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Asthma and Lower Airway Disease

Economic Impact of Allergic Diseases and Asthma—The HEAD Pan-European Registry

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ABSTRACT

The Health Economics of Allergic Diseases (HEAD) registry is a European-based registry developed by the European Academy of Allergy and Clinical Immunology in collaboration with national allergy societies to facilitate standardised allergic disease management. Using an observational design, this first registry-based study describes care patterns for allergic diseases and their impact on the healthcare system (diagnostic and management costs), society (missed work/school days and disability pension/support) and patients (out-of-pocket costs) in 778 adults and children with allergic rhinitis, asthma, atopic dermatitis and food allergy, from four countries (Belgium, Italy, Romania and Spain). The average total costs per patient and per year were €1329.55 ± 1947.39, with indirect costs of €338.68 ± 1629.61. Direct costs consisted of €82.74 ± 585.90 for hospitalisations, €17.50 ± 125.07 for the emergency department, €172.94 ± 323.17 for specialists, €22.70 ± 132.42 for primary care,

Abbreviations: AD, atopic dermatitis; AIT, allergen immunotherapy; AR, allergic rhinitis; ARIA, allergic rhinitis and its impact on asthma; COVID-19, coronavirus disease 2019; CRD, component-resolved diagnosis; CU, chronic urticaria; EAACI, European Academy of Allergy and Clinical Immunology; ED, emergency department; EMA, European Medicines Agency; FA, food allergy; HCRU, healthcare resource utilisation; HEAD, Health Economics of Allergic Diseases; LTRA, leukotriene receptor antagonist; NO, nitric oxide; OCS, oral corticosteroid; SCIT, subcutaneous allergen immunotherapy; SCORAD, SCORing Atopic Dermatitis; SD, standard deviation; SLIT, sublingual allergen immunotherapy; UEMS, European Union of Medical Specialists.

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See Appendix A for the HEAD Study Group.

€4.85 ± 136.84 for psychologists, €21.24 ± 82.47 for diagnosis and €104.81 ± 469.26 for treatments. Indirect costs were out-of-pocket consultation fees (€16.24 ± 106.40), medications (€161.90 ± 710.58), transportation (€44.15 ± 218.51), private insurance (€16.77 ± 157.91), avoidance (€8.65 ± 92.99) and environmental control (€99.33 ± 955.23). Adults missed 1.02 ± 3.20 workdays, children missed 0.53 ± 2.18 schooldays and burdened their families with 1.38 ± 13.83 lost days. There was a high degree of heterogeneity across countries for management patterns and for costs. The significant burden of allergic diseases calls for immediate action for better management.

1 | Introduction

Allergic diseases and asthma are among the most common chronic diseases, substantially contributing to the global health burden [1, 2]. In 2019, 262 million asthma cases and 171 million atopic dermatitis (AD) cases were reported globally, including 81 million children with asthma and 5.6 million children with AD [1, 2]. Data on asthma prevalence in children have been published with median values of 25% [3]. It is estimated that one in three people in Europe suffers from some form of chronic allergic disease, namely allergic rhinitis (AR), asthma, chronic rhinosinusitis, AD, chronic urticaria (CU), drug allergy (DA), food allergy (FA), eosinophilic oesophagitis or insect venom allergy [4–11].

Because the incidence and prevalence of allergic diseases increase, the resulting burden for many healthcare systems requires efficient management pathways coupled with sufficient provisions and increased awareness [12–20].

To deliver proper allergy care throughout Europe, it is necessary to evaluate the current management patterns and impact to identify gaps and barriers in their approach. A survey among European and non-European countries by the European Academy of Allergy and Clinical Immunology (EAACI) and the European Union of Medical Specialists (UEMS) section and allergologist board showed that in most countries, allergy care services are available but are highly heterogeneous in practices [21]. The same survey reported that allergy specialties do not exist or are just sub-specialties in many European countries. In addition, access to specialised care is challenging, with long waiting times and high costs. As a result, most allergic diseases are self-managed, treated by pharmacists or in primary care settings without proper allergy training, thus significantly impacting the quality of care and desired outcomes. The lack of political and societal awareness of the burden of allergic diseases and asthma also hampers care quality for these patients [14, 17, 19, 22, 23].

Estimating the true impact of allergic diseases is challenging due to incomplete and unrepresentative data [17, 19]. On the other hand, some practices may need to be appropriately evaluated in terms of cost-effectiveness outside the clinical trial framework in the long term, which would be necessary to standardise practices across Europe [24].

The overarching aims of the Health Economics of Allergic Diseases (HEAD) registry, established by the EAACI in 2021, are to harmonise allergic disease and asthma management and establish a structure for collaborative projects in these fields across European countries.

The aims of this cross-sectional study were to describe care patterns and estimate the impact of these diseases when considering direct medical costs (healthcare perspective), out-of-pocket costs for the patient (patient perspective) and all relevant costs to society (societal perspective). The assessment of care patterns and impact was stratified by disease and country.

2 | Methods

2.1 | Design

The design was cross-sectional. The observation period was set at 12 months. This is the baseline of a population-based multinational registry intended to run longitudinally hereafter.

2.2 | Population

To be included in the HEAD registry, patients needed to fulfil the following inclusion criteria: (a) specific diagnostic criteria for the following target allergic diseases: AR, asthma, AD, DA, FA and CU (Table S1); (b) any age/gender; (c) diagnosis in 2018 or before; and (d) at least one visit for the allergic disease during 2019 in the participating centres. The recruitment of allergy-specialised centres was done at the country level by country coordinators from the national allergy societies, trying to balance the representativeness of the populations attended and fidelity to the protocol. In principle, all centres were invited, but only a proportion, different in each country, accepted to participate.

The selection of 2019 as the cut-off year was due to the confounding effect of the Coronavirus disease 2019 (COVID-19) pandemic, which began disrupting all management pathways for allergic diseases and asthma in March 2020.

The centres were instructed to draw a random sampling of the patients attended in 2019. Random patient selection at the country level maintained the public/private ratio of specialised care centres to ensure representativeness. The target sample was 200 patients per disease and country. However, the target samples were not reached in all countries or diseases. Due to the data incompleteness, patients from Germany and the Czech Republic were not included in the final analysis. Similarly, pattern and impact analyses were not possible for DA and CU.

2.3 | Measurements and Variables

Standardised measures are fundamental for valid registry-based study results. The multinational HEAD registry thus employed

standard terminologies to ensure the same significance of information collected from different healthcare systems.

2.3.1 | Outcome 1: Care Patterns

The care pattern was defined by using specific assessments and management options for each disease and its associations. We characterised care patterns by assessing the frequency in which different diagnostic tests and management options are used (full list of considered tested and options are shown in Table S2).

2.3.2 | Outcome 2: Impact

The impact was studied over a 12-month period, with this time frame being the last full observation year before the pandemic (2018–2019). Therefore, data were collected for the interval between the last visit in 2019 (index visit) and a visit in 2018, occurring approximately 12 months before the last visit in 2019.

The results are presented in three levels:

- *Healthcare perspective*: direct medical costs (consultations, hospitalisations, visits to emergency department [ED]/specialist/primary care/psychologist, diagnostic tests, as well as pharmacological and non-pharmacologic interventions).
- *Societal perspective*: indirect costs represented by the value of production lost to society due to absence from work, days lost by families, school days missed by paediatric patients, disability and death.
- *Individual perspective*: indirect costs paid by the patient or their families related to the disease. Out-of-pocket costs were defined as additional costs not covered by insurance or other sources, directly impacting the family budget. The following data were collected: days lost by family members taking care of the sick person; out-of-pocket costs of diagnosis, medications, private insurance, transport to the specialised centre, lifestyle changes (e.g., special diet for FA, allergen avoidance or other environmental control) or other out-of-pocket costs.

2.4 | Statistical Analysis

Descriptive data were expressed by central tendency and dispersion measures or absolute frequency and percentages for quantitative and qualitative variables, respectively. Comparisons between countries were performed using the Kruskal–Wallis rank-sum test (continuous data) and chi-squared test (categorical data).

1. *Outcome 1—Care patterns*: For each disease, assessment or management option, use or pattern frequency was estimated with 95% confidence intervals. Comparisons between patient characteristics and treatment patterns were assessed by the chi-squared test for categorical variables and Kruskal–Wallis for continuous variables.
2. *Outcome 2—Impact*: The costs were obtained by surveying the country coordinators, who were instructed to search official databases in their respective countries. The currency for each cost was collected for each country and converted to Euro (€) of 2021, without inflation adjustment. For the cost analysis, we used the active substance, assumed that the same active ingredient had the same price, and the price per dose was calculated (in cases with multiple values for one active substance, we used the lowest value) [23]. The analysis did not include drugs listed under 'other drugs' and eye drops, gels, topical ointments and serums due to the difficulty of calculating dose costs. The price available for sublingual allergen immunotherapy (AIT) (SLIT) or subcutaneous AIT (SCIT) was that of a 10–12-month package. Therefore, the patient who received these compounds had a cost of 10–12 months (available price) since the computation period was 1 year (2018–2019). We assumed two adrenaline auto-injectors for long-term management for the whole study period. The total hospitalisation cost was calculated using the sum of visits and length of stay in intensive care unit or general ward. The total cost of specialist, primary care, psychologist or emergency department visits was determined by calculating the sum of the number of visits [25, 26].

Overall healthcare resource use utilisation (HCRU) was calculated as the sum of all costs (hospitalisations, ED visits, specialists, primary care visits and psychologist visits).

The total cost of diagnostic tests was determined by counting each diagnostic test used and multiplying it by its cost. The total treatment cost was the sum of the product price per dose of each active ingredient multiplied by the number of treatment days.

All statistical analyses were performed using a two-sided hypothesis at a 5% significance level, using the R statistical software, version 4.3.0 [27], with a two-sided hypothesis at a 5% significance level.

2.5 | Regulatory and Ethical Considerations

Regulatory and good clinical practice aspects followed the standards of the European Medicines Agency (EMA) and those of the Agency for Healthcare Research and Quality for multinational registries [28–31]. The registry ensured the European Union's and national regulations on data protection and storage (General Data Protection Regulation). Study procedures complied with the Declaration of Helsinki [29] and good clinical practice guidelines [31].

As data were collected during the pandemic in each country/centre, the institutional review board was asked about the possibility of written informed consent exemption for retrospective studies according to local regulations or telemedicine use procedures to obtain verbal consent and data collection.

