Original research

Chronic occupational exposures to irritants and asthma in the CONSTANCES cohort

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ABSTRACT

Objectives The impact of chronic occupational exposures to irritants on asthma remains discussed. We studied the associations between occupational exposures and asthma, with specific interest for chronic exposure to irritants, including disinfectants and cleaning products (DCPs) and solvents.

Methods Cross-sectional analyses included 115 540 adults (55% women, mean age 43 years, 10% current asthma) working at inclusion in the French population-based CONSTANCES cohort (2012–2020). Current asthma was defined by ever asthma with symptoms, medication or asthma attacks (past 12 months), and the asthma symptom score by the sum of 5 respiratory symptoms (past 12 months). Both lifetime and current occupational exposures were assessed by the Occupational Asthma-specific Job-Exposure Matrix. Associations were evaluated by gender using logistic and binomial negative regressions adjusted for age, smoking status and body mass index.

Results In women, associations were observed between current asthma and lifetime exposure to irritants (OR 1.05, 95% CI 1.00 to 1.11), DCPs (1.06, 95% CI 1.00 to 1.12) and solvents (1.06, 95% CI 0.98 to 1.14). In men, only lifetime exposure to DCPs (1.10, 95% CI 1.01 to 1.20) was associated with current asthma. Lifetime exposure to irritants was associated with higher asthma symptom score both in women (mean score ratio: 1.08, 95% CI 1.05 to 1.11) and men (1.11, 95% CI 1.07 to 1.15), especially for DCPs (women: 1.09, 95% CI 1.06 to 1.13, men: 1.21, 95% CI 1.15 to 1.27) and solvents (women 1.14, 95% CI 1.10 to 1.19, men: 1.10, 95% CI 1.05 to 1.15). For current exposures, no consistent associations were observed with current asthma and asthma symptom score.

Conclusions Lifetime occupational exposures to irritants were associated with current asthma and higher asthma symptom score. These exposures should be carefully considered in asthma management.

INTRODUCTION

Workplace exposures are an important contributor to the burden of adult asthma.[1 2] About 15% of adult asthma cases are caused by occupational exposures,[3] and 20% of adults with asthma have exacerbations at work.[3 4] Occupational asthma can be caused by sensitisers (eg, flours, latex, diisocyanates) and irritants.[1] Sensitiser-induced asthma,

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WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Chronic occupational exposure to irritants is common, but its impact on asthma remains discussed and few epidemiological studies considered this specific issue.

WHAT THIS STUDY ADDS

⇒ This study in 115 540 French adults brings new knowledge supporting a deleterious impact of chronic occupational exposures to irritants on current asthma and asthma symptoms.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Reduction of occupational exposure to irritants, including disinfectants/cleaning products and solvents, should be included in asthma prevention strategies and considered by clinicians in asthma management.

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which involves an immunological mechanism, is a well-known type of occupational asthma[5] and has largely been described in case series or surveillance programmes.[6] A second type of occupational asthma corresponds to asthma caused by non-immunological irritant mechanisms, which have not been precisely identified yet. Irritant-induced asthma can appear after a single acute exposure to very high levels of irritants (reactive airway dysfunction syndrome or Brooks' syndrome) but may also occur following a delayed onset after chronic exposures to irritants, even in the absence of high peak exposures.[7] The role of chronic exposures, whether in the past or currently, to irritants has been less documented[7] and is probably underestimated and involved in a substantial number of occupational asthma cases.[8] Because causality for chronic exposure irritant-induced asthma cannot be established with certainty at individual level (given the lack of appropriate clinical tests), epidemiological studies are particularly important to evaluate causality at population level.[7]

Only a limited number of studies have considered the impact on asthma of chronic occupational exposures to irritants as a broad category,[9] and they showed heterogeneous results. Among studies using the asthma-specific job exposure

matrix (AsJEM),[9] one study observed a positive association for physician-diagnosed asthma,[10] whereas three studies did not show any associations.[11–13] However, these studies[11–13] used a former version of the matrix,[9] which poorly evaluated chronic exposures to irritants. The AsJEM has been updated in 2018 and renamed as Occupational Asthma-specific JEM (OAsJEM) with a focus on improving assessment of irritant exposures.[14] Since then, the OAsJEM has been used in several epidemiological studies (https://oasjem.vjf.inserm.fr/paper-list/). Two of them studied associations of chronic occupational exposures to irritants with asthma,[15 16] and both found positive associations.

Irritant agents are frequent at work and include a wide variety of agents. Studies investigating specific agents have mostly focused on disinfectants and cleaning products (DCPs), which contain irritant substances, and are now recognised as a cause of asthma.[17–19] Among irritants, solvents are also commonly used in workplaces, but associations with asthma have been less documented.[15 20–22] In France, about 17% of workers are exposed to organic solvents,[23 24] which have been identified as causal agents of work-related asthma in the latest report from the National Network for Occupational Disease Vigilance and Prevention. Further epidemiological studies are still needed to evaluate the impact of chronic exposures to irritants, especially solvents, in asthma.

Therefore, we aimed to examine the association between chronic occupational exposures to irritants, including DCPs and solvents, evaluated by the OAsJEM,[14] and asthma, evaluated through dichotomous and semiquantitative standardised methods, in CONSTANCES, a large French population-based cohort.

MATERIALS AND METHODS
Study population
CONSTANCES is a French general population-based cohort.[25] Between 2012 and 2020, 220 000 participants aged 18–69 years were recruited in 21 Health Prevention Centers ('Centres d'examens de santé') across France. CONSTANCES included people affiliated to the main national health insurance (about 85% of the French population).[25] At enrolment, self-administered questionnaires were sent to participants to collect data including lifestyle, health, as well as a full job history where occupations were first coded according to the French classifications of occupations ('Profession et Catégories Socio-professionnelles', PCS 2003, https://www.insee.fr/fr/information/2400059) and of activities ('Nomenclature d'Activités Française', NAF, https://www.insee.fr/fr/information/2406147). Our analyses are based on inclusion data available in early 2022, totalising 205 203 participants enrolled since 2012.

