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TITLE

Estimate of the total costs of allergic rhinitis in specialized care based on real-world data: the FERIN Study

Running title: Real-world costs of allergic rhinitis

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Abstract

Background: Despite the socioeconomic importance of allergic rhinitis (AR), very few prospective studies have been performed under conditions of routine clinical practice and with a sufficiently long observation period outside the clinical trial scenario. We prospectively estimated the direct and indirect costs of AR in patients attending specialized clinics in Spain.

Methods: Patients were recruited at random from allergy outpatient clinics in 101 health centers throughout Spain over 12 months. We performed a multicenter, observational, prospective study under conditions of routine clinical practice. We analyzed direct costs from a funder perspective (health care costs) and from a societal perspective (health care and non–health care costs). Indirect costs (absenteeism and

presenteeism [productivity lost in the workplace]) were also calculated. The cost of treating conjunctivitis was evaluated alongside that of AR.

Results: The total mean cost of AR per patient-year (n=498) was 2,326.70 (direct, 553.80; indirect, 1,772.90). Direct costs were significantly higher in women (600.34 vs. 484.46, *P*=0.02). Total costs for intermittent AR were significantly lower than for persistent AR (1,484.98 vs 2,655.86, *P*<0.001). Total indirect costs reached 1,772.90 (presenteeism, 1,682.71; absenteeism, 90.19). The direct costs of AR in patients with intermittent asthma (507.35) were lower than in patients with mild-persistent asthma (719.07) and moderate-persistent asthma (798.71) (*P*=0.006).

Conclusions: The total cost of AR for society is considerable. Greater frequency of symptoms and more severe AR are associated with higher costs. Indirect costs are almost 3-fold direct costs, especially in presenteeism. A reduction in presenteeism would generate considerable savings for society.

Keywords

rhinitis; allergic; observational study; prospective study; health care costs.

Introduction

The increasing prevalence of allergic rhinitis (AR) during the second half of the twentieth century has placed this condition among the most prevalent chronic diseases in adolescents and young adults (1).

Often considered a trivial disease, AR causes major subjective discomfort (2-5), significant sleep impairment (6-8), and considerably reduced workplace productivity (9-

12) and school performance (13, 14). These characteristics and the high prevalence of AR (21.5% in Spain) (15) highlight the socioeconomic burden of the disease.

Studies on the cost of AR are subject to major methodological limitations (e.g., excessively small samples, short duration, and omission of key aspects, such as indirect costs) (16). Similarly, costs associated with disease duration are not calculated in accordance with the *Allergic Rhinitis and Its Impact on Asthma* (ARIA) guidelines (17).

Estimation of the overall costs of the disease involves quantification of the direct health costs generated by the disease itself and of the indirect costs, namely, days off work (absenteeism) and reduced workplace productivity (presenteeism) (17). Many cost studies omit these aspects, especially presenteeism; therefore, their results could prove inaccurate (18, 19). Despite the wealth of instruments that measure loss of productivity and the difficulty in selecting the optimal instrument (20, 21), researchers often choose the Work Productivity and Activity Impairment (WPAI) Questionnaire (22), which is free and fully validated in several languages (9, 23, 24).

Loss of productivity arising from AR is a key element of the socioeconomic burden of the disease. Results for presenteeism are homogeneous, showing a 25-30% reduction in work productivity during symptomatic periods (9-11, 24, 25).

Despite the socioeconomic importance of AR, results from prospective studies performed under conditions of routine clinical practice are lacking (i.e., outside the clinical trial setting) (17). The few published prospective studies are of insufficient duration or are based on small samples (16, 19), and the only suitably powered studies were controlled clinical trials (26, 27). However, these results do not accurately reflect real-world findings, since very few patients attending health centers fulfill trial inclusion criteria (28) and treatment options are more numerous (2, 29, 30). Therefore, we need wide-ranging observational studies to reproduce clinical practice and enable a

more accurate estimation of the costs associated with AR (31, 32, 33). A recent study covering a large population in Sweden provides a more general assessment of this problem (34).