3 | Results

Six countries recruited patients in the HEAD registry: Belgium, Czech Republic, Germany, Italy, Romania and Spain (Table S3).

The target samples and data completeness were not reached in all countries or diseases.

The study included 778 patients; 60% were females, with a mean age of 34 ± 21 years. AR was the most common diagnosis (441; 60%) and CU was the least frequent (81; 12%). Most patients reported never smoking (79%); 35% had a parental history of allergic diseases and 3.8% had occupational exposure to allergens. Sixty-six percent presented symptoms to indoor or outdoor allergens, most frequently due to pollen (45%) and house dust mites (37%). The most common comorbidity was gastro-oesophageal reflux (5.5%) (Table S4).

Overall, 40% had been diagnosed with a single allergic disease, while 5.1% presented four or more different allergic diseases among the targeted ones (Table S5). The most common association was between AR and asthma (38.0%), followed by AD with AR (15.9%) and FA with AR (15.4%) (Table S6).

3.1 | The Across-Country Average Impact of Allergic Diseases (AR, Asthma, AD and FA)

3.1.1 | Total Costs

Total healthcare costs per patient and year were €1329.55 (€3513.02), ranging from €532.58 in Romania to €2802.30 in Italy.

3.1.2 | Direct Medical Costs

Overall, treatments constituted the highest expense fraction (€546.89) and psychology visits the lowest (€6.23) (Table 1). Highest expense distribution varied across countries. For instance, Belgium had higher costs for diagnostic tests (€721.02) and hospitalisations (€524.39) than for treatments (€163.39), and Italy and Spain had high emergency visit costs (€520.00 and €306.10, respectively). Specialist visits were similarly distributed across countries. Regarding visits to psychologists, information was only available for Italy and Romania (Table 1).

3.1.3 | Societal Costs

On average, adult patients missed 1.61 (4.33) workdays, which translated to an average cost of €9.49 (72.90), while family members were burdened with 1.57 (15.41) lost days, equivalent to €30.00 (237.00) (Table 1). Paediatric patients missed 1.61 (4.33) school days (Table S12). Belgium reported the highest impact on patient families and the highest number of missed school days, and Italy had the highest impact on lost workdays.

3.1.4 | Individual Costs

The average indirect cost of allergic diseases ranged from €18.61 in Spain to €562.89 in Belgium (mean €201.56). On average, main costs were due to out-of-pocket medications (€118.74), followed by environmental control (€25.56) and costs of transportation to a specialised centre (€23.11) (Table 1). Belgium reported the highest out-of-pocket costs (€562.89), mainly resulting from private insurance, environmental control and medications. Romania had the highest out-of-pocket medication costs, and Italy presented the highest allergen avoidance costs.

Table 2 shows the impact of allergic diseases stratified by disease. Overall, asthma led to the highest costs, with €2240.83 (2620.34) per patient and year, followed by AD, with €1566.45 (5621.58).

3.2 | Allergic Rhinitis

3.2.1 | Description and Care Patterns

Of the 778 patients included in the study, 441 (56.7%) had an AR diagnosis, 56% were women, with a mean age of 31 ± 19 years. Most of them had never smoked (80%), and 27% had allergic and non-allergic comorbidities. The most frequent associations were with asthma (70%) and gastro-oesophageal reflux disease (6.1%). Parental history of allergic diseases was reported by 43% of patients, while 92% reported symptoms to allergens, mainly pollen (67%) and house dust (51%), as well as cat (25%) and dog epithelial (20%) (Table S7).

Except for Belgium, most AR patients were diagnosed by an allergist (72%) and had persistent (72%) and moderate-to-severe disease (63%), according to the allergic rhinitis and its impact on asthma (ARIA) duration and classification (28). The most common tests used to diagnose AR were skin prick tests (84%), serum total immunoglobulin E (IgE, 66%) and serum allergen-specific IgE (46%) (Table 3). More than 50% of Romanian and Spanish patients were reported to be diagnosed with component-resolved diagnosis (CRD).

Most AR patients were treated with oral antihistamines (78%), followed by intranasal corticosteroids (49%). Overall, SCIT and SLIT were prescribed in only 10% and 7.9% of patients, respectively, with Italy and Romania prescribing mainly SLIT and Spain SCIT (Table 3). There were no reports of oral corticosteroid (OCS) use in either country.

3.2.2 | Impact

The average annual impact per AR patient on healthcare costs was €538.06 (972.30), mainly composed of treatment costs (€278.03) and specialist visits (€129.31). There were significant differences between countries in terms of specialist visits, these costs being the highest in Romania (€185.98). Italy reported the highest primary care costs ($p = 0.001$) and HCRU costs ($p < 0.001$) (Table 4). Diagnostic tests and treatments resulted in an average cost of €56.98 ± 127.57 and €278.03 ± 737.68, respectively (Table 4). Diagnostic test (€127.02) and treatment (€463.73) costs were significantly higher in Spain than in other countries.

AR patients led to an average indirect cost of €173.04 (598.15), the highest being in Romania (€347.90), mainly due to out-of-pocket medications and private insurance payments, and the lowest indirect costs were found in Spain (€17.33) (Table 4). On average, adult patients missed 0.46 (1.80) workdays, which translated to an average cost of €4.41 (34.28), while family members were burdened with 0.70 (6.94) lost days, equivalent to

TABLE 1 | Impact of allergic diseases by country and by patient.

Impact (% of the total costs)	Across-country average, $n = 778$	Belgium, $n = 82$	Italy, $n = 104$	Romania, $n = 226$	Spain, $n = 177$	p
Healthcare impact (in €)	1329.55 (3513.02) (86.8%)	1750.75 (4553.92) (75.7%)	2802.30 (6390.0) (92.9%)	532.58 (1428.33) (69.7%)	1436.67 (2501.25) (98.7%)	< 0.001
Hospitalisations	106.22 (662.08)	524.39 (1278.75)	121.67 (925.66)	44.42 (411.46)	14.79 (193.23)	< 0.001
Emergency visits	198.37 (818.59)	115.85 (212.26)	520.0 (1707.36)	10.59 (85.86)	306.10 (731.89)	0.058
Specialist visits	222.01 (351.01)	211.59 (252.07)	380.00 (382.46)	183.20 (336.91)	196.62 (365.54)	< 0.001
Primary care visits	29.14 (149.43)	7.80 (31.70)	65.71 (162.21)	10.10 (24.21)	43.10 (233.51)	< 0.001
Psychologist visits	6.23 (155.05)	—	39.05 (390.39)	0.19 (3.08)	—	0.10
Diagnostic tests	198.22 (1573.11)	721.02 (4406.18)	82.05 (225.05)	65.33 (89.16)	220.17 (418.22)	< 0.001
Treatments	546.89 (2482.12)	163.39 (294.49)	1530.96 (5279.0)	213.46 (1009.52)	625.83 (1914.48)	< 0.001
Societal impact	39.50 (251.00) (2.6%)	243.99 (655.6) (10.5%)	49.22 (221.2) (1.6%)	20.13 (184.7) (2.6%)	15.23 (64.1) (1.0%)	0.008
Workdays lost	9.49 (72.90)	9.88 (89.4)	41.71 (180.1)	6.50 (21.40)	5.62 (35.20)	0.240
Days lost by family	30.00 (237.00)	234.11 (653.10)	7.51 (45.10)	13.63 (183.90)	9.61 (53.80)	0.020
Individual impact (in €)	201.56 (718.19) (13.2%)	562.89 (1138.47) (24.3%)	213.89 (535.49) (7.1%)	231.81 (844.36) (30.3%)	18.61 (74.30) (1.3%)	< 0.001
Out-of-pocket consultations	16.75 (86.15)	90.15 (213.26)	19.38 (73.03)	3.78 (16.48)	3.40 (21.72)	< 0.001
Out-of-pocket medications	118.74 (558.21)	112.06 (324.01)	137.46 (393.55)	202.26 (818.62)	7.78 (48.27)	< 0.001
Private insurance (not reimbursed)	21.53 (178.66)	144.63 (431.91)	3.01 (20.59)	8.12 (132.44)	—	< 0.001
Cost for environmental control at home	25.56 (158.19)	129.02 (411.96)	23.91 (73.80)	12.91 (62.79)	2.35 (34.26)	< 0.001
Cost for avoidance	6.60 (60.33)	3.66 (33.13)	30.13 (140.27)	2.37 (26.02)	1.43 (13.09)	0.002
Costs of transport to a specialised centre	23.11 (126.25)	91.17 (337.73)	25.21 (47.96)	15.02 (46.94)	5.97 (19.12)	< 0.001
Other out-of-pocket expenses	19.82 (82)	—	0.95 (9.76)	1.86 (19.69)	3.48 (26.39)	0.5
All costs	1531.11 (3714.23)	2313.64 (4760.95)	3016.18 (6708.83)	764.39 (1814.47)	1455.28 (2519.05)	< 0.001

Note: Data expressed as mean (SD). p-values from Kruskal–Wallis test.

TABLE 2 | Impact of allergic diseases by disease.

Impact (% of the total costs)	Allergic rhinitis, $n=441$	Asthma, $n=407$	Atopic dermatitis, $n=207$	Food allergy, $n=199$	p
Healthcare impact	538.06 (972.30) (72.5%)	2240.83 (2620.34) (93.6%)	1566.45 (5621.58) (84.0%)	1324.36 (2030.10) (89.0%)	<0.001
Hospitalisations	45.68 (536.23)	45.80 (409.76)	31.01 (352.18)	260.17 (807.65)	<0.001
Emergency visits	4.56 (68.23)	1420.10 (1442.23)	5.88 (48.51)	480.57 (421.92)	<0.001
Specialist visits	129.31 (183.27)	215.61 (262.54)	171.70 (306.62)	137.63 (164.38)	<0.001
Primary care visits	23.51 (107.26)	32.53 (119.14)	7.13 (29.85)	10.00 (39.75)	0.017
Psychologist visits	—	0.17 (2.96)	31.78 (352.22)	—	0.159
Diagnostic tests	56.98 (127.57)	176.23 (194.01)	348.66 (3522.48)	121.10 (298.60)	0.988
Treatments	278.03 (737.68)	312.10 (1699.09)	988.63 (4251.54)	314.89 (1876.50)	0.002
Societal impact	30.91 (281.90) (4.2%)	30.02 (93.54) (1,2%)	52.47 (203.04) (2.8%)	56.63 (267.92) (3,8%)	<0.001
Workdays lost	4.41 (34.28)	9.10 (42.13)	26.97 (154.86)	3.86 (16.18)	0.164
Days lost by family	26.49 (280.22)	20.92 (85.66)	25.50 (82.13)	52.77 (268.07)	<0.001
Individual impact	173.04 (598.15) (23.3%)	123.79 (392.98) (5.2%)	214.08 (521.84) (11.5%)	106.10 (296.27) (7.1%)	<0.001
Out-of-pocket consultations	5.85 (28.85)	8.05 (44.99)	27.14 (83.83)	18.86 (98.04)	<0.001
Out-of-pocket medications	120.92 (548.74)	65.26 (324.82)	111.31 (360.08)	21.61 (84.49)	<0.001
Private insurance (not reimbursed)	12.06 (127.24)	9.41 (71.61)	24.31 (111.29)	28.08 (127.24)	<0.001
Cost for environmental control at home	18.62 (105.64)	26.37 (127.69)	20.85 (88.72)	4.80 (42.33)	<0.001
Cost for avoidance	0.53 (6.26)	—	7.76 (72.47)	17.75 (103.12)	0.007
Costs of transport to a specialised centre	14.63 (54.30)	14.48 (55.02)	20.41 (72.41)	14.99 (64.73)	<0.001
Other out-of-pocket expenses	0.47 (6.27)	0.23 (3.07)	2.29 (14.34)	—	0.990
All costs	742.02 (1292.87)	2394.64 (2630.31)	1864.56 (5828.00)	1487.37 (2127.39)	<0.001

Note: Data expressed as mean (SD). p-values from multi-way ANOVA.