Asthma
Asthma was evaluated through dichotomous and semiquantitative approaches by standardised questionnaire at recruitment. We used standardised definitions of asthma similar to those previously used in European Community Respiratory Health Survey and in the Epidemiological study on the Genetics and Environments of Asthma.[26 27] Ever asthma was defined by a positive answer to the question 'have you ever had asthma?'. Current asthma was defined among participants with ever asthma by the report in the past 12 months of asthma attacks or symptoms (wheezing, woken up with chest tightness, attack of shortness of breath at rest, attack of shortness of breath after exercise and woken up by attack of shortness of breath), or use of an asthma treatment. We also considered age at asthma onset and

distinguished adult-onset asthma (>16 years) and childhood-onset asthma (≤16 years). As previously described and validated,[28] the asthma symptom score, a semiquantitative score ranging from 0 to 5, was defined as the sum of 5 asthma symptoms reported in the past 12 months: breathless while wheezing, woken up with chest tightness, attack of shortness of breath at rest, attack of shortness of breath after exercise and woken up by attack of shortness of breath.

Occupational exposures
After the transcoding of job history of all participants from PCS 2003 occupation codes into International Standard Classification of Occupation (ISCO)-88 codes (https://www.ilo.org/public/english/bureau/stat/isco/isco88/major.htm), the OAsJEM[14] was applied to job histories to estimate exposure to 30 agents assigned to 3 groups[14]: high-molecular-weight (HMW) sensitisers, low-molecular-weight (LMW) sensitisers and irritants (online supplemental table S1). The latter included a total of 19 specific agents, including organic solvents, bleach and cleaning products. Each exposure was evaluated in three levels: high (high probability of exposure and moderate to high intensity), medium (high probability and low intensity' or low probability and moderate to high intensity), no (unlikely to be exposed; low probability and low intensity). We studied five groups of exposures: the three main exposures of interest: irritants (large group), DCPs (indoor cleaning products, bleach and high-level chemical disinfectants) and organic solvents; and HMW sensitisers and LMW sensitisers (large groups), which are known asthmagens and were expected to be associated with asthma outcomes. We examined each exposure in two categories (exposed vs a reference group non-exposed to any exposure in the JEM) and three categories (medium exposure, high exposure vs non-exposed reference group). Two main temporalities were considered: lifetime and current exposures, corresponding to the maximum exposure level during the entire work history, and during the last 2 years, respectively. Among the 19 irritant agents, 9 agents were also classified as LMW sensitisers in the OAsJEM, because both mechanisms have been suggested (online supplemental table S1). When considering irritant exposures, sensitivity analyses excluding these nine agents were also performed.

Statistical analysis
Cross-sectional associations between occupational exposure estimated by the OAsJEM and asthma and the asthma symptom score were evaluated by logistic regressions (OR) and negative binomial regressions (mean score ratios (MSRs)), respectively. All analyses were adjusted for age, body mass index (BMI) and smoking status. As job tasks and asthma phenotypes may vary according to gender, all associations were assessed separately in women and men, and interaction tests were performed by fitting the interaction term in the models, as previously done in CONSTANCES.[22]

RESULTS
Population characteristics
We excluded participants without job history (n=34 098), not working at inclusion (n=47 085), without any respiratory data (n=1415) or without information on ISCO-88 job codes (n=1038), BMI or smoking status (n=6027) (online supplemental figure S1), yielding a population of 115 540 participants. We performed analyses on asthma symptom score for 111 892 participants and on current asthma for 107 299 subjects. Excluded participants differed from

Table 1 Description of study population

	Men n=51865	Women n=63675
Age, Mean, (SD)	43.3 (10.7)	43.0 (10.7)
BMI		
<25	53.2	67.1
25–29.9	36.4	22.2
≥30	10.4	10.7
Education		
<High school	19.6	15.0
High school	14.7	15.1
2–3 years postsecondary	27.9	32.9
4–5 years postsecondary	37.6	36.8
Other	0.2	0.2
Smoking habits		
Non-smoker	45.2	50.9
Former smoker	33.9	30.2
Current smoker	20.9	18.9
Asthma symptoms score		
0	71.7	67.8
1	17.4	19.8
2	6.2	7.1
3	2.6	3.0
4	1.3	1.5
5	0.8	0.8
Mean (SD)	0.5 (0.9)	0.5 (0.9)
Ever asthma	14.9	14.4
Current asthma	9.9	10.4
Asthma medication (in participants with current asthma)	71.7	69.0
Lifetime occupational exposures		
Irritants	43.2	37.0
DCPs	18.5	32.9
Organic solvents	29.8	18.2
HMW sensitisers	16.3	27.4
LMW sensitisers	31.5	34.1

Data are presented as % unless otherwise stated.
BMI, body mass index; DCPs, disinfectants and cleaning products; HMW, high molecular weight; LMW, low molecular weight.

and 40% were overweight or obese. More than 30% of the participants had at least one asthma symptom during the last 12 months, 14% had ever asthma and 10% had current asthma. According to OAsJEM estimates, 40% of the participants had lifetime exposure to irritants, including 25% to DCPs and 23% to organic solvents. Women were more exposed to DCPs and sensitisers than men. Men had higher proportions of occupational exposures to irritants in general and organic solvents.

Occupational exposures and current asthma

Among men, lifetime exposure to irritants was not associated with current asthma (table 2). We only observed a single and slight positive association between lifetime occupational exposure to DCPs and current asthma (OR 1.10, 95% CI 1.01 to 1.20). Among women, we observed weak but positive associations between lifetime exposure to irritants (OR 1.05, 95% CI 1.00 to 1.11) and current asthma, especially for DCPs (OR 1.06, 95% CI 1.00 to 1.12). When taking account of levels of exposures (figure 1), slightly higher associations were found for high exposures to irritants (OR 1.13, 95% CI 1.05 to 1.22) and DCPs (OR 1.17, 95% CI 1.08 to 1.26) and current asthma in women. When removing potential LMW sensitisers exposures from the irritant exposure category, we found similar significant results (online supplemental table S3). In contrast, for organic solvents, no dose–response association was observed according to exposure level. Interaction tests between gender and exposures were also performed. Significant interactions were observed for irritants and organic solvents (table 2).