We aim to reduce this information gap through a prospective evaluation of the use of resources in a broad sample of patients with AR treated at specialized clinics. The primary objective was to estimate the direct and indirect costs of AR in Spain. The secondary objectives were to evaluate the association between cost and severity and duration of AR and between cost and comorbidities (mainly asthma and conjunctivitis).

Methods

Study design

We performed a multicenter observational prospective study under conditions of routine clinical practice. The Ethics Committee of Hospital Clínic, Barcelona, Spain approved the study, and all the patients gave their written informed consent.

Study population

Patients were recruited consecutively from allergy outpatient clinics at 101 centers throughout Spain. The study lasted 19 months (7 for inclusion and 12 to evaluate consumption of resources by patients). Seasonal bias arising from exacerbations of AR was avoided by ensuring that recruitment covered 2 seasons (April to December 2009).

Patients had to fulfill all the inclusion criteria and none of the exclusion criteria. The inclusion criteria were age ≥18 years, diagnosis of AR, and attendance at a clinic because of AR (severity classified according to the modified ARIA criteria [35]). The exclusion criteria were nasal polyposis, major anatomic defects of the nasal cavity,

topical vasoconstrictors for more than 7 consecutive days during the previous month, major psychological-psychiatric disorders (major depression, excessive drug or alcohol consumption), permanent occupational disability, and inability to complete the questionnaires.

The minimum sample size for each degree of severity was 214 patients, which was necessary to perform the calculation with a 95% confidence interval and an accuracy of ± 75 for the mean cost of AR per patient, assuming a standard deviation of approximately 500. Losses to follow-up were estimated at approximately 20%. With 3 levels of severity, the minimum sample was 642 patients.

Data collection

AR was diagnosed by an allergologist and classified according to the modified ARIA guidelines as mild, moderate, or severe (35); frequency of symptoms was classified as intermittent or persistent according to ARIA (36). According to the traditional ARIA classification of AR, almost all patients had moderate-to-severe disease. In order to avoid this drawback, a modified classification has been proposed in which the moderate group is efficiently separated from the severe group (35). According to the modified classification, AR is considered moderate when 1-3 of the 4 ARIA criteria are fulfilled and severe when all 4 criteria are fulfilled.

The severity of asthma at the start of the study was classified according to the GINA recommendations as mild-intermittent, mild-persistent, moderate, and severe (http://ginasthma.org/wp-content/uploads/2016/01/GINA_Report_2015_Aug11-1.pdf).

Patients reported on drug consumption and visits to specialists and primary care. They were asked to record items as they occurred. The registers were completed quarterly over 1 year.

Direct health care costs were calculated considering visits to the doctor, complementary examinations, diagnostic tests, and specific immunotherapy (injected and sublingual) over 1 year. The results of AR-related diagnostic tests (skin tests, specific immunoglobulin E [IgE, both specific and by component], and challenge tests) and general diagnostic tests (lung function and imaging tests) performed during the observation period were recorded. Unit costs based on the prices in force in Spain were applied for each diagnostic test or visit to the doctor. Costs of pharmacologic treatment (rhinitis and conjunctivitis) and costs of immunotherapy were based on medication containers dispensed from the pharmacy. Non–health care direct costs (i.e. those associated with environmental control measures [dehumidifiers, acaricides, HEPA filters, and antimite covers]) were also calculated.

The Work Productivity and Activity Impairment: Allergy-Specific Questionnaire (WPAI-AS) (9) was used to calculate indirect costs based on AR-related absenteeism and presenteeism. WPAI-AS covers absenteeism, loss of productivity, overall loss of productivity, and restriction in activities of daily living calculated using procedures described elsewhere (22). A Spanish-language version of the WPAI questionnaire has been validated (23).

The analysis was performed from a funder perspective (health care costs) and from a societal perspective (health care and non–health care costs). Costs were expressed in euros for the year 2010.

The mean direct cost per patient was calculated based on the health care resources consumed and their unit costs (37, 38). Indirect costs were calculated using the human capital approach based on productivity lost during the study and by estimating the hourly cost of work lost with salary costs adjusted for sex and age (39) and assuming a cost of 0 for hours lost by students and unemployed persons.

