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Association between household cleaning product exposure in infancy and development of recurrent wheeze and asthma

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1 *Association between household cleaning product exposure in infancy and development of*
2 *recurrent wheeze and asthma*

3

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19

20

21 *Abstract*

22 *Objective:* Household chemicals may act as irritants in the lungs, however their association with
23 recurrent wheeze and asthma in children remains controversial. We aimed to investigate if
24 household cleaning product exposure in infancy is associated with recurrent wheezing and
25 asthma development in children.

26 *Methods:* We analyzed data from two cohorts: MARC-35 consisting of 815 children with history
27 of severe bronchiolitis in infancy, and MARC-43 consisting of 525 healthy children in infancy.
28 Frequency of use of cleaning product at the child's home during infancy was collected via
29 telephone interview with parents. Outcomes were recurrent wheezing by age 3 years and asthma
30 diagnosis at age 6 years.

31 *Results:* In MARC-35, there was no association between cleaning product exposure in infancy
32 and recurrent wheeze (adjusted HR= 1.01 [95% CI 0.66-1.54] for 4-7 days/week exposure
33 frequency), nor asthma (adjusted OR= 0.91 [95% CI 0.51-1.63]). In MARC-43, there was also
34 no association between cleaning product exposure in infancy and recurrent wheeze (adjusted
35 HR= 0.69 [95% CI 0.29-1.67] for 4-7 days/week exposure frequency).

36 *Conclusions:* We found no association between household cleaning product exposure in infancy
37 and later development of recurrent wheeze or asthma, even among children who are high-risk for
38 asthma due to history of severe bronchiolitis.

39

40 *Keywords:* Child, Disinfectants, Asthma, Bronchiolitis, Lung

41

42 *INTRODUCTION*

43 Recurrent wheezing episodes during early childhood are common, affecting as much as one-fifth
44 of children up to two years of age, worldwide (Alvarez-Alvarez et al. 2018). By age 5-6 years,
45 some of these children will develop asthma, which is a leading cause of chronic disease in this
46 age group, affecting more than 4 million people under the age of 18 in the US according to the
47 Centers for Disease Control and Prevention (CDC) (2022).

48 Recurrent wheeze and asthma share common environmental risk factors, such as secondhand
49 smoke, mold, dust mites and other indoor air pollutants (Beasley et al. 2015, Herr et al. 2012).
50 Disinfectants and cleaning products may irritate the pulmonary mucosa and have been associated
51 with increased risk of wheezing and asthma in adults, both in studies examining occupational
52 exposures (e.g. in cleaning workers) (Casas et al. 2022; Archangelidi et al. 2021; Dumas et al.
53 2021; Sit et al. 2022; Sejbaek et al. 2021; De Troeyer et al. 2022) and exposures during house
54 cleaning (Casas et al. 2022; Lemire et al. 2022; Pacheco Da Silva et al. 2023; Pacheco Da Silva
55 et al. 2022; Weinmann et al. 2017; Zock et al. 2007). More recently, the impact of early-life
56 exposure to cleaning products on children's respiratory health has also been investigated (Casas
57 et al. 2022). In children, it is important to investigate both wheezing and asthma as outcomes,
58 since not all children that wheeze will develop asthma in the future (Mikeš et al. 2019). It is also
59 important to investigate the association of cleaning product use with recurrent wheezing (a risk
60 factor for asthma) as opposed to transient wheezing symptoms (Casas et al. 2022). While several
61 studies consistently found associations with increased risk of various types of wheezing (Casas et
62 al. 2013a; Herr et al. 2012; Henderson et al. 2008; Sherriff et al. 2005, Mikeš et al. 2019), only
63 one study (Parks et al. 2020) investigated specifically recurrent wheeze in children as an

64 outcome. In addition, the findings are inconsistent for childhood asthma as an outcome (Mikeš et
65 al. 2019; Nickmilder et al. 2007; Parks et al. 2020).

