

DR GIZEM PAMUK (Orcid ID : 0000-0002-1401-1777)

Article type : Letter to the Editor

The economic burden of allergic comorbidities in pediatric severe asthma

Gizem Pamuka, MD, Muriel Le Bourgeoisa, MD, Rola Abou Taama, MD, Antoine Neurazb,c,d, MD-PhD, Jacques de Blicc,c, MPH-PhD, Christophe Delacourta,c, MPH-PhD, and Guillaume Lezmia,c MD-PhD

Affiliations: aAP-HP, Hôpital Necker-Enfants Malades, Department of Pediatric Pulmonology and Allergy, Paris, France; bAP-HP, Hôpital Necker-Enfants Malades, Department of Medical Informatics; c University of Paris, Faculty of medicine, Paris, France; and d INSERM UMRS 1138, Team 22, Centre de Recherche des Cordeliers

Address correspondence to: Gizem Pamuk, AP-HP, Hôpital Necker-Enfants Malades, Department of Pediatric Pulmonology and Allergy, 149 rue de Sèvres 75015 Paris, France, [gizem.pamuk@aphp.fr], +33 1 44 49 48 38.

Funding Source: No external funding for this manuscript.

Financial Disclosure: The authors have indicated they have no financial relationships relevant to this article to disclose.

Conflict of Interest: The authors have indicated they have no potential conflicts of interest to disclose.

To the Editor:

Severe asthma (SA) affects less than 5% of the pediatric asthma population but is considered to account for approximately half of total pediatric asthma healthcare costs. Allergic comorbidities, including food allergies (FA) and allergic rhinitis (AR), are frequent in children with SA (1). The presence of FA and AR increases asthma severity (1–6) and medication use (4–6). Treating AR improves asthma symptoms (3). However, the economic burden of allergic comorbidities in children with SA has been poorly studied. We aimed to quantify the costs associated with management of allergic comorbidities in children with severe asthma, and to

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1111/PAI.13532](https://doi.org/10.1111/PAI.13532)

This article is protected by copyright. All rights reserved

compare such costs in children with severe and non-severe asthma (NSA). Children with SA, defined as those requiring step 4 or 5 of treatment of the Global Initiative for Asthma (GINA), regularly followed in the Department of Pediatric Pulmonology of Necker Hospital were included as previously described (7). Participants were consecutively recruited during outpatient visits between May 1, 2018 and October 30, 2018. The diagnosis of SA, FA, or AR was made by a physician according to guidelines (8-10). A physician-guided questionnaire was completed with parents to assess individual expenditures related to asthma and allergic comorbidities in the previous six months. Parental claims were confirmed by analysis of the medical records. The methods are detailed elsewhere (7). First, we determined the direct, indirect, and global costs of SA over a six-month period (7) (see Supplemental information and Supplemental Table 1) and then assessed the allergy-related costs. This included anti-allergic medications (oral antihistamines, steroid nasal sprays, anti-allergic eye drops, adrenaline autoinjectors, and allergen immunotherapy), anti-IgE treatment, scheduled ambulatory or hospital outpatient visits to an allergist, pulmonologist, ophthalmologist, or dermatologist, skin tests, blood tests for allergy-specific IgE, and day care unit (DCU) admissions for oral food challenge (OFC) (7). Categorical variables are expressed as absolute and relative frequencies and continuous variables as means and confidence intervals. The 95% confidence intervals (95%CI) were estimated by the bootstrapping method. Analyses were performed using R Statistical Software version 4.0.3 and the boot package (11). We computed the mean for each variable and subgroup using the ordinary bootstrap method with 1,000 repetitions and its bootstrapped 95%CI using the percentile method (12). Parents were informed and accepted to participate in the study. The local ethical committee confirmed that Institutional Review Board approval was not required.

