



HAL
open science

Factors Associated with Asthma Severity in Children: Data from the French COBRAPed Cohort

Guillaume Lezmi, Stéphanie Lejeune, Isabelle Pin, Sylvain Blanchon, Naïm Bouazza, Valérie Jolaine, Christophe Marguet, Véronique Houdoin, Patrick Berger, Michael Fayon, et al.

► **To cite this version:**

Guillaume Lezmi, Stéphanie Lejeune, Isabelle Pin, Sylvain Blanchon, Naïm Bouazza, et al.. Factors Associated with Asthma Severity in Children: Data from the French COBRAPed Cohort. *Journal of Allergy and Clinical Immunology: In Practice*, 2021, 9 (5), pp.1969-1979. 10.1016/j.jaip.2020.12.027 . hal-03238438

HAL Id: hal-03238438

<https://u-paris.hal.science/hal-03238438>

Submitted on 9 May 2023

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 **Factors associated with asthma severity in children: data from the French COBRAPed**

2 **Cohort**

3

4 **Guillaume Lezmi, MD, PhD^{1,2}§, Stéphanie Lejeune, MD^{3,4}§, Isabelle Pin, MD⁵, Sylvain**

5 **Blanchon, MD, PhD⁶, Naïm Bouazza, PhD⁷, Valérie Jolaine, MD⁷, Christophe Marguet, MD,**

6 **PhD⁸, Véronique Houdoin, MD, PhD⁹, Patrick Berger, MD, PhD¹⁰, Michael Fayon, MD,**

7 **PhD¹¹, Jean-Christophe Dubus, MD, PhD¹², Philippe Reix, MD, PhD¹³, Mathieu Pellan, MD¹⁴,**

8 **Jacques Brouard, MD, PhD¹⁵, Raphael Chiron, MD¹⁶, Lisa Giovannini-Chami, MD, PhD¹⁷,**

9 **Antoine Deschildre, MD^{3,4}, Jacques de Blic, MD, PhD^{1,2}, on behalf of the COBRAPed Study**

10 **Group.**

11 **§ Both authors contributed equally to this work**

12

13 *¹ Université de Paris, Institut Necker Enfants Malades, Equipe Immunorégulation et*
14 *Immunopathologie, Inserm UMR1151, CNRS UMR8253, F-75015, Paris France.*

15 *² Service de Pneumologie et Allergologie Pédiatriques, AP-HP, Hôpital Necker-Enfants*
16 *Malades, F-75015, Paris, France.*

17 *³Univ. Lille, CHU Lille, Pediatric pulmonology and allergy department. Hôpital Jeanne de*
18 *Flandre, Lille, France.*

19 *⁴Univ. Lille, LIRIC UMR 995 Inserm, Clinical Investigation Center, CIC-1403-Inserm-CHU, Lille,*
20 *France*

21 *⁵Pédiatrie. CHU Grenoble Alpes; INSERM, Institute for Advanced Biosciences; Université*
22 *Grenoble Alpes; Grenoble, France.*

23 *⁶Children Hospital, Pediatric Pulmonology and Allergology Unit CHU Toulouse, Toulouse,*
24 *France*

25 ⁷Paris Descartes Necker - Cochin Clinical Research Unit, Assistance Publique-Hôpitaux de
26 Paris, Paris, France

27 ⁸EA3830-GHRV, Rouen University, France, Pediatric Respiratory and Allergic Diseases, CF
28 reference center, Rouen University Hospital-Charles Nicolle, Rouen, France

29 ⁹Robert Debré Hospital, Pediatric Pulmonology and Allergology, University of Paris, Paris,
30 France, University of Paris Diderot, Sorbonne Paris Cité, INSERM UMR S976, Paris, France.

31 ¹⁰Univ. Bordeaux, Centre de Recherche Cardio-Thoracique de Bordeaux, INSERM, U1045,
32 Bordeaux, France

33 ¹¹CHU de Bordeaux, Unité de pneumologie pédiatrique, Centre d'Investigation Clinique (CIC
34 1401), Bordeaux, France

35 ¹²Unité de pneumopédiatrie CHU Timone-Enfants, Aix-Marseille Université, IRD MEPHI, IHU
36 Méditerranée-Infection, Marseille, France

37 ¹³Service de Pneumologie, Allergologie et Mucoviscidose Pédiatrique, CHU de Lyon, Lyon,
38 France. UMR 5558 (EMET), CNRS, LBBE, Université de Lyon, Villeurbanne, France.

39 ¹⁴Service de Pédiatrie, CHU Jean Verdier, Bondy, France

40 ¹⁵Service de Pédiatrie Médicale, CHU Caen, Caen, France. Groupe de Recherche sur
41 l'Adaptation Microbienne (GRAM 2.0), Normandie Université, Caen, France

42 ¹⁶Pediatric department, Montpellier university Hospital, Montpellier, France

43 ¹⁷Pediatric Pulmonology Department, Lénal University Hospital, Nice, France

44

45 Dr. Lezmi reports personal fees from novartis pharma, personal fees from Astra zeneca, personal fees from
46 YSSUP research, during the conduct of the study; personal fees from DBV technologies, personal fees from
47 Aimune therapeutics, outside the submitted work; Dr. Lejeune reports grants from GSK, grants from
48 Stallergènes, grants from Chiesi, grants from Novartis, grants from MundiPharma, grants from Chancellerie
49 des Universités de Paris (legs Gaston Poix), during the conduct of the study; other from Novartis Pharma,
50 grants from Astra Zeneca, personal fees from Mayoli-Spindler, personal fees from Icomed, personal fees from
51 ALK-Abello, other from Novartis, outside the submitted work; Dr. PIN reports other from NOVARTIS, other
52 from ASTRA ZENECA, non-financial support and other from AGIRàdom, outside the submitted work; Dr .
53 BLANCHON has nothing to disclose; N. BOUAZZA reports grants from GSK, grants from Stallergènes, grants
54 from Chiesi, grants from Novartis, grants from MundiPharma, grants from Chancellerie des Universités de
55 Paris (legs Gaston Poix), during the conduct of the study; V.Jolaine reports grants from GSK, grants from
56 Stallergènes, grants from Chiesi, grants from Novartis, grants from MundiPharma, grants from Chancellerie
57 des Universités de Paris (legs Gaston Poix), during the conduct of the study; Pr. MARGUET reports personal
58 fees and non-financial support from NOVARTIS, personal fees and non-financial support from ALK, non-
59 financial support from GSK, personal fees and non-financial support from TEVA, personal fees from MYLAN
60 (MEDA), during the conduct of the study; Dr. Houdouin reports grants from GSK, grants from Stallergènes,
61 grants from Chiesi, grants from Novartis, grants from MundiPharma, grants from Chancellerie des Universités
62 de Paris (legs Gaston Poix), during the conduct of the study; Dr. Berger reports grants from GSK, grants from
63 Stallergènes, grants from Chiesi, grants from Novartis, grants from MundiPharma, grants from Chancellerie
64 des Universités de Paris (legs Gaston Poix), during the conduct of the study; grants, personal fees and non-
65 financial support from Novartis, personal fees and non-financial support from Chiesi, grants, personal fees and
66 non-financial support from Boehringer Ingelheim, personal fees and non-financial support from AstraZeneca,
67 personal fees and non-financial support from Sanofi, personal fees from Menarinni, personal fees from TEVA,
68 personal fees from Clrcassia, outside the submitted work; Pr. FAYON reports grants from GSK, grants from
69 Stallergènes, grants from Chiesi, grants from Novartis, grants from MundiPharma, grants from Chancellerie
70 des Universités de Paris (legs Gaston Poix), during the conduct of the study; Pr. Dubus reports grants from
71 GSK, grants from Stallergènes, grants from Chiesi, grants from Novartis, grants from MundiPharma, grants
72 from Chancellerie des Universités de Paris (legs Gaston Poix), during the conduct of the study; Dr. reix reports
73 grants from GSK, grants from Stallergènes, grants from Chiesi, grants from Novartis, grants from
74 MundiPharma, grants from Chancellerie des Universités de Paris (legs Gaston Poix), during the conduct of the
75 study; Dr. Pellan reports grants from GSK, grants from Stallergènes, grants from Chiesi, grants from Novartis,
76 grants from MundiPharma, grants from Chancellerie des Universités de Paris (legs Gaston Poix), during the
77 conduct of the study; Pr. BROUARD has nothing to disclose; Dr. Chiron has nothing to disclose; Dr.
78 Giovannini-chami reports personal fees from novartis pharma, grants and personal fees from Astra zeneca,
79 from Stallergènes, personal fees from Sanofi, during the conduct of the study; Dr. DESCHILDRE reports
80 personal fees and other from Novartis, personal fees and other from ALK, personal fees from TEVA, personal
81 fees from GSK, grants and personal fees from stallergenes greer , personal fees and other from CHIESI,
82 personal fees from Aimmune Therapeutics, personal fees and other from DBV Technologies, other from Astra
83 Zeneca, other from Mylan , other from Nutricia , personal fees from Nestlé Health Science, outside the
84 submitted work; Pr. de BLIC reports grants from GSK, grants from Stallergènes, grants from Chiesi, grants
85 from Novartis, grants from MundiPharma, grants from Chancellerie des Universités de Paris (legs Gaston
86 Poix), during the conduct of the study.