We also made analyses considering the age at asthma onset (childhood-onset (≤16 years), adult-onset (>16 years)). The association of DCPs with current asthma was slightly more pronounced for childhood-onset asthma in men (online supplemental table S4), whereas associations of irritants and DCPs with current asthma were significant only for adult-onset asthma in women (online supplemental table S5). No other significant associations were observed.

For known sensitisers, we found weak but positive associations between lifetime exposures to HMW sensitisers and current asthma in both men and women, whereas no association was observed for LMW sensitisers (table 3).

Last, regarding associations between current occupational exposures to irritants and current asthma, results were less consistent (online supplemental table S6). We did not find positive associations and even observed some inverse associations in men and women. We also observed inverse associations between current exposures to sensitisers and current asthma in men and women.

included participants in terms of age, sex, BMI, education or smoking habits but no differences were seen regarding asthma outcomes (online supplemental table S2). The mean age was approximately 43 years and 55% of the participants were women. The characteristics of the participants by gender are presented in table 1. Two-thirds of the participants had more than a high school degree, about 20% were current smokers

Table 2 Associations between lifetime occupational exposure to irritants, DCPs, organic solvents and current asthma or asthma symptom score

	Current asthma					Asthma symptom score				
	Men (n=47873)		Women (n=59426)			Men (n=50438)		Women (n=61454)		
	n	OR (95% CI)	n	OR (95% CI)	P interaction	n	Mean score ratio (95% CI)	n	Mean score ratio (95% CI)	P interaction
Ref	26922	1	37157	1		28504	1	43315	1	
Irritants	20515	0.97 (0.91 to 1.03)	21847	**1.05 (1.00 to 1.11)**	0.01	21471	**1.11 (1.07 to 1.15)**	22525	**1.08 (1.05 to 1.11)**	0.14
DCPs	6898	**1.10 (1.01 to 1.20)**	18197	**1.06 (1.00 to 1.12)**	0.87	7164	**1.21 (1.15 to 1.27)**	18725	**1.09 (1.06 to 1.13)**	0.005
Organic solvents	11471	0.93 (0.87 to 1.01)	8282	1.06 (0.98 to 1.14)	0.002	11944	**1.10 (1.05 to 1.15)**	8472	**1.14 (1.10 to 1.19)**	0.27

Logistic regressions and binomial negative regressions adjusted for age, BMI and smoking habits. Results in boldface are statistically significant.
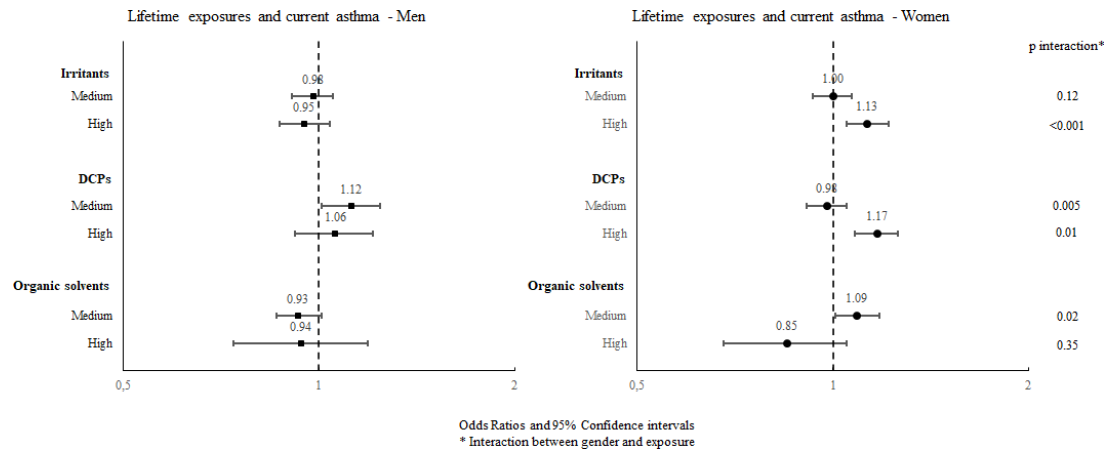BMI, body mass index; DCPs, disinfectants and cleaning products.

Figure 1 Associations between lifetime occupational exposure to irritants and current asthma according to exposure level. DCPs, disinfectants and cleaning products.

Occupational exposures and asthma symptom score

In men, we observed significant and positive associations between all irritant exposures and higher mean asthma symptom scores (table 2). In addition, associations were higher for high-level exposures (MSR ranging from 1.18 to 1.28) than for medium-level exposures (MSR ranging from 1.07 to 1.17) (figure 2).

Regarding the asthma symptom score in women, we observed significant positive associations for lifetime occupational exposures (in two classes) to irritants, DCPs and organic solvents with MSR ranging from 1.08 to 1.14 (table 2). When discriminating medium and high levels of exposures to irritants and DCPs, MSRs were higher for the latter (figure 2). Regarding, interaction tests between gender and exposures, we observed significant interactions for exposures to DCPs and not for irritants and organic solvents (table 2), contrary to results obtained for current asthma. Medium levels of irritants and DCPs were associated with significantly higher MSRs in men than in women, whereas no interaction by gender was observed for high-level exposures (figure 2). When excluding potential LMW sensitisers exposures from the irritant category, we found similar results (online supplemental table S3).

For known sensitisers, we also observed positive associations between lifetime exposure to both HMW and LMW sensitisers and a higher asthma symptom score in women and men (table 3).