Forty-eight children with SA and 26 with NSA were included. Their general characteristics are summarized in Table 1. The mean overall cost of SA was €3,982.00 over the six-month study period (7). For children with allergic SA, the mean cost attributed to allergic comorbidities was €2,803.00 representing 48.1% of the direct SA costs and 45.8% of the global SA costs (Supplemental figure 1). The mean global and direct costs of SA were higher for children with allergic comorbidities than for those without (€4,645.95 vs. €1,076.26, $p = 0.02$; €4,477.08 vs. €944.71 $p = 0.01$; respectively) (Table 2). However, these figures partially reflect the actual economic contribution of allergic comorbidities in children with allergic SA. For those requiring omalizumab, the economic burden of allergic comorbidities was €5,057.00 representing 74.1% of direct SA costs and 71.6% of global SA costs. In this group, omalizumab was the main driver of costs, representing 73.6% of direct SA costs and 71.5% of global SA costs. For children with allergic SA not requiring omalizumab, the economic burden of allergic comorbidities was €174.50 representing 17.8% of direct SA costs and 15.8% of global SA

costs (Supplemental figure 1). When the cost of omalizumab was not taken into consideration, the economic burden of allergic comorbidities was not significantly different between children with allergic SA requiring omalizumab vs. those who did not (€153.30 vs. €174.50, $p = 0.99$). Moreover, when costs related to omalizumab treatment were excluded, the mean global and direct costs of SA for children with allergic comorbidities were not significantly different from those without (€2,006.00 vs. €950.70, $p = 0.43$ and €1,837.00 vs. €819.10, $p = 0.28$, respectively). However, the burden of allergic comorbidities expressed as a percentage of direct and global SA costs was lower for children with SA requiring omalizumab than those who did not (3% vs. 17.8%, $p < 0.01$ and 2.9% vs. 15.8%, $p < 0.01$, respectively).

Global, direct, and indirect costs did not differ between children with NSA, with or without allergic comorbidity (Table 3). For children with allergic NSA, the mean cost of allergic comorbidities was €139.57, representing 40.8% of the asthma direct costs and 34.7 % of the asthma global costs (Supplemental figure 1). Thus, regardless of omalizumab use, the difference between the mean cost of allergic comorbidities for children with allergic SA and that for those with allergic NSA was not statistically significant (€163.11 vs. €139.57, $p = 0.19$). However, the economic burden of allergic comorbidities was greater for children with NSA than those with SA: 40.8% vs 9.8% of direct costs and 34.7% vs. 8.9% of global costs, respectively (both $p < 0.01$). Finally, the economic burden of allergic comorbidities was not significantly different between children with allergic SA not requiring omalizumab and those with allergic NSA (€174.50 vs. €139.57, $p = 0.29$).

This study shows that the costs attributed to allergic comorbidities for children with SA are substantial and mostly driven by omalizumab but are minor when omalizumab is not taken into account. The economic burden of allergic comorbidities was not significantly different between children with allergic SA not requiring omalizumab and those with allergic NSA. The global and direct costs of children with allergic SA were higher than those of children with non-allergic SA. This finding confirms that the presence of allergic comorbidities increases the costs of asthma management (13). Our study had several limitations. Only a small number of children were included. However, we included children with well-defined doctor-confirmed SA, with and without omalizumab, reflecting the heterogeneity of this population. The burden of allergic comorbidities may be misestimated particularly in children with SA under omalizumab. This treatment may improve allergic symptoms such as those of allergic rhinitis, and thus reduce the use of H1-antihistamines or local corticosteroids and affect the number of consultation to allergist or ENT. The cost of omalizumab is substantial, thus omalizumab increases the economic burden of the treatment in children with SA. On the

