



HAL
open science

Chronic occupational exposures to irritants and asthma in the CONSTANCES cohort

Guillaume Sit, Laurent Orsi, Yuriko Iwatsubo, Brigitte Dananché, Florence Orsi, Marcel Goldberg, Benedicte Leynaert, Rachel Nadif, Céline Ribet, Nicolas Roche, et al.

► To cite this version:

Guillaume Sit, Laurent Orsi, Yuriko Iwatsubo, Brigitte Dananché, Florence Orsi, et al.. Chronic occupational exposures to irritants and asthma in the CONSTANCES cohort. Occupational and Environmental Medicine, 2024, 81 (3), pp.129-135. 10.1136/oemed-2023-109100 . inserm-04486088

HAL Id: inserm-04486088

<https://inserm.hal.science/inserm-04486088v1>

Submitted on 3 Jun 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

1 **CHRONIC OCCUPATIONAL EXPOSURES TO IRRITANTS AND**
2 **ASTHMA IN THE CONSTANCES COHORT**

3 Guillaume SIT^a, Laurent ORSI^a, Yuriko IWATSUBO^b, Brigitte DANANCHE^a, Florence
4 ORSI^a, Marcel GOLDBERG^{c,d}, Bénédicte LEYNAERT^a, Rachel NADIF^a, Céline RIBET^{c,d},
5 Nicolas ROCHE^e, Yves ROQUELAURE^f, Raphaëlle VARRASO^a, Marie ZINS^{c,d}, Corinne
6 PILORGET^b, Nicole LE MOUAL^a, Oriane DUMAS^a

- 7
8 a. Université Paris-Saclay, UVSQ, Univ. Paris-Sud, Inserm, Équipe d'Épidémiologie
9 respiratoire intégrative, CESP, 94807, Villejuif, France
10 b. Santé publique France Direction Santé Environnement Travail, 94415 Saint-Maurice,
11 France
12 c. Université de Paris Cité, Université Paris-Saclay, UVSQ, Inserm, UMS 11, Cohortes
13 Epidémiologiques en population, 94807, Villejuif, France.
14 d. Faculty of Medicine, University of Paris, 75006 Paris, France
15 e. APHP Centre-Université de Paris, Hôpital et Institut Cochin, Service de Pneumologie,
16 75014 Paris, France
17 f. UNIV Angers, CHU Angers, Univ Rennes, Inserm, EHESP, Irset (Institut de
18 recherche en santé, environnement et travail) UMR_S1085, F-49000 Angers, France
19

20 **Corresponding Author:**

21 **Oriane Dumas**

22 Université Paris-Saclay, UVSQ, Univ. Paris-Sud, Inserm, Équipe d'Épidémiologie respiratoire
23 intégrative, CESP, 16, avenue Paul Vaillant Couturier, 94807, Villejuif, France

24 **e-mail address: orianne.dumas@inserm.fr**

25 **Phone number: +33 1 45 59 53 57**

26
27 **Key words: Current asthma, Asthma Symptom score, Occupational exposure, Solvents,**
28 **Cleaning products and disinfectants, Job-exposure matrix, Population-based cohort**

29 **Abstract**

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

34 **Methods.** Cross-sectional analyses included 115,540 adults (55% women, mean age 43 years,
35 10% current asthma) working at inclusion in the French population-based CONSTANCES
36 cohort (2012-2020). Current asthma was defined by ever asthma with symptoms, medication
37 or asthma attacks (past 12 months), and the asthma symptom score by the sum of 5 respiratory
38 symptoms (past 12 months). Both lifetime and current occupational exposures were assessed
39 by the Occupational Asthma-specific Job-Exposure Matrix (OAsJEM). Associations were
40 evaluated by gender using logistic and binomial negative regressions adjusted for age, smoking
41 status and body mass index.

42 **Results.** In women, associations were observed between current asthma and lifetime exposure
43 to irritants (odds ratio: 1.05, 95%CI 1.00-1.11), DCPs (1.06, 1.00-1.12) and solvents (1.06,
44 0.98-1.14). In men, only lifetime exposure to DCPs (1.10, 1.01-1.20) was associated with
45 current asthma. Lifetime exposure to irritants was associated with higher asthma symptom score
46 both in women (mean score ratio: 1.08, 95%CI 1.05-1.11) and men (1.11, 1.07-1.15), especially
47 for DCPs (women: 1.09, 1.06-1.13, men: 1.21, 1.15-1.27) and solvents (women: 1.14, 1.10-
48 1.19, men: 1.10, 1.05-1.15). For current exposures, no consistent associations were observed
49 with current asthma and asthma symptom score.

