mechanisms, other biological mechanisms could be involved: cleaning products/disinfectants are mixtures of substances that can be irritants or sensitizers[23] and pesticides have been associated with allergic asthma in some studies.[19] Studies with a larger sample size would be needed to precise the relationships for these subgroups and specific agents.

The association between current occupational exposure to irritants and CA1, and not with lifetime exposure might be related to the endotype definition. Indeed, since respiratory endotypes included clinical characteristics assessed over the last 12 months, reflecting the current activity of the disease, stronger associations were expected with current exposure rather than with past exposure. However, larger studies would be needed to study more accurately the temporal relationship between occupational exposures and endotypes. In addition, although CA1 included mostly participants with adult-onset asthma, we could not differentiate occupational asthma and work-exacerbated asthma, and the observed association may reflect both types of work-related asthma. We did not observe an association between occupational exposure to LMW agents and CA1 nor the other endotypes. These results are consistent with the hypothesis of different biological mechanism for LMW agents, possibly involving a specific immune response, with or without specific IgE production.[24 25]

The OAsJEM evaluated chronic exposure to low/moderate levels of irritants, considered as non-accidental, and not peaks of exposure to irritants. The exposures estimated by the OAsJEM were completed by an expert reassessment step. Both the OAsJEM and the reassessment step have been developed by favouring specificity for high level of exposure rather than sensitivity.[14 26 27] This trade-off between sensitivity and specificity generally increases the positive predictive ability of a JEM.[26] However, it also reduces the number of subjects classified as exposed, thus possibly decreasing statistical power to detect associations. Nonetheless, our results were almost similar whatever the exposure estimation. Although the possibility of unmeasured confounding can never be ruled out, our analyses were adjusted for the confounders (age, sex, smoking status) usually used in the literature to study the relationships between occupational exposure and asthma, and further adjustment for BMI in a sensitivity analysis led to similar results. Analyses were not adjusted for education level or socioeconomic status as adding these variables may result in overadjustment in models investigating health effects of occupational exposures, and lead to biased results.[28] Finally, previous analyses in this cohort have suggested a healthy worker effect,[29] which may have led to underestimated or null associations. However, it is notable that we observed a positive association between current exposure and endotype CA1 despite this potential bias.

To our knowledge, this study is the first to investigate the association between occupational exposure to irritants and respiratory endotypes identified by cluster analysis integrating personal, clinical, functional and biological characteristics. Among 2030 healthcare workers, Su *et al* identified five asthma clusters using hierarchical clustering and differentially associated with five clusters of irritant exposures.[30] However, the asthma clusters were identified without integrating biological markers and exposure was restricted to cleaning products, making direct comparison with our results difficult. Other studies conducted in clinical settings performed cluster analysis of occupational asthma integrating biological markers (FeNO,[31] blood level of neutrophils and eosinophils[32]), and studied occupational exposures to specific agents (diisocyanates) or groups of High Molecular Weight or LMW agents,[31 32] but did not include patients with irritant-induced asthma.

Statistical clustering approaches are useful to identify disease endotypes based on a large number of clinical and biological characteristics in the context of highly heterogeneous diseases such as asthma. However, addressing the stability of the resulting clusters and their clinical interpretation is always challenging.

Thus, comparison with studies using a priori definitions of asthma phenotypes/endotypes is important. Our results are consistent with previous studies which examined individually some of the asthma characteristics included in the definition of endotypes in relation to occupational exposure to irritants. The endotype CA1 was predominantly characterised by adult-onset asthma, poor lung function and respiratory symptoms. Previous studies have shown associations between cleaning products with respiratory symptoms and lower lung function among asthmatics[22] or lung function decline independently of asthma.[21 33] Exposure to vapours, dust, gas and fumes, agents generally considered as irritants, has been associated with poor lung function or lung function decline in many studies.[33 34]

CA1 was also characterised by a high level of FlOPs, a biomarker of damages related to oxidative stress. In the EGEA study,[9] we previously reported that among men without asthma, occupational exposure to irritants and chemicals was associated with higher level of plasma FlOPs. A few other studies investigated the association between biomarkers related to oxidative stress and occupational asthma induced by irritants. Corradi *et al*[7] showed that exhaled breath condensate (EBC) H_2O_2 level, was significantly higher in hospital cleaners as compared with controls. Casimirri *et al*[35] showed that EBC malondialdehyde level was higher among cleaners compared with non-exposed controls. In contrast, Vizcaya *et al*[10] did not observe an association between occupational exposure to cleaning products and 8-isoprostanes, another biomarker of lipid peroxidation. Although these studies differ in terms of biological compartment and type of biological marker (ROS, lipid peroxidation), overall results including ours support the role of oxidative stress as one potential mechanism by which occupational exposure to irritants may affect asthma.