Last, regarding associations between current occupational exposures to irritants and asthma symptom score, we found positive associations in men and women but weaker than associations obtained with lifetime exposures (online supplemental table S6). We also found inverse associations between current exposures to sensitisers and asthma symptom score in women.

DISCUSSION

In a large French population-based study, we found that lifetime occupational exposures to irritants were associated with a higher asthma symptom score in women and men. Lifetime occupational exposures to irritants were also associated with slightly increased risk of current asthma in women; in men, positive associations with current asthma were only suggested for DCPs. Overall, our results bring new support for an association between chronic occupational exposures to irritants and asthma.

Results from previous epidemiological works on this question using JEMs were inconsistent. Two studies used the OAsJEM and found associations between chronic exposure to irritants and a specific asthma endotype characterised by neutrophilic inflammation and oxidative stress[16] and current adult-onset asthma.[15] Among studies using the former asthma-specific JEM, which evaluated less accurately irritant exposures, most did not detect associations between occupational exposures to low/moderate levels of irritants and asthma,[11] its severity[12] or its development,[13] although one reported a positive association with current asthma.[10]

Table 3 Associations between lifetime occupational exposure to known sensitisers and current asthma or asthma symptom score

	Current asthma					Asthma symptoms score				
	Men (n=47 873)		Women (n=59 426)			Men (n=50 438)		Women (n=61 454)		
	n	OR (95% CI)	n	OR (95% CI)	P interaction	n	Mean score ratio (95% CI)	n	Mean score ratio (95% CI)	P interaction
Ref	26 922	1	37 157	1		28 504	1	43 315	1	
HMW sensitisers	38 174		51 180			35 019		52 958		
Exposed	6240	**1.12 (1.02 to 1.22)**	14 023	1.05 (0.98 to 1.11)	0.41	6515	**1.16 (1.10 to 1.23)**	14 471	**1.05 (1.02 to 1.09)**	0.001
Medium	3893	**1.09 (0.98 to 1.22)**	6670	1.00 (0.91 to 1.09)	0.51	4063	**1.17 (1.09 to 1.24)**	6704	**1.05 (1.01 to 1.10)**	0.01
High	2347	**1.16 (1.02 to 1.33)**	7533	**1.09 (1.00 to 1.18)**	0.94	2452	**1.16 (1.07 to 1.25)**	7767	**1.06 (1.01 to 1.11)**	0.04
LMW sensitisers	39 307		50 950			41 377		52 711		
Exposed	12 385	0.96 (0.89 to 1.03)	13 793	1.03 (0.96 to 1.09)	0.04	12 873	**1.09 (1.05 to 1.14)**	14 224	**1.04 (1.00 to 1.08)**	0.06
Medium	9353	0.95 (0.88 to 1.03)	12 333	1.03 (0.97 to 1.11)	0.12	9733	**1.06 (1.02 to 1.12)**	12 714	**1.03 (1.00 to 1.07)**	0.28
High	3032	0.99 (0.87 to 1.12)	1460	0.96 (0.81 to 1.14)	0.67	3140	**1.18 (1.10 to 1.27)**	1510	1.09 (0.99 to 1.19)	0.15

Logistic regressions and binomial negative regressions adjusted for age, BMI and smoking habits. Results in boldface are statistically significant.
BMI, body mass index; HMW, high molecular weight; LMW, low molecular weight.
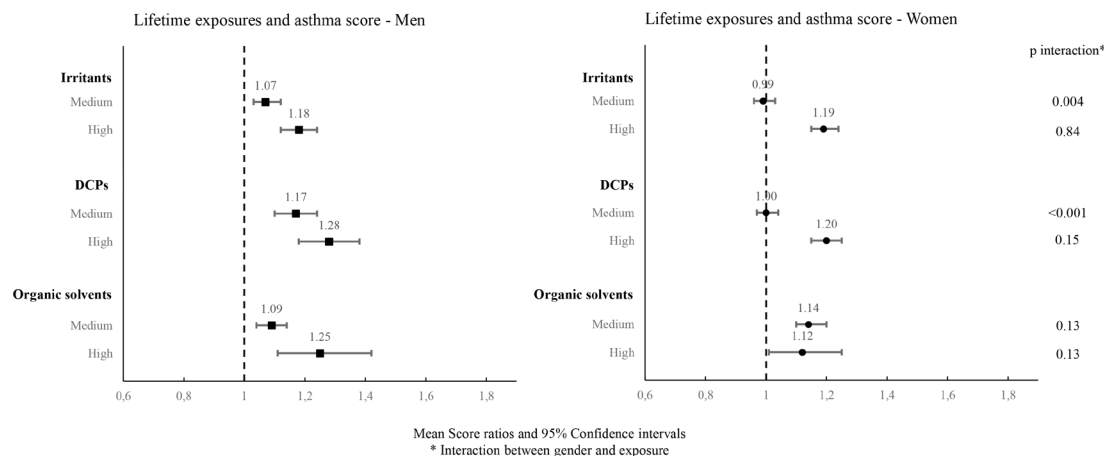
Figure 2 Associations between lifetime occupational exposure to irritants and asthma symptom score according to exposure level. DCPs, disinfectants and cleaning products.

In the past 10 years, evidence has increased for a deleterious role of DCPs in asthma. Our results are consistent with previous occupational epidemiological studies among healthcare workers and cleaners, which found associations between exposures to DCPs, estimated mostly with questionnaires, and asthma[19 29] and a meta-analysis concluding that occupational exposures to cleaning products are associated with a higher risk of asthma.[18] These results are also homogeneous with the scarce studies in population-based cohorts using the updated OAsJEM, which suggested associations of chronic occupational exposure to DCPs with asthma and its control[15 16] or older works with the AsJEM[30] or the N-JEM,[17] adapted from the AsJEM for Northern countries.