87

88

89 **Funding information**

90 This study was funded by the “Chancellerie des Universités de Paris (legs Gaston Poix)” and
91 grants from GSK, Stallergènes, Chiesi, Novartis, and Mundi Pharma Laboratories.

92 **Correponding author:**

93 Jacques de Blic, AP-HP, Hôpital Necker-Enfants Malades, Service de Pneumologie et

94 Allergologie Pédiatriques, Université Paris Descartes, Paris, France.

95 +33144494838

96 deblicj@gmail.com

97

98

99 **Highlight Box**

100 1. What is already known about this topic? Environmental factors and allergic disorders are
101 associated with the severity of pediatric severe asthma.

102 2. What does this article add to our knowledge? We found that factors associated with
103 asthma severity in children may differ according to age. In preschoolers, environmental
104 factors are predominant, whereas allergic disorders are mainly involved at school age.

105 3. How does this study impact current management guidelines? Our results highlight the
106 need to explore household exposure at least in preschoolers, and confirm the importance of
107 controlling associated allergic disorders.

108

109 **Key words:** Severe asthma, preschool, school-age, phenotype

110

111 **Word count: 2998**

112 **Abstract word count: 220**

113 **Number of figures: 2**

114 **Number of tables: 6**

115

116 **List of abbreviations**

117 ACT: Asthma Control Test

118 AD: atopic dermatitis

119 AR: allergic rhinitis

120 BD: bronchodilator

121 BMI: body mass index

122 FA: food allergy

123 FeNO: fractional exhaled nitric oxide

124 FVC: forced vital capacity

125 GER: gastroesophageal reflux

126 GINA: Global Initiative for Asthma

127 ICS: inhaled corticosteroids

128 ICU: intensive care unit

129 FEV1: forced expiratory volume in the first second

130 LABA: long-acting β -agonist

131 LRTA: Leukotriene receptor antagonist

132 NSA: non-severe asthma

133 NSRW: non-severe recurrent wheeze

134 PAQLQ: Pediatric Asthma Quality-of-Life Questionnaire

135 SA: severe asthma

136 SRW: severe recurrent wheeze

137 SABA: short-acting β -agonist

138 SHS: second hand smoke

139 SPT: skin-prick test

140 WA: weeks of amenorrhea

141 **Abstract**

142 **Background:** Severe asthma (SA) in children is a complex, heterogeneous disease, associated
143 with a considerable burden in children. However, factors influencing asthma severity are
144 poorly described and may differ according to age.

145 **Objective:** To determine whether factors associated with asthma severity differ between
146 preschoolers with severe recurrent wheeze (SRW) and school-age children with SA.

147 **Patients and methods:** Data from the French multicenter prospective observational cohort
148 of preschool (3-6 years) children with SRW and non-severe recurrent wheeze (NSRW) and
149 school-age (7-11 years) children with SA and non-severe asthma (NSA) (COBRAPed) were
150 analyzed.

151 **Results:** 131 preschool children (92 SRW and 49 NSRW) and 207 school-age children (92 SA
152 and 115 NSA) were included. In both univariable and multi-variable analysis, SRW was
153 associated with SHS exposure (multi-variable analysis, OR [95%CI], 29.8 [3.57-3910]), and
154 exposure to mold/dampness at home (multi-variable analysis: OR [95%CI], 4.22 [1.25-18.2])
155 compared with NSRW. At school-age, history of atopic dermatitis and food allergy were
156 more frequent in children with SA than in those with NSA. Multi-variable analysis confirmed
157 that SA was associated with a history of food allergy (OR: 5.01 [2.23-11.9]).

158 **Conclusion:** Our data suggest that factors influencing asthma severity may differ according
159 to age. In preschool children with SRW, second-hand smoke and exposure to mold are
160 predominant, whereas associated allergic disorders are mainly involved in SA at school age.

161

162

163 **Introduction**

164 Pediatric asthma is a heterogeneous condition with multiple phenotypes associated with
165 different mechanisms or endotypes, both in preschool [1–4] and at school-age [5–8]. Asthma
166 is well controlled for most children with low-to-medium doses of inhaled corticosteroids
167 (ICS) and when modifiable factors are addressed. Severe asthma (SA) and severe recurrent
168 wheeze (SRW) [9, 10], were defined by the need for high doses of ICS and an additional
169 controller medication to maintain control or persistent poor control despite appropriate
170 treatment [11]. Although those entities affect less than 5% of children with asthma, their
171 burden in terms of symptoms, alteration of quality of life, and economic costs is
172 disproportionately high [12–14]. Recent studies have described multiple phenotypes of SA
173 and SRW, with variable degrees of allergic sensitization and different patterns of airway
174 inflammation [15–17]. Factors influencing asthma severity throughout childhood are poorly
175 understood [18], and it remains unclear whether SA and SRW are driven by common
176 pathological processes.

177 Better characterization of the factors associated with asthma severity is crucial to improve
178 the management of patients and move forward in precision medicine. The Pediatric Cohort
179 of Bronchial Obstruction and Asthma (COBRAPed) is a French multicenter prospective
180 observational cohort of preschool (3-6 years) and school-age children (7-12 years) with
181 asthma, providing clinical, biological, and functional data with longitudinal follow-up. Design
182 and inclusions were conducted in parallel with the adult COBRA cohort [19].

183 The main objectives of this cross-sectional exploratory analysis were to describe the baseline
184 characteristics of the population and to identify factors associated with asthma severity in
185 preschool and school-age children.

186

187 **Patients and methods**

188 COBRAPed is a prospective, observational cohort study initiated in France, between April
189 2014 and November 2017 (Figure 1). Institutional ethical approval (CPP Ile de France 1) and
190 written informed consent from parents / caregivers of all participants were obtained. The
191 study is registered in ClinicalTrial.gov (NCT02114034). Data presented in this article are
192 those obtained at inclusion.

193 **Cohorts**

194 Two cohorts of preschool (3-6 years) and school-aged children (7-12 years) were enrolled in
195 12 pediatric tertiary care centers across France. Children were included consecutively during
196 their follow-up. The diagnosis of asthma was made according to the GINA guidelines by
197 specialized pediatric asthma physicians[20].

198 Preschool children with SRW and school-age children with SA were defined as those with
199 persistent symptoms or requiring a short-acting β -agonist (SABA) ≥ 3 days a week for ≥ 3
200 months AND/OR frequent or severe exacerbations in the previous year (≥ 1 severe
201 exacerbation requiring admission to an intensive care unit (ICU); ≥ 2 exacerbations requiring
202 hospital admissions and intravenous medications, and/or a ≥ 3 -day course of oral steroids)
203 AND/OR persistent airflow obstruction in school-age children (Forced Expiratory Volume in
204 the first second (FEV1) $< 80\%$ and/or airway resistance $> 150\%$ of predicted values), despite
205 being prescribed high doses of inhaled corticosteroids (ICS) (≥ 800 $\mu\text{g}/\text{day}$ budesonide or
206 equivalent) and another controller therapy (long-acting β -agonist (LABA) or leukotriene
207 receptor antagonist (LRTA)) [11]. Children under medium-to-high doses of ICS and
208 omalizumab were also included in the SRW or SA groups. Preschool children with NSRW and
209 school-age children with NSA were defined as children with ≤ 1 severe exacerbation
210 (requiring a course of steroids) in the past year AND no hospital admission during the

211 previous year AND no recurrent chronic symptoms AND normal lung function, with no more
212 than low-medium doses of ICS (<500 µg/day budesonide or equivalent), with or without
213 other controller medication.

214 All children with SRW and SA were followed for at least three months before inclusion to
215 exclude other diagnoses, treat comorbidities, reduce environmental exposure, optimize
216 asthma control, and assess medication adherence and inhalation technique.

217 Non-inclusion criteria were: asthma exacerbation within the previous four weeks, history of
218 bronchopulmonary dysplasia, post-infection chronic lung disease, vocal cord dysfunction,
219 lung malformation, tracheomalacia, cystic fibrosis, primary ciliary dyskinesia, immune
220 deficiency, foreign body inhalation, or congenital cardiac disease. Children were not
221 included if the physician-based assessment showed poor adherence and/or technique
222 based on asthma history and demonstration of inhaler use.

223 Study assessments

224 Baseline data collected by physicians included: i) demographics and anthropometrics; ii)
225 family history of allergic disorders, including atopic dermatitis (AD), asthma, food allergy
226 (FA), allergic rhinitis (AR); iii) past medical history, including associated allergic disorders (AD,
227 AR, FA), comorbidities (symptomatic gastro-oesophageal reflux), and history of
228 hospitalization for at least one episode of bronchiolitis before the age of 2 years; iv)
229 parental-reported environmental exposure, including pre and post-natal smoke exposure,
230 carpet, visible mold/dampness at home [21], pet ownership, fuel heat; v) current asthma
231 history, including symptoms and medications. For asthma control, the Childhood Asthma
232 Control Test (ACT) for children ≤12 years [22, 23] and Global Initiative for Asthma (GINA)
233 criteria [24] were used. Assessment of quality of life for school-age children aged 7-12 years
234 was performed with the specific Pediatric Asthma Quality-of-Life Questionnaire (PAQLQ)

235 [25]. Adherence and inhalation techniques were assessed by physicians in charge of the
236 child. Symptomatic gastroesophageal reflux (GER) was diagnosed on the basis of suggestive
237 symptoms, AND/OR positive pH monitoring AND/OR endoscopy AND/OR positive response
238 to anti-acid therapy.