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

53 **KEY MESSAGES**

54 **-What is already known on this topic?**

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

57 **-What this study adds?**

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

60 **-How this study might affect research, practice or policy?**

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

64 INTRODUCTION

65 Workplace exposures are an important contributor to the burden of adult asthma [1,2].
66 About 15% of adult asthma cases are caused by occupational exposures [3], and 20% of adults
67 with asthma have exacerbations at work [3,4]. Occupational asthma can be caused by sensitizers
68 (e.g., flours, latex, diisocyanates) and irritants [1,5]. Sensitizer-induced asthma, which involves
69 an immunologic mechanism, is a well-known type of occupational asthma [6]. and has largely
70 been described in case series or surveillance programs [7]. A second type of occupational
71 asthma corresponds to asthma caused by non-immunological irritant mechanisms, which have
72 not been precisely identified yet. Irritant-induced asthma can appear after a single acute
73 exposure to very high levels of irritants (reactive airway dysfunction syndrome (RADS), or
74 Brooks' syndrome), but may also occur following a delayed onset after chronic exposures to
75 irritants, even in absence of high peak exposures [8–10]. The role of chronic exposures, whether
76 in the past or currently, to irritants has been less documented [9,10] and is probably
77 underestimated and involved in a substantial number of occupational asthma cases [11].
78 Because causality for chronic exposure irritant-induced asthma cannot be established with
79 certainty at individual level (given the lack of appropriate clinical tests), epidemiological
80 studies are particularly important to evaluate causality at population level [8,9].

81 Only a limited number of studies have considered the impact on asthma of chronic
82 occupational exposures to irritants as a broad category [8,12], and they showed heterogeneous
83 results. Among studies using the asthma-specific job exposure-matrix (AsJEM) [12], one study
84 observed a positive association for physician diagnosed asthma [13], whereas three studies did
85 not show any associations [14–16]. However, these studies [14–16] used a former version of
86 the matrix [12], which poorly evaluated chronic exposures to irritants. The AsJEM has been
87 updated in 2018 and renamed as Occupational Asthma-specific JEM (OAsJEM) with a focus
88 on improving assessment of irritant exposures [17]. Since then, the OAsJEM has been used in
89 several epidemiological studies (<https://oasjem.vjf.inserm.fr/paper-list/>). Two of them studied
90 associations of chronic occupational exposures to irritants with asthma [18,19], and both found
91 positive associations.

92 Irritant agents are frequent at work and include a wide variety of agents. Studies
93 investigating specific agents have mostly focused on Disinfectants and Cleaning Products
94 (DCPs), which contain irritant substances, and are now recognized as a cause of asthma [20–
95 23]. Among irritants, solvents are also commonly used in workplaces, but associations with

96 asthma have been less documented [18,24–26]. In France, about 17% of workers are exposed
97 to organic solvents [27,28], which have been identified as causal agents of work-related asthma
98 in the latest report from the National Network for Occupational Disease Vigilance and
99 Prevention (RNV3P). Further epidemiological studies are still needed to evaluate the impact of
100 chronic exposures to irritants, especially solvents, in asthma.

101 Therefore, we aimed to examine the association between chronic occupational
102 exposures to irritants, including DCPs and solvents, evaluated by the OAsJEM [17], and
103 asthma, evaluated through dichotomous and semi-quantitative standardized methods, in
104 CONSTANCES, a large French population-based cohort.

105 **MATERIALS AND METHODS**

106 *Study population*

107 CONSTANCES is a French general population-based cohort [29]. Between 2012 and
108 2020, 220,000 participants aged 18–69 years were recruited in 21 Health Prevention Center
109 (‘Centres d’examens de santé’) across France. CONSTANCES included people affiliated to the
110 main national health insurance (about 85% of the French population) [29]. At enrolment, self-
111 administered questionnaires were sent to participants to collect data including lifestyle, health,
112 as well as a full job history where occupations were first coded according to the French
113 classifications of occupations (‘Profession et Catégories Socio-professionnelles’, PCS 2003,
114 <https://www.insee.fr/fr/information/2400059>) and of activities (‘Nomenclature d’Activités
115 Française’, NAF, <https://www.insee.fr/fr/information/2406147>). Our analyses are based on
116 inclusion data available in early 2022, totalizing 205,203 participants enrolled since 2012.

117 *Asthma*

118 Asthma was evaluated through dichotomous and semi-quantitative approaches by
119 standardized questionnaire at recruitment. We used standardized definitions of asthma similar
120 to those previously used in European Community Respiratory Health Survey (ECRHS) and in
121 the Epidemiological study on the Genetics and Environments of Asthma (EGEA) [30,31]. Ever
122 asthma was defined by a positive answer to the question “have you ever had asthma?”. Current
123 asthma was defined among participants with ever asthma by the report in the past 12 months of
124 asthma attacks or symptoms (wheezing, woken up with chest tightness, attack of shortness of
125 breath at rest, attack of shortness of breath after exercise, and woken up by attack of shortness
126 of breath), or use of an asthma treatment. We also considered age at asthma onset and
127 distinguished adult-onset asthma (>16 years) and childhood-onset asthma (≤16 years). As

128 previously described and validated [32], the asthma symptom score, a semi-quantitative score
129 ranging from 0 to 5, was defined as the sum of 5 asthma symptoms reported in the past 12
130 months: breathless while wheezing, woken up with chest tightness, attack of shortness of breath
131 at rest, attack of shortness of breath after exercise, and woken up by attack of shortness of
132 breath.