other hand, our results may provide a real-life picture of the economic burden of allergic comorbidities in this heterogeneous group. In addition, our study was performed in a tertiary-care center. Thus, the children with NSA may not be representative of community children. This may bias the estimation because allergic comorbidities may have been more frequently assessed in a tertiary center than in ambulatory settings, and management may differ, including the prescription of allergen immunotherapy. Our estimation was based on parental declarations, with a potential memory bias and a risk of misestimation of certain expenditures. We limited this risk by analyzing the medical records, which confirmed the parental claims. The best design would have been to obtain the data of children selected by a physician from the NHI. However, this approach is rarely authorized in France. Moreover, the study covered a short period of time including winter and two months of spring, which may lead to underestimation of costs related to seasonal allergy treatments. In addition, the number of children under allergen immunotherapy was small (1 in the group of children with allergic SA vs. 4 children with allergic NSA ($p = 0.03$)). Finally, one limitation of our study is that the uncertainty associated with each item may induce misestimation of costs.

In summary, this study is the first to precisely analyze the proportion of costs attributed to allergic comorbidities in pediatric SA. As expected, allergy-related costs are mainly driven by omalizumab. However, for children with allergic SA who do not require omalizumab, the economic contribution of allergic comorbidities to SA costs is relatively small.

The authors declare they have no conflicts of interest.

References

1. Deschildre A, Marguet C, Salleron J, Pin I, Rittié J-L, Derelle J, et al. Add-on omalizumab in children with severe allergic asthma: a 1-year real life survey. *Eur Respir J.* 1 nov 2013;42(5):1224.
2. Just J, Gouvis-Echraghi R, Rouve S, Wanin S, Moreau D, Annesi-Maesano I. Two novel, severe asthma phenotypes identified during childhood using a clustering approach. *Eur Respir J.* juill 2012;40(1):55-60.
3. Deliu M, Belgrave D, Simpson A, Murray CS, Kerry G, Custovic A. Impact of rhinitis on asthma severity in school-age children. *Allergy.* nov 2014;69(11):1515-21.

4. Schwindt CD, Tjoa T, Floro JN, McLaren C, Delfino RJ. Association of Atopy to Asthma Severity and Medication Use in Children. *J Asthma*. janv 2006;43(6):439-46.
5. Wang J, Visness C, Sampson H. Food allergen sensitization in inner-city children with asthma. *J Allergy Clin Immunol*. mai 2005;115(5):1076-80.
6. Friedlander JL, Sheehan WJ, Baxi SN, Kopel LS, Gaffin JM, Ozonoff A, et al. Food Allergy and Increased Asthma Morbidity in a School-Based Inner-City Asthma Study. *J Allergy Clin Immunol Pract*. sept 2013;1(5):479-84.
7. Pamuk G, Le Bourgeois M, Abou Taam R, de Blic J, Delacourt C, Lezmi G. The economic burden of severe asthma in children: a comprehensive study. *J Asthma*. 21 août 2020; In Press.
8. Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C, et al. EAACI Food Allergy and Anaphylaxis Guidelines: diagnosis and management of food allergy. *Allergy*. août 2014;69(8):1008-25.
9. Seidman MD, Gurgel RK, Lin SY, Schwartz SR, Baroody FM, Bonner JR, et al. Clinical Practice Guideline: Allergic Rhinitis. *Otolaryngol Neck Surg*. févr 2015;152(1_suppl):S1-43.
10. 2018 GINA Report, Global Strategy for Asthma Management and Prevention.
11. Angelo Canty and Brian Ripley (2017). *boot: Bootstrap R (S-Plus) Functions*. R package version 1.3-20.
12. Davison, A. C. & Hinkley, D. V. (1997) *Bootstrap Methods and Their Applications*. Cambridge University Press, Cambridge. ISBN 0-521-57391-2
13. Schramm B, Ehlken B, Smala A, Quednau K, Berger K, Nowak D. Cost of illness of atopic asthma and seasonal allergic rhinitis in Germany: 1-yr retrospective study. *Eur Respir J*. janv 2003;21(1):116-22.

Table 1. General characteristics of children with SA according to allergy status.