66 If household cleaning product exposure does indeed increase the risk for recurrent wheeze and
67 asthma in children, this is a modifiable environmental exposure that would be important to
68 counsel families to avoid, especially among children who are already high risk for asthma, such
69 as those with a history of severe bronchiolitis in infancy (Meissner 2016).

70 We aimed to investigate if household cleaning product exposure during infancy is associated
71 with increased risk of (i) recurrent wheezing by age 3 years, and (ii) asthma at age 6 years.

72

73 *METHODS*

74 *Study Design*

75 The 35th Multicenter Airway Research Collaboration (MARC-35) and the 43rd Multicenter
76 Airway Research Collaboration (MARC-43) are two ongoing prospective multicenter cohort
77 studies of US children (Geller et al. 2021; Hasegawa et al. 2016). Briefly, MARC-35 is a cohort
78 of 921 children from 17 sites across 14 US states that were recruited during three consecutive
79 winter seasons (from November 1 to April 30, 2011-2014) during a hospitalization with
80 bronchiolitis during their first year of life and followed-up until age 6 years (Geller et al. 2021;
81 Hasegawa et al. 2016). MARC-43 is a cohort of 599 healthy children in infancy (i.e., without
82 known major medical conditions or previous hospitalization for a breathing problem), recruited
83 during a well-child or other clinical visit in 4 sites (subset of the 17 centers in MARC-35) in
84 2017, and followed-up until age 6 years. Parents/guardians of all children provided informed
85 consent and all participating hospitals had local approval of their institutional review board.

86 MARC-35 participants and MARC-43 participants were followed longitudinally via structured
87 parent telephone interviews every six months (biannual), conducted by trained interviewers.

88 *Exposure*

89 Exposure to cleaning product in the first year of life was collected via telephone interviews with the
90 families when the child was aged 42 and 54 months. The question about cleaning products was
91 adapted from the European Community Respiratory Health Survey (ECRHS) (Zock et al. 2007).
92 We used answers primarily from the 42-month interview, and if data was missing, we used
93 answers from the 54-month interview. Parents were asked, “During your child’s first year of life,
94 how often did anyone use cleaning products (for example, cleaning sprays, bleach, multi-purpose
95 cleaners) at home?”. Responses were categorized as <1 day/week, 1-3 days/week and 4-7
96 days/week.

97 *Outcomes*

98 Recurrent wheeze by age 3 years was defined as at least 2 corticosteroid-requiring exacerbations
99 in 6 months or having at least 4 wheezing episodes in 1 year that last at least 1 day and affect
100 sleep, based on parent report (National Asthma Education and Prevention Program 2007), as
101 described in detail elsewhere (Dumas et al. 2019). Briefly, at each follow-up interview, data were
102 collected about the child’s prescribed medication (i.e., inhaled corticosteroids or montelukast)
103 and “breathing problem” episodes (which were defined specifically to the parents) since the last
104 follow-up interview. For each reported breathing problem, parents were also asked about the date
105 when the breathing problem started and about the medication used. These data were compiled to
106 assess recurrent wheezing by age 3 years.

107 Age 6-year asthma was based on a commonly used epidemiologic asthma definition, consisted of
108 parent report of clinician-diagnosed asthma by age 6 years and the presence of either asthma
109 medications or asthma symptoms during age 5.0-5.9 years (Geller et al. 2021). The parent report
110 of clinician-diagnosed asthma was validated in a subset population of MARC-35 cohort, and
111 demonstrated high sensitivity and specificity when compared to medical record data (Geller et al.
112 2021)

113 Data on recurrent wheeze by age 3 years was available in both cohorts. At the time of analyses,
114 data on age 6-year asthma was only available in MARC-35.