Regarding solvents, we observed significant associations between lifetime exposures and a higher asthma symptom score in both men and women. Fewer significant associations were found for current asthma than for the asthma symptom score. Our results are consistent with a previous work in CONSTANCES using self-reported exposure to solvents, and a population-based solvent-specific JEM,[22] a case–control study in Norway and a cohort study in Singapore which observed associations between occupational exposures to solvents and asthma.[20 21]

In our analyses, we used two standardised definitions of asthma: current asthma and the asthma symptom score. Compared with a dichotomous definition of asthma, the semiquantitative score, which defines asthma as a continuum, increases power to identify risk factors for asthma.[28] In particular, this score does not include the term 'asthma', with the aim to further decrease possible diagnostic bias due to challenges in asthma diagnosis,[28 31] and leading to both underdiagnosis and overdiagnosis of the disease.[32] When studying occupational exposures, this score is particularly relevant because occupational asthma is under-recognised in clinical practice. Using the asthma symptom score may help revealing associations by including subjects not identified as asthmatics.[1 28] In our results, associations between exposures and respiratory outcomes differed between asthma symptom score and current asthma. Although MSRs and OR are not directly comparable, we observed more significant associations between occupational exposures and the asthma symptom score than with current asthma. This disparity supports our hypothesis that occupational asthma is under-recognised.[33] Occupational exposures to irritants may also be associated with a specific asthma phenotype, which is less documented and may not commonly be recognised as asthma. This was previously suggested in a study of healthcare

workers, in which exposure to disinfection products was associated with a profile 'undiagnosed/untreated asthma' (identified by hierarchical clustering), characterised by numerous asthma symptoms, but low proportion of physician-diagnosed asthma and moderate use of asthma medications.[34]

In our study, we applied the recently updated asthma-specific JEM (OAsJEM)[14] to assess occupational exposures. In occupational epidemiological studies, using a JEM, rather than a questionnaire to assess exposure, is considered to reduce the risk of differential misclassification between participants with or without the disease of interest. However, using a JEM could also induce non-differential misclassification, partly due to disparities in tasks and work conditions between subjects within a same job, which may be taken into account only by applying a job-task-exposure matrix.[35] Transcoding operations which converted PCS 2003 French job codes into ISCO-88 international job codes could also introduce misclassification. In a previous work in the French NutriNet-Santé cohort, where jobs were directly coded into ISCO-88 classification (no transcoding), positive and higher associations were observed between occupational exposures to irritants estimated with the OAsJEM and current adult-onset asthma.[15] Associations between occupational exposures and asthma also differed according to gender. We found more positive associations between lifetime occupational exposures to irritants and current asthma in women than in men, but associations between irritant exposures and asthma symptom score were generally stronger in men than in women, with significant interactions in some cases. These differences could be explained by disparities in jobs and also tasks between women and men within the same job.[36] Distinct sex-related pathophysiological mechanisms might also contribute to these discrepancies between men and women.[37 38]

We observed more positive and stronger associations with asthma when studying lifetime exposures than for current exposures. Furthermore, in contrast to lifetime exposures, we observed some inverse associations between current exposures and both current asthma and symptom score. This difference in findings for current and lifetime exposure was observed not only for exposure to irritants, but also for well-known sensitisers (HMW and LMW agents), especially in women. This phenomenon could partly be explained by a healthy worker effect, which implies that working people are in better health than non-working people and asthmatics with more symptoms could avoid more often tasks and jobs exposing them to irritants. This

selection bias can act at two levels: at recruitment (hire effect) and during employment (survivor effect).[39] In our study, the weaker associations observed with current exposures compared with lifetime exposures could be explained by the fact that the subjects with asthma or asthma symptoms have left past occupations with exposures that could worsen their health status. It has been suggested that selection bias during employment is more important for women than for men.[39] Beyond inverse associations observed when investigating current exposure, a healthy worker effect (including hire effect) may have generally led to an underestimation of associations in our study, and partly explain the modest associations observed. Interestingly, associations observed for irritants exposure were of similar magnitude or higher than those observed for HMW and LMW sensitisers, which are well-known causes of occupational asthma.

This work is one of the first to assess associations between occupational exposures to irritants, using the updated OAsJEM, and asthma and asthma symptom score in a large general population cohort. One of the main strengths is the large size of the cohort, which favours the detection of even modest associations. One original feature of the analyses is to evaluate asthma according to several standardised definitions in a cohort from the general population and not in a specific occupational sample (eg, healthcare workers and cleaners). However, our study was limited by its cross-sectional design, which prevents determining accurately whether exposure occurred before or after asthma onset. In women, associations between irritant exposures and current asthma were restricted to current adult-onset asthma, but in men, DCPs exposures were associated with current childhood-onset asthma. A lower statistical power with two times less current adult asthma in men than in women could partly explain the absence of significant associations with adult-onset asthma in men. These findings probably also reflect an impact of occupational exposures on both new-onset asthma and the activity or aggravation of a pre-existing (including childhood onset) disease, which both have important consequences at individual and society level.[1] Despite the use of a JEM to limit recall bias with respect to exposure assessment, recall bias with respect to occupational history may still have occurred. However, the collection of occupational histories has been shown to be a reliable and valid method.[40] Finally, our conclusions are limited by the relatively low observed associations with ORs/MSR of 1.10–1.30, which should be interpreted with caution. More longitudinal data and improved assessment of exposure to specific agents are needed to clarify the role of irritants in asthma.

CONCLUSION

The results of this cross-sectional analysis in a large population-based cohort support the hypothesis of a deleterious role of chronic exposure to irritants, particularly DCPs and solvents, with regard to current asthma and asthma symptom score. These data suggest that irritant exposures, which are very common at the workplace, should be reduced to protect workers' respiratory health through industry-specific exposure reduction strategies. Clinicians should consider occupational exposures to irritants as a potential risk factor and recommend to avoid such exposures in patients with asthma or asthma-like symptoms.

