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Differential healthcare direct costs of asthma and chronic rhinosinusitis with nasal polyps in Catalonia (Spain)

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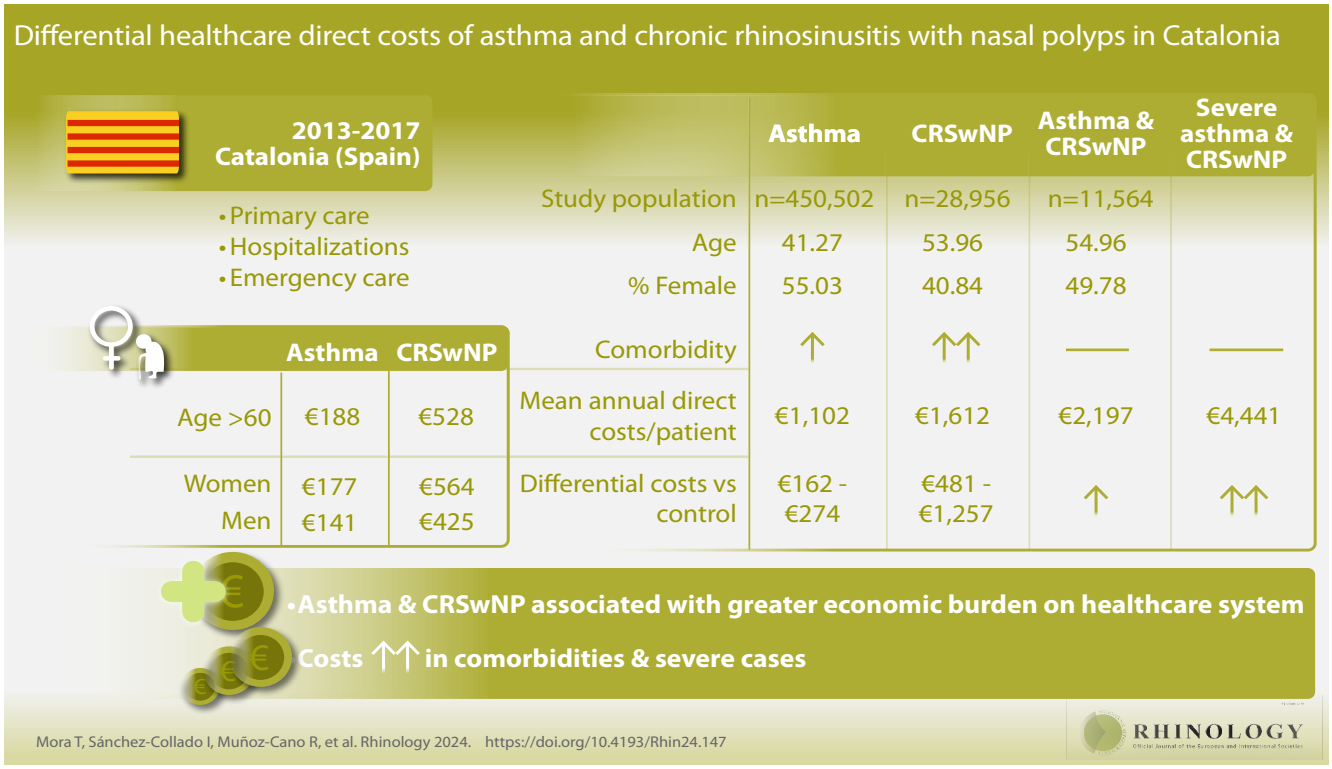

Abstract

Introduction: This study compares the direct healthcare costs associated with asthma and chronic rhinosinusitis with nasal polyps (CRSwNP) from 2013 to 2017 in Catalonia (Spain) with a population control group without these conditions.

Methods: A population administrative database containing healthcare information was used. The database contained information on primary care, hospitalisations, and emergency care from 2013 to 2017 in Catalonia. The unit cost of each healthcare procedure was imputed using a complete list of public prices for primary care services, hospital, and speciality services. Differential costs were estimated using a finite mixture model.

Results: Individuals diagnosed with asthma or CRSwNP showed a higher incidence of comorbidities than the control group. Mean annual direct costs per patient were €1,102 for asthma, €1,612 for CRSwNP and €2,197 for those with both conditions. According to our estimations, differential costs were €162 - €274 for patients with asthma and €481 - €1,257 for patients with CRSwNP compared to the reference population. These costs were significantly higher when asthma and CRSwNP coexist and especially in their severe condition.

Conclusion: This population-based study revealed that asthma and CRSwNP are associated with great economic burdens for healthcare systems. These costs were significantly higher when comorbidity was present (asthma and CRSwNP) and especially in their severe condition (€4,441).