€26.49 (280.22) (Table 4). Paediatric patients missed 2.77 (12.33) school days (Table S8). Belgium reported the highest number of missed school days and the cost of days lost by the family, and Italy presented the highest cost of missed workdays.

3.3 | Asthma

3.3.1 | Description and Care Patterns

The HEAD registry included 407 patients with asthma; 56% were women, with a mean age of 34 ± 20 years. The majority never smoked (77%); 38% of patients had a parental history of atopic disease, 4.7% recounted occupational exposure and 83% presented symptoms in response to indoor or outdoor allergens, with pollen and house dust mites being the most common (56% and 50%, respectively) (Table S9). The most frequently associated disease was AR (74%), followed by 8.6% gastro-oesophageal reflux disease and 7.1% rhinosinusitis with nasal polyps. Most patients were partially controlled (Table 5) and 241 (72%) experienced no exacerbations during the study period, with an average exacerbation number of 0.5 (0.5).

In 60% of cases, patients were diagnosed by an allergist. Commonly employed diagnostic tests, without specifying a specific asthma type, were spirometry (88%), bronchodilator test (55%), skin prick test (69%), serum total IgE (62%) and CRD (48%). Exhaled nitric oxide (NO) was frequently measured in Belgium (75%), while no

TABLE 3 | Allergic rhinitis: diagnosis, severity, health care resources and treatment by country.

Variable	Across-country average, $n = 441$	Belgium, $n = 49$	Italy, $n = 45$	Romania, $n = 117$	Spain, $n = 107$	p
Who made the diagnosis?						
Allergist	318 (72%)	9 (18%)	35 (78%)	104 (89%)	55 (51%)	<0.001
Pulmonologist	30 (6.8%)	26 (53%)	0 (0%)	4 (3.4%)	0 (0%)	<0.001
Paediatrician	61 (14%)	11 (22%)	9 (20%)	5 (4.3%)	36 (34%)	<0.001
Internal Medicine	1 (0.2%)	1 (2.0%)	0 (0%)	0 (0%)	0 (0%)	0.138
Primary care	6 (1.4%)	1 (2.0%)	0 (0%)	1 (0.9%)	3 (2.8%)	0.527
ENT Surgeon	3 (0.7%)	1 (2.0%)	0 (0%)	2 (1.7%)	0 (0%)	0.421
Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—
Number of diagnostic professionals	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.138
ARIA duration						
Intermittent	110 (28%)	23 (62%)	31 (70%)	15 (13%)	33 (38%)	<0.001
Persistent	287 (72%)	14 (38%)	13 (30%)	100 (87%)	54 (62%)	
ARIA severity						
Mild	146 (37%)	30 (79%)	25 (56%)	35 (31%)	43 (51%)	<0.001
Moderate-to-severe	248 (63%)	8 (21%)	20 (44%)	78 (69%)	42 (49%)	
VAS						
2018	6.0 (4.0–8.0)	5.0 (1.0–8.0)	4.5 (3.0–8.2)	7.0 (4.0–8.0)	6.0 (4.0–8.0)	0.007
2019	4.0 (3.0–7.0)	5.0 (2.0–8.0)	4.0 (3.0–6.0)	3.0 (2.0–5.00)	5.0 (3.0–8.0)	0.058
Diagnostic tests (ever performed)						
Nasal endoscopy	14 (3.2%)	6 (12%)	2 (4.4%)	3 (2.6%)	2 (1.9%)	0.016
Nasal lavage	2 (0.5%)	0 (0%)	0 (0%)	2 (1.7%)	0 (0%)	0.326
Nasal brushing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—
PNIF	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—
Rhinomanometry	19 (4.3%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	0.577
Acoustic rhinometry	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—
Nasal hyper-reactivity test	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—
Nasal NO	7 (1.6%)	5 (10%)	0 (0%)	0 (0%)	0 (0%)	<0.001
Skin prick test	371 (84%)	34 (69%)	45 (100%)	109 (93%)	79 (74%)	<0.001
Serum total IgE	291 (66%)	27 (55%)	37 (82%)	81 (69%)	77 (72%)	0.036
Serum allergen-specific IgE	204 (46%)	30 (61%)	35 (78%)	34 (29%)	73 (68%)	<0.001

(Continues)

TABLE 3 | (Continued)

Variable	Across-country average, $n = 441$	Belgium, $n = 49$	Italy, $n = 45$	Romania, $n = 117$	Spain, $n = 107$	p
Component resolved diagnosis in serum	169 (38%)	6 (12%)	13 (29%)	59 (50%)	55 (51%)	<0.001
Blood eosinophils	20 (4.5%)	0 (0%)	1 (2.2%)	7 (6.0%)	0 (0%)	0.021
Microbiological tests	17 (3.9%)	11 (22%)	0 (0%)	0 (0%)	1 (0.9%)	<0.001
Other	102 (23%)	2 (4.1%)	34 (76%)	7 (6.0%)	43 (40%)	<0.001
Number of diagnostic tests	3.0 (1.0–4.0)	3.0 (1.0–4.0)	4.0 (4.0–5.0)	3.0 (1.0–4.0)	4.0 (1.5–5.0)	<0.001
Pharmacological interventions						
Intranasal decongestants	6 (1.4%)	1 (2.0%)	0 (0%)	3 (2.6%)	2 (1.9%)	0.762
Intranasal antihistamines	10 (2.3%)	2 (4.1%)	1 (2.2%)	2 (1.7%)	2 (1.9%)	0.803
Intranasal cromones	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—
Oral antihistamines	343 (78%)	37 (76%)	34 (76%)	85 (73%)	82 (77%)	0.918
Intranasal corticosteroids	217 (49%)	28 (57%)	30 (67%)	70 (60%)	72 (67%)	0.508
Intranasal corticosteroid + antihistamine	20 (4.5%)	0 (0%)	1 (2.2%)	16 (14%)	0 (0%)	<0.001
Oral corticosteroids	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—
LTRA	44 (10.0%)	12 (24%)	0 (0%)	19 (16%)	13 (12%)	0.005
SCIT	46 (10%)	0 (0%)	3 (6.7%)	5 (4.3%)	36 (34%)	<0.001
SLIT	35 (7.9%)	1 (2.0%)	15 (33%)	15 (13%)	2 (1.9%)	<0.001
Other	18 (4.1%)	5 (10%)	4 (8.9%)	6 (5.1%)	3 (2.8%)	0.215
Other health care resources						
Hospitalisations	5 (2.4%)	0 (0%)	2 (4.7%)	3 (12%)	0 (0%)	0.203
Specialist visits	120 (74%)	15 (71%)	19 (50%)	6 (86%)	10 (38%)	<0.001
ED visits	3 (1.5%)	1 (4.0%)	1 (2.3%)	0 (0%)	1 (2.8%)	0.412
Primary care visits	95 (44%)	2 (8.7%)	10 (23%)	35 (92%)	16 (40%)	0.019
Psychologist visits	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—

Note: Data expressed as *n* (%) or as median (P25-P75). The *p*-value was calculated with Pearson's chi-squared, Fisher's exact test or the Kruskal–Wallis rank-sum test.
Abbreviations: ARIA, allergic rhinitis and its impact on asthma; ED, emergency department; ENT, ear–nose–throat; IgE, immunoglobulin E; LTRA, leukotriene receptor antagonists; NO, nitric oxide; PNIF, PEAK nasal inspiratory flow; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; VAS, visual analogue scale.

TABLE 4 | Allergic rhinitis impact, overall and by country.

Impact (% of the total costs)	Across-country average, $n = 441$	Belgium, $n = 49$	Italy, $n = 45$	Romania, $n = 117$	Spain, $n = 107$	p
Healthcare impact	538.06 (972.30) (72.5%)	242.28 (320.64) (39.5%)	552.43 (1507.12) (88.0%)	493.44 (544.87) (58.3%)	716.27 (1199.20) (97.4%)	< 0.001
HCRU costs	203.05 (613.00)	75.10 (101.76)	509.44 (1504.14)	209.71 (256.29)	125.51 (233.51)	< 0.001
Costs of hospitalisations	45.68 (536.23)	—	283.89 (1406.48)	14.96 (98.39)	—	0.13
Cost of specialist visits	129.31 (183.27)	72.45 (97.39)	143.33 (159.76)	185.98 (235.28)	87.48 (134.49)	< 0.001
Costs of ED visits	4.56 (68.23)	1.02 (7.14)	26.67 (178.89)	—	1.87 (19.33)	0.5
Cost of primary care visits	23.51 (107.26)	1.63 (11.43)	55.56 (140.71)	8.77 (17.40)	36.17 (157.28)	0.001
Cost of psychologist visits	—	—	—	—	—	—
Diagnostic tests	56.98 (127.57)	20.73 (31.87)	26.22 (43.87)	19.93 (22.30)	127.02 (198.47)	< 0.001
Nasal endoscopy	0.69 (6.22)	—	1.38 (9.25)	0.55 (5.95)	0.88 (6.40)	0.7
Nasal lavage	0.04 (0.68)	—	—	0.10 (1.11)	—	—
Nasal brushing	—	—	—	—	—	—
PINF	—	—	—	—	—	—
Rhinomanometry	—	—	—	—	—	—
Acoustic rhinometry	—	—	—	—	—	—
Nasal hyperreactivity test	—	—	—	—	—	—
Nasal NO	—	—	—	—	—	—
Skin prick tests	20.63 (63.48)	15.51 (25.58)	8.37 (13.11)	7.76 (15.97)	42.21 (103.33)	0.001
Serum-specific IgE	22.32 (74.09)	2.78 (5.79)	12.00 (24.27)	2.58 (6.98)	57.20 (119.26)	< 0.001
Serum total IgE	5.87 (11.26)	2.45 (5.70)	2.43 (4.60)	4.21 (5.24)	10.69 (16.99)	< 0.001
Component-resolved diagnosis	4.65 (47.37)	—	1.50 (3.03)	0.97 (4.19)	12.13 (81.25)	< 0.001
Blood eosinophils	2.53 (4.67)	—	0.54 (1.89)	3.09 (5.02)	3.93 (5.39)	< 0.001
Microbiological tests	0.24 (2.05)	—	—	0.66 (3.34)	—	—
Treatments	278.03 (737.68)	146.44 (317.80)	16.76 (19.90)	263.80 (423.21)	463.73 (1146.07)	< 0.001
LTRA	14.20 (55.50)	20.11 (60.28)	—	3.80 (11.60)	28.77 (83.57)	0.067