Statistical analysis

We performed a descriptive analysis of the study population at the baseline visit. Continuous variables were described using the mean±SD; categorical variables were described using absolute numbers and percentages.

Estimated costs were compared between groups of patients (according to severity of AR and frequency of symptoms) using the *t* test or analysis of variance depending on the number of groups to be compared. When the conditions for application of the tests were not met, Box-Cox transformations were performed. The Bonferroni correction was used for pairwise comparison. Cost trends were evaluated according to the degree of severity. Statistical significance was set at 5% in all the analyses.

The results were analyzed by intention to treat with respect to the total number of evaluable patients, i.e., those who attended the baseline visit and had been followed for ≥6 consecutive months.

Results

Of the 646 patients recruited, 498 were evaluable. Data from the remainder (23% of the total) were considered insufficient. Patients were considered dropouts if they did not provide the information requested in the questionnaires for more than 2 consecutive trimesters.

Mean age was 32.2±9.32 years (59.8% women, 92.2% Caucasian). As for occupational status, 79.4% of patients were registered for work (although 8.7% were unemployed). Students made up 16.1% of the population and homemakers and pensioners 4.6%. With respect to smoking, 15.9% of patients were active smokers, 14.5% were ex-smokers, and 69.7% nonsmokers.

In most cases, AR was moderate (71.1%), and symptoms were mostly persistent (71.9%). The prevalence of asthma was 38.6% (mild-intermittent in 22.7%, mild-persistent in 10.4%, and moderate in 5.4%). No severe asthma was recorded. As for allergy, 43% of patients were sensitive to only 1 group of allergens, mainly pollens. The remainder were sensitive to ≥2 groups (Table 1).

The mean total cost of AR per patient-year was 2,326.70± 3,013.93, of which 553.80± 540.70 corresponded to direct costs and 1,772.90± 2,906.20 to indirect costs. Direct costs accounted for approximately 24% of total costs and indirect costs 76%.

Direct costs were significantly higher among women (600.34± 625.04 vs. 484.46± 372.84 per patient-year, P=0.02). However, no statistically significant differences according to sex were found for total or indirect costs. No differences were found in total or indirect costs by educational level (no formal eduction, primary, secondary, or university). Similarly, no statistically significant differences were found in total or direct costs by time since diagnosis of AR (≤1 year vs. >1 year). Significant differences were observed in total and indirect costs according to smoking status: costs were higher for smokers and ex-smokers than for nonsmokers, although the results of pairwise comparisons were not significant. Direct costs increased with the degree of allergic sensitization, although the differences were not statistically significant (507.25, 577.84, and 597.87 for patients allergic to 1, 2, and ≥3 groups of allergens, respectively).

Total, direct, and indirect costs by duration and severity of AR

The total cost of intermittent AR was 1,484.98±1,996.05 per patient-year, and that of persistent AR was 2,655.86±3,272.34 per patient-year (P<0.001). Significant differences were also observed for direct and indirect costs (Figure 1a).

Analysis of costs by degree of severity revealed a statistically significant upward trend. Pairwise comparisons showed differences in total and indirect costs between patients with severe AR and patients with mild/moderate AR.

Components of direct costs by duration and severity of AR

Total direct costs differed significantly between persistent and intermittent AR, with higher values in persistent AR for all types of costs except for diagnostic tests, hospitalizations, and non–health care costs (Table 2). Although the differences in direct costs by degree of severity did not reach statistical significance, costs associated with visits to the doctor and immunotherapy tended to be significantly higher in more severe disease (Table 3).

Components of indirect costs by duration and severity of AR

Mean absenteeism was 0.93 (3.12) days per year overall, with no differences between patients in terms of duration or severity of AR.

Mean presenteeism was 137.35±225.80) hours per patient-year. However, statistically significant differences were observed, with a greater number of hours for persistent AR than for intermittent AR (160.71±243.88 vs. 69.13±125.10, P<0.001) and higher presenteeism in more severe AR, with values of 85.15±162.07, 125.85±204.14, and 179.71±276.63 hours for mild, moderate, and severe AR, respectively (P=0.032).