133 *Occupational exposures*

134 After the transcoding of job history of all participants from PCS 2003 occupation codes
135 into International Standard Classification of Occupation (ISCO)-88 codes
136 (<https://www.ilo.org/public/english/bureau/stat/isco/isco88/major.htm>), the OAsJEM [17] was
137 applied to job histories to estimate exposure to 30 agents assigned to 3 groups [17]: High
138 Molecular Weight (HMW) sensitizers, Low Molecular Weight (LMW) sensitizers and irritants
139 (Table S1). The latter included a total of 19 specific agents, including organic solvents, bleach
140 and cleaning products. Each exposure was evaluated in 3 levels: high (high probability of
141 exposure and moderate to high intensity), medium (high probability and low intensity' or low
142 probability and moderate to high intensity), no (unlikely to be exposed; low probability and low
143 intensity). We studied 5 groups of exposures: the 3 main exposures of interest: irritants (large
144 group), DCPs (indoor cleaning products, bleach and high-level chemical disinfectants) and
145 organic solvents; and HMW sensitizers and LMW sensitizers (large groups) which are known
146 asthmagens and were expected to be associated with asthma outcomes. We examined each
147 exposure in 2 categories (exposed vs a reference group non-exposed to any exposure in the
148 JEM) and 3 categories (medium exposure, high exposure, vs non-exposed reference group).
149 Two main temporalities were considered: lifetime and current exposures, corresponding to the
150 maximum exposure level during the entire work history, and during the last 2 years,
151 respectively. Among the 19 irritant agents, nine agents were also classified as low molecular
152 weight (LMW) sensitizers in the OAsJEM, because both mechanisms have been suggested
153 (Table S1). When considering irritant exposures, sensitivity analyses excluding these nine
154 agents were also performed.

155 *Statistical analysis*

156 Cross-sectional associations between occupational exposure estimated by the OAsJEM
157 and asthma and the asthma symptom score, were evaluated by logistic regressions (Odds ratio
158 (OR)) and negative binomial regressions (Mean Scores ratios (MSR)) respectively. All analyses
159 were adjusted for age, body mass index (BMI), and smoking status. As job tasks and asthma
160 phenotypes may vary according to gender, all associations were assessed separately in women

161 and men, and interaction tests were performed by fitting the interaction term in the models, as
162 previously done in CONSTANCES [26].

163 **RESULTS**

164 *Population characteristics*

165 We excluded participants without job history (n=34,098), not working at inclusion
166 (n=47,085), without any respiratory data (n=1,415), or without information on ISCO-88 job
167 codes (n= 1,038), BMI or smoking status (n=6,027) (Figure S1), yielding a population of
168 115,540 participants. We performed analyses on asthma symptom score for 111,892
169 participants and on current asthma for 107,299 subjects. Excluded participants differed from
170 included participants in terms of age, sex, BMI, education or smoking habits but no differences
171 were seen regarding asthma outcomes (Table S2). The mean age was approximately 43 years
172 and 55% of the participants were women. The characteristics of the participants by gender are
173 presented in Table 1. Two-thirds of the participants had more than a high school degree, about
174 20% were current smokers and 40% were overweight or obese. More than 30% of the
175 participants had at least one asthma symptom during the last 12 months, 14% had ever asthma
176 and 10% had current asthma. According to OAsJEM estimates, 40% of the participants had
177 lifetime exposure to irritants, including 25% to DCPs and 23% to organic solvents. Women
178 were more exposed to DCPs and sensitizers than men. Men had higher proportions of
179 occupational exposures to irritants in general and organic solvents.

180 *Occupational exposures and current asthma*

181 Among men, lifetime exposure to irritants was not associated with current asthma (Table
182 2). We only observed a single and slight positive association between lifetime occupational
183 exposure to DCPs and current asthma (OR 1.10, 95% CI 1.01-1.20). Among women, we
184 observed weak but positive associations between lifetime exposure to irritants (OR 1.05, 95%
185 CI 1.00-1.11) and current asthma, especially for DCPs (OR 1.06, 95% CI 1.00-1.12). When
186 taking account of levels of exposures (Figure 1), slightly higher associations were found for
187 high exposures to irritants (OR 1.13, 95% CI 1.05-1.22) and DCPs (OR 1.17, 95% CI 1.08-
188 1.26) and current asthma in women. When removing potential LMW sensitizers exposures from
189 the irritant exposure category, we found similar significant results (Table S3). In contrast, for
190 organic solvents, no dose-response association was observed according to exposure level.
191 Interaction tests between gender and exposures were also performed. Significant interactions
192 were observed for irritants and organic solvents (Table 2).

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

198 For known sensitizers, we found weak but positive associations between lifetime
199 exposures to HMW sensitizers and current asthma in both men and women, whereas no
200 association were observed for LMW sensitizers (Table 3).

201 Last, regarding associations between current occupational exposures to irritants and
202 current asthma, results were less consistent (Table S6). We did not find positive associations
203 and even observed some inverse associations in men and women. We also observed inverse
204 associations between current exposures to sensitizers and current asthma in men and women.

205 ***Occupational exposures and asthma symptom score***

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

210 Regarding the asthma symptom score in women, we observed significant positive
211 associations for lifetime occupational exposures (in 2 classes) to irritants, DCPs and organic
212 solvents with MSR ranging from 1.08 to 1.14 (Table 2). When discriminating medium and high
213 levels of exposures to irritants and DCPs, MSR were higher for the latter (Figure 2). Regarding,
214 interaction tests between gender and exposures, we observed significant interactions for
215 exposures to DCPs and not for irritants and organic solvents (Table 2), contrary to results
216 obtained for current asthma. Medium levels of irritants and DCPs were associated with
217 significantly higher mean score ratios in men than in women, whereas no interaction by gender
218 was observed for high-level exposures (Figure 2). When excluding potential LMW sensitizers
219 exposures from the irritant category, we found similar results (Table S3).