Characteristics	SA	Allergic SA	Non allergic SA	P
n	48	39	9	
Gender				
Male/female	30/18	25	5	0.65
Age (years)	13.4 [10.73 - 16.18]	14.30 [11.00 - 16.40]	11.30 [8.75 - 13.75]	0.03
BMI (kg/m ²)	19.37 [17.14 - 21.91]	19.95 [17.12 - 22.32]	18.08 [16.94 - 19.60]	0.16
Comorbid diseases				
Atopic dermatitis	15 (31.2%)	15 (38.5%)	0 (0)	0.02
Food allergy	8 (16.6%)	8 (20.5%)	0 (0)	0.14
Allergic rhinitis+/-conjunctivitis	37 (77%)	37 (95%)	0 (0)	< 0.01
Nasal polyps	1 (2.1%)	1 (2.5%)	0 (0)	0.67
Sinusitis	3 (6.3%)	3 (7.7%)	0 (0)	0.41
Gastroesophageal reflux disease	14 (29.1%)	13 (33.3%)	1 (11.1%)	0.19
Obstructive sleep apnea syndrome	1 (2.1%)	1 (2.5%)	0 (0)	0.67
1 allergic comorbidity	24 (50%)	24 (61.5%)		
2 allergic comorbidities	11 (22.9%)	11 (28.2%)		
3 allergic comorbidities	4 (8.3%)	4 (10.3%)		
Influenza vaccination, n (%)	21 (43.7%)	18 (46.1%)	3 (33.3%)	0.49
Utilization of treatments				

Dose of ICS (µg/d flu eq.)	500 [500-500]	500 [500-500]	500 [450-500]	0.54
LABA, n (%)	42 (87.5%)	34 (87.1%)	8 (88.8%)	0.91
Nebulization for maintenance treatment, n (%)	7 (14.6%)	5 (12.8%)	2 (22.2%)	0.49
Leukotriene antagonist, n (%)	26 (54.1%)	20 (51.3%)	6 (66.6%)	0.41
Long term antibiotic treatment, n (%)	3 (6.3%)	2 (5.1%)	1 (11.1%)	0.53
Anti-Ig E, n (%)	22 (45.8%)	21 (53.8%)	1 (11.1%)	0.02
Allergen Immunotherapy, n (%)	1 (2.1%)	1 (2.5%)	0 (0)	0.66
Rehabilitation, n (%)	2 (4.2%)	1 (2.5%)	1 (11.1%)	0.27
Patients having outpatient clinical and laboratory tests, n (%)				
Spirometry	35 (72.9%)	28 (71.8%)	7 (77.7%)	0.73
At hospital	35 (72.9%)	28 (71.8%)	7 (77.7%)	0.73
In ambulatory	1 (2.1%)	1 (2.5%)	0 (0)	0.67
skin test for allergy	12 (25%)	10 (25.6%)	2 (22.2%)	0.85
blood test for allergy-specific IgE	15 (31.2%)	13 (33.3%)	2 (22.2%)	0.53
chest X-ray	6 (12.5%)	5 (12.8%)	1 (11.1%)	0.90
ENT endoscopy	4 (8.4%)	4 (10.2%)	0 (0)	0.33
pHmetry	2 (4.2%)	2 (5.1%)	0 (0)	0.51
Emergency department visit, n (%)	11 (22.9%)	10 (25.6%)	1 (11.1%)	0.36