Data on absenteeism and presenteeism showed that total indirect costs reached a mean of 1,772.90± 2,906.20 per patient-year. Of these, 1,682.71± 2,845.47 corresponded to presenteeism and 90.19± 303.05 to absenteeism (Table 4).

Statistically significant differences were observed in total and indirect costs of presenteeism, for both degree of severity and duration of AR. In contrast, no significant differences were observed between patients for costs generated by absenteeism in terms of severity and duration of AR.

Comorbidity of AR

We analyzed the effect of asthma on cost of AR. Patients with asthma had total and indirect costs similar to those of patients who did not have asthma, with higher direct costs (605.67± 520.64 vs. 522.96± 551.35), although the difference was not statistically significant. Statistically significant differences were only observed for drug costs (excluding immunotherapy), with values of 95.19± 164.41 vs. 52.45± 81.49 for patients with and without asthma, respectively (P<0.001).

Significant differences were not observed for total or indirect costs between degrees of severity of asthma. However, significant differences were observed for direct costs (P=0.006). Intermittent asthma generated direct costs of 507.35± 543.61 per patient-year; these rose to 719.07± 447.41 in mild-persistent asthma and to 798.71± 468.20 in moderate-persistent asthma. Pairwise comparisons revealed significant differences between the direct costs associated with intermittent asthma and mild-persistent or moderate-persistent asthma. In contrast, no significant differences were observed between moderate-persistent asthma and mild-persistent asthma.

The presence of other comorbidities (, atopic dermatitis, urticaria, food allergy, otitis, sinusitis) was only associated with statistically significant differences (P<0.05) for direct costs in patients with food allergy. Compared with patients with no comorbidities, these costs were higher for food allergy.

Discussion

From a societal perspective, the costs of AR in a hospital clinic are considerable. Overall mean cost per patient-year was over 2,300, which is relevant given the high prevalence of AR in developed countries (2, 40). Furthermore, the magnitude of the costs in the present study was associated with the severity and duration of AR, as reported in retrospective studies (41, 42).

To our knowledge, no prospective studies on AR have been performed over a 12-month period under conditions of routine clinical practice in a specialized clinic. At least 1 similar published study analyzed seasonal AR in a small sample over a 6-month period, although it only took into account direct costs (43). Cardell et al. (34) recently provided a more general perspective of the magnitude of the social burden of AR. Prospective studies lasting ≥6 months have been performed in the trial setting (27), although the therapeutic options are very limited and do not reflect current practice. Of note, most patients with AR take several drugs simultaneously, mainly antihistamines and intranasal corticosteroids (29). Furthermore, it has been argued that primary care patients differ from trial patients, since only a small number fulfill the inclusion criteria (28), thus reducing the external validity of the results. Consequently, studies performed under real-world conditions are necessary (16, 28, 31, 32, 44). Our multicenter prospective study was based on careful selection of patients and respect for conditions

of routine clinical practice in a specialized clinic in order to provide real-world evidence.

We applied the modified ARIA classification (35) and observed differences in indirect costs between the 3 degrees of severity, specifically for costs associated with presenteeism, thus highlighting the discriminative capacity of the classification.

The direct costs of severe AR were higher than those of moderate AR, and the costs of moderate AR were higher than those of mild AR, indicating a trend towards increasing costs with increasing severity, although the differences were not statistically significant. We observed significant differences in the costs of medical care and the costs of drug therapy and immunotherapy. The direct costs of persistent AR were considerably higher than those of intermittent AR (mainly medical care, drugs, and immunotherapy). The association between direct costs and severity has been reported elsewhere (27) and is foreseeable, as is the association with duration of AR (41). In our opinion, the calculation of costs per patient depending on the degree of severity could enable more accurate calculation of total costs for a specific community. Furthermore, it could help to direct therapy toward patients with more severe AR and thus reduce the social burden, which is particularly high in terms of indirect costs.