220 For known sensitizers we also observed positive associations between lifetime exposure
221 to both HMW and LMW sensitizers and a higher asthma symptom score in women and men
222 (Table 3).

223 Last, regarding associations between current occupational exposures to irritants and
224 asthma symptom score, we found positive associations in men and women but weaker than
225 associations obtained with lifetime exposures (Table S6). We also found inverse associations
226 between current exposures to sensitizers and asthma symptom score in women.

227 **DISCUSSION**

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

234 Results from previous epidemiological works on this question using JEMs were
235 inconsistent. Two studies used the OAsJEM, and found associations between chronic exposure
236 to irritants and a specific asthma endotype characterized by neutrophilic inflammation and
237 oxidative stress [19] and current adult-onset asthma [18]. Among studies using the former
238 asthma-specific JEM, which evaluated less accurately irritant exposures, most did not detect
239 associations between occupational exposures to low/moderate levels of irritants and asthma
240 [14], its severity [15] or its development [16], although one reported a positive association with
241 current asthma [13].

242 In the past 10 years, evidence has increased for a deleterious role of DCPs in asthma.
243 Our results are consistent with previous occupational epidemiological studies among healthcare
244 workers and cleaners which found associations between exposures to DCPs, estimated mostly
245 with questionnaires, and asthma [23,33] and a meta-analysis concluding that occupational
246 exposures to cleaning products are associated with a higher risk of asthma [22]. These results
247 are also homogeneous with the scarce studies in population-based cohorts using the updated
248 OAsJEM which suggested associations of chronic occupational exposure to DCPs with asthma
249 and its control [18,19] or older works with the AsJEM [34] or the N-JEM [21], adapted from
250 the AsJEM for Northern countries.

251 Regarding solvents, we observed significant associations between lifetime exposures
252 and a higher asthma symptom score in both men and women. Fewer significant associations
253 were found for current asthma than for the asthma symptom score. Our results are consistent

254 with a previous work in CONSTANCES using self-reported exposure to solvents, and a
255 population-based solvent-specific JEM [26], a case-control study in Norway and a cohort study
256 in Singapore which observed associations between occupational exposures to solvents and
257 asthma [24,25].

258 In our analyses, we used two standardized definitions of asthma: current asthma and the
259 asthma symptom score. Compared to a dichotomous definition of asthma, the semi-quantitative
260 score, which defines asthma as a continuum, increases power to identify risk factors for asthma
261 [32]. In particular, this score does not include the term “asthma”, with the aim to further
262 decrease possible diagnostic bias due to challenges in asthma diagnosis [32,35], and leading to
263 both under- and over-diagnosis of the disease [36]. When studying occupational exposures, this
264 score is particularly relevant because occupational asthma is under-recognized in clinical
265 practice. Using the asthma symptom score may help revealing associations by including
266 subjects not identified as asthmatics [1,32]. In our results, associations between exposures and
267 respiratory outcomes differed between asthma symptom score and current asthma. Although
268 mean score ratios and odds ratio are not directly comparable, we observed more significant
269 associations between occupational exposures and the asthma symptom score than with current
270 asthma. This disparity supports our hypothesis that occupational asthma is under-recognized
271 [37]. Occupational exposures to irritants may also be associated with a specific asthma
272 phenotype, which is less documented and may not commonly be recognized as asthma. This
273 was previously suggested in a study of healthcare workers, in which exposure to disinfection
274 products was associated with a profile “undiagnosed/untreated asthma” (identified by
275 hierarchical clustering), characterized by numerous asthma symptoms, but low proportion of
276 physician diagnosed asthma, and moderate use of asthma medications [38].

277 In our study, we applied the recently updated asthma-specific JEM (OAsJEM) [17] to
278 assess occupational exposures. In occupational epidemiological studies, using a JEM, rather
279 than a questionnaire to assess exposure, is considered to reduce the risk of differential
280 misclassification between participants with or without the disease of interest. However, using
281 a JEM could also induce non-differential misclassification, partly due to disparities in tasks and
282 work conditions between subjects within a same job, which may be taken into account only by
283 applying a job-task-exposure matrix [39]. Transcoding operations which converted PCS 2003
284 French job codes into ISCO-88 international job codes could also introduce misclassification.
285 In a previous work in the French NutriNet-Santé cohort, where jobs were directly coded into
286 ISCO-88 classification (no transcoding), positive and higher associations were observed

287 between occupational exposures to irritants estimated with the OAsJEM and current adult-onset
288 asthma [18]. Associations between occupational exposures and asthma also differed according
289 to gender. We found more positive associations between lifetime occupational exposures to
290 irritants and current asthma in women than in men, but associations between irritant exposures
291 and asthma symptom score were generally stronger in men than in women, with significant
292 interactions in some cases. These differences could be explained by disparities in jobs and also
293 tasks between women and men within the same job [40]. Distinct sex-related
294 pathophysiological mechanisms might also contribute to these discrepancies between men and
295 women [41,42].