(Continues)

TABLE 4 | (Continued)

Impact (% of the total costs)	Across-country average, $n = 441$	Belgium, $n = 49$	Italy, $n = 45$	Romania, $n = 117$	Spain, $n = 107$	p
Oral antihistamine	21.80 (42.70)	38.38 (63.59)	10.91 (15.14)	14.05 (27.37)	27.21 (49.29)	0.5
Intranasal decongestants	36.10 (636.60)	—	—	1.10 (9.39)	106.09 (1097.39)	0.7
Intranasal corticosteroids	40.60 (92.30)	63.46 (161.89)	5.85 (8.11)	56.82 (79.90)	27.01 (73.17)	0.002
Intranasal steroid + antihistamine	—	—	—	—	—	
SCIT	97.00 (252.50)	—	—	34.19 (162.50)	250.79 (353.85)	—
SLIT	68.40 (279.80)	24.49 (171.43)	—	153.85 (402.91)	23.86 (173.68)	—
Societal impact	30.91 (281.90) (4.2%)	175.22 (703.59) (28.6%)	11.03 (65.38) (1.7%)	4.63 (14.10) (0.5%)	1.93 (9.54) (0.2%)	0.044
Workdays lost	4.41 (34.28)	8.27 (57.86)	10.38 (65.34)	3.57 (12.05)	1.07 (5.81)	0.001
Days lost by family	26.49 (280.22)	166.96 (703.21)	0.65 (4.35)	1.05 (7.80)	0.86 (7.01)	< 0.001
Individual impact	173.04 (598.15) (23,3%)	195.82 (428.45) (31,9%)	63.84 (93.33) (10.2%)	347.90 (914.95) (38.8%)	17.33 (60.21) (2.3%)	< 0.001
Out-of-pocket consultations	5.85 (28.85)	20.73 (60.63)	3.00 (17.90)	5.21 (20.66)	0.93 (9.67)	0.003
Out-of-pocket medications	120.92 (548.74)	41.07 (130.44)	32.29 (44.01)	290.72 (875.70)	9.09 (45.38)	< 0.001
Other out-of-pocket health	0.47 (6.26)	—	2.22 (14.91)	0.43 (4.62)	—	0.4
Private insurance	12.02 (127.04)	30.82 (94.38)	3.38 (22.35)	18.46 (199.69)	—	< 0.001
Environmental control at home	18.62 (105.64)	63.27 (231.79)	15.80 (70.75)	15.90 (68.81)	2.34 (24.17)	0.004
Avoidance	0.53 (6.26)	—	—	1.11 (9.63)	0.37 (3.87)	0.7
Transport to a specialised centre	14.63 (54.30)	39.94 (120.09)	7.16 (22.49)	16.07 (37.06)	4.60 (12.21)	0.4
Total costs	742.02 (1292.87)	613.32 (1037.39)	627.30 (1596.59)	845.97 (1339.57)	735.53 (1210.11)	0.023

Note: Data are expressed as n (%) or mean € (SD); the p-value is from Pearson's chi-squared, Fisher's exact test or the Kruskal–Wallis rank-sum test.
Abbreviations: ED, emergency department; HCRU, healthcare resource utilisation; IgE, immunoglobulin E; LTRA, leukotriene receptor antagonists; NO, nitric oxide; PNIF, Peak nasal inspiratory flow; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

patient underwent this diagnostic test in Romania. Blood eosinophils were measured in only 0.5% of cases (Table 5).

Most patients were treated with the combination of inhaled corticosteroid-long-acting beta-agonists (ICS-LABA) (67%), followed by leukotriene receptor antagonist (LTRA) (29%), with only 7% receiving biologicals. A similarly low level of AIT prescription as for AR was noted: 6.1% for SCIT and 4.2% for SLIT, with a trend to prescribe SCIT in Spain and SLIT in Italy. Vaccination level (flu vaccine, etc.) was also very low (2%) (Table 5).

3.3.2 | Impact

The average annual cost of an asthma patient to the healthcare system was €2240.83 (€2620.34), the resources used during exacerbations representing the most important part of the cost. Italy had the highest costs for specialist visits (€361.54), exacerbation HCRU (€4800.00) and primary care visits (€87.18) (Table 6). The diagnostic test costs were highest in Belgium (€273.09) and lowest in Italy (€109.37). The average cost for asthma control treatment was €831.66 and the highest in Italy (Table 6). There were country differences in the use of ICS ($p = 0.045$), ICS-LABA ($p < 0.001$) and long-acting antimuscarinic agents (LAMAs) ($p = 0.047$). The average cost for treating asthma exacerbations was €28.96, which was the highest in Italy (Table 6).

Regarding individual costs, asthma patients incurred an average cost of €123.79, the highest cost being in Belgium, followed by Romania and Italy (Table 6). Out-of-pocket consultation costs were significantly higher in Belgium (€35.16) and out-of-pocket medications in Romania (€135.55). On average, adult patients missed 1.23 (3.56) workdays, which translated to an average cost of €9.10 (42.13), whereas family members were burdened with 0.75 (2.87) lost days, equivalent to €20.92 (85.66) (Table 6). Paediatric patients missed 3.04 (6.26) school days (Table S8). Belgium reported the highest number of missed school days and cost of days lost by the family, whereas Spain reported the highest cost of missed workdays.

3.4 | Atopic Dermatitis

3.4.1 | Description and Care Patterns

The registry included 207 AD patients, of which 55% were women, with a mean age of 24 ± 18 years, 80% never smoked, 44% had a parental history of atopic disease, and 72% presented symptoms with indoor or outdoor allergens, with pollen and house dust mites being the more common allergens (49% and 41%). The most frequent allergic disease associations were with AR (65%) and asthma (60%) (Table S10).

Diagnosis was performed by allergists (39%), dermatologists (27%) or paediatricians (27%). In Belgium, most cases were diagnosed by dermatologists, in Romania by allergists and by paediatricians in Italy and Spain. The most common diagnostic tests were skin prick tests (59%) and serum total IgE (58%). Serum-specific IgE and blood eosinophils were recommended in one-third of cases. SCORing Atopic Dermatitis (SCORAD) was reported for 27% of cases, mainly in Romania and Italy. Microbiological tests were used in only 3.9% of cases (Table 7).

Most patients (62%) received topical corticosteroids, followed by oral antihistamines (35%), with only 8% receiving biologicals, mainly in Italy. The rate of systemic steroid or immunosuppressant use was very low (1.9%, respective 4.8%). Forty-five percent experienced AD flares during the study period, with an average exacerbation number of 0.9 ± 0.9, with 0.3 ± 0.3 flares requiring OCS.

3.4.2 | Impact

AD burdened the healthcare system with an average of €1566.45, ranging from €147.00 in Romania to €6266.07 in Italy. In Romania, costs mainly came from HCRU, while in Italy, they resulted from treatments and, more specifically, from the use of biologicals (Table 8). The average costs for treating an AD flare were €1.11 (4.25) and the highest cost was in Italy.

Individual costs amounted to €214.08, with the largest expense being out-of-pocket medications. On average, adult patients missed 3.33 (9.08) workdays, which translated to an average cost of €26.97 (154.86), while family members were burdened with 0.74 (2.47) lost days, equivalent to €25.50 (82.13) (Table 8). Paediatric patients missed 1.32 (3.56) school days (Table S8). Belgium reported the highest number of missed school days and the cost of days lost by the family, whereas Italy reported the highest cost of missed workdays.

3.5 | Food Allergy

3.5.1 | Description and Care Patterns

The registry included 199 FA patients; 57% were women, with a mean age of 24 ± 18 years. More than half of the patients also had AR (63%), almost half had AD (49%), and 48% reported a parental history of atopic diseases (Table S11). Seventy-six percent of patients had no allergic comorbidities (Table S11). Peanuts and hazelnuts were the most common allergens (16% each), followed by milk, apple and walnuts (14%) (Table S12).

FA diagnosis was mainly performed by allergists (65%) and paediatricians (25%) (Table 9). Most patients had serum total IgE determinations (64%), LDH (lactate dehydrogenase) (61%) and skin prick tests (58%) for diagnosis. Twenty-nine percent (29%) were diagnosed with an open-food challenge, and only two patients were subjected to a double-blind food challenge.

Forty-seven percent (47%) used adrenaline auto-injectors, and 41% participated in educational sessions (Table 9). They had, on average, 10 ± 4 oral immunotherapy sessions. Fifty-eight percent experienced no episodes during the study period, 36% presented one episode and 6.1% underwent two episodes.

3.5.2 | Impact

FA patients burdened healthcare with an average of €1324.36 (€2030.10), significantly higher in Italy. The entries of this

TABLE 5 | Asthma: diagnosis, control of symptoms and treatment by country.