239 Atopy was defined by the presence of at least one positive skin-prick test (SPT) (wheal
240 diameter ≥ 3 mm) and/or specific IgE levels (≥ 0.35 Ku/l) against common airborne and/or
241 food allergens.

242 Lung function was assessed in children aged ≥ 4 years. Measures were performed in
243 accordance with ATS/ERS guidelines [26, 27]. The predicted values and Z-scores were
244 calculated from the Global Lung function Initiative predictive equations [28]. Reversibility
245 was assessed after administration of short acting bronchodilator (BD) (400 μ g Salbutamol)
246 and defined as an increase in FEV1 $> 12\%$ between pre and post bronchodilator values.
247 Fractional exhaled nitric oxid (FeNO) was measured in school-age children, and a minimum
248 of two measurements were performed. Data were expressed as parts per billion (ppb).

249 Statistical analysis

250 R version 3.3.1 statistical software was used for statistical analysis (R Core Team (2016)
251 Vienna, Austria). Continuous variables are presented as medians [interquartile range], and
252 categorical variables as numbers (%). Comparisons of quantitative data were performed
253 using Wilcoxon-Mann-Whitney tests. Categorical variables were analysed using the chi-
254 square test or Fisher exact test as appropriate. No imputation of missing data was
255 performed. Multivariable logistic regression analyses were performed to assess risk factors
256 for SRW and SA. Multi-variable models were first built with the inclusion of all variables not
257 involved in the definition of SRW or SA (Asthma history in Table 1 and Table 2) with
258 univariate p-values < 0.1 (See Table 1, 3 and 4). Then, selection of the final variables with the

259 best fit for each multi-variable model (*i.e.*, for preschool and school-age children) was
260 achieved by backward stepwise elimination using Aikaiki's information criterion. A p-value <
261 0.05 was considered statistically significant.

262 **Results**

263 **Subjects**

264 Overall, 348 patients were recruited (male: 68%), including 141 (40.5%) preschool and 207
265 (59.5%) school-age children (Figure 2). Among preschool children, 92 (65.2%) had SRW and
266 49 (34.8%) had NSRW. Among school-age children, 92 (44.4%) had SA and 115 (56.6%) had
267 NSA. Six pairs of siblings were included, amongst which three were included in the same age-
268 matched and severity-matched cohort. Overall, baseline demographic characteristics were
269 comparable between children with SRW and SA and those with milder disease (Table 1),
270 except that school-age children with SA were slightly older at inclusion than those with NSA
271 (10.0 [9.0-11.0] vs 9.0 [8.0-11.0] years, $p=0.017$) and breastfeeding during infancy was less
272 frequent in SA than in NSA (61.1% vs 77.9%, $p=0.014$). The general characteristics of the
273 children are summarized in Table 2.

274

275 **Factors associated with severe recurrent wheeze in preschool children**

276 Birth weight was lower in preschool children with SRW than in those with NSRW (3100 g
277 [2685-3467] vs 3370 g [3100-3520], $p=0.011$) (Table 1). Prenatal smoke exposure did not
278 differ between children with SRW and NSRW.

279 Exposure to second hand smoke (SHS) and visible mold/dampness was more frequent in
280 preschool children with SRW than in those with NSRW (25.8% vs 2.0%, $p<0.001$; 28.3% vs
281 8.3%, $p=0.012$, respectively) (Table 3).

282 A family history of atopy was present in 85.3% of preschoolers. The family atopy status was
283 not associated with severity, except for AD in siblings, which was more frequent in preschool
284 children with SRW than in those with NSRW (41.0% vs 18.6%, $p=0.021$).

285 Atopy was common in preschool children (64.3%), and there was no difference in associated
286 atopic disorders between SRW and NSRW (Table 4). No difference was observed in the
287 frequency of symptomatic GER among preschoolers.

288 Multivariable logistic regression analysis showed an association between SRW and birth
289 weight (OR [95%CI]: 0.34 [0.14-0.75] per unit, kg, increase), second-hand smoke exposure
290 (OR [95%CI]: 29.8 [3.57-3910]), the presence of visible mold/dampness at home (OR [95%CI]:
291 4.22 [1.25-18.2]), and atopic dermatitis in siblings (OR [95%CI]: 3.02 [1.19-8.29]) (Table 5).

292

293 **Factors associated with severe asthma in school-age children**

294 No difference in prenatal environment and birth weight (Table 1), as well as postnatal
295 environment (Table 3) was observed between SA and NSA.

296 A family history of atopy was also frequent in school-age children: 84.8%. The family atopy
297 status was not associated with SA. The number of residents at home was higher in children
298 with SA than in those with NSA (5 [4-6] vs 4 [4-5], $p < 0.01$).

299 Atopy was present in 83.0% of school-age children, and history of AD and FA were more
300 frequent in SA than in those with NSA (48.9% vs 26.1%, $p < 0.01$; 31.1% vs 13.5%, $p < 0.01$,
301 respectively). Symptomatic GER was more frequent in school-age children with SA than in
302 NSA (21.7% vs 8.7%, $p = 0.014$) (Table 4).

303 Multivariable logistic regression analysis of school-age children showed an association
304 between the number of residents at home (OR [95%CI]: 1.54 [1.18-2.06]), fuel-based heating
305 (OR [95%CI]: 16.7 [2.76-322]), and history of food allergies (OR [95%CI]: 5.01 [2.23-11.9])
306 (Table 6).

307

308

309 **Discussion**

310 We initiated the first prospective French cohort of asthmatic children including preschoolers
311 with SRW and school-age children with SA to identify factors associated with asthma severity
312 in these two groups. We observed that factors influencing severity differed between
313 preschoolers and school-age children. In preschoolers, SRW was preferentially associated
314 with pejorative environmental factors, such as SHS exposure and mold/dampness at home,
315 whereas at school age, SA was preferentially associated with allergic sensitization and
316 comorbidities.

317 We observed that preschoolers with SRW were more frequently exposed to visible
318 mold/dampness at home than those with NSRW, as supported by previous studies, showing
319 that preschoolers exposed to dampness at home were at high risk of developing asthma
320 symptoms, regardless of their atopy status [29]. Regarding SHS, several studies, among
321 which a survey conducted in over 20,000 children (median age 4.4 years) have also shown
322 that maternal smoking increased the risk of emergency-department visits for asthma [30].

323 Overall, our results highlight the potential effects of indoor factors and pollutants in the
324 severity of preschool asthma and the need to explore household exposure in this population.

325 Furthermore, preschoolers with SRW had lower birth weights than those with a milder
326 disease, as opposed to comparable Z-scores for body mass index (BMI) at inclusion. Prenatal
327 smoke exposure has previously been associated with increased airway responsiveness and
328 reduced lung function in childhood [31, 32]. More experimental and epidemiologic studies
329 are needed to determine the mechanisms underlying the influence of antenatal exposure,
330 growth, and birth weight on the subsequent development of asthma and development of
331 lung function.

332 Despite stringent inclusion criteria, preschoolers with SRW may be a heterogeneous group.
333 Various evolution phenotypes of preschoolers with SRW may emerge during the prospective
334 follow-up of the cohort. Preschoolers with a multiple and early sensitization phenotype have
335 been previously identified to have a high-risk evolution profile, including severe
336 exacerbations and hospital admissions for exacerbations [33]. Our results raise the
337 hypothesis that this trajectory may also be influenced by early harmful environmental
338 exposures.

339 At school-age, the magnitude of allergic sensitization against food or airborne allergens has
340 been associated with asthma severity in previous studies [6, 34–36]. Furthermore, the
341 association of allergic disorders, such as AR [37], IgE-mediated FA [38, 39], and AD [40],
342 appears to increase asthma severity. Although our study was cross-sectionnal, our results
343 also suggest that allergic mechanisms may worsen the clinical expression of asthma in
344 school-age children with allergic disorders. Allergic rhinitis is a classical factor associated
345 with asthma severity [12]. However, this was not the case in our study, possibly due to the
346 high prevalence of AR in both SA and NSA. One could also hypothesize that the severity of
347 AR, rather than its presence, may affect asthma severity [34, 37]. Although frequently
348 observed in preschoolers with SRW, allergic disorders and sensitization were only associated
349 with asthma severity at school age.

350 Our data support the hypothesis that factors associated with severity may differ between
351 preschoolers and school-age children, or have a different impact depending on the age of
352 children and the duration of the disease. Here, we described patients based on data
353 collection at inclusion. The impact of an environmental risk factor and the phenotypic
354 features may change over time [41]. New sensitizations and comorbidities may develop in
355 certain children. These distinct phenotypes may be associated with different baseline

356 endotypes leading to varying severity between preschool and school-age children. The
357 prospective follow-up that we initiated will provide further insights into the disease
358 trajectory of these children and the evolution of allergic disorders, lung function, and
359 asthma severity.