296 We observed more positive and stronger associations with asthma when studying
297 lifetime exposures than for current exposures. Furthermore, in contrast to lifetime exposures,
298 we observed some inverse associations between current exposures and both current asthma and
299 symptom score. This difference in findings for current and lifetime exposure was observed not
300 only for exposure to irritants, but also for well-known sensitizers (HMW and LMW agents),
301 especially in women. This phenomenon could partly be explained by a healthy worker effect,
302 which implies that working people are in better health than non-working people and asthmatics
303 with more symptoms could avoid more often tasks and jobs exposing them to irritants. This
304 selection bias can act at two levels: at recruitment (hire effect) and during employment (survivor
305 effect) [43]. In our study, the weaker associations observed with current exposures compared
306 to lifetime exposures could be explained by the fact that the subjects with asthma or asthma
307 symptoms have left past occupations with exposures that could worsen their health status. It
308 has been suggested that selection bias during employment is more important for women than
309 for men [43]. Beyond inverse associations observed when investigating current exposure, a
310 healthy worker effect (including hire effect) may have generally led to an underestimation of
311 associations in our study, and partly explain the modest associations observed. Interestingly,
312 associations observed for irritants exposure were of similar magnitude or higher than those
313 observed for HMW and LMW sensitizers, which are well-known causes of occupational
314 asthma.

315 This work is one of the first to assess associations between occupational exposures to
316 irritants, using the updated OAsJEM, and asthma and asthma symptom score in a large general
317 population cohort. One of the main strengths is the large size of the cohort, which favours the
318 detection of even modest associations. One original feature of the analyses is to evaluate asthma
319 according to several standardized definitions in a cohort from the general population and not in

320 a specific occupational sample (e.g., healthcare workers and cleaners). However, our study was
321 limited by its cross-sectional design, which prevents determining accurately whether exposure
322 occurred before or after asthma onset. In women, associations between irritant exposures and
323 current asthma were restricted to current adult-onset asthma, but in men DCPs exposures were
324 associated with current childhood-onset asthma. A lower statistical power with 2 times less
325 current adult-asthma in men than in women could partly explain the absence of significant
326 associations with adult-onset asthma in men. These findings probably also reflect an impact of
327 occupational exposures on both new onset asthma and the activity or aggravation of a pre-
328 existing (including childhood-onset) disease, which both have important consequences at
329 individual and society level [1]. Despite the use of a JEM to limit recall bias with respect to
330 exposure assessment, recall bias with respect to occupational history may still have occurred.
331 However, collection of occupational histories has been shown to be a reliable and valid method
332 [44]. Finally, our conclusions are limited by the relatively low observed associations with
333 ORs/MSR of 1.10 to 1.30 which should be interpreted with caution. More longitudinal data and
334 improved assessment of exposure to specific agents are needed to clarify the role of irritants in
335 asthma.

336 **CONCLUSION**

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

344

345 **Acknowledgments:** The authors thank the “Caisse nationale d’assurance maladie des
346 travailleurs salariés” (CNAMTS), the “Centres d’examens de santé » of the French Social
347 Security where cohort participants were included and the CONSTANCES respiratory group.

348 **Authors’ contributions:** GS contributed to the analysis and interpretation of the data, and
349 primary manuscript preparation. BD, FO, MG, CR, and MZ contributed to acquisition and
350 interpretation of the data and critical revision of the manuscript. LO, YI, BL, RN, NR, YR,
351 RV, CP were involved in the data interpretation and critical revision of the manuscript. NLM
352 and OD developed the study hypotheses, and contributed to data interpretation, primary
353 manuscript preparation and critical revision of the manuscript. All authors approved the final
354 version of the manuscript.

355 **Funding sources:** The CONSTANCES Cohort Study was funded by the Caisse nationale
356 d’assurance maladie des travailleurs salariés (CNAMTS), and benefits from a grant from the
357 French Commissariat général à l’investissement (ANR-11-INBS-0002). CONSTANCES also
358 receives funding from MSD and L’Oréal managed by INSERM-Transfert. Guillaume SIT has
359 benefited from a PhD scholarship, co-funded by DIM Qi2 (Domaine d’Intérêt Majeur Qi2,
360 Réseau de recherche Qualité de l’air en Ile-de-France) with the support of the Ile-de-France
361 Region and University of Paris-Saclay, France. This study was partly supported by The French
362 National Research Program for Environmental and Occupational Health of Anses (2020/01/047
363 – CONETRE).