115 *Covariates*

116 Data on covariates were collected during enrollment or follow-up parental interviews. We
117 considered asthma risk factors known in the literature and confounders commonly included in
118 similar studies. Additional factors were considered if they were both known asthma risk factors,
119 and associated with exposure in our cohorts (suggestive association with $p \leq 0.20$ in at least one
120 cohort). In the main model (Model 1), we adjusted for sex, race/ethnicity, median household
121 income, number of siblings, and breastfeeding. In Model 2, we further adjusted for cesarian-
122 section and maternal smoking during pregnancy.

123 *Data analysis*

124 We used Cox proportional hazards models in both cohorts when the outcome was recurrent
125 wheezing (time to event analysis). We used logistic regression models to study the association
126 between cleaning product exposure and asthma in MARC-35. A two-sided $P < 0.05$ was
127 considered statistically significant.

128 *RESULTS*

129 *Children with history of severe bronchiolitis in infancy (MARC-35)*

130 Out of 921 children, 837 (91%) parents responded to the 42-month or 54-month interviews. We
 131 further excluded 22 children with missing data for the question on cleaning habits at both
 132 interviews. Non-respondents/excluded participants, compared to those included, did not differ
 133 for sex, ethnicity, or recurrent wheezing by age 3 years (all $p > 0.15$).

134 There were 815 children with available data in MARC-35 for analyses of recurrent wheezing by
 135 age 3 years, and 804 children for analyses of asthma by age 6 years. A total of 268 children
 136 (33%) had recurrent wheezing, and 222 (28%) had asthma. In this population, 10% of the parents
 137 reported that cleaning products were used in the home <1 day/week, 54% 1-3 days/week, and
 138 36% 4-7 days/week. Participant's characteristics according to household cleaning habits are
 139 summarized in Table 1. In MARC-35, participant's characteristics associated with higher
 140 household use of cleaning products were: Hispanic and non-Hispanic black ethnicity, median
 141 household income <\$40,000, higher number of children in the home and no breastfeeding.

Table 1. Participant's characteristics according to household use of cleaning products, cohort of infants hospitalized for bronchiolitis (MARC-35)

	All (n=815)	Less than once a week (n=79)	1-3 days/week (n=442)	4-7 days/week (n=294)	p
Female sex	40 (n=330)	39	41	39	0.85
Race/ethnicity					
Non-Hispanic white	46 (n=375)	61	46	41	0.007
Non-Hispanic black	23 (n=181)	10	24	23	
Hispanic	29 (n=238)	24	27	34	
Non-Hispanic other	2 (n=21)	5	3	2	
Median household income by ZIP code					
<\$40,000	30 (n=241)	14	31	32	0.04

\$40,000 to \$79,999	20 (n=160)	22	21	18	
≥\$80,000	23 (n=187)	33	23	21	
Missing	28 (n=227)	32	26	29	
Housing type					0.95
House	70 (n=573)	73	70	70	
Apartment	27 (n=220)	24	28	27	
Other	3 (n=22)	3	2	3	
Premature birth (≤37 weeks)	18 (n=145)	15	17	20	0.52
Cesarean section	34 (n=275)	28	33	38	0.20
Number of children in the home					
1	22 (n=177)	27	22	20	0.01
2	38 (n=314)	51	39	35	
3+	40 (n=324)	23	39	45	
Daycare attendance*	52 (n=414)	58	52	51	0.55
Breastfeeding†	48 (n=373)	62	48	45	0.03
Maternal smoking during pregnancy	14 (n=111)	13	14	14	0.96
Passive smoke exposure during early life (≤2 years)	15 (n=126)	19	16	14	0.59
Parental history of asthma	33 (n=268)	34	34	31	0.77
*3% missing data. †6% missing data Results are presented as percentages (observed proportion in the study population and within each exposure frequency), unless otherwise specified.					