360 The burden of SRW and SA has been demonstrated in previous studies to be high in terms of
361 symptoms and medication requirement [6, 12, 42]. Although children with SA were slightly
362 older than those with NSA in our study, they had a more severe asthma trajectory, with
363 more admissions for severe exacerbations or ICU admissions in childhood, and had worse
364 lung function. It is therefore unlikely that this age difference affected the results. Hence, our
365 data suggest that children with SRW/SA may display a more severe course of the disease
366 than their counterparts throughout childhood. These findings are supported by observations
367 from the SARP cohort, showing that a history of ICU admission or intubation was associated
368 with SA at school-age [6], although not observed in the U-Biopred cohort [12]. Furthermore,
369 it has been shown that asthmatic children with severe exacerbations in infancy display
370 poorer lung function, not only in the preschool years but also later [43].

371 Our study had several limitations. First, we did not include healthy control subjects.
372 However, we aimed to determine factors associated with severity. Thus, children with milder
373 disease were appropriate controls. Because the recruitment was conducted in tertiary-care
374 centers, the children with NSW and NSA in our study may not be representative of all
375 children with mild/moderate recurrent asthma or wheeze followed in primary care.
376 However, children with SRW and SA constituted a representative sample of French children
377 with SRW/SA. We cannot exclude that certain preschool wheezers had transient symptoms
378 and that certain patients with recurrent wheeze may outgrow their condition, in particular
379 among those with low exposure to environmental triggers and low sensitization rates.

380 Transient wheeze is generally defined as beginning and ending before the age of three years
381 [24, 44, 45]. The inclusion of children older than three years limited this potential bias.
382 Moreover, the high proportion of sensitization observed in preschoolers with SRW increased
383 their likelihood of having persistent symptoms [24, 46, 47]. SRW in preschoolers may not
384 progress to SA in school-age children. In a previous study, we reported that preschoolers
385 with SRW displayed persistent asthma at school-age in 72% of cases, but that asthma
386 severity decreased over time [16]. Preschoolers with SRW and school-age children with SA
387 may display distinct phenotypes and endotypes, as suggested by studies showing specific
388 features in bronchial biopsies, such as the predominance of neutrophils in preschoolers with
389 SRW [4]. Our findings that factors associated with SRW in preschoolers and SA in children
390 may differ support this hypothesis. Furthermore, the definition of severity in the preschool
391 years, based on the persistence of symptoms and/or exacerbations despite high doses of ICS
392 and a second controller therapy, was chosen in accordance with the stepwise-approach
393 guidelines. High-dose treatment was used as a feature to define SRW by extension of the the
394 definition of the SA guidelines [11]. Although there is little evidence of a beneficial effect of
395 medium-to-high doses of ICS in the preschool age, ICS dose escalation is still the
396 recommended approach in asthma guidelines, including the possibility of a high-dose trials
397 [11, 20, 24, 48].

398 Second, no objective measurements of indoor allergen, mold/dampness or outdoor
399 pollution levels were performed during home visits. Our results were based on parental
400 descriptions of exposure, which may not be accurate [11]. The impact of pollutants and their
401 differential effects in subgroups of patients may have therefore been misestimated.
402 Furthermore, the number of children included varied among centers and there may have
403 been a geographical bias for the assessment of air pollution, which differed between cities.

404 In addition, adherence was not assessed with objective measures, which may have
405 overestimated the frequency of SRW and SA. We limited this bias by not including cases with
406 confirmed poor adherence / inhaler technique in those groups and by applying a strict
407 definition for SRW and SA. Finally, we did not classify preschoolers according to previous
408 classifications of wheezing phenotypes, such as early transient wheeze, persistent wheeze,
409 late-onset wheeze, or episodic or multiple-trigger wheeze. Early transient wheeze was not
410 adapted to our population consisting of children of ≥ 3 years of age. It has been reported
411 that the episodic and multiple-trigger wheeze phenotypes may not be stable over time [20,
412 49]. Finally, it has been shown that viral wheezers and multiple-trigger wheezers display the
413 same pattern of remodeling and airway inflammation and that multiple-trigger wheezers
414 and severe intermittent wheezers have similar inflammatory profiles during acute
415 exacerbations and eight weeks later [4, 50].

416 The COBRAPed study describes a subsequent and well-characterised sample of 2 clinical
417 entities: preschool recurrent wheezing and school-age children with asthma in France. Our
418 analysis of baseline characteristics suggests that factors influencing asthma severity may
419 differ between preschoolers and school-age children. Some of them may be targets for
420 prevention. Improving environmental factors, especially in the preschool years, and
421 preventing the development of allergic disorders may therefore prevent or improve the
422 prognosis of SRW and SA.

423

424 ***Members of the COBRAPed Study Group:***

425 Dr Rola Abou-Taam (CHU Necker-Enfants Malades), Dr Muriel Le Bourgeois (CHU Necker-
426 Enfants Malades), Dr Alice Hadchouel-Duvergé (CHU Necker-Enfants Malades), Dr David
427 Drummond (CHU Necker-Enfants Malades), Pr Christophe Delacourt (CHU Necker-Enfants
428 Malades), Dr Marie-Alexandra Alyanakian (CHU Necker-Enfants Malades), Pr Lucienne
429 Chatennoud (CHU Necker-Enfants Malades), Dr Caroline Thumerelle (CHU Lille), Dr Clémence
430 Mordacq (CHU Lille), Dr Irina Badiu-Decleyre (CHU Lille), Dr Cécile Bonnel (CHU Lille), Dr
431 Laure Delbecque (CHU Lille), Dr Laurent Beghin, PhD (CHU Lille), Mrs Graziella Mingardi (CHU
432 Lille), Mrs Caroline Tournegros (CHU Grenoble Alpes), Dr Léa Roditis (CHU Toulouse), Dr
433 Stéphanie Wanin (Robert Debré Hospital, Paris), Dr Marie Noelle Lebras (Robert Debré
434 Hospital, Paris), Dr Stéphane Debelleix (CHU Bordeaux), Dr Valérie Siao (CHU Bordeaux), Mrs
435 Marine Servat (CHU Bordeaux, Hôpital Haut-Lévêque), Mr Guillaume Simon (CHU Bordeaux,
436 Hôpital Pellegrin-Enfants), Dr Patricia El Boustany (CHU Marseille Timone-Enfants), Dr
437 Emmanuelle Bosdure (CHU Marseille Timone-Enfants), Dr Julie Mazenq (CHU Marseille
438 Timone-Enfants), Dr Isabelle Cabon (CHU Marseille Timone-Enfants), Dr Camille Ohlmann
439 (CHU Lyon), Dr Stéphanie Vrielynck (CHU Lyon), Dr Virginie Jubin (CHU Lyon), Dr Sylvie-Anne
440 André Gomez (CHU Lyon), Dr Marie-Christine Werck Gallois (CHU Lyon).

441 ***Acknowledgements***

442 The authors would like to thank the patients and their families for their participation in the
443 study, as well as all nurses, physicians and clinical research coordinators who were involved
444 in the COBRAPed study group.

445

446

447 **References**

- 448 1. Saglani S, Payne DN, Zhu J, Wang Z, Nicholson AG, Bush A, Jeffery PK. Early detection of
449 airway wall remodeling and eosinophilic inflammation in preschool wheezers. *Am. J.*
450 *Respir. Crit. Care Med.* 2007; 176: 858–864.
- 451 2. Just J, Gouvis-Echraghi R, Couderc R, Guillemot-Lambert N, Saint-Pierre P. Novel severe
452 wheezy young children phenotypes: boys atopic multiple-trigger and girls nonatopic
453 uncontrolled wheeze. *J. Allergy Clin. Immunol.* 2012; 130: 103-110.e8.
- 454 3. Guiddir T, Saint-Pierre P, Purenne-Denis E, Lambert N, Laoudi Y, Couderc R, Gouvis-
455 Echraghi R, Amat F, Just J. Neutrophilic Steroid-Refractory Recurrent Wheeze and
456 Eosinophilic Steroid-Refractory Asthma in Children. *J Allergy Clin Immunol Pract* 2017;
457 5: 1351-1361.e2.
- 458 4. Lezmi G, Gosset P, Deschildre A, Abou-Taam R, Mahut B, Beydon N, de Blic J. Airway
459 Remodeling in Preschool Children with Severe Recurrent Wheeze. *Am. J. Respir. Crit.*
460 *Care Med.* 2015; 192: 164–171.
- 461 5. Barbato A, Turato G, Baraldo S, Bazzan E, Calabrese F, Panizzolo C, Zanin ME, Zuin R,
462 Maestrelli P, Fabbri LM, Saetta M. Epithelial damage and angiogenesis in the airways of
463 children with asthma. *Am. J. Respir. Crit. Care Med.* 2006; 174: 975–981.
- 464 6. Fitzpatrick AM, Teague WG, Meyers DA, Peters SP, Li X, Li H, Wenzel SE, Aujla S, Castro
465 M, Bacharier LB, Gaston BM, Bleecker ER, Moore WC, National Institutes of
466 Health/National Heart, Lung, and Blood Institute Severe Asthma Research Program.
467 Heterogeneity of severe asthma in childhood: confirmation by cluster analysis of
468 children in the National Institutes of Health/National Heart, Lung, and Blood Institute
469 Severe Asthma Research Program. *J. Allergy Clin. Immunol.* 2011; 127: 382-389.e1-13.
- 470 7. Just J, Gouvis-Echraghi R, Rouve S, Wanin S, Moreau D, Annesi-Maesano I. Two novel,
471 severe asthma phenotypes identified during childhood using a clustering approach. *Eur.*
472 *Respir. J.* 2012; 40: 55–60.
- 473 8. Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches.
474 *Nat. Med.* 2012; 18: 716–725.
- 475 9. Kaiser SV, Huynh T, Bacharier LB, Rosenthal JL, Bakel LA, Parkin PC, Cabana MD.
476 Preventing Exacerbations in Preschoolers With Recurrent Wheeze: A Meta-analysis.
477 *Pediatrics* 2016; 137.
- 478 10. Bingham Y, Sanghani N, Cook J, Hall P, Jamalzadeh A, Moore-Crouch R, Bush A, Fleming
479 L, Saglani S. Electronic adherence monitoring identifies severe preschool wheezers who
480 are steroid responsive. *Pediatr. Pulmonol.* 2020; .
- 481 11. Hedlin G, Bush A, Lødrup Carlsen K, Wennergren G, De Benedictis FM, Melén E, Paton J,
482 Wilson N, Carlsen K-H, Problematic Severe Asthma in Childhood Initiative group.
483 Problematic severe asthma in children, not one problem but many: a GA2LEN initiative.
484 *Eur. Respir. J.* 2010; 36: 196–201.