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

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

371

372 **REFERENCES**

- 373 1 Tarlo SM, Lemiere C. Occupational Asthma. *N Engl J Med.* 2014;370:640–9.
- 374 2 GBD 2016 Occupational Chronic Respiratory Risk Factors Collaborators. Global and
375 regional burden of chronic respiratory disease in 2016 arising from non-infectious airborne
376 occupational exposures: a systematic analysis for the Global Burden of Disease Study 2016.
377 *Occup Environ Med.* 2020;77:142–50.
- 378 3 Blanc PD, Annesi-Maesano I, Balmes JR, *et al.* The Occupational Burden of Nonmalignant
379 Respiratory Diseases. An Official American Thoracic Society and European Respiratory
380 Society Statement. *Am J Respir Crit Care Med.* 2019;199:1312–34.
- 381 4 Henneberger PK, Redlich CA, Callahan DB, *et al.* An Official American Thoracic Society
382 Statement: Work-Exacerbated Asthma. *Am J Respir Crit Care Med.* 2011;184:368–78.
- 383 5 Kurt OK, Basaran N. Occupational Exposure to Metals and Solvents: Allergy and Airway
384 Diseases. *Curr Allergy Asthma Rep.* 2020;20:38.
- 385 6 Maestrelli P, Henneberger PK, Tarlo S, *et al.* Causes and Phenotypes of Work-Related
386 Asthma. *Int J Environ Res Public Health.* 2020;17:4713.
- 387 7 Vandenplas O, Godet J, Hurdubaea L, *et al.* Are high- and low-molecular-weight
388 sensitizing agents associated with different clinical phenotypes of occupational asthma?
389 *Allergy.* 2019;74:261–72.
- 390 8 Vandenplas O, Wiszniewska M, Raulf M, *et al.* EAACI position paper: irritant-induced
391 asthma. *Allergy.* 2014;69:1141–53.
- 392 9 Ronsmans S, Le Moual N, Dumas O. Update on irritant-induced occupational asthma. *Curr*
393 *Opin Allergy Clin Immunol.* 2023;23:63–9.
- 394 10 Bernstein JA, Dumas O, de Blay F, *et al.* Irritant-Induced Asthma and Reactive Airways
395 Dysfunction Syndrome. In: Tarlo SM, Vandenplas O, Bernstein DI, *et al.*, eds. *Asthma in*
396 *the workplace.* Boca Raton, FL: CRC Press 2021:251–60.
- 397 11 Reilly MJ, Wang L, Rosenman KD. The Burden of Work-related Asthma in Michigan,
398 1988–2018. *Ann Am Thorac Soc.* 2020;17:284–92.
- 399 12 Kennedy SM. Development of an asthma specific job exposure matrix and its application
400 in the epidemiological study of genetics and environment in asthma (EGEA). *Occup*
401 *Environ Med.* 2000;57:635–41.
- 402 13 Dumas O, Laurent E, Bousquet J, *et al.* Occupational irritants and asthma: an Estonian
403 cross-sectional study of 34 000 adults. *Eur Respir J.* 2014;44:647–56.
- 404 14 Zock J-P, Cavallé N, Kromhout H, *et al.* Evaluation of specific occupational asthma risks
405 in a community-based study with special reference to single and multiple exposures. *J Expo*
406 *Sci Environ Epidemiol.* 2004;14:397–403.
- 407 15 Le Moual N, Siroux V, Pin I, *et al.* Asthma Severity and Exposure to Occupational
408 Asthmogens. *Am J Respir Crit Care Med.* 2005;172:440–5.

- 409 16 Hoy RF, Burgess JA, Benke G, *et al.* Occupational Exposures and the Development of
410 New-onset Asthma: A Population-based Cohort Study From the Ages of 13 to 44 Years. *J*
411 *Occup Environ Med.* 2013;55:235–9.
- 412 17 Le Moual N, Zock J-P, Dumas O, *et al.* Update of an occupational asthma-specific job
413 exposure matrix to assess exposure to 30 specific agents. *Occup Environ Med.*
414 2018;75:507–14.
- 415 18 Sit G, Varraso R, Fezeu LK, *et al.* Occupational exposures to irritants and sensitizers,
416 asthma and asthma control in the NutriNet-Santé cohort. *The Journal of Allergy and*
417 *Clinical Immunology: In Practice.* 2022;10:3220–7.
- 418 19 Andrianjafimasy MV, Febrissy M, Zerimech F, *et al.* Association between occupational
419 exposure to irritant agents and a distinct asthma endotype in adults. *Occup Environ Med.*
420 2022;79:155–61.
- 421 20 Abrahamsen R, Fell AKM, Svendsen MV, *et al.* Association of respiratory symptoms and
422 asthma with occupational exposures: findings from a population-based cross-sectional
423 survey in Telemark, Norway. *BMJ Open.* 2017;7:e014018.
- 424 21 Lillienberg L, Andersson E, Janson C, *et al.* Occupational Exposure and New-onset Asthma
425 in a Population-based Study in Northern Europe (RHINE). *Ann Occup Hyg.* 2013;57:482–
426 92.
- 427 22 Archangelidi O, Sathiyajit S, Consonni D, *et al.* Cleaning products and respiratory health
428 outcomes in occupational cleaners: a systematic review and meta-analysis. *Occup Environ*
429 *Med.* 2021;78:604–17.
- 430 23 Dumas O, Gaskins AJ, Boggs KM, *et al.* Occupational use of high-level disinfectants and
431 asthma incidence in early- to mid-career female nurses: a prospective cohort study. *Occup*
432 *Environ Med.* 2021;78:244–7.
- 433 24 Torén K, Balder B, Brisman J, *et al.* The risk of asthma in relation to occupational
434 exposures: a case control study from a Swedish city. *Eur Respir J.* 1999;13:496–501.
- 435 25 LeVan TD, Koh W-P, Lee H-P, *et al.* Vapor, Dust, and Smoke Exposure in Relation to
436 Adult-Onset Asthma and Chronic Respiratory Symptoms - The Singapore Chinese Health
437 Study. *Am J Epidemiol.* 2006;163:1118–28.
- 438 26 Sit G, Letellier N, Iwatsubo Y, *et al.* Occupational Exposures to Organic Solvents and
439 Asthma Symptoms in the CONSTANCES Cohort. *Int J Environ Res Public Health.*
440 2021;18:9258.
- 441 27 Pilorget C, Lagarrigue R, Houot M. Évolution de l'exposition professionnelle aux solvants
442 oxygénés, pétroliers et chlorés en France entre 1999 et 2013. Résultats du programme
443 Matgéné. *Bull Epidemiol Hebd (Paris).* 2018;12–13:234–40.
- 444 28 Lucas D, Robin C, Vongmany N, *et al.* Main Causal Agents of Occupational Asthma in
445 France, Reported to the National Network for Occupational Disease Vigilance and
446 Prevention (RNV3P) 2001–2018. *Annals of Work Exposures and Health.* 2023;67:297–
447 302.