Participants in CA1 were also characterised by a high level of neutrophil counts. To our knowledge, few studies investigated the role of non-eosinophilic inflammation in irritant-induced asthma.[36 37] In the Lifelines cohort, occupational exposures to chemicals and pesticides were associated with a lower count of neutrophils at baseline, but no association was found in the longitudinal analysis.[38] In contrast, in EGEA, Matulonga *et al*[36] reported an association between frequent use of bleach for home cleaning and high neutrophil counts in women with current asthma. In a murine model of irritant-induced asthma, McGovern *et al*[37] showed that neutrophils were significantly increased after exposure of mice to chlorine gas, a well-known irritant agent. Our results were consistent with the latter findings, suggesting a role of neutrophilic inflammation, in addition to oxidative stress, as potential mechanisms by which occupational exposure to irritants may affect asthma. This hypothesis appears especially relevant since these two mechanisms are closely related.[7] In addition, the absence of association between irritants and the endotype characterised by allergic sensitisation and high IgE level (CA3) observed in our study is consistent with the hypothesis of a non-allergic/non-immunologic mechanism of irritant-induced asthma.[2]

CONCLUSION

Overall, our study shows that occupational exposure to irritants, including chronic low-to-moderate level of exposure, is related to an asthma endotype characterised by poor lung function, respiratory symptoms, high level of FlOPs and neutrophil counts. Our results provide additional knowledge on the biological mechanisms of irritant-induced asthma, suggesting oxidative stress and neutrophilic inflammation as potential mechanisms. They support the usefulness of distinct asthma endotypes when studying risk factors for asthma. If replicated, our findings may help improving the recognition and management of irritant-induced work-related asthma. Other studies, in an epidemiological or clinical setting, and possibly including additional relevant pathways for irritant-induced asthma, such as neurogenic inflammation involving transient receptor potential channels[39] would be useful to further characterise asthma endotypes related to irritant exposures.

Author affiliations
[1]Université Paris-Saclay, UVSQ, Univ. Paris-Sud, Inserm, Équipe d'Épidémiologie respiratoire intégrative, CESP, 94807, Villejuif, Île-de-France, France
[2]LIPADE, Université Paris 5 Descartes, Paris, Île-de-France, France
[3]Univ. Lille, ULR 4483 - IMPECS, CHU Lille, F-59000 Lille, Lille, France
[4]Institut Pasteur de Lille, F-59000, Lille, France
[5]Industrial hygiene consulting, Courlaoux, France
[6]Utrecht University, Division of Environmental Epidemiology, Institute for Risk Assessment Sciences, Utrecht, Netherlands
[7]Toxibio-consultant, Lescar, France
[8]Aarhus University, Department of Public Health, Environment, Occupation and Health, Danish Ramazzini Centre, Aarhus, Denmark
[9]National Research Centre for the Working Environment, Kobenhavn, Denmark
[10]Universite Grenoble Alpes, Inserm, CNRS, Team of environmental epidemiology applied to Reproduction and Respiratory health, IAB, Grenoble, France
[11]Institute for Global Health (ISGlobal) and Universitat Pompeu Fabra (UPF), Barcelona, Spain

Acknowledgements EGEA cooperative group. Coordination: VS (epidemiology, PI since 2013); FD (genetics); IP (clinical aspects); RN (biology); F Kauffmann (PI 1992-2012). Respiratory epidemiology: Inserm ex-U 700, Paris: M Korobaeff (Egea1), F Neukirch (Egea1); Inserm ex-U 707, Paris: I Annesi-Maesano (Egea1-2); Inserm U 1018, Villejuif: O Dumas, F Kauffmann, N Le Moual, R Nadif, MP Oryszczyn (Egea1-2), R Varraso; Inserm U 1209 Grenoble: J Lepeule, V Siroux. Genetics: Inserm ex-U 393, Paris: J Feingold; Inserm UMR 1124, Paris: E Bouzigon, MH Dizier, F Demenais; CNG, Evry: I Gut (now CNAG, Barcelona, Spain), M Lathrop (now Univ McGill, Montreal, Canada). Clinical centers: Grenoble: I Pin, C Pison; Lyon: D Ecochard (Egea1), F Gormand, Y Pacheco;Marseille: D Charpin (Egea1), D Vervloet (Egea1-2); Montpellier: J Bousquet; Paris Cochin: A Lockhart (Egea1), R Matran (now in Lille); Paris Necker: E Paty (Egea1-2), P Scheinmann (Egea1-2); Paris-Trousseau: A Grimfeld (Egea1-2), J Just. Data management and quality: Inserm ex-U155, Paris: J Hochez (Egea1); Inserm U 1018, Villejuif: N Le Moual, L Orsi; Inserm ex-U780, Villejuif: C Ravault (Egea1-2); Inserm ex-U794, Evry: N Chateigner (Egea1-2); Inserm UMR 1124, Paris: H Mohamdi; Inserm U1209, Grenoble: A Boudier, J Quentin (Egea1-2). The authors thank all those who participated to the setting of the study and on the various aspects of the examinations involved: interviewers, technicians for lung function testing and skin prick tests, blood sampling, IgE determinations, coders, those involved in quality control, data and sample management and all those who supervised the study in all centers. The authors are grateful to the three CIC-Inserm of Necker, Grenoble and Marseille who supported the study and in which participants were examined. They are also grateful to the biobanks in Lille (CIC Inserm), and at Annemasse (Etablissement français du sang) where biological samples are stored. They are indebted to all the individuals who participated, without whom the study would not have been possible. We thank Theodore Lytras, Eva Andersson, Linnéa Lillienberg and Geza Benke for their contribution to the update of the asthma-specific job-exposure matrix (OAsJEM).

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ORCID iDs
Miora Valérie Andrianjafimasy http://orcid.org/0000-0002-5791-0772
Hans Kromhout http://orcid.org/0000-0002-4233-1890
Nicole Le Moual http://orcid.org/0000-0002-2723-5569
Orianne Dumas http://orcid.org/0000-0001-8423-2826

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