- 485 12. Fleming L, Murray C, Bansal AT, Hashimoto S, Bisgaard H, Bush A, Frey U, Hedlin G,
486 Singer F, van Aalderen WM, Vissing NH, Zolkipli Z, Selby A, Fowler S, Shaw D, Chung KF,
487 Sousa AR, Wagers S, Corfield J, Pandis I, Rowe A, Formaggio E, Sterk PJ, Roberts G, U-
488 BIOPRED Study Group. The burden of severe asthma in childhood and adolescence:
489 results from the paediatric U-BIOPRED cohorts. *Eur. Respir. J.* 2015; 46: 1322–1333.
- 490 13. Delmas M-C, Marguet C, Raheison C, Nicolau J, Fuhrman C. [Admissions for pediatric
491 asthma in France]. *Arch Pediatr* 2013; 20: 739–747.
- 492 14. Chipps BE, Zeiger RS, Borish L, Wenzel SE, Yegin A, Hayden ML, Miller DP, Bleecker ER,
493 Simons FER, Szefer SJ, Weiss ST, Haselkorn T, TENOR Study Group. Key findings and
494 clinical implications from The Epidemiology and Natural History of Asthma: Outcomes
495 and Treatment Regimens (TENOR) study. *J. Allergy Clin. Immunol.* 2012; 130: 332-
496 342.e10.
- 497 15. Malmström K, Malmberg LP, O’Reilly R, Lindahl H, Kajosaari M, Saarinen KM, Saglani S,
498 Jahnsen FL, Bush A, Haahtela T, Sarna S, Pelkonen AS, Mäkelä MJ. Lung function, airway
499 remodeling, and inflammation in infants: outcome at 8 years. *Ann. Allergy Asthma
500 Immunol.* 2015; 114: 90–96.
- 501 16. Lezmi G, Deschildre A, Abou Taam R, Fayon M, Blanchon S, Troussier F, Mallinger P,
502 Mahut B, Gosset P, de Blic J. Remodelling and inflammation in preschoolers with severe
503 recurrent wheeze and asthma outcome at school age. *Clin. Exp. Allergy* 2018; 48: 806–
504 813.
- 505 17. Lezmi G, Abou-Taam R, Garcelon N, Dietrich C, Machavoine F, Delacourt C, Adel-Patient
506 K, Leite-de-Moraes M. Evidence for a MAIT-17-high phenotype in children with severe
507 asthma. *J. Allergy Clin. Immunol.* 2019; 144: 1714-1716.e6.
- 508 18. Ramratnam SK, Bacharier LB, Guilbert TW. Severe Asthma in Children. *J Allergy Clin
509 Immunol Pract* 2017; 5: 889–898.
- 510 19. Pretolani M, Soussan D, Poirier I, Thabut G, Aubier M, COBRA Study Group, COBRA
511 cohort Study Group. Clinical and biological characteristics of the French COBRA cohort
512 of adult subjects with asthma. *Eur. Respir. J.* 2017; 50.
- 513 20. Global Initiative for Asthma (GINA). 2020 Report: Global strategy for asthma
514 management and prevention. <https://ginasthma.org/> (last accessed: August 2020). .
- 515 21. Jaakkola JJK, Hwang B-F, Jaakkola N. Home dampness and molds, parental atopy, and
516 asthma in childhood: a six-year population-based cohort study. *Environ. Health
517 Perspect.* 2005; 113: 357–361.
- 518 22. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, Murray JJ, Pendergraft
519 TB. Development of the asthma control test: a survey for assessing asthma control. *J.
520 Allergy Clin. Immunol.* 2004; 113: 59–65.

- 521 23. Liu AH, Zeiger R, Sorkness C, Mahr T, Ostrom N, Burgess S, Rosenzweig JC, Manjunath R.
522 Development and cross-sectional validation of the Childhood Asthma Control Test. *J.*
523 *Allergy Clin. Immunol.* 2007; 119: 817–825.
- 524 24. 2012-GINA.pdf [Internet]. [cited 2020 Feb 12]. Available from:
525 <https://ginasthma.org/wp-content/uploads/2019/01/2012-GINA.pdf>.
- 526 25. Juniper EF, Guyatt GH, Feeny DH, Ferrie PJ, Griffith LE, Townsend M. Measuring quality
527 of life in children with asthma. *Qual Life Res* 1996; 5: 35–46.
- 528 26. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P,
529 van der Grinten CPM, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R,
530 Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J, ATS/ERS Task Force.
531 Standardisation of spirometry. *Eur. Respir. J.* 2005; 26: 319–338.
- 532 27. Beydon N, Davis SD, Lombardi E, Allen JL, Arets HGM, Aurora P, Bisgaard H, Davis GM,
533 Ducharme FM, Eigen H, Gappa M, Gaultier C, Gustafsson PM, Hall GL, Hantos Z, Healy
534 MJR, Jones MH, Klug B, Lødrup Carlsen KC, McKenzie SA, Marchal F, Mayer OH, Merkus
535 PJFM, Morris MG, Oostveen E, Pillow JJ, Seddon PC, Silverman M, Sly PD, Stocks J, et al.
536 An official American Thoracic Society/European Respiratory Society statement:
537 pulmonary function testing in preschool children. *Am. J. Respir. Crit. Care Med.* 2007;
538 175: 1304–1345.
- 539 28. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, Enright PL, Hankinson JL, Ip
540 MSM, Zheng J, Stocks J, ERS Global Lung Function Initiative. Multi-ethnic reference
541 values for spirometry for the 3-95-yr age range: the global lung function 2012
542 equations. *Eur. Respir. J.* 2012; 40: 1324–1343.
- 543 29. Pekkanen J, Hyvärinen A, Haverinen-Shaughnessy U, Korppi M, Putus T, Nevalainen A.
544 Moisture damage and childhood asthma: a population-based incident case-control
545 study. *Eur. Respir. J.* 2007; 29: 509–515.
- 546 30. Farber HJ, Batsell RR, Silveira EA, Calhoun RT, Giardino AP. The Impact of Tobacco
547 Smoke Exposure on Childhood Asthma in a Medicaid Managed Care Plan. *Chest* 2016;
548 149: 721–728.
- 549 31. Bjerg A, Hedman L, Perzanowski M, Lundbäck B, Rönmark E. A strong synergism of low
550 birth weight and prenatal smoking on asthma in schoolchildren. *Pediatrics* 2011; 127:
551 e905-912.
- 552 32. Cohen RT, Raby BA, Van Steen K, Fuhlbrigge AL, Celedón JC, Rosner BA, Strunk RC,
553 Zeiger RS, Weiss ST, Childhood Asthma Management Program Research Group. In utero
554 smoke exposure and impaired response to inhaled corticosteroids in children with
555 asthma. *J. Allergy Clin. Immunol.* 2010; 126: 491–497.
- 556 33. Simpson A, Tan VYF, Winn J, Svensén M, Bishop CM, Heckerman DE, Buchan I, Custovic
557 A. Beyond atopy: multiple patterns of sensitization in relation to asthma in a birth
558 cohort study. *Am. J. Respir. Crit. Care Med.* 2010; 181: 1200–1206.