Variable	Across-country average, $n = 407$	Belgium, $n = 55$	Italy, $n = 39$	Romania, $n = 112$	Spain, $n = 82$	p
Who made the diagnosis?						
Allergist	244 (60%)	8 (15%)	28 (72%)	85 (76%)	39 (48%)	< 0.001
Pulmonologist	66 (16%)	32 (58%)	4 (10%)	21 (19%)	2 (2.4%)	< 0.001
Paediatrician	55 (14%)	14 (25%)	8 (21%)	5 (4.5%)	24 (29%)	< 0.001
Internal medicine	2 (0.5%)	1 (1.8%)	1 (2.6%)	0 (0%)	0 (0%)	0.227
Primary care	5 (1.2%)	3 (5.5%)	0 (0%)	0 (0%)	2 (2.4%)	0.061
ENT surgeon	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—
Other	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—
Diagnostic tests (ever performed)						
Spirometry	358 (88%)	47 (85%)	38 (97%)	107 (96%)	61 (74%)	< 0.001
Bronchodilator test	223 (55%)	33 (60%)	35 (90%)	63 (56%)	37 (45%)	< 0.001
Airway hyperreactivity test	29 (7.1%)	8 (15%)	11 (28%)	0 (0%)	10 (12%)	< 0.001
Exhaled NO	167 (41%)	41 (75%)	5 (13%)	0 (0%)	28 (34%)	< 0.001
IOS	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—
Body plethysmography	12 (2.9%)	4 (7.3%)	3 (7.7%)	0 (0%)	0 (0%)	0.002
Skin prick tests	279 (69%)	33 (60%)	36 (92%)	92 (82%)	42 (51%)	< 0.001
Serum total IgE	253 (62%)	34 (62%)	32 (82%)	74 (66%)	52 (63%)	0.162
Serum allergen specific IgE	175 (43%)	32 (58%)	33 (85%)	30 (27%)	54 (66%)	< 0.001
Component resolved diagnosis in serum	195 (48%)	25 (45%)	26 (67%)	66 (59%)	45 (55%)	0.194
Blood eosinophils	2 (0.5%)	1 (1.8%)	0 (0%)	1 (0.9%)	0 (0%)	0.590
Sputum cellularity	59 (14%)	11 (20%)	9 (23%)	7 (6.3%)	12 (15%)	0.017
Chest X-rays	16 (3.9%)	9 (16%)	2 (5.1%)	0 (0%)	0 (0%)	< 0.001
HRCT	23 (5.7%)	2 (3.6%)	1 (2.6%)	11 (9.8%)	0 (0%)	0.013
Therapeutic trial with steroids	1 (0.2%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0.665
Microbiology tests	39 (9.6%)	3 (5.5%)	1 (2.6%)	0 (0%)	12 (15%)	< 0.001
Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—
Control of symptoms (2018)						
Daytime symptoms	126 (39%)	20 (43%)	8 (22%)	36 (40%)	29 (48%)	0.069
Night awakening	82 (25%)	10 (21%)	3 (8%)	15 (17%)	21 (34%)	0.012
Need of rescue treatment	88 (27%)	16 (34%)	6 (16%)	17 (19%)	29 (48%)	< 0.001
Activity limitation	147 (45%)	17 (36%)	6 (16%)	30 (34%)	25 (41%)	0.084
Control of symptoms (2019)						
Daytime symptoms	77 (23%)	10 (22%)	5 (14%)	33 (31%)	13 (22%)	0.162
Night awakening	46 (14%)	6 (13%)	3 (8%)	13 (12%)	10 (17%)	0.607

(Continues)

TABLE 5 | (Continued)

Variable	Across-country average, $n = 407$	Belgium, $n = 55$	Italy, $n = 39$	Romania, $n = 112$	Spain, $n = 82$	p
Need of rescue treatment	57 (17%)	8 (18%)	5 (13%)	21 (20%)	15 (25%)	0.532
Activity limitation	101 (30%)	9 (20%)	—	27 (25%)	14 (24%)	0.008
Pharmacological interventions						
ICS	71 (17%)	6 (11%)	4 (10%)	20 (18%)	12 (15%)	0.543
LABA	9 (2.2%)	0 (0%)	0 (0%)	0 (0%)	1 (1.2%)	0.472
Ultra-LABA	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—
ICS-LABA	272 (67%)	35 (64%)	33 (85%)	77 (69%)	45 (55%)	0.011
ICS-ultra LABA	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)	1 (1.2%)	0.472
LAMA	22 (5.4%)	1 (1.8%)	1 (2.6%)	6 (5.4%)	11 (13%)	0.023
ICS-LABA-LAMA	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—
LABA-LAMA	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—
Ultra LABA-LAMA	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—
LTRA	116 (29%)	28 (51%)	4 (10%)	55 (49%)	20 (24%)	< 0.001
Biologicals	29 (7.1%)	1 (1.8%)	1 (2.6%)	6 (5.4%)	10 (12%)	0.049
OCS as controller	4 (1.0%)	0 (0%)	0 (0%)	2 (1.8%)	0 (0%)	0.367
SCIT	25 (6.1%)	0 (0%)	0 (0%)	2 (1.8%)	22 (27%)	< 0.001
SLIT	17 (4.2%)	0 (0%)	9 (23%)	4 (3.6%)	1 (1.2%)	< 0.001
Vaccination	9 (2.2%)	3 (5.5%)	1 (2.6%)	5 (4.5%)	0 (0%)	0.227
Other	55 (14%)	17 (31%)	7 (18%)	9 (8.0%)	8 (9.8%)	< 0.001
Other health resources						
Hospitalisations	6 (3.0%)	2 (6.9%)	0 (0%)	4 (16%)	0 (0%)	0.105
Specialist visits	122 (78%)	23 (100%)	30 (94%)	3 (60%)	19 (76%)	< 0.001
ED visits	15 (7.4%)	4 (14%)	1 (2.5%)	2 (7.4%)	7 (19%)	0.056
Primary care visits	99 (47%)	3 (12%)	18 (49%)	44 (96%)	11 (33%)	< 0.001
Psychologist visits	1 (0.6%)	0 (0%)	0 (0%)	1 (17%)	0 (0%)	0.681

Note: Data are expressed as n (%). the p-value was calculated using Pearson's chi-squared test.
Abbreviations: ED, emergency department; ENT, ear-nose-throat; HRCT, high-resolution computed tomography; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IOS, impulse oscillometry; LABA, Long-acting Beta-antagonists; LAMA, long-acting muscarinic antagonists; LTRA, leukotriene receptor antagonists; NO, nitric oxide; OCS, oral corticosteroids; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

cost were evenly distributed across HCRU, diagnostics and treatment, except in Belgium and Italy, where hospitalisation and acute episode costs mainly drove the costs, respectively (Table 10).

Individual costs amounted to a mean €106.10 (296.27) and were significantly higher in Belgium. On average, adult patients missed 0.30 (0.90) workdays, which translated to an average cost of €3.86 (16.18), while family members were burdened with 3.43 (30.39) lost days, translated to €52.77 (268.07) (Table 10). Paediatric patients missed 2.61 (5.61) school days (Table S8). Romania reported the highest cost of days lost by the family, Belgium the highest number of missed school days, and Italy the highest cost of missed workdays, although it was not possible to consider all the multidisciplinary professionals involved.

4 | Discussion

This registry-based study described care patterns for allergic diseases and their impact on healthcare systems, society and individuals, with valuable insights into the economic burden of allergic diseases and asthma across Europe. The analysis included costs of diagnosis and management, missed work/school days, disability pensions and out-of-pocket expenses. Patients with one or more of the following conditions were included: AR, asthma, AD and FA.

TABLE 6 | Asthma impact, overall and by country.

Impact (% of the total costs)	Across-country average	Belgium, $n=55$	Italy, $n=39$	Romania, $n=112$	Spain, $n=82$	p
Healthcare impact	2240.83 (2620.34) (93.6%)	924.30 (529.31) (73.0%)	6276.46 (4105.51) (98.7%)	1192.99 (1803.95) (87.4%)	2635.67 (1039.34) (98.6%)	0.011
HCRU costs	1928.00 (2458.00)	729.00 (281.00)	5812.00 (4069.00)	889.00 (1514.00)	2302.00 (756.00)	<0.001
Costs of hospitalisations	45.80 (409.76)	72.73 (377.84)	—	82.05 (600.58)	—	0.2
Exacerbation-related HCRU	1401.03 (1430.77)	400.00 (0.00)	4800.00 (0.00)	563.36 (0.00)	1600.00 (0.00)	<0.001
Costs of specialist visits	215.61 (262.54)	110.00 (129.24)	361.54 (140.70)	203.09 (241.50)	234.15 (354.23)	<0.001
Costs of ED visits	19.07 (137.29)	7.27 (35.25)	15.38 (96.08)	4.40 (33.13)	48.78 (242.54)	0.13
Costs of primary care visits	32.53 (119.14)	5.09 (24.41)	87.18 (128.10)	13.83 (21.31)	50.49 (197.03)	<0.001
Costs of psychologist visits	0.17 (2.96)	—	—	0.45 (4.75)	—	—
Diagnostic tests	176.23 (194.01)	273.09 (230.53)	109.37 (64.35)	119.40 (87.04)	220.67 (265.76)	<0.001
Spirometry	103.45 (134.37)	256.36 (228.53)	61.26 (25.01)	79.47 (65.73)	53.71 (53.90)	<0.001
Bronchodilator test	14.17 (26.17)	—	21.67 (25.87)	20.31 (34.41)	11.71 (16.40)	<0.001
Airway hyperreactivity test	1.65 (8.22)	—	2.58 (11.23)	—	4.57 (12.86)	<0.001
Exhaled NO	7.86 (28.38)	—	1.93 (12.06)	—	26.69 (47.77)	<0.001
Body plethysmography	0.17 (2.09)	—	1.29 (5.61)	—	—	—
Chest X-rays	1.29 (5.36)	—	1.93 (6.79)	1.08 (4.55)	2.14 (7.06)	0.2
Therapeutic trial with CS	0.12 (2.07)	—	—	0.31 (3.33)	—	—
Skin prick tests	14.16 (55.94)	10.91 (21.02)	5.15 (10.27)	6.47 (14.61)	31.10 (100.16)	0.029
Serum-specific IgE	25.07 (94.74)	2.76 (5.81)	9.23 (21.93)	2.03 (5.87)	79.02 (165.43)	<0.001
Serum total IgE	4.74 (6.81)	3.05 (6.06)	3.09 (6.62)	4.12 (5.75)	7.50 (7.91)	<0.001
Blood eosinophils	3.29 (5.46)	—	1.24 (2.01)	4.94 (6.88)	4.21 (5.01)	<0.001
Microbiological tests	0.38 (194.01)	—	—	0.99 (3.50)	—	—
Asthma controllers	321.10 (1699.00)	54.90 (97.93)	831.66 (4050.49)	180.36 (1202.01)	449.06 (572.32)	<0.001
OCS	0.767 (13.00)	—	—	1.97 (20.87)	—	0.7