Emergency department visit per patient	0.81 (39/48)	0.95 (37/39)	0.22 (2/9)	
Day Care Unit admission, n (%)	3 (6.3%)	3 (7.7%)	0 (0)	0.41
Hospitalization, n (%)	4 (8.4%)	3 (7.7%)	1 (11.1%)	0.76
in emergency unit	2 (4.2%)	1 (2.5%)	1 (11.1%)	0.27
in pulmonology unit	2 (4.2%)	2 (5.1%)	0 (0)	0.51
Urgent (unscheduled) physician visit in ambulatory, n (%)	21 (43.7%)	18 (46.1%)	3 (33.3%)	0.49
Scheduled physician visit, n (%)				
Hospital outpatient visit				
To pulmonologist/allergist	43 (89.6%)	34 (87.1)	9 (100%)	0.27
To ENT specialist	4 (8.4%)	4 (10.2%)	0 (0)	0.33
To dermatologist	2 (4.2%)	2 (5.1%)	0 (0)	0.51
To ophtalmologist	1 (2.1%)	1 (2.5%)	0 (0)	0.67
Ambulatory visit				
To general practitioner	6 (12.5%)	4 (10.2%)	2 (22.2%)	0.34
To pediatrician	4 (8.4%)	3 (7.7%)	1 (11.1%)	0.76
To pulmonologist	4 (8.4%)	4 (10.2%)	0 (0)	0.33
To allergist	1 (2.1%)	1 (2.5%)	0 (0)	0.67
To ENT specialist	5 (10.4%)	4 (10.2%)	1 (11.1%)	0.96
To dermatologist	0 (0)	0 (0)	0 (0)	

To ophtalmologist

1 (2.1%)

1 (2.5%)

0 (0)

0.67

SA: severe asthma, NSA: non-severe asthma, BMI: body mass index, ICS: inhaled corticosteroids, $\mu\text{g}/\text{d}$ flu eq: $\mu\text{g}/\text{day}$ in fluticasone equivalent, LABA: long-acting beta-2 agonist, ENT: ear nose throat

Categorical variables are expressed as absolute and relative frequencies and continuous variables as medians and quartiles. The 95% confidence intervals (95%CI) were estimated.

Table 2. Estimated costs (€) for children with SA according to allergy status during the six-month study period

	Allergic SA (n = 39)	Non allergic SA (n = 9)	p*
Direct costs	Mean [95% CI]	Mean [95% CI]	
Medications	2,967.04 [1,877.92- 4,280.15]	430.19 [208.93-758.51]	0.06
Anti-allergic medications	46.15 [19.15-81.40]	0 [0-0]	< 0.01
Oral antihistamines	5.41 [4.18-6.68]	0 [0-0]	< 0.01
Steroid nasal sprays	5.10 [3.68-6.60]	0 [0-0]	< 0.01
Anti-allergic eye drops	1.00 [0.39-1.80]	0 [0-0]	0.056
Adrenaline autoinjectors	23.26 [3.55-49.82]	0 [0-0]	0.27
Allergen immunotherapy	11.52 [0.00-34.55]	0 [0-0]	0.67
Asthma Rescue treatment			
SABA (MDI or DPI)	22.76 [17.29-28.70]	7.67 [6.06-9.20]	< 0.01
SABA (nebulizer solution)	18.66 [5.02-38.52]	8.09 [1.67-17.08]	0.91
Ipratropium bromide in nebulizer solution	4.65 [0.40-10.92]	6.14 [0.00-18.41]	0.83

Oral corticosteroids	5.48 [3.95-7.06]	2.94 [2.14-3.74]	0.23
Asthma Maintenance treatment			
Inhaled corticosteroid ($\pm$ LABA) treatment (MDI, DPI)	127.48 [104.85-148.81]	111.72 [76.54-146.46]	0.89
Inhaled corticosteroid (nebulizer solution)	34.40 [10.32-63.55]	42.76 [0.00-112.72]	0.93
Leukotriene modifiers	42.27 [28.56-56.36]	62.71 [31.36-92.42]	0.17
Long-term antibiotic treatment	2.13 [0.00-5.81]	4.64 [0.00-13.91]	0.53
Anti-Ig E	2,640.38 [1,582.43-3,921.76]	156.43 [0.00-469.29]	0.02
Influenza vaccination	4.67 [3.11-6.22]	3.37 [0.00-6.74]	0.50
Medical devices ^a	58.87 [31.56-87.10]	0 [0-0]	< 0.01
Urgent (unscheduled) physician visit in ambulatory	39.74 [21.15-64.10]	22.22 [0.00-44.44]	0.49
Scheduled physician visits	82.67 [65.39-100.36]	64.89 [37.00-92.99]	0.41
Hospital outpatient visits	58.00 [44.09-72.92]	43.33 [28.00-58.67]	0.48
To pulmonologist/allergist	52.26 [39.44-65.79]	43.33 [28.00-58.67]	0.76
To ENT specialist	2.87 [0.72-5.74]	0 [0-0]	0.33
To dermatologist	1.44 [0.00-3.59]	0 [0-0]	0.52