142

143 There was no significant association between cleaning product exposure in infancy and recurrent
144 wheeze (adjusted HR=0.79 [95% CI 0.52-1.20] and 1.01 [95% CI 0.66-1.54] for 1-3 and 4-7
145 days/week exposure frequency, respectively), nor asthma (adjusted OR= 0.81 [95% CI 0.46-
146 1.42] and 0.91 [95% CI 0.51-1.63]). (Table 2)

Table 2. Association between household use of cleaning products and recurrent wheezing / asthma, cohort of infants hospitalized for bronchiolitis (MARC-35, n=815)			
	Less than once a week (n=79)	1-3 days/week (n=442)	4-7 days/week (n=294)
<i>Recurrent wheezing, n (%)</i>	28 (35%)	135 (31%)	105 (36%)
Adjusted HR, model 1	1	0.79 (0.52-1.19)	1.02 (0.67-1.56)
Adjusted HR, model 2	1	0.79 (0.52-1.20)	1.01 (0.66-1.54)
<i>Asthma*, n (%)</i>	22 (29%)	114 (26%)	86 (29%)
Adjusted OR, model 1	1	0.82 (0.47-1.44)	0.94 (0.53-1.67)
Adjusted OR, model 2	1	0.81 (0.46-1.42)	0.91 (0.51-1.63)
HR: hazard ratio; OR: odds ratio. *Analyses performed in 790 children. Model 1: adjusted for sex, race/ethnicity, median household income, number of siblings, breastfeeding. Model 2: adjusted for sex, race/ethnicity, median household income, number of siblings, breastfeeding, c-section, maternal smoking during pregnancy Missing values for confounders were handled by including a missing value category for variables with $\geq 3\%$ missing data (breastfeeding and household income), and by exclusion for variables with $< 3\%$ missing data (9 missing observation on c-section; model 2 included n=806 observations).			

148

149 *Healthy children in infancy (MARC-43)*

150 Out of 599 children, 527 (88%) parents responded to the 42-month or 54-month interviews. We
 151 further excluded 2 children with missing data for the question on cleaning habits at both
 152 interviews. Non-respondents/excluded participants, compared to those included did not differ for
 153 sex, ethnicity, or recurrent wheezing by age 3 years (all $p > 0.15$).

154 There were 525 children with available data in MARC-43 of which 38 children (7%) had
 155 recurrent wheezing. In this population, 18% of the parents reported that cleaning products were
 156 used in the home < 1 day/week, 49% 1-3 days/week, and 33% 4-7 days/week. Participant's
 157 characteristics according to household cleaning habits are summarized in Table 3. Similarly to
 158 MARC-35, in MARC-43, characteristics associated with higher household cleaning product use

159 were: Hispanic and non-Hispanic black ethnicity, median household income <\$40,000, higher
 160 number of children in the home and no breastfeeding.

Table 3. Participant's characteristics according to household use of cleaning products, cohort of healthy infants (MARC-43)

	All (n=525)	Less than once a week (n=94)	1-3 days/week (n=259)	4-7 days/week (n=172)	p
Female sex	49 (n=259)	45	48	54	0.28
Race/ethnicity					
Non-Hispanic white	44 (n=233)	68	41	36	<0.001
Non-Hispanic black	30 (n=155)	11	31	37	
Hispanic	21 (n=111)	15	21	24	
Non-Hispanic other	5 (n=26)	6	6	2	
Median household income by ZIP code					
<\$40,000	33 (n=171)	22	31	40	<0.001
\$40,000 to \$79,999	11 (n=60)	12	13	9	
≥\$80,000	34 (n=178)	55	32	25	
Missing	22 (n=116)	11	24	26	
Housing type*					
House	70 (n=366)	66	72	69	0.60
Apartment	30 (n=155)	34	28	30	
Premature birth (≤37 weeks)	10 (n=54)	9	12	9	0.61
Cesarean section	32 (n=170)	26	33	35	0.27
Number of children in the home					
1	39 (n=205)	56	42	25	<0.001
2	33 (n=175)	30	33	36	
3+	28 (n=145)	14	25	39	
Daycare attendance	60 (n=314)	65	59	58	0.53
Breastfeeding*	64 (n=333)	73	64	59	0.08
Maternal smoking during pregnancy	9 (n=47)	6	8	12	0.18
Passive smoke exposure during early life (≤2 years)	7 (n=37)	3	7	9	0.23
Parental history of asthma	31 (n=162)	33	29	33	0.53

*1% missing data.