(Continues)

TABLE 6 | (Continued)

Impact (% of the total costs)	Across-country average	Belgium, $n=55$	Italy, $n=39$	Romania, $n=112$	Spain, $n=82$	p
ICS	9.59 (39.00)	1.06 (7.87)	5.47 (31.60)	13.21 (48.20)	12.31 (40.09)	0.045
LABA	—	—	—	—	—	—
ICS LABA	58.98 (155.40)	6.37 (33.10)	173.58 (245.57)	12.11 (28.96)	103.76 (205.13)	<0.001
LAMA	24.73 (146.40)	—	4.21 (26.30)	10.89 (55.79)	69.97 (261.59)	0.047
LTRA	35.71 (83.80)	47.47 (84.15)	11.13 (42.53)	18.48 (30.35)	63.04 (128.50)	0.10
Biologicals	128.84 (1630.60)	—	637.27 (3979.72)	109.41 (1157.85)	—	0.4
SCIT	62.50 (207.70)	—	—	14.29 (106.42)	199.99 (332.30)	—
SLIT	—	—	—	—	—	—
Exacerbation treatment costs	28.96 (275.60)	1.22 (5.00)	71.32 (440.95)	26.05 (266.51)	32.53 (281.55)	0.2
Societal impact	30.02 (93.54)	86.89 (169.41)	11.23 (25.61)	12.96 (33.94)	24.12 (84.75)	0.044
Workdays lost	9.10 (42.13)	7.36 (54.61)	9.73 (23.53)	8.79 (28.46)	10.38 (54.11)	0.001
Days lost by family	20.92 (85.66)	79.53 (164.04)	1.50 (6.52)	4.17 (20.12)	13.74 (67.31)	<0.001
Individual impact	123.79 (392.98)	254.73 (489.31)	71.51 (110.25)	158.77 (507.07)	13.06 (49.61)	<0.001
Out-of-pocket consultations	8.05 (44.99)	35.16 (97.40)	0.10 (0.31)	3.39 (12.68)	—	<0.001
Out-of-pocket medications	65.26 (324.82)	43.68 (124.35)	17.18 (73.44)	135.55 (503.95)	6.59 (34.97)	<0.001
Other out-of-pocket health	0.23 (3.07)	—	—	0.58 (4.92)	—	0.4
Private insurance	9.41 (71.61)	49.27 (158.92)	0.03 (0.16)	—	—	<0.001
Environmental control at home	26.37 (127.69)	89.09 (265.57)	43.59 (90.45)	6.65 (40.53)	3.05 (27.61)	<0.001
Avoidance	—	—	—	—	—	—
Transport to a specialised centre	14.48 (55.02)	37.53 (114.89)	10.62 (13.43)	12.59 (29.86)	3.43 (11.08)	<0.001
Total costs	2394.64 (2630.31)	1265.92 (897.96)	6359.21 (41029.52)	1364.71 (1895.73)	2672.85 (1085.19)	<0.001

Note: Data are expressed in mean (SD). p-values were obtained with the Kruskal–Wallis rank-sum test.
Abbreviations: ED, emergency department; HCRU, healthcare resource utilisation; ICS, inhaled corticosteroids; IgE, immunoglobulin E; LABA, Long-acting Beta-antagonists; LAMA, long-acting muscarinic antagonists; LTRA, leukotriene receptor antagonists; NO, nitric oxide; OCS, oral corticosteroids; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

TABLE 7 | Atopic dermatitis: diagnosis and treatment by country.

Variable	*n* = 207	Belgium, *n* = 29	Italy, *n* = 22	Romania, *n* = 30	Spain, *n* = 48	*p*
Who made the diagnosis?						
Allergist	81 (39%)	4 (14%)	0 (0%)	28 (93%)	7 (15%)	< 0.001
Dermatologist	56 (27%)	16 (55%)	8 (36%)	1 (3.3%)	6 (13%)	< 0.001
Paediatrician	56 (27%)	10 (34%)	15 (68%)	1 (3.3%)	24 (50%)	< 0.001
Internal medicine	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—
Primary care	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—
Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—
Diagnostic tests (ever performed)						
SCORAD	56 (27%)	0 (0%)	10 (45%)	15 (50%)	8 (17%)	< 0.001
IGA	27 (13%)	0 (0%)	15 (68%)	0 (0%)	0 (0%)	< 0.001
EASI	20 (9.7%)	0 (0%)	19 (86%)	0 (0%)	1 (2.1%)	< 0.001
BSA affected (%)	14 (6.8%)	0 (0%)	7 (32%)	0 (0%)	1 (2.1%)	< 0.001
Skin prick tests	123 (59%)	16 (55%)	15 (68%)	23 (77%)	17 (35%)	0.002
Serum total IgE	121 (58%)	18 (62%)	16 (73%)	22 (73%)	15 (31%)	< 0.001
Serum-specific IgE (whole extract)	66 (32%)	15 (52%)	14 (64%)	5 (17%)	12 (25%)	< 0.001
Blood eosinophils	65 (31%)	5 (17%)	16 (73%)	16 (53%)	13 (27%)	< 0.001
LDH	13 (6.3%)	0 (0%)	13 (59%)	0 (0%)	0 (0%)	< 0.001
Microbiology tests	8 (3.9%)	0 (0%)	1 (4.5%)	1 (3.3%)	0 (0%)	0.372
Others	33 (16%)	14 (48%)	3 (14%)	7 (23%)	1 (2.1%)	< 0.001
Pharmacological interventions						
Oral antihistamines	73 (35%)	12 (41%)	15 (68%)	10 (33%)	16 (33%)	0.035
Topical corticosteroids	129 (62%)	18 (62%)	16 (73%)	14 (47%)	25 (52%)	0.232
Topical crisaborole	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—
Topical immunosuppressants	30 (14%)	4 (14%)	9 (41%)	3 (10%)	4 (8.3%)	0.004
Systemic immunosuppressants	10 (4.8%)	0 (0%)	2 (9.1%)	0 (0%)	3 (6.3%)	0.194
Biologicals	17 (8.2%)	0 (0%)	9 (41%)	0 (0%)	1 (2.1%)	< 0.001
Systemic corticosteroids	4 (1.9%)	0 (0%)	1 (4.5%)	1 (3.3%)	1 (2.1%)	0.726
Phototherapy	8 (3.9%)	1 (3.4%)	0 (0%)	0 (0%)	1 (2.1%)	0.661
Others	24 (12%)	11 (38%)	2 (9.1%)	8 (27%)	0 (0%)	< 0.001
Other health resources						
Hospitalisations	1 (0.7%)	1 (4.0%)	0 (0%)	0 (0%)	0 (0%)	0.068
Specialist visits	58 (45%)	15 (68%)	16 (84%)	0 (0%)	3 (23%)	< 0.001
ED visits	4 (2.8%)	1 (4.0%)	1 (4.8%)	1 (17%)	1 (5.3%)	0.794
Primary care visits	25 (18%)	1 (4.3%)	4 (19%)	1 (17%)	3 (18%)	0.083
Psychologist visits	2 (1.5%)	0 (0%)	2 (9.5%)	0 (0%)	0 (0%)	0.013

Note: Data are expressed as *n* (%). The *p*-value is from Pearson's chi-squared test.
Abbreviations: BSA, body surface area; EASI, Eczema Area and Severity Index; ED, emergency department; IGA, investigator's global assessment; IgE, immunoglobulin E; LDH, lactate dehydrogenase; SCORAD, Scoring of Atopic Dermatitis.

TABLE 8 | Atopic dermatitis impact, overall and by country.

Impact (% of the total costs)	Across-country average	Belgium	Italy	Romania	Spain	*p*
Healthcare impact	1566.45 (5621.58) (84.0%)	1751.12 (7440.20) (79.4%)	6266.07 (9385.31) (86.7%)	147.00 (116.75) (71.8%)	188.06 (369.15) (79.2%)	< 0.001
HCRU costs	259.61 (740.50)	263.45 (767.20)	877.27 (1342.86)	57.01 (49.66)	100.83 (323.90)	< 0.001
Costs of hospitalisations	31.01 (352.18)	137.93 (742.78)	—	—	—	0.3
Costs of specialist visits	171.70 (306.62)	122.41 (123.63)	586.36 (375.81)	53.99 (47.81)	85.00 (289.70)	< 0.001
Costs of ED visits	17.99 (162.16)	1.72 (9.28)	81.82 (383.76)	2.35 (12.86)	8.33 (57.74)	> 0.9
Costs of primary care visits	7.13 (29.85)	1.38 (7.43)	22.73 (52.84)	0.67 (3.67)	7.50 (31.25)	0.12
Costs of psychologist visits	31.78 (352.22)	—	186.36 (852.05)	—	—	—
Diagnostic tests costs	348.66 (3522.48)	1408.83 (7429.94)	37.45 (48.78)	36.12 (35.48)	46.11 (87.66)	0.095
SCORAD	6.24 (25.89)	—	—	15.84 (35.61)	6.88 (30.69)	< 0.001
IGA	—	—	—	—	—	
EASI	0.08 (0.88)	—	—	—	0.21 (1.44)	—
BSA affected (%)	0.04 (0.44)	—	—	—	0.10 (0.72)	—
LDH	0.37 (1.54)	—	2.20 (3.21)	—	—	—
Skin prick tests	11.34 (29.55)	16.55 (27.29)	5.70 (10.77)	5.16 (3.17)	14.63 (42.53)	0.2
Serum-specific IgE	11.90 (31.65)	6.90 (10.84)	19.09 (42.97)	2.52 (6.53)	17.50 (40.97)	0.3
Serum total IgE	316.11 (3521.28)	1385.38 (7426.65)	7.96 (13.59)	6.83 (4.91)	4.61 (8.65)	0.5
Blood eosinophils	2.41 (3.97)	—	2.50 (3.21)	5.03 (5.11)	2.19 (3.78)	< 0.001
Microbiological tests	0.17 (1.95)	—	—	0.74 (4.04)	—	—
Treatment costs	988.63 (4251.54)	78.84 (93.34)	5463.47 (9210.94)	55.75 (80.92)	70.37 (98.29)	< 0.001
Oral antihistamines	16.92 (49.13)	19.26 (52.49)	37.51 (63.19)	7.75 (37.49)	11.79 (44.71)	0.002
Topical corticosteroids	46.14 (48.15)	46.34 (48.82)	56.73 (48.31)	38.40 (47.83)	46.00 (48.46)	—
Topical crisaborole	—	—	—	—	—	—
Topical immunosuppressants	14.88 (34.88)	13.24 (33.69)	39.27 (48.31)	9.60 (29.29)	8.00 (26.81)	—
Systemic immunosuppressants	15.93 (140.86)	—	83.43 (337.40)	—	4.58 (24.27)	0.2
Biologicals	894.69 (4231.83)	—	5246.14 (9232.58)	—	—	—
OCS (chronic use)	0.07 (0.78)	—	0.40 (1.89)	—	—	—