To ophtalmologist	0.72 [0.00-2.15]	0 [0-0]	0.67
Ambulatory visits	24.67 [11.88-39.18]	21.56 [5.33-40.56]	0.84
To general practitioner	7.05 [0.64-16.67]	11.11 [0.00-27.78]	0.36
To pediatrician	4.72 [0.00-11.79]	5.11 [0.00-15.33]	0.76
To pulmonologist	5.51 [1.23-11.03]	0 [0-0]	0.33
To allergist	1.23 [0.00-3.69]	0 [0-0]	0.67
To ENT specialist	4.92 [1.23-9.85]	5.33 [0.00-16.00]	0.96
To dermatologist	0 [0-0]	0 [0-0]	
To ophtalmologist	1.23 [0.00-3.69]	0 [0-0]	0.67
Outpatient Clinical and Laboratory tests	119.87 [88.01-149.78]	65.68 [37.54-100.86]	0.50
spirometry	73.06 [55.20-90.92]	63.32 [35.18-98.50]	0.65
skin test for allergy	7.38 [2.95-11.82]	0 [0-0]	0.57
blood test for allergy-specific IgE	27.68 [14.90-40.45]	0 [0-0]	0.53
chest X-rays	4.37 [0.55-8.73]	2.36 [0.00-7.09]	0.87
ENT endoscopy	2.95 [0.74-5.91]	0 [0-0]	0.33
pHmetry	4.43 [0.00-11.08]	0 [0-0]	0.52
Day care unit admissions	126.18 [0.00-281.31]	0 [0-0]	0.41
Emergency department visits	621.41 [235.13-1,158.85]	145.56 [0.00-436.67]	0.34
Hospitalizations	73.58 [0.00-180.50]	57.94 [0.00-173.82]	0.68

in emergency unit	13.37 [0.00-40.11]	57.94 [0.00-173.82]	0.27
in pulmonology unit	60.21 [0.00-163.90]	0 [0-0]	0.52
Rehabilitation	387.72 [0.00-1,163.17]	158.23 [0.00-474.68]	0.29
Management of allergic comorbidities^	2,803.00 [146.3-5135]	0 [0-0]	<0.01
Total	4,477.08 [3,065.53- 5,978.44]	944.71 [336.24-1,836.08]	0.01
Indirect costs			
<i>Asthma-related School loss (days)</i>	13.87 [7.49-22.33]	3.67 [1.89-5.56]	0.29
Asthma-related work loss of the father (€)	94.87 [39.85-165.08]	41.11 [0.00-98.67]	0.56
<i>Asthma-related work loss of the father (days)</i>	1.28 [0.54-2.23]	0.56 [0.00-1.33]	0.56
Asthma-related work loss of the mother (€)	74.00 [41.74-117.64]	90.44 [16.44-205.56]	0.99
<i>Asthma-related work loss of the mother (days)</i>	1.00 [0.56-1.59]	1.22 [0.22-2.78]	0.99

Total	168.87 [92.97-267.54]	131.56 [16.44-312.44]	0.52
Global Costs = Direct + Indirect costs	4,645.95 [3,169.12- 6,235.34]	1,076.26 [481.97-1,888.65]	0.02