Key words: direct health costs, economic burden, asthma, chronic rhinosinusitis with nasal polyps

Introduction

Asthma is the most prevalent chronic lung disease. It affects people of all ages, with a peak incidence in childhood [1]. The prevalence of asthma in Europe is 8.2% in adults and 9.4% in children, with striking geographical variations [2]. Specifically, in Catalonia (Spain), in 2017, asthma prevalence was 6.3% [3] and 0.41% for CRSwNP [4].

Asthma is a lifelong condition with a wide range of clinical presentations, from mild to severe forms, requiring extensive emergency care, frequent hospital admissions, and many missed school- or work- days. Therefore, this disease is a significant public health concern that burdens patients and healthcare systems [5]. The economic burden of asthma is mainly related to outpatient visits, hospital admissions, treatments, and assessments. However, indirect costs, such as work-related losses, are more significant than direct health costs [5].

Estimates of the economic impact of asthma differ widely among studies, depending on the region, type of healthcare system, and the database used, among other factors. A population-based study including 10,237 people from the U.S. showed an incremental annual medical cost per capita of $3,266 [6]. A mean total cost per patient of €1,583 was found in a real-world evaluation of the economic impact of persistent asthma in Europe [7]. In a prospective study conducted in Spain, the total societal cost of asthma was €1,726 per patient annually [6] and €7,472 in a retrospective study in patients with severe asthma [8].

Another factor increasing asthma-related expenditures is the concurrent treatment of its comorbidities [5]. Chronic rhinosinusitis (CRS) is one of the most reported comorbidities [9], sharing a similar pathophysiology with asthma [10]. CRS is a group of disorders characterised by the inflammation of the nasal mucosa and paranasal sinuses. CRS with nasal polyps (CRSwNP), one of the main CRS phenotypes, presents a high symptom burden. The estimated prevalence of CRS in adults is 10.9% (range 6.9–27.1) in Europe [11], and CRSwNP represents approximately 20–30% of CRS cases [12]. However, prevalence estimates for CRSwNP may be underestimated [13].

CRSwNP is a significant burden for patients, significantly impairing their quality of life and daily living activities [14], particularly in patients with comorbidities or those requiring repeated corticosteroid treatment or sinonasal surgery [13]. The impact of CRSwNP on health-related quality of life is higher than that of angina or chronic heart failure [15] and is similar to chronic diseases such as asthma [16]. Its high degree of chronicity and the frequent coexistence of comorbidities in patients with CRSwNP means that it requires substantial healthcare resource use, resulting in a high economic burden [17]. In a retrospective, case-control study, the average total annual costs for patients with CRSwNP were $8,004 in the U.S. [15]. In Europe, total direct costs per patient/year were €1,501 in a cross-sectional study for the Netherlands [18]. Strictly related to those who had surgery, health direct costs in England were £2,173 [19].

This study used a large-scale retrospective database to compare the healthcare costs associated with asthma and CRSwNP from 2013 to 2017 in Catalonia (Spain) to those without these diseases. Since no other study has compared healthcare expenditures related to CRSwNP and asthma, and there is no cost estimation of CRSwNP management in Spain, our analysis strongly contributes to the existing literature. It estimates the economic burden of patients with asthma, CRSwNP, or both conditions in the Spanish healthcare system. This can help to identify areas that would benefit from enhanced optimisation of healthcare resource use.

Materials and methods

Data sources and study population

We conducted a retrospective longitudinal observational study to compute the differential costs associated with asthma and CRSwNP management in Catalonia (Spain). To this end, we used a population administrative database from the Agència de Qualitat i Avaluació Sanitàries de Catalunya (AQuAS, Agency for Health Quality and Assessment of Catalonia). This database contains healthcare information from several public providers (primary healthcare centres, hospitals, and emergency rooms). The Ethics Committee of Hospital Clínic (Barcelona, Catalonia, Spain) approved the study.

The study population comprised all Catalonia residents entitled to the public health insurance covered by the statutory Spanish National Health System from 2013 to 2017, diagnosed with asthma or CRSwNP at primary, hospital, or emergency care levels. The control group comprised a large group of individuals of different ages, sexes, and health-sanitary areas from the population of different ages and sexes who matched individuals without asthma or CRSwNP. Since most patients with CRSwNP are aged ≥18 years, we only considered adults with CRSwNP; there was no age limit for patients with asthma and the control groups. The total population consisted of 1,221,184 individuals.

The database contained information on primary care, hospitalisations, and emergency care from 2013 to 2017. Entries in the database comprise a patient's identifier, the date of the visit (and length in case of hospitalisations) and all diagnoses and procedures associated with the visit. Identifiers allow the linkage of patients' information across datasets submitted by different healthcare providers and to demographic information, including gender, age, drug co-payment level (related to socioeconomic status), nationality, date of death, and sanitary health area (elementary territorial unit through which primary health care services are organized).