- 559 34. Pongracic JA, Krouse RZ, Babineau DC, Zoratti EM, Cohen RT, Wood RA, Khurana
560 Hershey GK, Kercksmar CM, Gruchalla RS, Kattan M, Teach SJ, Johnson CC, Bacharier LB,
561 Gern JE, Sigelman SM, Gergen PJ, Togias A, Visness CM, Busse WW, Liu AH.
562 Distinguishing characteristics of difficult-to-control asthma in inner-city children and
563 adolescents. *J. Allergy Clin. Immunol.* 2016; 138: 1030–1041.
- 564 35. Sharples J, Gupta A, Fleming L, Bossley CJ, Bracken-King M, Hall P, Hayward A, Puckey
565 M, Balfour-Lynn IM, Rosenthal M, Bush A, Saglani S. Long-term effectiveness of a
566 staged assessment for paediatric problematic severe asthma. *Eur. Respir. J.* 2012; 40:
567 264–267.
- 568 36. Just J, Saint-Pierre P, Gouvis-Echraghi R, Laoudi Y, Roufai L, Momas I, Annesi Maesano I.
569 Childhood allergic asthma is not a single phenotype. *J. Pediatr.* 2014; 164: 815–820.
- 570 37. Togias A, Gergen PJ, Hu JW, Babineau DC, Wood RA, Cohen RT, Makhija MM, Khurana
571 Hershey GK, Kercksmar CM, Gruchalla RS, Liu AH, Wang E, Kim H, Lamm CI, Bacharier LB,
572 Pillai D, Sigelman SM, Gern JE, Busse WW. Rhinitis in children and adolescents with
573 asthma: Ubiquitous, difficult to control, and associated with asthma outcomes. *J.*
574 *Allergy Clin. Immunol.* 2019; 143: 1003-1011.e10.
- 575 38. Friedlander JL, Sheehan WJ, Baxi SN, Kopel LS, Gaffin JM, Ozonoff A, Fu C, Gold DR,
576 Phipatanakul W. Food allergy and increased asthma morbidity in a School-based Inner-
577 City Asthma Study. *J Allergy Clin Immunol Pract* 2013; 1: 479–484.
- 578 39. Deschildre A, Marguet C, Salleron J, Pin I, Rittié J-L, Derelle J, Taam RA, Fayon M,
579 Brouard J, Dubus JC, Siret D, Weiss L, Pouessel G, Beghin L, Just J. Add-on omalizumab
580 in children with severe allergic asthma: a 1-year real life survey. *Eur. Respir. J.* 2013; 42:
581 1224–1233.
- 582 40. Fitzpatrick AM, Gaston BM, Erzurum SC, Teague WG. Features of severe asthma in
583 school-age children: Atopy and increased exhaled nitric oxide. *J Allergy Clin Immunol*
584 2006; 118: 1218–1225.
- 585 41. Ross KR, Gupta R, DeBoer MD, Zein J, Phillips BR, Mauger DT, Li C, Myers RE,
586 Phipatanakul W, Fitzpatrick AM, Ly NP, Bacharier LB, Jackson DJ, Celedón JC, Larkin A,
587 Israel E, Levy B, Fahy JV, Castro M, Bleecker ER, Meyers D, Moore WC, Wenzel SE,
588 Jarjour NN, Erzurum SC, Teague WG, Gaston B. Severe asthma during childhood and
589 adolescence: A longitudinal study. *J. Allergy Clin. Immunol.* 2020; 145: 140-146.e9.
- 590 42. Teague WG, Phillips BR, Fahy JV, Wenzel SE, Fitzpatrick AM, Moore WC, Hastie AT,
591 Bleecker ER, Meyers DA, Peters SP, Castro M, Coverstone AM, Bacharier LB, Ly NP,
592 Peters MC, Denlinger LC, Ramratnam S, Sorkness RL, Gaston BM, Erzurum SC, Comhair
593 SAA, Myers RE, Zein J, DeBoer MD, Irani A-M, Israel E, Levy B, Cardet JC, Phipatanakul
594 W, Gaffin JM, et al. Baseline Features of the Severe Asthma Research Program (SARP III)
595 Cohort: Differences with Age. *J Allergy Clin Immunol Pract* 2018; 6: 545-554.e4.
- 596 43. Belgrave DCM, Buchan I, Bishop C, Lowe L, Simpson A, Custovic A. Trajectories of lung
597 function during childhood. *Am. J. Respir. Crit. Care Med.* 2014; 189: 1101–1109.

- 598 44. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and
599 wheezing in the first six years of life. The Group Health Medical Associates. *N. Engl. J.*
600 *Med.* 1995; 332: 133–138.
- 601 45. Savenije OE, Granell R, Caudri D, Koppelman GH, Smit HA, Wijga A, de Jongste JC,
602 Brunekreef B, Sterne JA, Postma DS, Henderson J, Kerkhof M. Comparison of childhood
603 wheezing phenotypes in 2 birth cohorts: ALSPAC and PIAMA. *J. Allergy Clin. Immunol.*
604 2011; 127: 1505-1512.e14.
- 605 46. Sly PD, Boner AL, Björkstén B, Bush A, Custovic A, Eigenmann PA, Gern JE, Gerritsen J,
606 Hamelmann E, Helms PJ, Lemanske RF, Martinez F, Pedersen S, Renz H, Sampson H, von
607 Mutius E, Wahn U, Holt PG. Early identification of atopy in the prediction of persistent
608 asthma in children. *Lancet* 2008; 372: 1100–1106.
- 609 47. Illi S, von Mutius E, Lau S, Niggemann B, Grüber C, Wahn U, Multicentre Allergy Study
610 (MAS) group. Perennial allergen sensitisation early in life and chronic asthma in
611 children: a birth cohort study. *Lancet* 2006; 368: 763–770.
- 612 48. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, Adcock IM, Bateman ED, Bel
613 EH, Bleecker ER, Boulet L-P, Brightling C, Chané P, Dahlen S-E, Djukanovic R, Frey U,
614 Gaga M, Gibson P, Hamid Q, Jajour NN, Mauad T, Sorkness RL, Teague WG.
615 International ERS/ATS guidelines on definition, evaluation and treatment of severe
616 asthma. *Eur. Respir. J.* 2014; 43: 343–373.
- 617 49. Raaymakers MJA, Brand PLP, Landstra AM, Brouwer ML, Balemans WAF, Niers LEM,
618 Merkus PJFM, Boehmer ALM, Kluytmans JAJW, de Jongste JC, Pijnenburg MWH,
619 Vaessen-Verberne AAPH. Episodic viral wheeze and multiple-trigger wheeze in
620 preschool children are neither distinct nor constant patterns. A prospective multicenter
621 cohort study in secondary care. *Pediatr. Pulmonol.* 2019; 54: 1439–1446.
- 622 50. Lejeune S, Pichavant M, Engelmann I, Beghin L, Drumez E, Le Rouzic O, Dessein R,
623 Rogeau S, Beke T, Kervoaze G, Delvart C, Ducoin H, Pouessel G, Le Mée A, Boileau S,
624 Roussel J, Bonnel C, Mordacq C, Thumerelle C, Gosset P, Deschildre A. Severe preschool
625 asthmatics have altered cytokine and anti-viral responses during exacerbation. *Pediatr*
626 *Allergy Immunol* 2020; .

627

628

629 **Figure legends**

630 **Figure 1. Prospective follow-up of the children included in the COBRAPed study**

631 SA: severe asthma, SRW: Severe recurrent wheeze, NSA: Non-severe asthma, NSRW: Non-severe
632 recurrent wheeze, ACT: Asthma control test, PAQLQ: Pediatric Asthma Quality of Life, FeNO:
633 fractional exhaled nitric oxide, SPT: skin prick tests. Data were collected if the exams were performed
634 within the 3 months prior to inclusion.

635

636 **Figure 2. Flow-chart of the population**

637 SA: Severe Asthma; NSA: Non-Severe Asthma, SRW: Severe recurrent wheeze, NSRW: Non-severe
638 recurrent wheeze

	Preschool children				School-Age children			
	Total population 141	Severe Recurrent Wheeze92	Non-severe Recurrent Wheeze 49	p-value	Total population 207	Severe Asthma 92	Non-severe Asthma 115	p-value
Demographics								
Age, y	5.0 [4.0, 6.0]	5.0 [4.0, 6.0]	5.0 [4.0, 6.0]	0.25	9.0 [8.0, 11.0]	10.0 [9.0, 11.0]	9.0 [8.0, 11.0]	0.017
Male gender	96 (68.1)	63 (68.5)	33 (67.3)	0.99	138/207 (66.7)	65/92 (70.7)	73/115 (63.5)	0.35
Caucasian	100/134 (74.6)	64/90 (71.1)	36/44 (81.8)	0.26	124/192 (64.6)	52/84 (61.9)	72/108 (66.7)	0.59
Anthropometrics								
Z score for BMI	n = 140 0.3 [-0.5, 1.1]	n = 91 0.4 [-0.6, 1.3]	n = 49 0.3 [-0.3, 0.8]	0.37	n = 207 0.7 [-0.5, 1.9]	n = 92 0.6 [-0.5, 1.7]	n = 115 0.8 [-0.4, 2.1]	0.26
Past medical history								
Gestational age at birth, wa	39.0 [38.0, 40.0]	38.0 [37.8, 40.0]	39.0 [38.0, 40.0]	0.48	39.0 [37.5, 40.0]	39.0 [37.0, 40.0]	39.0 [38.0, 40.0]	0.45
Birth weight, g	n = 136 3180 [2800, 3505]	n = 88 3100 [2685, 3467]	n = 48 3370 [3100, 3520]	0.011	n = 195 3252.5 [2880.0, 3667.5]	n = 90 3200.0 [2872.5, 3600.0]	n = 105 3300.0 [2890.0, 3700.0]	0.17
Breastfeeding	n = 139	n = 90	n = 49		n = 200	n = 91	n = 109	
Mother smoke during pregnancy	77/138 (55.8) 22/141 (15.6)	45/89 (50.6) 18/92 (19.6)	32/49 (65.3) 4/49 (8.2)	0.14 0.13	143/203 (70.4) 21/205 (10.2)	55/90 (61.1) 11/92 (12.0)	88/113 (77.9) 10/113 (8.8)	0.014 0.62
Asthma history								
Age at first wheeze (months)	5.0 [2.0, 8.0] n = 117	4.0 [2.0, 7.2] n = 80	6.0 [3.0, 8.0] n = 37	0.082	5.0 [2.0, 10.0] n = 145	4.0 [3.0, 9.0] n = 69	6.0 [2.0-11.2] n = 76	0.37
At least one admission for bronchiolitis	43/122 (35.2)	38/83 (45.8)	5/39 (12.8)	0.00081	50/149 (33.6)	31/72 (43.1)	19/77 (24.7)	0.028
No. of admissions for asthma exacerbation in childhood	1.0 [0.0, 4.0] n = 140	3.0 [0.0, 5.0] n = 91	0.0 [0.0, 1.0] n = 49	< 0.0001	1.0 [0.0-3.0] n = 203	2.5 [1.0, 5.0] n = 90	0.0 [0.0-1.0] n = 113	< 0.001
At least one ICU admission	26/140 (18.6)	25/91 (27.5)	1/49 (2)	0.00053	53/206 (25.7)	35/91 (38.5)	18/115 (15.7)	< 0.001