SA: severe asthma, DPI: dry powder inhaler, MDI: metered dose inhaler, SABA: short-acting beta-2 agonist, LABA: long-acting beta-2 agonist, ^a inhalation chamber, peak flow meter and nebulizer, ENT: ear nose throat, [^]: The costs resulting from the management of allergic comorbidities include the costs related to anti-allergic medications (oral antihistamines, steroid nasal sprays, anti-allergic eye drops, adrenaline autoinjectors, and allergen immunotherapy), anti-IgE treatment, scheduled ambulatory or hospital outpatient visits to an allergist, pulmonologist, ophthalmologist, or dermatologist, skin tests, blood tests for allergy-specific IgE, and day care unit (DCU) admissions for oral food challenge (OFC).

* Mann Whitney U

Categorical variables are expressed as absolute and relative frequencies and continuous variables as means and confidence intervals. The 95% confidence intervals (95%CI) were estimated by the bootstrapping method.

Table 3. General characteristics and estimated costs (€) for children with NSA according to allergy status during the six-month study period

	Allergic NSA	Non allergic NSA	p*
Characteristics			
n	14	12	
Comorbid diseases			
Atopic dermatitis	5 (35.7%)	0 (0)	
Food allergy	3 (21.4%)	0 (0)	
Allergic rhinitis+/-conjunctivitis	13 (92.8%)	0 (0)	
1 allergic comorbidity	8 (57.1%)		
2 allergic comorbidities	5 (35.7%)		
3 allergic comorbidities	1 (7.1%)		
Direct costs			
	Mean [95% CI]	Mean [95% CI]	
Medications	160.18 [74.67-276.59]	86.49 [48.86-132.97]	0.49
Anti-allergic medications	76.29 [6.85-178.68]	0 [0-0]	<0.01
Oral antihistamines	4.11 [2.21-6.01]	0 [0-0]	<0.01
Steroid nasal sprays	2.37 [0.83-4.22]	0 [0-0]	<0.01
Anti-allergic eye drops	0.10 [0.00-0.29]	0 [0-0]	0.36

Adrenaline autoinjectors	10.65 [0.00-37.75]	0 [0-0]	0.38
Allergen immunotherapy	59.85 [2.03-141.41]	0 [0-0]	0.054
Asthma Rescue treatment			
SABA (MDI or DPI)	6.93 [4.61-9.43]	5.93 [4.27-7.73]	0.79
SABA (nebulizer solution)	0.83 [0.00-2.48]	0 [0-0]	0.37
Ipratropium bromide in nebulizer	0 [0-0]	0 [0-0]	
Oral corticosteroids	2.01 [0.80-3.55]	1.40 [0.60-2.20]	0.87
Asthma Maintenance treatment			
Inhaled corticosteroid ($\pm$ LABA)	67.26 [36.07-103.79]	60.54 [35.96-86.46]	0.92
treatment (MDI, DPI)			
Inhaled corticosteroid (nebulizer solution)	0 [0-0]	0 [0-0]	
Leukotriene modifiers	0 [0-0]	16.09 [0.00-39.61]	0.13
Long-term antibiotic treatment	0 [0-0]	0 [0-0]	
Influenza vaccination	4.33 [1.46-7.22]	2.53 [0.00-5.05]	0.37
Medical devices ^a	1.89 [0.00-3.79]	2.21 [0.02-4.42]	0.86
Urgent (unscheduled) physician visit in ambulatory	0 [0-0]	4.17 [0.00-10.42]	0.13
Scheduled physician visits	52.00 [31.15-72.85]	29.42 [19.34-39.00]	0.14
Hospital outpatient visits	27.86 [14.00-47.71]	23.33 [14.00-35.00]	0.98
To pulmonologist/allergist	25.86 [14.00-41.71]	23.33 [14.00-35.00]	0.98
To ENT specialist	0 [0-0]	0 [0-0]	