The presence of specific comorbidities increases direct and indirect costs, as observed for asthma (43), especially moderate and severe asthma (42). This observation is consistent with our results, possibly because patients with asthma have more severe AR, although we were unable to demonstrate this. Concomitant allergic conjunctivitis also seems to increase costs or, at least, to reduce workplace productivity and increase consumption of health care resources (12). We assessed the costs of treatment of rhinitis and conjunctivitis together, since most patients with rhinitis also had conjunctivitis.

Indirect costs were 3 times as high as direct costs, i.e., much higher than reported elsewhere (16, 27). Previous studies have shown the high indirect costs generated by AR, which were evaluated in terms of work productivity and exceeded those of other chronic diseases such as asthma, diabetes, and coronary disease (11, 24). We found statistically significant differences in indirect costs between the different degrees of severity according to the modified ARIA classification (35), mainly owing to higher presenteeism in severe AR. Previous studies had already found differences in presenteeism between mild and moderate-severe AR (9). Furthermore, it is noteworthy that in the calculation of indirect costs, no amount was attributed to unemployed persons, students, or homemakers, since they did not generate income; therefore, the calculation in money terms underestimates the impact of the disease on activities of daily living. This observation could explain why the differences between the indirect costs of moderate and severe AR do not reach statistical significance. Other studies have evaluated these costs using arbitrary measures, namely loss of time for usual daily activities (27), although their methodology is not standardized and not commonly used in Spain.

The loss of productivity measured using specific questionnaires has proven quite homogeneous in studies in Europe and the USA (20%–30% during symptomatic periods of AR) (10, 11, 24, 25). This loss of productivity can exceed that caused by other chronic diseases such as diabetes or arterial hypertension (10). Absenteeism, measured as days of work lost due to AR, is also similar between studies, where average annual absenteeism ranges from 2 to 4 days (11, 24, 27). Our results were considerably lower for absenteeism and higher for presenteeism.

Many studies on costs do not calculate the loss of work productivity using validated questionnaires, thus limiting global assessment, since this loss clearly accounts for the

largest component of indirect costs (11, 24, 26). Calculation of total indirect costs is of paramount importance: in addition to being the largest component of total costs, it is also that which can be best modified through the health system using timely application of optimal therapy. The economic impact on society of a reduction in even part of AR-associated presenteeism could be enormous. For example, in Sweden, it was calculated that reduction in loss of work productivity to the equivalent of 1 working day would generate an annual saving of 528 million (11). Given wage costs in Spain, a 20% reduction in lost productivity could generate an annual saving of 2.9 billion.

Recent studies have calculated the direct costs of asthma in Spain to be 1,533 (95% CI, 1,133–1,946) per patient-year (45), whereas those of AR reached 554 per patient-year. Given that the prevalence of AR is 4–5 times higher than that of asthma, the direct costs of AR for the whole population are thought to be considerably higher than those of asthma. These results agree with those of other authors (11). Total costs, however, are not similar for both conditions, since presenteesim is not calculated in previous studies.

Our study is subject to a series of limitations. First, the study population only included patients who had attended specialized clinics. We excluded patients treated exclusively in primary care and patients who bypass their doctor and seek help directly at the pharmacy. Consequently, less sick patients may have not been included. In addition, the possibility that our study population contained a lower number of individuals with mild AR makes it difficult to evaluate them. On the other hand, local variations in costs of medical assistance and diagnostic or therapeutic procedures should be borne in mind before extrapolating results to other countries. Moreover, we did not include a control group owing to the difficulty in finding a representative nonallergic population in allergology clinics.

A further limitation of our study is the loss of 23% of cases, which is slightly higher than the expected 20%, although the effect on the final results is not necessarily relevant.

Lost productivity can be translated into monetary units for the calculation of indirect costs in several ways. We used the human capital approach, where costs are calculated by multiplying workdays lost by the mean salary earned (20). Lost work productivity can be calculated using various methods, and a wide variety of questionnaires are available (21). We used the WPAI questionnaire because it had been validated in Spanish (23) and is open access.