Results are presented as percentages (observed proportion in the study population and within each exposure level).

161
162 There was no significant association between cleaning product exposure in infancy and recurrent
163 wheeze (adjusted HR=0.46 [95% CI 0.20-1.09] and 0.69 [95% CI 0.29-1.67] for 1-3 and 4-7
164 days/week exposure frequency, respectively) (Table 4).

Table 4. Association between household use of cleaning products and recurrent wheezing / asthma, cohort of healthy infants (MARC-43, n=525)

	Less than once a week (n=94)	1-3 days/week (n=259)	4-7 days/week (n=172)
<i>Recurrent wheezing, n (%)</i>	10 (11%)	14 (5%)	14 (8%)
Adjusted HR, model 1	1	0.46 (0.20-1.07)	0.70 (0.29-1.67)
Adjusted HR, model 2	1	0.46 (0.20-1.09)	0.69 (0.29-1.67)

HR: hazard ratio.

Model 1: adjusted for sex, race/ethnicity, median household income, number of siblings, breastfeeding.

Model 2: adjusted for sex, race/ethnicity, median household income, number of siblings, breastfeeding, c-section, maternal smoking during pregnancy.

Missing values for confounders were handled by including a missing value category for variables with $\geq 3\%$ missing data (household income), and by exclusion for variables with $< 3\%$ missing data (6 missing values for breastfeeding; models 1-2 included n=519 observations).

165
166 **DISCUSSION**
167 In two prospective multicenter cohorts of US children, we did not find an association between
168 cleaning product exposure and respiratory outcomes, both in children with high risk for asthma
169 due to history of severe bronchiolitis in infancy, and in children with no specific risk for asthma.
170 Previous studies examining wheezing outcomes were quite consistent for an association with
171 early life exposure to cleaning products, regardless of the wheezing phenotype analyzed (Casas
172 et al. 2022; Casas et al. 2013a; Herr et al. 2012; Henderson et al. 2008; Sherriff et al. 2005,
173 Mikeš et al. 2019; Parks et al. 2020). Our study, however, specifically examined the outcome

174 recurrent wheezing, with the aim to distinguish children with high risk of developing asthma
175 from children with transient wheezing symptoms, which may explain discrepancies with
176 previous literature studying more common wheezing phenotypes (Casas et al. 2022).

177 In studies examining childhood asthma, the results have been more conflicting (Mikeš et al.
178 2019; Parks et al. 2020). In a Canadian birth cohort, higher use of cleaning products in infancy
179 was associated with increased risk of asthma at age 3 years, although reliable asthma diagnosis is
180 difficult at this age (Parks et al. 2020). In contrast, among Czech children, Mikes et al. (2019) did
181 not find an association between cleaning product use during infancy and school-age asthma.
182 They hypothesized that these results may be due to low number of events in the study
183 population. A novelty of our study was to include a cohort of children with a history of severe
184 bronchiolitis in infancy (MARC-35 cohort), which is a predictor of long-term respiratory
185 morbidity, including increased rates of recurrent wheezing and asthma (Meissner 2016).
186 Accordingly, 28% of these children were diagnosed as having asthma at age 6 years. Despite the
187 increased power, we did not find any association with exposure to cleaning products, which
188 suggests that this factor did not further increase risk of asthma in this high-risk population.