1 **Table 1. Baseline characteristics of the population**

2 Data are expressed as medianq [IQR] or frequencies (%). Comparisons of quantitative data were performed using Wilcoxon-Mann-Whitney tests. Categorical variables were
3 analysed using the chi-square test or Fisher exact test, as appropriate.

4 *BMI: body mass index, WA: weeks of amenorrhea, ICU: intensive care unit.*

5
6
7
8
9

	Preschool children				School-Age children			
	Total population 141	Severe Recurrent Wheeze 92	Non-severe Recurrent Wheeze 49	p-value	Total population 207	Severe Asthma 92	Non-severe Asthma 115	p-value
Asthma history in the past year								
≥ 3 exacerbations	82/137 (59.9)	79/89 (88.8)	3/48 (6.2)	< 0.0001	68/204 (33.3)	60/90 (66.7)	8/114 (7.0)	< 0.001
No. of cumulated days of oral steroids	18.0 [10.0, 30.0] n=106	20.0 [12.0, 30.5] n=88	5.5 [4.2, 9.5] n=18	< 0.0001	10.0 [4.0, 20.0] n=106	15.0 [10.0, 25.0] n=70	4.0 [3.0, 5.0] n=36	< 0.001
No. of emergency visits for acute asthma	1 [0, 3] n=138	1 [0, 4] n=90	0 [0, 1] n=48	< 0.0001	0 [0, 1] n=206	0 [0, 2] n=91	0 [0,0] n=115	< 0.001
Asthma control								
ACT score	n=135 20.0 [16.0, 23.0]	n=90 18.0 [14.0, 20.0]	n=45 23.0 [22.0, 25.0]	< 0.0001	n=207 21.0 [16.0, 24.0]	n=92 18.0 [13.8, 22.0]	n=115 23.0 [20.0, 24.5]	< 0.001
PAQLQ								
Total	NA	NA	NA	-	n=203 6.0 [4.8, 6.7]	n=91 5.2 [3.7, 6.5]	n=112 6.3 [5.5, 6.8]	< 0.001
Activity limitation	NA	NA	NA	-	5.2 [3.6, 6.6]	4.5 [3.0, 6.3]	5.7 [4.0, 6.7]	0.007
Emotion	NA	NA	NA	-	6.4 [5.2, 7.0]	5.5 [4.3, 6.6]	6.7 [6.0, 7.0]	< 0.001
Symptoms	NA	NA	NA	-	6.0 [4.8, 6.9]	5.4 [3.4, 6.6]	6.5 [5.5, 7.0]	< 0.001
Lung function								
FEV1 pre-BD (% predicted)	105 [93, 119] n=86	101 [91, 119] n=48	109 [98, 116] n=38	0.29	97 [88, 106] n=203	93 [80, 103] n=90	99 [90, 107] n=113	0.002
FEV1 post-BD (% predicted)	113 [90, 123] n=66	110 [94, 123] n=33	113 [103, 124] n=33	0.23	102 [94, 113] n=167	98 [87, 113] n=75	103 [96, 112] n=92	0.054
FEV1 pre-BD (Zscore)	-0.1 [-0.9, 0.9] n=87	-0.3 [-1.3, 0.8] n=48	0.0 [-0.5, 0.9] n=39	0.16	-0.3 [-1.2, 0.5] n=196	-0.7 [-1.9, 0.2] n=86	0.1 [-0.8, 0.7] n=110	< 0.001
FEV1 post-BD (Zscore)	0.4 [-0.6, 1.3] n=68	0.4 [-0.8, 1.1] n=34	0.3 [-0.2, 1.4] n=34	0.31	0.2 [-0.7, 0.9] n=162	-0.1 [-1.1, 0.8] n=72	0.4 [-0.3, 1.0] n=90	0.037
FEV1/FVC pre-BD (%)	91 [84, 95] n=84	92 [83, 96] n=47	90 [85, 94] n=37	0.61	85 [78, 90] n=200	82 [75, 91] n=89	86 [81, 90] n=111	0.011
FEV1/FVC post-BD (%)	91 [87, 97] n=62	91 [87, 98] n=29	91 [88, 95] n=33	0.71	89 [84, 93] n=155	88 [81, 91] n=69	89 [86, 94] n=86	0.022
FEV1/FVC pre-BD (Zscore)	0.0 [-1.0, 0.7] n=87	0.0 [-1.2, 1.1] n=48	-0.1 [-0.9, 0.4] n=39	0.61	-0.7 [-1.5, 0.2] n=191	-1.0 [-1.9, 0.0] n=83	-0.6 [-1.2, 0.2] n=108	0.001
FEV1/FVC post-BD (Zscore)	0.1 [-0.7, 0.6] n=67	-0.3 [-0.8, 0.6] n=33	0.2 [-0.7, 0.6] n=34	0.77	-0.1 [-0.7, 0.6] n=161	-0.5 [-1.3, 0.4] n=71	0.2 [-0.6, 0.8] n=90	0.002
Post-BD FEV1 reversibility	12/67 (17.9)	8/33 (24.2)	4/34 (11.8)	0.31	40/167 (24)	25/75 (33.3)	15/92 (16.3)	0.017
FeNO (ppb)	NA	NA	NA		14.1 [7.0, 29.5] n=90	12.0 [6.3, 35.5] n=39	16.9 [7.0, 28.1] n=51	0.64
Asthma therapy								
ICS	131/141 (92.9)	92/92 (100)	39/49 (79.6)	0.00050	168/207 (81.2)	92/92 (100)1000	76/115 (66.1)	< 0.001
ICS doses, µg/day. eq Budesonide	1000 [500, 1600] n=131	1000 [950, 2000] n=92	400 [400, 450] n=39	< 0.0001	800 [400, 1000] n=168	[800, 1213] n=92	400 [250, 500] n=76	< 0.001
ICS + LABA	56/140 (40.0)	41/91 (45.1)	15/49 (30.6)	0.14	124/207 (59.9)	75/92 (81.5)	49/115 (42.6)	< 0.001
Leukotriene modifier	77/141 (54.6)	68/92 (73.9)	9/49 (18.4)	< 0.0001	79/207 (38.2)	59/92 (64.1)	20/115 (17.4)	< 0.001
Maintenance oral corticosteroids	5/141 (3.5)	5/92 (5.4)	0/49 (0.0)	0.16	0/207 (0.0)	0/92 (0.0)	0/115 (0.0)	NA

Immunotherapy	3/141 (2.1)	1/92 (1.1)	2/49 (4.1)	0.28	16/207 (7.7)	6/92 (6.5)	10/115 (8.7)	0.75
Omalizumab	6/141 (4.3)	6/92 (6.5)	0/49 (0.0)	0.093	29/207 (14.0)	29/92 (31.5)	0/115 (0.0)	< 0.001

1 **Table 2. General characteristics of the population at inclusion.**

2 Data are expressed as medians [IQR] or frequencies (%).

3 Comparisons were not performed for criteria that were included in the definition.

4 Comparisons of quantitative data were performed using Wilcoxon-Mann-Whitney tests. Categorical variables were analysed using the chi-square test or Fisher exact test, as
5 appropriate.