In conclusion, the total costs of AR in a hospital clinic are considerable. Both these costs and the high prevalence of the disease underline the socioeconomic burden of AR. Indirect costs are 3 times higher than direct costs. Most indirect costs correspond to presenteeism. Costs are associated with the duration and severity of AR: the more severe and persistent forms have the highest costs.

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Author contributions

All the authors have contributed in patient´s inclusion and article review.

Conflicts of interest

Non interest conflict for any author

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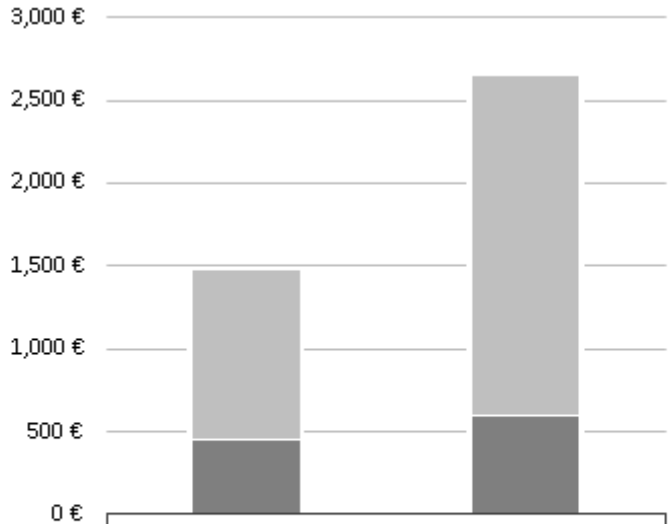
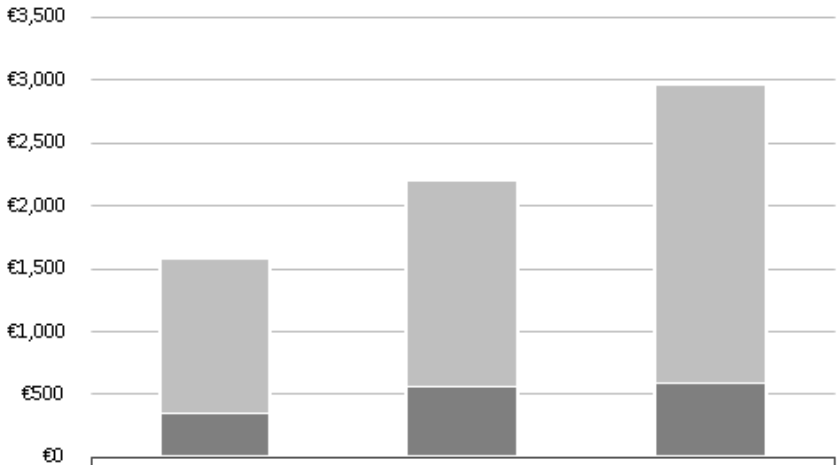
Figure 1. Total, direct, and indirect costs of allergic rhinitis according to duration (a) and severity (b)

Fig 1a Costs of AR according to disease duration (mean costs per patient and year)



	Intermittent	Persistent	
Indirect Costs	1,036.00 €	2,061.07 €	p < 0,001
Direct costs	448.98 €	594.79 €	p = 0,007
Total costs	1,484.98 €	2,655.86 €	p < 0,001

Fig 1b Costs of AR according to disease severity (mean costs per patient and year)



	Mild	Moderate	Severe	p for trend
Indirect Costs	1,235.98 €	1,639.49 €	2,368.20 € [ab]	p = 0,012
Direct costs	349.22 €	560.00 €	597.08 €	p = 0,060
Total costs	1,585.20 €	2,199.49 €	2,965.28 € [ab]	p = 0,006

a. p< 0,05 compared with mild severity.
b. p< 0,05 compared with moderate severity.