- 448 29 Goldberg M, Carton M, Descatha A, *et al.* CONSTANCES: a general prospective
449 population-based cohort for occupational and environmental epidemiology: cohort profile.
450 *Occupational and Environmental Medicine*. 2017;74:66–71.
- 451 30 Cazzoletti L, Marcon A, Janson C, *et al.* Asthma control in Europe: A real-world evaluation
452 based on an international population-based study. *Journal of Allergy and Clinical*
453 *Immunology*. 2007;120:1360–7.
- 454 31 Kauffmann F, Dizier M-H. EGEA (Epidemiological study on the Genetics and
455 Environment of Asthma, bronchial hyperresponsiveness and atopy)-design issues. *Clinical*
456 *& Experimental Allergy*. 1995;25:19–22.
- 457 32 Sunyer J, Pekkanen J, Garcia-Esteban R, *et al.* Asthma score: predictive ability and risk
458 factors. *Allergy*. 2007;62:142–8.
- 459 33 Caridi MN, Humann MJ, Liang X, *et al.* Occupation and task as risk factors for asthma-
460 related outcomes among healthcare workers in New York City. *Int J Hyg Environ Health*.
461 2019;222:211–20.
- 462 34 Le Moual N, Carsin A-E, Siroux V, *et al.* Occupational exposures and uncontrolled adult-
463 onset asthma in the European Community Respiratory Health Survey II. *Eur Respir J*.
464 2014;43:374–86.
- 465 35 Louis R, Satia I, Ojanguren I, *et al.* European Respiratory Society guidelines for the
466 diagnosis of asthma in adults. *Eur Respir J*. 2022;60:2101585.
- 467 36 Aaron SD, Boulet LP, Reddel HK, *et al.* Under-diagnosis and Over-diagnosis of Asthma.
468 *Am J Respir Crit Care Med*. 2018;198:1012–20.
- 469 37 Tiotiu AI, Novakova S, Labor M, *et al.* Progress in Occupational Asthma. *Int J Environ*
470 *Res Public Health*. 2020;17:4553.
- 471 38 Su F-C, Friesen MC, Humann M, *et al.* Clustering asthma symptoms and cleaning and
472 disinfecting activities and evaluating their associations among healthcare workers. *Int J*
473 *Hyg Environ Health*. 2019;S1438463918310174.
- 474 39 Quinot C, Dumas O, Henneberger P, *et al.* Development of a job-task-exposure matrix to
475 assess occupational exposure to disinfectants among US nurses. *Occup Environ Med*.
476 2017;74:130–7.
- 477 40 Eng A, Cheng S, Mannelje A, *et al.* Gender differences in occupational exposure patterns.
478 *Occup Environ Med*. 2011;68:888–94.
- 479 41 Becklake MR, Kauffmann F. Gender differences in airway behaviour over the human life
480 span. *Thorax*. 1999;54:1119–38.
- 481 42 Leynaert B, Real FG, Idrose NS, *et al.* Gender differences and sex-related hormonal factors
482 in asthma. *Asthma in the 21st Century*. Academic Press 2022:63–86.
- 483 43 Le Moual N, Kauffmann F, Eisen EA, *et al.* The Healthy Worker Effect in Asthma: Work
484 May Cause Asthma, but Asthma May Also Influence Work. *American Journal of*
485 *Respiratory and Critical Care Medicine*. 2008;177:4–10.

486 44 Teschke K. Occupational exposure assessment in case-control studies: opportunities for
487 improvement. *Occup Environ Med.* 2002;59:575–94.
488

489 Table 1 : Description of study population

	Men n = 51,865	Women n = 63,675
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	20.7	15.0
High school	14.7	15.1
2-3 years post-secondary	27.9	32.9
4-5 years post-secondary	39.4	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	71.8	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 Sensitizers	16.3	27.4
LMW Sensitizers	31.5	34.1

490 Data are presented as % unless otherwise stated;

491 BMI = Body Mass Index; HMW = High Molecular Weight; LMW = Low Molecular Weight;

492 DCPs = Disinfectants Cleaning Products

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 = 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	26,922	1	37,157	1		28,504	1	43,315	1	
Irritants	20,515	0.97 [0.91-1.03]	21,847	1.05 [1.00-1.11]	0.01	21,471	1.11 [1.07-1.15]	22,525	1.08 [1.05-1.11]	0.14
DCPs	6,898	1.10 [1.01-1.20]	18,197	1.06 [1.00-1.12]	0.87	7,164	1.21 [1.15-1.27]	18,725	1.09 [1.06-1.13]	0.005
Organic solvents	11,471	0.93 [0.87-1.01]	8,282	1.06 [0.98-1.14]	0.002	11,944	1.10 [1.05-1.15]	8,472	1.14 [1.10-1.19]	0.27