6 *ACT: asthma control test, PAQLQ: pediatric asthma quality of life questionnaire, NA: Not available, FEV1: forced expiratory volume in 1 s, BD: bronchodilator, FVC: forced
7 vital capacity, FeNO: fractional exhaled nitric oxide, ICS: inhaled corticosteroids, LABA: long-acting β -agonist.*

	Preschool children				School-Age children			
	Total population 141	Severe Recurrent Wheeze 92	Non-severe Recurrent Wheeze 49	p-value	Total population 207	Severe Asthma 92	Non-severe Asthma 115	p-value
Type of child care								
Community childcare before the age of 3 y	57/141 (59.6)	42/92 (45.7)	15/49 (30.6)	0.12	63/203 (31.0)	25/91 (27.5)	38/112 (33.9)	0.40
Environment								
Home:								
Rural	37/141 (26.9)	24/92 (26.1)	13/49 (26.5)	0.81	51/206 (24.8)	24/92 (26.1)	27/114 (23.7)	0.49
Semi-rural	25/141 (17.7)	15/92 (16.3)	10/49 (20.4)		43/206 (20.9)	22/92 (23.9)	21/114 (18.4)	
Urban	79/141 (56.0)	53/92 (57.6)	26/49 (53.1)		112/206 (54.4)	46/92 (50.0)	66/114 (57.9)	
No. of residents at home	4 [4-5] n=140	4 [4-5] n=91	4 [4-5] n=49	0.46	4 [4, 5] n=206	5 [4-6] n=92	4 [4-5] n=114	0.004
Smoker	NA	NA	NA	NA	0/201 (0.0)	0/90 (0.0)	0/111 (0.0)	NA
Second-hand smoke exposure	24/138 (17.4)	23/89 (25.8)	1/49 (2.0)	0.00098	14/201 (7.0)	9/90 (10.0)	5/111 (4.5)	0.21
Carpet at home	26/141 (18.4)	13/92 (14.1)	13/49 (26.5)	0.11	38/206 (18.4)	16/92 (17.4)	22/114 (19.3)	0.86
Visible mold/dampness at home	30/140 (21.4)	26/92 (28.3)	4/48 (8.3)	0.012	36/205 (17.6)	17/92 (18.5)	19/113 (17.0)	0.90
Pet ownership	62/141 (44.0)	43/92 (46.7)	19/49 (38.8)	0.47	114/206 (55.3)	54/92 (58.7)	60/114 (52.6)	0.47
Fuel heat	11/140 (7.9)	9/91 (9.9)	2/49 (4.1)	0.33	11/206 (5.3)	9/92 (9.8)	2/114 (1.8)	0.015

1

2 **Table 3. Impact of environmental factors**

3 Data are expressed as medians [IQR] or frequencies (%). Comparisons of quantitative data were performed using Wilcoxon-Mann-Whitney tests. Categorical variables were
4 analysed using the chi-square test or Fisher exact test, as appropriate.

5

6

	Preschool children				School-Age children			
	Total population 141	Severe Recurrent Wheeze 92	Non-severe Recurrent Wheeze 49	p-value	Total population 207	Severe Asthma 92	Non-severe Asthma 115	p-value
Family atopy status								
Atopy in 1 or 2 parents or siblings	116/136 (85.3)	75/88 (85.2)	41/48 (85.4)	0.99	167/197 (84.8)	75/88 (85.2)	92/109 (84.4)	0.99
Parental asthma	71/136 (52.2)	44/88 (50.0)	27/48 (56.2)	0.60	80/200 (40.0)	43/91 (47.3)	37/109 (33.9)	0.077
Parental atopic dermatitis	42/140 (30.0)	25/91 (27.5)	17/49 (34.7)	0.49	70/204 (34.3)	32/92 (34.8)	38/112 (33.9)	0.99
Parental immediate food allergy	14/140 (10.0)	10/91 (11.0)	4/49 (8.2)	0.77	17/204 (8.3)	6/92 (6.5)	11/112 (9.8)	0.55
Parental allergic rhinitis	69/139 (49.6)	47/91 (51.6)	22/48 (45.8)	0.64	101/204 (49.5)	43/92 (46.7)	58/112 (51.8)	0.56
Asthma in siblings	53/122 (43.4)	41/81 (50.6)	12/41 (29.3)	0.040	77/182 (42.3)	37/85 (43.5)	40/97 (41.2)	0.87
Atopic dermatitis in siblings	40/121 (33.1)	32/78 (41.0)	8/43 (18.6)	0.021	67/183 (36.6)	35/84 (41.7)	32/99 (32.3)	0.25
Immediate food allergy in siblings	20/124 (16.1)	15/82 (18.3)	5/42 (11.9)	0.51	21/182 (11.5)	14/84 (16.7)	7/98 (7.1)	0.076
Allergic rhinitis in siblings	35/119 (29.4)	27/79 (34.2)	8/40 (20.0)	0.16	54/175 (30.9)	24/79 (30.4)	30/96 (31.2)	0.99
Allergic sensitization								
Atopy	74/115 (64.3)	44/72 (61.1)	30/43 (69.8)	0.46	151/182 (83.0)	70/82 (85.4)	81/100 (81.0)	0.56
≥ 1 positive SPT or sp IgE to airborne allergen	68/114 (59.6)	39/71 (54.9)	29/43 (67.4)	0.26	143/179 (79.9)	67/80 (83.8)	76/99 (76.8)	0.33
≥ 1 positive SPT or sp IgE to food allergen	13/97 (13.4)	8/59 (13.6)	5/38 (13.2)	0.99	32/147 (21.8)	20/69 (29.0)	12/78 (15.4)	0.072
Total IgE (Ku/L)	101 [29, 347] n=124	89 [26, 300] n=84	129 [42, 428] n=40	0.37	369 [126, 774] n=190	443 [141, 982] n=87	311 [108, 666] n=103	0.053
Blood eosinophils count (n/mm ³)	220 [120-500] n=111	215 [115-425] n=72	300 [135-600] n=39	0.31	400 [200, 700] n=149	400 [200, 770] n=69	390 [200, 600] n=80	0.40
Associated allergic disorders								
History of food allergy	20/136 (14.7)	13/88 (14.8)	7/48(14.6)	0.99	43/201 (21.4)	28/90 (31.1)	15/111 (13.5)	0.004
History of allergic rhinitis	70/140 (50.0)	43/92 (46.7)	27/48 (56.2)	0.37	152/207 (73.4)	71/92 (77.2)	81/115 (70.4)	0.35
History of atopic dermatitis	49/141 (34.8)	33/92 (35.9)	16/49 (32.7)	0.84	75/207 (36.2)	45/92 (48.9)	30/115 (26.1)	0.001
Comorbidities								
Symptomatic gastro-oesophageal reflux	31/141 (22.0)	24/92 (26.1)	7/49 (14.3)	0.16	30/207 (14.5)	20/92 (21.7)	10/115 (8.7)	0.014

1

2 Table 4. Atopy and associated disorders

3 Data are expressed as medians [IQR] or frequencies (%). Comparisons of quantitative data were performed using Wilcoxon-Mann-Whitney tests. Categorical variables were
4 analysed using the chi-square test or Fisher exact test, as appropriate.

5

6

1
2
3

	Adjusted OR (95% CI)	p-value
Birth weight (<i>per unit, kg, increase</i>)	0.34 (0.14 - 0.75)	0.007
Second-hand smoke exposure: <i>yes vs. no</i>	29.8 (3.57 - 3910)	< 0.001
Visible mold/dampness at home: <i>yes vs. no</i>	4.22 (1.25 - 18.2)	0.019
Atopic dermatitis in siblings: <i>yes vs. no</i>	3.02 (1.19 - 8.29)	0.02

4

Table 5. Multi-variable analysis to assess risk factors for severe recurrent wheeze in preschool children

5

OR: Odds Ratio, ICU: intensive care unit.

6

Variables considered before the backward elimination procedure: birth weight, second-hand smoke exposure, visible mold/dampness at home, asthma in siblings, atopic dermatitis in siblings.

7

8

9

10

11

12

13

14

15

16

17

18

19

20

	Adjusted OR (95% CI)	p-value
Age (<i>per unit, year, increase</i>)	1.22 (1.00 – 1.49)	0.045
Breastfeeding: <i>yes vs. no</i>	0.33 (0.16 – 0.67)	0.002
N° of residents at home: (<i>per unit increase</i>)	1.54 (1.18 – 2.06)	0.002
Fuel heat: <i>yes vs. no</i>	16.7 (2.76 - 322)	0.011
Parental asthma: <i>yes vs. no</i>	1.56 (0.80 – 3.05)	0.19
History of food allergy: <i>yes vs. no</i>	5.01 (2.23 – 11.9)	< 0.001

1
2 **Table 6. Multi-variable analysis to assess risk factors for severe asthma in school-age children**

3 *OR: Odds Ratio, SPT: skin-prick test.*

4 *Variables considered before the backward elimination procedure: age, breastfeeding, number of residents at home, fuel heat, parental asthma, immediate food allergy in*
5 *siblings, ≥ 1 positive SPT or specific IgE to food allergen, total IgE (Ku/L), history of food allergy, diagnosed atopic dermatitis, symptomatic gastro-esophageal reflux.*

6
7
8
9
10
11
12
13

	Inclusion	Follow-up		Visit 6-7 years	Visit 12 years	Visit 17-18 years
		SA and SRW: Every 6 months	NSA and NSRW: Every year			
All children						
Clinical assessment	X	X	X	X	X	X
ACT Questionnaire	X	X	X	X	X	X
PAQL Questionnaire	X	X	X	X	X	X
Lung function +- FeNO	X	X	X	X	X	X
SPT	X			X	X	X
Eosinophil count, vitamin D, total and specific IgE	X			X	X	X
ISAC® chip	X			X	X	X
Genomic DNA extraction	X			X	X	X
Children with SRW and SA						
Humoral immune status	X	According to: history, hospital center protocols and evolution				
Thoracic computerized tomography scan	X					
Ear, Nose and Throat Examination	X					
Sinus computerized tomography scan (after the age of 7 years)	X					
Intraesophageal pH measurement	X					
Bronchoscopy and bronchoalveolar lavage +- bronchial brushing	X					
Induced sputum	X					