Table 1. Clinical data

Years since diagnosis of AR (Mean ± SD)		9.6±7.9
Severity of AR according to modified ARIA classification (Valero, Ferrer et al. 2007)	Mild	6.8%
	Moderate	71.1%
	Severe	22.1%
Duration of AR according to the ARIA classification	Intermittent	28.1%
	Persistent	71.9%
Treatment of AR at baseline	Nonsedating oral antihistamines	93.6%
	Ocular topical antihistamines	24.5%
	Intranasal corticosteroids	81.1%
	Antileukotrienes	6.0%
	Immunotherapy	44.2%
Sensitization to allergens at baseline	Mites	49.8%
	Fungi	8.4%
	Pollens	80.3%
	Animal dander	39.4%
Comorbidities	Asthma	38.6%
	Allergic conjunctivitis	81.9%
	Food allergy	9.8%
	Atopic dermatitis	6.4%

Table 2. Total direct costs of AR according to disease duration

	Intermittent (n=140)		Persistent (n=358)		p Value
	Mean	**SD**	**Mean**	**SD**	
Direct health care costs,	**435.64**	**±463.81**	**580.17**	**±557.66**	0.007
Visits to the doctor	134.12	±168.22	209.12	±273.24	0.003
Diagnostic tests	166.25	±380.25	166.76	±390.91	0.989
Drug therapy	45.62	±78.93	77.88	±134.22	0.008
Immunotherapy	89.65	±123.73	123.03	±141.99	0.015
Hospitalizations	0.00	–	3.38	±63.97	0.532
Non–health care direct costs[1]	**13.34**	**±32.12**	**14.62**	**±33.88**	0.702
Total direct costs	**448.98**	**±469.64**	**594.79**	**±561.36**	**0.007**

[1]Non–health care direct costs are those associated with environmental control measures (dehumidifiers, acaricides, HEPA filters, and antimite covers). Expressed as mean costs per patient and year.

Table 3. Total direct costs of allergic rhinitis according to disease severity

	Mild (n=34)		Moderate (n=354)		Severe (n=110)		p Value for trend
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Direct health care costs,	**331.62**	**± 346.14**	**546.79**	**± 556.95**	**580.48**	**± 505.94**	0.061
Visits to the doctor	118.35	± 129.91	177.04	± 190.47	244.98[ab]	± 397.53	0.003
Diagnostic tests	72.76	± 144.38	188.50	± 448.77	125.21	± 142.56	0.760
Drug therapy	41.77	± 86.02	70.36	± 127.07	72.16	± 114.60	0.360
Immunotherapy	98.75	± 127.99	107.47	± 137.88	138.14	± 138.76	0.043
Hospitalizations	0.00	–	3.42	± 64.34	0.00	–	0.768
Non–health care direct costs[1]	**17.59**	**± 37.58**	**13.21**	**± 30.87**	**16.60**	**± 39.37**	0.708
Total direct costs	**349.22**	**± 356.76**	**560.00**	**± 560.99**	**597.08**	**± 510.12**	**0.060**

[1]Non–health care direct costs are those associated with environmental control measures (dehumidifiers, acaricides, HEPA filters, and antimite covers).
[a]$p<0.05$ compared with the group with mild allergic rhinitis.
[b]$p<0.05$ compared with the group with moderate allergic rhinitis.
Expressed as mean costs per patient and year.

Table 4. Total indirect costs of AR according to disease duration and severity

	Cost of hours not worked because of absence from the workplace (absenteeism),		Cost of hours of work lost in the workplace (presenteeism),		Total indirect costs,	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
According to the duration of AR						
Intermittent	99.06	± 307.84	936.94	± 1798.78	1036.00	± 1907.16
Persistent	86.72	± 301.52	1.974.35	± 3115.87	2061.07	± 3169.50
p value	0.683		<0.001		<0.001	
According to the severity of AR						
Mild	56.45	± 215.54	1.179.53	± 2539.87	1235.98	± 2533.51
Moderate	98.52	± 320.82	1.540.97	± 2608.19	1639.49	± 2674.02
Severe	73.83	± 265.52	2.294.37[ab]	± 3523.15	2368.20[ab]	± 3592.40
p value for trend	0.852		0.010		0.012	

[a]p<0.05 compared with mild severity.
[b]p<0.05 compared with moderate severity.