Contributors GS contributed to the analysis and interpretation of the data, and primary manuscript preparation. GS acts as the guarantor for this work. BD, FO, MG, CR and MZ contributed to acquisition and interpretation of the data and critical revision of the manuscript. LO, YI, BL, RN, NR, YR, RV and CP were involved in the data interpretation and critical revision of the manuscript. NLM and OD developed the study hypotheses and contributed to data interpretation, primary manuscript preparation and critical revision of the manuscript. All authors approved the final version of the manuscript.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and the CONSTANCES cohort received legal authorisation from the French National Data Protection Authority (no. 910486) and the ethical approval from the Institutional Review Board of the National Institute for Medical Research (no.01-011). All participants gave informed consent to participate. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Data can be provided on reasonable request after approval by the CONSTANCES scientific committee.

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ONLINE SUPPLEMENT

CHRONIC OCCUPATIONAL EXPOSURES TO IRRITANTS AND ASTHMA IN THE CONSTANCES COHORT

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ETHICS STATEMENT

The CONSTANCES cohort received ethical approval from the French National Data Protection Authority (authorisation no. 910486) and the Institutional Review Board of the National Institute for Medical Research (authorisation no. 01-011). All participants gave informed consent to participate.

Figure S1: Selection of study population

Supplemental material

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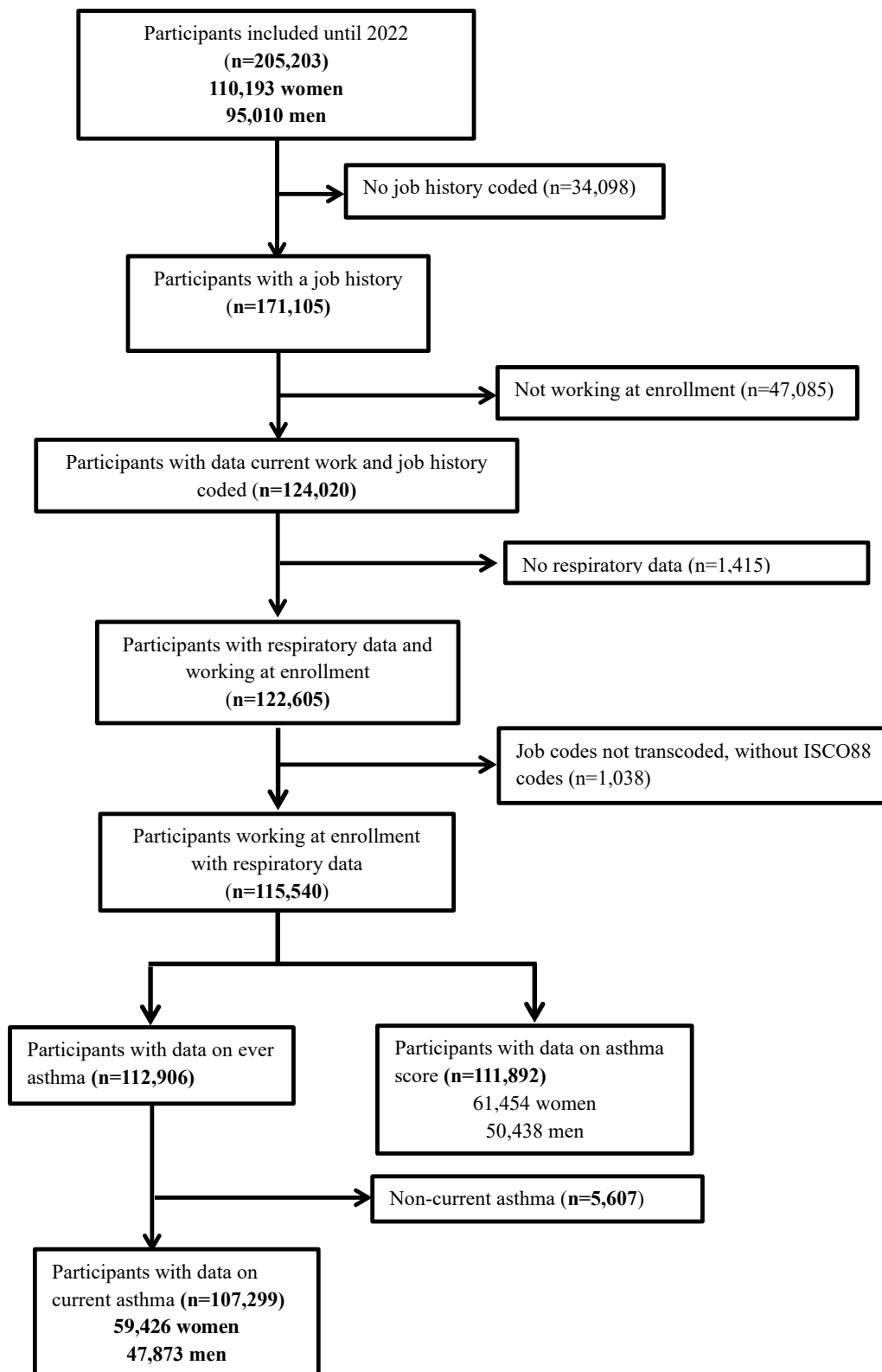
Table S1: List of individual agents classified in 3 large groups in the new occupational asthma-specific JEM (OAsJEM)

Agents, n=30	HMW sensitizer	LMW Sensitizer	Irritant
Animals	1		
Fish/shellfish	1		
Flour	1		
Foods	1		
Plant-related dusts	1		
House dust mites	1		
Storage mites	1		
Plant mites	1		
Enzymes	1		
Latex	1		
Textiles	1		1
Moulds			1
Endotoxin			1
Drugs	1	1	
High-level chemical disinfectants		1	1
Aliphatic amines		1	1
Isocyanates		1	1
Acrylates		1	1
Epoxy resins		1	1
Persulfates/henna		1	1
Wood		1	1
Metal		1	1
Metal working fluids		1	1
Herbicides			1
Insecticides			1
Fungicides			1
Indoor cleaning			1
Bleach			1
Organic solvents			1
Exhaust fumes			1