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

Table 3 : Associations between lifetime occupational exposure to known sensitizers 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	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	26,922	1	37,157	1		28,504	1	43,315	1	
HMW Sensitizers	38,174		51,180			35,019		52,958		
Exposed	6,240	1.12 [1.02-1.22]	14,023	1.05 [0.98-1.11]	0.41	6,515	1.16 [1.10-1.23]	14,471	1.05 [1.02-1.09]	0.001
Medium	3,893	1.09 [0.98-1.22]	6,670	1.00 [0.91-1.09]	0.51	4,063	1.17 [1.09-1.24]	6,704	1.05 [1.01-1.10]	0.01
High	2,347	1.16 [1.02-1.33]	7,533	1.09 [1.00-1.18]	0.94	2,452	1.16 [1.07-1.25]	7,767	1.06 [1.01-1.11]	0.04
LMW Sensitizers	39,307		50,950			41,377		52,711		
Exposed	12,385	0.96 [0.89-1.03]	13,793	1.03 [0.96-1.09]	0.04	12,873	1.09 [1.05-1.14]	14,224	1.04 [1.00-1.08]	0.06
Medium	9,353	0.95 [0.88-1.03]	12,333	1.03 [0.97-1.11]	0.12	9,733	1.06 [1.02-1.12]	12,714	1.03 [1.00-1.07]	0.28
High	3,032	0.99 [0.87-1.12]	1,460	0.96 [0.81-1.14]	0.67	3,140	1.18 [1.10-1.27]	1,510	1.09 [0.99-1.19]	0.15

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

Figure 1 : Associations between lifetime occupational exposure to irritants and current asthma according to exposure level

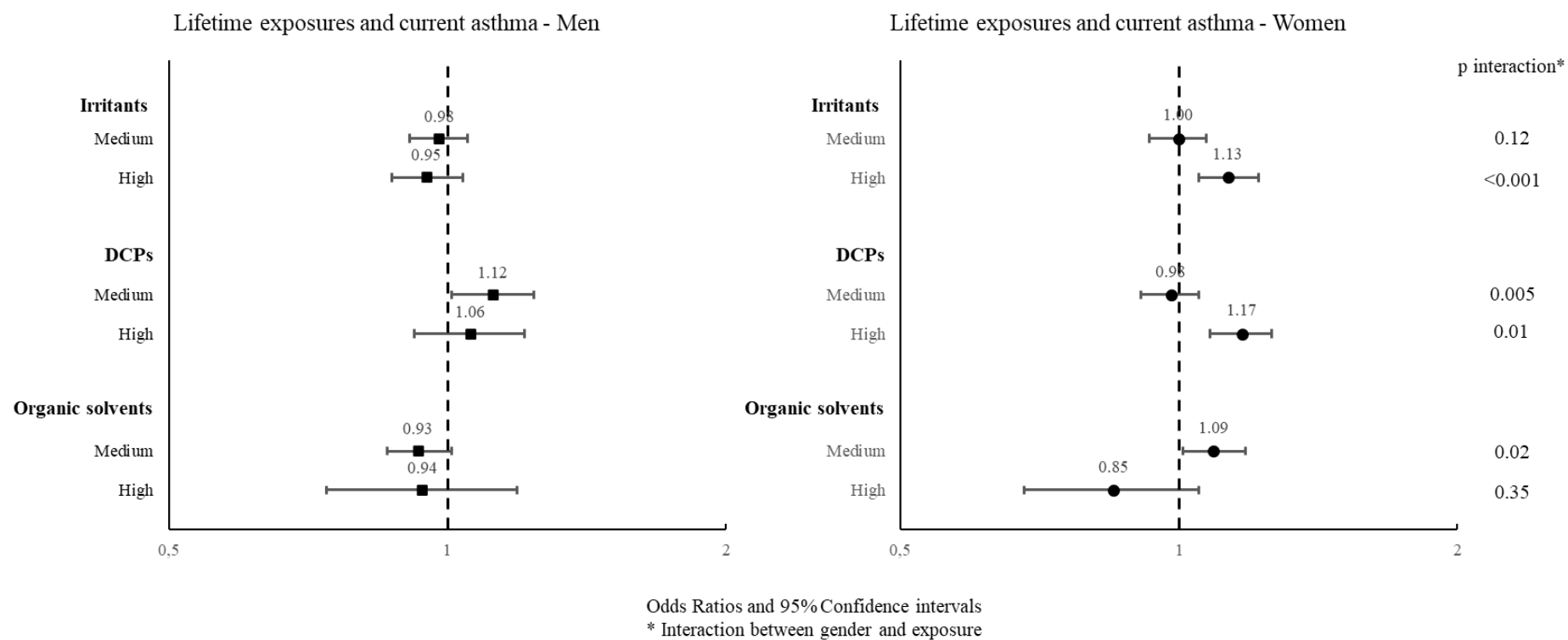


Figure 2 : Associations between lifetime occupational exposure to irritants and asthma symptom score according to exposure level