(Continues)

TABLE 8 | (Continued)

Impact (% of the total costs)	Across-country average	Belgium	Italy	Romania	Spain	*p*
Phototherapy	—	—	—	—	—	
Flare treatment costs	1.11 (4.25)	—	3.78 (8.22)	0.47 (1.71)	0.94 (3.58)	0.023
Societal impact	52.47 (203.04) (3.3%)	76.81 (126.39) (3.5%)	179.18 (446.06) (2.5%)	8.47 (16.33) (4.1%)	7.19 (49.80) (3.0%)	< 0.001
Workdays lost	26.97 (154.86)	—	147.32 (357.00)	7.93 (16.47)	—	< 0.001
Days lost by family	25.50 (82.13)	76.81 (126.39)	31.85 (94.47)	0.55 (2.08)	7.19 (49.80)	< 0.001
Individual impact	214.08 (521.84) (11.5%)	376.49 (501.36) (17.1%)	669.05 (957.29) (9,2%)	46.83 (109.06) (22.9%)	11.97 (48.45) (5.0%)	< 0.001
Out-of-pocket consultations	27.14 (83.83)	61.24 (116.15)	65.23 (133.36)	0.50 (2.74)	5.73 (28.82)	< 0.001
Out-of-pocket medications	111.31 (360.08)	86.29 (166.26)	520.77 (728.93)	13.33 (50.74)	—	< 0.001
Other out-of-pocket health	2.29 (14.34)	—	—	2.67 (10.48)	4.50 (21.95)	0.4
Private insurance	24.31 (111.29)	107.93 (217.44)	0.27 (0.70)	—	—	< 0.001
Environmental control at home	20.85 (88.72)	64.14 (149.20)	—	27.67 (101.36)	—	< 0.001
Avoidance	7.76 (72.47)	—	45.50 (173.82)	—	—	—
Transport to a specialised centre	20.41 (72.41)	56.90 (135.54)	37.27 (61.80)	2.67 (10.15)	1.74 (7.33)	< 0.001
Total costs	1864.56 (5944.29)	2204.42 (7382.92)	7230.21 (10,089.98)	204.65 (178.57)	237.42 (489.31)	< 0.001

Note: Data are expressed in mean (SD). *p*-values are obtained from the Kruskal–Wallis rank-sum test.
Abbreviations: BSA, body surface area; EASI, Eczema Area and Severity Index; ED, emergency department; HCRU, healthcare resource utilisation; IGA, Investigator's Global Assessment; LDH, lactate deshydrogenase; OCS, oral corticosteroid; SCORAD, Scoring of Atopic Dermatitis.

TABLE 9 | Food allergy: diagnosis and treatment by country.

Variable	$n = 199$	Belgium, $n = 35$	Italy, $n = 25$	Romania, $n = 12$	Spain, $n = 78$	p
Who made the diagnosis?						
Allergist	130 (65%)	19 (54%)	25 (100%)	10 (83%)	33 (42%)	< 0.001
Pulmonologist	14 (7.0%)	14 (40%)	0 (0%)	0 (0%)	0 (0%)	< 0.001
Paediatrician	50 (25%)	8 (23%)	1 (4.0%)	1 (8.3%)	38 (49%)	< 0.001
Internal medicine	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—
Primary care	1 (0.5%)	0 (0%)	1 (4.0%)	0 (0%)	0 (0%)	0.169
ENT surgeon	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—
Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—
Diagnostic tests (ever performed)						
Skin prick tests	116 (58%)	5 (14%)	25 (100%)	6 (50%)	64 (82%)	< 0.001
Prick-by prick	64 (32%)	26 (74%)	13 (52%)	2 (17%)	22 (28%)	< 0.001
Open food challenge test	57 (29%)	19 (54%)	0 (0%)	3 (25%)	24 (31%)	< 0.001
Double-blind food challenge test	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—
BAT	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—
Serum total IgE	127 (64%)	27 (77%)	24 (96%)	5 (42%)	55 (71%)	0.004
Component resolved diagnosis	84 (42%)	16 (46%)	22 (88%)	3 (25%)	31 (40%)	< 0.001
Serum-specific IgE (whole extract)	29 (15%)	16 (46%)	1 (4.0%)	0 (0%)	10 (13%)	< 0.001
Blood eosinophils	50 (25%)	4 (11%)	4 (16%)	5 (42%)	29 (37%)	0.012
Serum tryptase	104 (52%)	25 (71%)	24 (96%)	3 (25%)	52 (67%)	0.818
Others	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)	1 (1.3%)	< 0.001
Long-term interventions						
Adrenaline auto-injector	93 (47%)	21 (60%)	21 (84%)	5 (42%)	41 (53%)	0.026
Oral immunotherapy	28 (14%)	14 (40%)	0 (0%)	2 (17%)	11 (14%)	< 0.001
Sublingual immunotherapy	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—
Biologicals	4 (2.0%)	0 (0%)	0 (0%)	0 (0%)	4 (5.1%)	0.285
Educational sessions	82 (41%)	18 (51%)	21 (84%)	6 (50%)	31 (40%)	0.002
Others	92 (46%)	7 (20%)	5 (20%)	4 (33%)	39 (50%)	0.004
Other health resources						
Hospitalisations	19 (12%)	15 (58%)	0 (0%)	2 (29%)	2 (8.7%)	< 0.001
Specialist visits	79 (57%)	21 (91%)	20 (83%)	1 (20%)	11 (69%)	< 0.001
ED visits	18 (11%)	1 (3.8%)	4 (16%)	4 (36%)	8 (28%)	0.300
Primary care visits	31 (20%)	3 (13%)	2 (8.0%)	3 (38%)	9 (36%)	0.162
Psychologist visits	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—

Note: Data are expressed as *n* (%). the *p*-value is from Pearson's chi-squared test.
Abbreviations: BAT, basophil activation test; BSA, body surface area; EASI, Eczema Area and Severity Index; ED, emergency department; ENT, ear, nose and throat; IGA, investigator's global assessment; IgE, immunoglobulin E; SCORAD, scoring of atopic dermatitis.

TABLE 10 | Food allergy impact, overall and by country.

	Across-country averagen = 199	Belgium, *n* = 35	Italy, *n* = 25	Romania, *n* = 12	Spain, *n* = 78	*p*
Healthcare impact	1324.36 (2030.10)	1311.46 (1475.93)	1817.85 (551.56)	631.46 (353.08)	1278.57 (2597.00)	< 0.001
HCRU costs	888.37 (866.33)	1223.43 (1426.30)	1544.00 (433.09)	489.59 (328.12)	589.23 (417.36)	< 0.001
Costs of hospitalisations	260.17 (807.65)	1000.00 (1371.99)	—	72.94 (170.34)	40.38 (318.99)	< 0.001
Acute episode HCRU costs	442.60 (363.46)	100.00 (0.00)	1200.00 (0.00)	140.84 (0.00)	400.00 (0.00)	< 0.001
Costs of specialist visits	137.63 (164.38)	118.57 (115.10)	204.00 (129.03)	199.52 (238.02)	115.38 (174.53)	0.003
Costs of ED visits	37.97 (141.76)	1.43 (8.45)	120.00 (300.00)	70.42 (130.89)	23.08 (71.94)	0.029
Costs of PC visits	10.00 (39.75)	3.43 (11.36)	20.00 (81.65)	5.87 (14.52)	10.38 (28.94)	0.5
Costs of psychologist visits	—	—	—	—	—	—
Diagnostic tests costs	121.10 (298.60)	63.77 (62.83)	93.85 (380.32)	49.15 (53.21)	166.63 (347.36)	< 0.001
Skin prick tests	18.03 (44.32)	5.71 (19.75)	4.02 (9.39)	5.28 (10.01)	30.00 (57.31)	< 0.001
Prick-by prick	7.83 (17.67)	22.86 (27.93)	2.01 (4.70)	4.11 (12.18)	3.53 (9.85)	0.001
Open food challenge test	8.67 (28.68)	—	—	22.20 (43.38)	13.25 (34.85)	0.006
Double-blind food challenge test	—	—	—	—	—	—
Serum-specific IgE	66.44 (262.25)	12.34 (12.32)	81.60 (358.70)	9.45 (27.33)	94.62 (300.16)	0.009
Serum total IgE	6.32 (7.75)	9.14 (9.73)	2.63 (4.77)	1.71 (3.99)	6.94 (7.31)	< 0.001
BAT	—	—	—	—		
Serum tryptase	3.47 (12.74)	13.71 (23.65)	—	—	0.51 (2.22)	< 0.001
Component-resolved diagnosis	9.03 (69.00)	—	3.60 (15.02)	4.73 (8.55)	15.48 (95.08)	0.003
Blood eosinophils	1.33 (3.18)	—	—	1.68 (3.91)	2.31 (3.88)	< 0.001
Long-term treatment costs	314.89 (1876.50)	24.26 (26.95)	180.00 (129.90)	92.73 (70.05)	522.71 (2590.72)	< 0.001
Adrenaline auto-injector	28.40 (37.60)	11.40 (9.44)	—	34.04 (42.07)	44.25 (42.31)	< 0.001
Biologicals	204.00 (1857.30)	—	—	—	392.31 (2569.03)	—
Educational sessions	82.50 (130.10)	12.86 (22.17)	180.00 (129.90)	58.68 (66.01)	86.15 (145.88)	< 0.001

(Continues)

TABLE 10 | (Continued)

	Across-country averagen = 199	Belgium, *n* = 35	Italy, *n* = 25	Romania, *n* = 12	Spain, *n* = 78	*p*
Acute episode treatment costs	0.28 (1.62)	0.34 (2.03)	0.01 (0.07)	0.73 (2.51)	0.27 (1.53)	0.83
Societal impact	56.63 (267.92)	126.13 (210.85)	11.68 (32.65)	256.25 (861.94)	9.14 (38.22)	0.001
Workdays lost	3.86 (16.18)	—	11.68 (32.65)	4.78 (11.31)	2.95 (11.34)	0.09
Days lost by family	52.77 (268.07)	126.13 (210.85)	—	251.47 (863.39)	6.19 (35.10)	< 0.001
Individual impact	106.10 (296.27)	332.37 (492.63)	83.08 (224.74)	145.00 (297.06)	5.96 (22.41)	< 0.001
Out-of-pocket consultations	18.86 (98.04)	74.74 (193.11)	0.12 (0.60)	—	2.69 (16.72)	< 0.001
Out-of-pocket medications	21.61 (84.49)	60.34 (96.32)	—	85.83 (232.08)	1.28 (11.32)	< 0.001
Other out-of-pocket health	—	—	—	—	—	
Private insurance	28.08 (127.24)	120.29 (244.00)	0.08 (0.40)	—	—	< 0.001
Environmental control at home	4.80 (42.33)	20.57 (86.70)	—	—	—	—
Avoidance	17.75 (103.12)	8.57 (50.71)	74.52 (226.64)	41.67 (116.45)	—	0.002
Transport to a specialised centre	14.99 (64.73)	47.86 (124.80)	8.36 (12.11)	17.50 (57.54)	1.98 (5.73)	< 0.001
Total costs	1487.37 (2127.39)	1770.30 (1832.55)	1912.63 (594.12)	1033.43 (1290.92)	1293.94 (2600.31)	< 0.001

Abbreviations: BAT, basophil activation test; HCRU, healthcare resource utilisation; IgE, immunoglobulin E; PC, primary care.