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Table S2: Description of included and excluded populations

	Included n = 115,540	Missing asthma status n =1,415	Missing BMI or smoking status n = 6,027	Missing -job transcoded codes (ISCO88) n = 1,038
Age, Mean, (sd)	43.1 (10.7)	46.5 (13.7)*	44.3 (10.8)*	43.0 (11.0)
Women	55.1	51.7*	54.7	34.3*
BMI		*		
<25	60.9	46.3	.	39.6
25-29.9	28.6	32.5	.	25.5
≥30	10.5	21.2	.	35.0
Education		*	*	
< High school	17.6	44.6	21.2	42.5
High school	14.9	15.4	14.9	23.2
2-3 years post-secondary	29.3	18.5	26.9	23.0
4-5 years post-secondary	38.0	21.1	36.8	11.0
Other	0.2	0.4	0.2	0.3
Smoking habits		*		*
Non smoker	48.3	52.0	.	39.5
Former smoker	31.9	32.0	.	25.5
Current smoker	19.8	16.0	.	35.0
Asthma symptoms score				
0	69.6	.	68.3	68.6
1	18.7	.	19.8	18.1
2	6.7	.	6.9	7.4
3	2.8	.	2.8	3.1
4	1.4	.	1.3	2.0
5	0.8	.	0.9	0.8
Current asthma	10.2	.	9.4	11.2

Data are presented as % unless otherwise stated;
BMI = Body Mass Index;
*p<0.05 for chi square test/Student test

4

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Table S3: Associations between lifetime occupational exposure to irritants and current asthma or asthma symptom score, after excluding exposures also classified as potential LMW sensitizers

	Current asthma					Asthma symptom score				
	Men (n = 47,873)		Women (n = 59,426)			Men (n = 50,438)		Women (n = 61,454)		
	n	Odds Ratio (95% CI)	n	Odds Ratio (95% CI)	p inter	n	Mean Score Ratio (95% CI)	n	Mean Score Ratio (95% CI)	p inter
Ref	26922	1	37157	1		28504	1	43315	1	
Irritants <u>without</u> LMW sensitizers	45985		57549			48451		59483		
Exposed	19063	0.96 [0.90-1.02]	20392	**1.07 [1.01-1.13]**	<0.001	19947	**1.12 [1.08-1.16]**	20996	**1.10 [1.07-1.14]**	0.35
Medium	12732	0.97 [0.91-1.04]	11149	1.02 [0.95-1.10]	0.31	13399	**1.09 [1.05-1.13]**	11564	1.03 [0.99-1.07]	0.01
High	6331	0.93 [0.85-1.02]	9243	**1.14 [1.06-1.22]**	<0.001	6548	**1.16 [1.09-1.22]**	9432	**1.19 [1.15-1.24]**	0.61

5

Table S4: Associations between lifetime occupational exposures and current asthma according to age of onset in men

	No asthma (ref)	Childhood onset asthma (≤16 years)		Adult onset asthma (>16 years)	
	n=43,115	n=3,282	Odds ratio (IC95%)	n=1,141	Odds ratio (IC95%)
Irritants	42,736	3,249		1,122	
Ref.	24,232	1,869	1	649	1
Exposed	18,504	1,380	0.97 [0.90-1.04]	473	0.91 [0.81-1.03]
Medium	11,404	881	0.99 [0.91-1.07]	300	0.95 [0.83-1.09]
High	7,100	499	0.94 [0.85-1.04]	173	0.85 [0.71-1.00]
DCPs	30,352	2,410		824	
Ref.	24,232	1,869	1	649	1
Exposed	6,120	541	*1.09 [0.99-1.21]*	175	1.03 [0.87-1.22]
Medium	3,860	363	**1.13 [1.00-1.27]**	113	1.08 [0.88-1.32]
High	2,260	178	1.03 [0.88-1.21]	62	0.96 [0.73-1.25]
Organic solvents	34,640	2,587		915	
Ref.	24,232	1,869	1	649	1
Exposed	10,408	718	0.93 [0.85-1.02]	266	0.90 [0.78-1.05]
Medium	9,654	663	0.93 [0.84-1.02]	250	0.92 [0.79-1.06]
High	754	55	1.00 [0.75-1.32]	16	0.74 [0.45-1.22]
HMW Sensitizers	29,759	2,363		812	
Ref.	24,232	1,869	1	649	1
Exposed	5,527	494	**1.11 [1.00-1.23]**	163	1.07 [0.90-1.27]
Medium	3,453	318	*1.13 [0.99-1.28]*	87	0.92 [0.73-1.15]
High	2,074	176	1.09 [0.92-1.28]	76	**1.32 [1.04-1.69]**
LMW Sensitizers	35,435	2,653		956	
Ref.	24,232	1,869	1	649	1
Exposed	11,203	784	0.94 [0.86-1.03]	307	0.97 [0.84-1.11]
Medium	8,464	598	0.94 [0.85-1.03]	229	0.96 [0.82-1.12]
High	2,739	186	0.94 [0.80-1.10]	78	0.98 [0.77-1.25]

Logistic regressions adjusted for age, BMI and smoking status

n=335 participant with missing age of asthma onset

6

Table S5: Associations between lifetime occupational exposures and current asthma according to age of onset in women