189 The fact that the children are indirectly exposed to cleaning products (in contrast to adults who
190 do cleaning tasks themselves) may also contribute to our results. For instance, Bédard et al.
191 (2014) found that current asthma was increased in women directly involved in cleaning activities
192 at home, while no association was found in those having the house cleaned by household help. In
193 children, some of the previous studies reported associations between maternal use of cleaning
194 products during pregnancy, which may represent a more direct (prenatal) exposure for the child,
195 and respiratory outcomes (Casas et al. 2013a; Henderson et al. 2008). Similar findings have been
196 suggested for maternal occupational exposure to cleaning products, prior to conception and

197 during pregnancy, although results vary across studied outcomes (Forster et al. 2023; Kojima et
198 al. 2022; Tjalvin et al. 2022). This emphasizes the importance of collecting data on use of
199 cleaning products at different exposure windows in future studies.

200 Our study also has some limitations. Firstly, exposure was assessed through parental report only,
201 which makes it susceptible to both differential and non-differential misclassification.
202 Furthermore, we assessed exposure retrospectively and there was a gap between when the
203 exposure occurred (first year of life) and when we asked parents about it (when the children were
204 either 42 or 54 months old). However, differential misclassification or “recall bias” (parents
205 recalling information differently according to their children’s health) is unlikely to explain the
206 absence of association observed in our study, since it would likely cause an overestimation of the
207 association. In contrast, the observed associations may have been underestimated because of
208 non-differential misclassification. However, parental report is commonly used in similar studies.
209 In our study, the question asked was simple (general use of cleaning products in the home), as
210 we thought parents would be more likely to remember these general habits than specific types of
211 products. We did not collect detailed data on the type of chemicals and the form of products used
212 during the cleaning, in contrast with previous studies that used composite scores based on
213 different cleaning agents use (Mikes et al. 2019; Parks et al. 2020; Bédard et al. 2014; Casas et
214 al. 2013a; Henderson et al. 2008) or distinguishing products used in spray form, which lead to a
215 higher degree of inhalation when compared to liquid products (Casas et al. 2013b). However, it
216 is important to note that even the more detailed questionnaires are still subject to
217 misclassification bias since many parents do not know the exact composition of each product
218 used at home. Our study also did not address whether the child was at home or not during the
219 cleaning, nor the ventilation condition during the cleaning. Although these factors are likely to

220 modulate the children exposure levels, experimental studies have shown that the air
221 concentrations of volatile organic compounds reach the background level 1–2 hours after cleaning
222 product application, and that some compounds are further released slowly from the surfaces,
223 creating potential for exposure hours after the cleaning activities are performed (Bello, 2009).
224 The impact of the composition and form of cleaning products merits further investigation in
225 children, as well as the conditions in the environment while the cleaning product use happens,
226 such as ventilation. Future studies should also focus on addressing the association between
227 household cleaning product exposure and recurrent wheezing, as opposed to more common types
228 of wheezing, such as transient.

229

230 *CONCLUSIONS*

231 In conclusion, we found no association between household cleaning product exposure in infancy
232 and later development of recurrent wheeze or asthma, even among children who are high-risk for
233 asthma due to a history of severe bronchiolitis. Our results contradict previous literature,
234 especially regarding the recurrent wheezing outcome. Therefore, further studies are needed to
235 determine whether early life exposure to cleaning products is mainly associated with transient
236 wheezing symptoms in early childhood or has long-term impact on children's respiratory health.

237

238 *DECLARATIONS*

239 *Competing interests:* The authors have no competing interests to declare that are relevant to the
240 content of this article.

241 *Data availability:* The datasets analyzed during the current study are not publicly available due
242 to privacy or ethical restrictions but are available from the corresponding author on reasonable
243 request.

244 *Author contributions:* All authors contributed to the study conception and design. Material
245 preparation, data collection and analysis were performed by Oriane Dumas. The first draft of
246 the manuscript was written by Isis F. Baroni and all authors commented on previous versions of
247 the manuscript. All authors read and approved the final manuscript.

248 *Ethics approval:* All participating hospitals had local approval of their institutional review board.

249 *Consent to participate:* Informed consent was obtained from legal guardians.

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