The average total costs per patient and year were €1531, with €202 corresponding to the individual's burden. Healthcare costs (€1329) were primarily driven by treatments (€546) and specialist visits (€222). Adults missed 1.61 workdays, children 6.81 school days and family members lost 1.57 days caring for patients. Asthma had the highest disease burden, with an annual cost of €2757 per patient.

Economic evaluation results are not easily generalisable due to differences in economic circumstances, approved indications, insurance decisions, local guidelines according to the existence of training or allergology specialisation and healthcare systems between countries. However, different studies have shown that, despite geographical differences, allergic diseases, especially asthma, are among the main contributors to the increase in healthcare expenditures [21, 32, 33].

Our findings revealed a substantial economic burden associated with allergic diseases, with an average annual cost of €1531.11 per patient. This figure encompasses both direct and indirect healthcare costs that individuals and society bear. The fact that healthcare costs account for €1329 of the total amount (88.8%) underscored the significant strain these conditions place on healthcare systems, as well as household finances due to out-of-pocket expenses [26, 34]. Concerning HCRU, our results demonstrated that treatments and specialist visits were the primary drivers of healthcare costs, accounting for €546 and €222, respectively. Even if AIT is part of the cost, it is the only disease-modifying treatment with a precise duration period available for allergic disorders that would reduce healthcare costs, improve symptoms and decrease the need for pharmacotherapy due to its prolonged effect [35]. The societal impact of allergic diseases represents 2.6% of the total cost and is evident with the productivity loss observed. Adults missed an average of 1.61 workdays yearly, while children lost 6.81 school days. Additionally, family members lost 1.57 days caring for patients, indicating a ripple effect extending beyond the affected individuals. The productivity loss associated with allergic diseases has significant implications for individuals and society. Allergic conditions lead to substantial absenteeism and presenteeism, ultimately affecting work performance and quality of life [36]. These findings emphasise the need for effective management strategies that not only alleviate symptoms but also minimise daily life disruptions. The study revealed that individuals bear an average of €201.56 in out-of-pocket expenses annually (13.2% of the total). While this represents a smaller proportion of the total costs, it

is not insignificant and may represent a financial challenge for some patients, potentially affecting treatment adherence and quality of life.

Among the allergic conditions studied, asthma emerged as the most burdensome, with an annual cost of €2757 per patient, with €831.66 spend on asthma controller medication. This finding aligns with previous research highlighting the significant economic impact of asthma. For example, in the United Stated the analysis of the 2008–2013 household component of the Medical Expenditure Panel Survey reported an annual per-person incremental medical cost of asthma of $3266 (in 2015 U.S. dollars), of which $1830 was attributable to prescription medication, $640 to office visits, $529 to hospitalisations, $176 to hospital-based outpatient visits and $105 to emergency room visits [37]. The resources used during exacerbations represented the most important part of the costs, suggesting that targeted interventions for asthma management could yield substantial financial benefits. Patients with asthma have incremental mean differences in different resources (outpatient and emergency department visits and hospitalisations), and direct and indirect costs are associated with asthma severity [38]. Real-world studies have demonstrated in patients with persistent asthma that allergy is associated with greater healthcare resource utilisation and expenditures, with medication being the largest expense component [21, 33, 39]. This suggests that optimising prevention (patient education on the use of inhaler devices), and treatment strategies as well as improving specialist care efficiency could lead to cost reductions without compromising patient outcomes. We also report significant absenteeism related to asthma, similar to the data reported by the United States where total annual school and work days lost due to asthma ranged from 22.4 thousand (Wyoming) to 1.5 million days (California) and absenteeism costs ranged from $4.4 million (Wyoming) to $345 million (California) [40].

The average annual impact per AR patient on healthcare costs was €538.06, mainly composed of treatment costs and specialist visits. This result is similar to the FERIN study, conducted in Spain reporting direct costs of €553, but lower than the TOTALL study, conducted in Sweden, reporting direct costs of €210.3 [13, 41].

AD burdened the healthcare system with an average of €1566.45, ranging from €147.00 in Romania to €6266.07 in Italy. The results align well with a systematic review conducted in European countries reporting direct medical costs ranging between €307 and €6993 per person and per year [42]. Similar to our results, prescription medications and specialist dermatologist visits were the main contributors, and costs increased with disease severity or with uncontrolled disease. The highest cost incurred by AD in our study was related to the use of biologicals, similar to the total direct costs of €5191 (€4382–6019) per patient per year reported for patients with AD using systemic immunosuppressive treatment [43].

In our study, FA patients burdened healthcare with an average of €1324.36, similar to the data reported by the EuroPrevall study (2016 international dollar per patient) [44], but significantly higher than the data recently reported for Australia, where the total Medicare cost associated with FA from age 1 to 4 years was estimated to be €411.0 (95% CI €261.5–€549.0) per child [45]. Of note, these data come from a population-based longitudinal study, while our data are cross-sectional and retrospective. However, we report similar out-of-pocket costs (€106.10) to another Australian study ($129) [46].

These findings have important implications for healthcare policy and clinical practice. They underscored the need for improved prevention strategies to reduce the incidence of allergic diseases, more efficient diagnostic and treatment pathways to minimise healthcare costs, and support systems for patients and families to reduce the societal impact.

They need to be weighed against the reality of each health system. It is important to note that healthcare costs are reimbursed differently in different countries. In Belgium, for example, even though healthcare costs are quite high, patients are fully reimbursed, meaning that they have good access to care despite the financial and societal burden. Also, some results, like the high percentage of patients diagnosed by an allergist, may not be representative because, in some countries, such as Belgium, this speciality does not exist, and the specialists consulted are usually pneumologists.

Visits to psychologists are critical due to emotional disorders accompanying allergic diseases [47]. However, psychology visits account for the lowest costs, very likely because they are not contemplated in the public or private systems, or if accessible, the waiting lists or the shortages make it impossible in reality [48].

Unlike clinical trials, registries reflect diverse, real-world populations, offering valuable insights for everyday practice [49], a key strength of the HEAD registry. As an international registry, HEAD considers variability in management patterns across geographic regions due to multiple factors, including differences in approved indications, insurance decisions and local clinical guidelines.

Indirect costs often strongly influence the economic evaluation of healthcare programmes. Due to the assumptions' limitations, cost results may be underestimated.

This was a cross-sectional study with a 12-month observation period nested in a population-based multinational registry. The main limitations of cross-sectional studies derive from their high sensitivity to biases, mainly selection (non-representative sample) and information (key study variables measured, collected or interpreted inaccurately) bias. The study's observational nature and the COVID-19 context may have made data collection for indirect costs difficult (recall bias). On the other hand, the observational nature could have favoured data underreporting. The possible inaccuracy of the diagnostic coding and other comorbidities, or the lack of any variable that could influence the results, should also be considered a limitation. Therefore, group comparisons should be carefully interpreted, and cost estimates may be underestimated due to the assumptions' limitations. Moreover, the analysis does not incorporate population weighting and the costs reported represent unadjusted averages based on the study sample. Thus, the representativeness and generalisability of the findings is of low certainty. Furthermore, the results need validation by the upcoming prospective data collection by the registry.

Even though the diseases studied have different distributions by age as some were more prevalent in childhood and others in adulthood, the analysis could not be carried out by strata due to the small sample size of some illnesses. Consequently, the economic estimates by the global disease could introduce bias, with the average being skewed towards the group with the largest patient number (either children or adults).

The study focused on direct costs and some aspects of indirect costs. Future research could explore intangible expenses, such as the impact on quality of life, to provide a more comprehensive picture of the total burden of allergic diseases.

As the burden of allergic disorders continues to rise across several factors may be manipulated to mitigate risk. An opportune window in immunological development appears to exist in early life whereby certain exposures may promote or prevent the development of an allergic disease [5, 50]. There is a growing interest in building patients' capacities to self-manage their chronic health conditions. Increasing allergy literacy as a complement of interrelated dimensions combining knowledge of allergy, safe and self-regulatory behaviours, with the capacity to seek support or treatment might further help to alleviate the disease burden [5, 51, 52].

In conclusion, this registry-based study demonstrated the substantial economic burden of allergic diseases across Europe with a high degree of heterogeneity between countries. The findings highlighted the need for improved management strategies and policy interventions to reduce this burden on healthcare systems, society and individuals. By addressing these challenges, we will be able to work towards more efficient and effective care for patients with allergic diseases, ultimately improving outcomes and reducing costs.

Author Contributions

Ioana Agache, Maria Torres, Paulo Jorge Nogueira and Loreto Carmona: conceptualisation; methodology; roles/writing – original draft; and writing – review and editing. **Loreto Carmona, Paulo Jorge Nogueira and Maria Miguel Oliveira:** methodology; formal analysis; roles/writing – original draft; and writing – review and editing. All the remaining authors: investigation; methodology and writing – review and editing.

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Conflicts of Interest

I.A. reports Deputy Editor of *Allergy* journal. All the other authors report no COI.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Appendix A

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