	Current asthma (n=47,538)				
	No asthma (réf)	Childhood onset asthma (≤16 years)		Adult onset asthma (>16 years)	
	n=53,243	n=3,296	Odds ratio (IC95%)	n=2,292	Odds ratio (IC95%)
Irritants	52,854	3,276		2,281	
Ref.	33,435	2,000	1	1,374	1
Exposed	19,419	1,276	1.01 [0.94-1.09]	907	*1.08 [0.99-1.17]*
Medium	11,205	723	0.98 [0.90-1.07]	472	1.01 [0.91-1.13]
High	8,214	553	1.06 [0.96-1.17]	435	**1.16 [1.04-1.30]**
DCPs	49,594	3,061		2,145	
Ref.	33,435	2,000	1	1,374	1
Exposed	16,159	1,061	1.01 [0.93-1.09]	771	**1.09 [1.00-1.20]**
Medium	9,122	575	0.94 [0.85-1.04]	387	1.02 [0.91-1.15]
High	7,037	486	1.10 [0.99-1.22]	384	**1.18 [1.05-1.33]**
Organic solvents	40,790	2,478		1,718	
Ref.	33,435	2,000	1	1,374	1
Exposed	7,355	478	1.02 [0.92-1.13]	344	1.05 [0.93-1.19]
Medium	6,402	428	1.06 [0.95-1.18]	307	1.08 [0.95-1.22]
High	953	50	0.79 [0.59-1.05]	37	0.88 [0.63-1.24]
HMW Sensitizers	45,923	2,822		1,943	
Ref.	33,435	2,000	1	1,374	1
Exposed	12,488	822	1.02 [0.94-1.11]	569	1.06 [0.96-1.17]
Medium	5,794	382	0.96 [0.86-1.08]	251	1.02 [0.89-1.18]
High	6,694	440	1.07 [0.96-1.20]	318	1.08 [0.96-1.23]
LMW Sensitizers	45,752	2,748		1,950	
Ref.	33,435	2000	1	1,374	1
Exposed	12,317	748	0.96 [0.88-1.05]	576	1.08 [0.98-1.19]
Medium	11,010	667	0.97 [0.89-1.06]	518	1.08 [0.98-1.20]
High	1307	81	0.89 [0.70-1.12]	58	1.04 [0.79-1.36]

Logistic regressions adjusted for age, BMI and smoking status

n=595 participant with missing age of asthma onset

Table S6: Associations between current occupational exposure and current asthma or asthma symptom score

| | Current Asthma | | | | | Asthma symptom score | | | | |
| | Men (n = 47,873) | | Women (n = 59,426) | | | Men (n = 50,438) | | Women (n = 61,454) | | |
	n	Odds Ratio (95% CI)	n	Odds Ratio (95% CI)	p Inter	N	Mean Score Ratio (95% CI)	n	Mean Score Ratio (95% CI)	p Inter
Ref	34,863	1	43,996	1		36,863	1	45,550	1	
Irritants	47,310		58,564			49,846		55,589		
Exposed	12,447	**0.93 [0.87-1.00]**	14,568	0.98 [0.92-1.04]	0.13	12,943	**1.07 [1.03-1.12]**	15,004	1.01 [0.97-1.04]	0.001
Medium	8,298	0.94 [0.87-1.02]	9,173	0.96 [0.89-1.04]	0.48	8,701	**1.06 [1.02-1.11]**	9,530	**0.92 [0.89-0.97]**	<0.001
High	4,149	0.90 [0.81-1.01]	5,395	1.00 [0.91-1.10]	0.07	4,282	**1.10 [1.04-1.17]**	5,474	**1.14 [1.09-1.20]**	0.39
DCPs	38,538		56,148			40,701		58,075		
Exposed	3,675	1.08 [0.97-1.20]	12,182	0.98 [0.92-1.05]	0.27	3,838	**1.11 [1.03-1.17]**	12,525	1.02 [0.98-1.05]	0.02
Medium	2,315	*1.13 [0.99-1.29]*	7,357	0.96 [0.89-1.04]	0.04	2,434	**1.08 [1.00-1.17]**	7,646	**0.93 [0.89-0.97]**	<0.001
High	1,360	0.99 [0.83-1.19]	4,825	1.02 [0.93-1.12]	0.17	1,404	**1.14 [1.03-1.26]**	4,879	**1.16 [1.10-1.22]**	0.80
Organic solvents	41,196		48,012			43,457		49,642		
Exposed	6,333	**0.89 [0.81-0.97]**	8,150	0.93 [0.84-1.04]	0.31	6,594	**1.05 [1.00-1.11]**	4,092	**1.05 [1.00-1.12]**	0.93
Medium	6,079	**0.89 [0.81-0.97]**	3,910	0.96 [0.86-1.08]	0.11	6,344	1.05 [0.99-1.10]	3,694	**1.06 [1.00-1.13]**	0.79
High	254	0.91 [0.60-1.40]	379	**0.68 [0.47-0.98]**	0.23	250	1.20 [0.95-1.50]	398	0.98 [0.83-1.17]	0.14
HMW Sensitizers	38,174		53,633			40,339				
Exposed	3,311	**1.15 [1.03-1.29]**	9,637	0.94 [0.87-1.01]	0.004	3,476	**1.06 [1.00-1.14]**	10,017	**0.94 [0.91-0.98]**	0.002
Medium	2,151	**1.17 [1.02-1.33]**	4,500	**0.88 [0.79-0.98]**	0.04	2,259	1.07 [0.99-1.16]	4,692	**0.93 [0.88-0.99]**	0.004
High	1,160	1.13 [0.94-1.36]	5,137	0.99 [0.90-1.09]	0.94	1,217	1.06 [0.95-1.18]	5,325	0.96 [0.91-1.01]	0.10
LMW Sensitizers	41,551		53,110			43,836		55,064		
Exposed	6,688	**0.91 [0.84-1.00]**	9,174	0.93 [0.87-1.01]	0.48	6,973	**1.05 [1.00-1.10]**	9,514	**0.95 [0.91-0.99]**	0.002
Medium	5,468	**0.90 [0.82-0.99]**	8,491	0.95 [0.88-1.02]	0.08	5,717	1.02 [0.97-1.08]	8,798	**0.96 [0.92-1.00]**	0.04
High	1,220	0.97 [0.80-1.18]	683	**0.77 [0.59-1.00]**	0.14	1,256	**1.15 [1.03-1.28]**	716	**0.88 [0.77-1.00]**	0.002

Logistic regressions and binomial negative regressions adjusted for age, BMI and smoking habits

8