To dermatologist	2.00 [0.00-6.00]	0 [0-0]	
To ophthalmologist	0 [0-0]	0 [0-0]	
Ambulatory visits	24.14 [11.93-39.21]	6.08 [0.00-14.25]	0.059
To general practitioner	5.36 [0.00-14.29]	2.08 [0.00-6.25]	0.64
To pediatrician	0 [0-0]	0 [0-0]	
To pulmonologist	0 [0-0]	0 [0-0]	0.11
To allergist	11.93 [0.00-25.50]	0 [0-0]	
To ENT specialist	6.86 [0.00-17.14]	4.00 [0.00-12.00]	
To dermatologist	0 [0-0]	0 [0-0]	
Outpatient Clinical and Laboratory tests	54.46 [24.26-93.45]	52.77 [26.38-79.15]	0.75
spirometry	36.18 [18.09-58.80]	52.77 [26.38-79.15]	0.35
skin test for allergy	12.34 [4.11-20.57]	0 [0-0]	0.01
blood test for allergy-specific IgE	5.93 [0.00-17.79]	0 [0-0]	0.39
chest X-rays	0 [0-0]	0 [0-0]	
ENT endoscopy	0 [0-0]	0 [0-0]	
pHmetry	0 [0-0]	0 [0-0]	
Day care unit admissions	0 [0-0]	0 [0-0]	
Emergency department visits	0 [0-0]	109.17 [0.00-327.50]	0.32
Hospitalizations	37.25 [0.00-111.74]	0 [0-0]	0.39

in emergency unit	37.25 [0.00-111.74]	0 [0-0]	0.39
in pulmonology unit	0 [0-0]	0 [0-0]	
Rehabilitation	0 [0-0]	0 [0-0]	
Management of allergic comorbidities^	139.57 [44.96-278.64]	0 [0-0]	< 0.01
Total	305.78 [163.16-471.01]	284.22 [143.35- 511.07]	0.86
Indirect costs			
<i>Asthma-related School loss (days)</i>	1.57 [0.71-2.64]	1.58 [0.71-2.75]	0.61
Asthma-related work loss of the father (€)	31.71 [0.00-74.00]	18.50 [0.00-37.00]	0.97
<i>Asthma-related work loss of the father (days)</i>	0.43 [0.00-1.00]	0.25 [0.00-0.50]	0.97
Asthma-related work loss of the mother (€)	31.71 [5.29-63.43]	49.33 [18.50-80.17]	0.36
<i>Asthma-related work loss of the mother (days)</i>	0.43 [0.07-0.86]	0.67 [0.25-1.08]	0.36
Total	63.43 [15.86-121.57]	67.83 [30.83-104.83]	0.86

Global Costs = Direct + Indirect costs	369.21 [202.73-547.35]	352.05 [195.74-577.62]	0.98
---	------------------------	------------------------	------

NSA: non severe asthma, DPI: dry powder inhaler, MDI: metered dose inhaler, SABA: short-acting beta-2 agonist, LABA: long-acting beta-2 agonist, ^a inhalation chamber, peak flow meter and nebulizer, ENT: ear nose throat, [^]: The costs resulting from the management of allergic comorbidities include the costs related to anti-allergic medications (oral antihistamines, steroid nasal sprays, anti-allergic eye drops, adrenaline autoinjectors, and allergen immunotherapy), anti-IgE treatment, scheduled ambulatory or hospital outpatient visits to an allergist, pulmonologist, ophthalmologist, or dermatologist, skin tests, blood tests for allergy-specific IgE, and day care unit (DCU) admissions for oral food challenge (OFC).

* Mann Whitney U

Categorical variables are expressed as absolute and relative frequencies and continuous variables as means and confidence intervals. The 95% confidence intervals (95%CI) were estimated by the bootstrapping method.