Diagnoses were classified according to the International Classification of Diseases diagnostic manual, 9th revision (ICD-9). The database stores diagnoses hierarchically, associating the primary diagnosis to each visit and listing all secondary diagnoses. Heal-

thcare procedures (HCPs) were defined and classified according to the ICD-9 Clinical Modification (ICD-9-CM), with 2,800 HCPs identified in the dataset.

Assignment of healthcare procedure costs

The unit cost of each HCP was imputed using a list of public prices approved in 2013 by the Catalan Healthcare Service. This list included unit prices or tariffs for standard primary care services such as general practitioner visits, speciality and hospital services, and psychiatric and mental health services. As no other list of public prices has been published in Catalonia and, considering that very few HCP prices have been updated after 2013, the approved 2013 public prices were used as the main resource to impute the cost of HCPs.

Most HCP prices were set according to the Diagnostic Related Group (DRG), which include prices for a wide range of procedures, such as surgical implants or infections. The Department of Health in Catalonia distinguishes between four groups of hospitals based on resource use and structural capacity (i.e., number of beds), with prices for each DRG varying between them. Specifically, the Department of Health sets a unified price for group 1 (isolated basic general hospitals and complementary hospitals) and group 2 (basic general hospitals), a price for those hospitals belonging to group 3 (referral hospitals), and a different one for hospitals classified as group 4 (high technology hospitals and monographic hospitals). As the dataset indicates the hospital at which individuals were treated every time they required hospital care, the corresponding DRG cost established for that group of hospitals is used.

In cases where no tariff was established in Catalonia by the Department of Health, we assigned the price of the DRG. It is often possible to determine the appropriate HCP by considering the group of hospitals where it was performed. When an HCP could be assigned to more than one DRG, the average cost across all possible DRGs by groups of hospitals was taken. If neither the unit price nor the DRG price by the hospital's group was found within Catalonia, we used the platform eSalud (an online and up-to-date database of Spanish healthcare costs) to search for prices in other regions in Spain in any available year. Since prices in eSalud are deflated using either the 2018 or 2019 Consumer Price Index, we inputted the updated price. Imputed prices were deflated to 2017 levels, using each year's corresponding Health Consumer Price Index. Drug costs were considered from the funder's perspective (cost incurred by the provider) and not discounting any co-payments. We excluded individuals who passed away during the study period and those whose total average yearly costs were above the 95th percentile from the analysis since these groups may distort the average behaviour and represent extreme cases.

Econometric methodology

To compute the differential costs of an individual with asthma or CRSwNP, we must consider two relevant factors: (i) the econometric technique to be used and the control units, and (ii) the factors associated with higher costs to be included in the regressions and the inclusion of specific comorbidities. Besides considering potential confounders, the asymmetric distribution of the variable costs and the fact that there is certain bimodality in the distributions should be considered to ensure the most suitable methodology is utilised. We estimated our models using alternative methods that provide complementary approaches: propensity score matching, two-part models, and Finite Mixture Models (FMM). The first method focuses on finding units that serve as a control (the overall population does not represent a control group per se). In contrast, two-part models consider the estimation separately in the two parts of the distribution (low costs as opposed to high costs). The FMM model usually fits better for cost analyses that often have high degrees of asymmetry due to the presence of individuals with high costs, which complicates the comparison of averages. Our model has also been estimated considering control individuals obtained using the neighbourhood matching technique. We considered two/three latent classes for FMM models to explain the different parts of the distribution. For our approach, the first part of the positive costs is relevant and not affected by heavy users or healthcare resources. An extensive explanation of the use of these kinds of models for the determinants of healthcare costs can be found in [20].

Our identification strategy is based on instrumenting diagnosis by the probability of being diagnosed. For this purpose, for everyone, we compute the most visited healthcare provider defined by number of yearly visits. Then, for each healthcare provider unit, we calculate the probability of being diagnosed with either asthma or CRSwNP ($prop_j$). This probability is the ratio between the number of visits related to asthma or CRSwNP against the total number of yearly visits to that healthcare provider. This step is shown in Equation (2). We considered all units of public healthcare providers *(j)* (primary care centres, hospitals, and emergency rooms) present in Catalonia. Equation (1) shows the model estimated that explains total medical costs.

$Y_i = X_i \beta + diag_{i,j} \gamma 1 + abs_i + \varepsilon_i$ (1) $diag_{i,j} = prop_j + X_i \delta + u_i$ (2) where Y_i indicates the total direct healthcare costs of the individual *i*, while X_i is a set of observable characteristics (sex, age, nationality, co-payment rates and out-of-pocket limits per person) and some comorbidities, such as the existence in the patient's record of visits due to: non-specific allergy, hypertension, diabetes, dyslipidaemia, anxiety, ischemic disease, overweight condition, depression, alcohol-related diseases, or chronic obstructive pulmonary disease (COPD). $diag_{i,j}$ captures a diagnosis of asthma or CRSwNP at each healthcare provider unit (*j*). We have considered fixed effects that may affect prescribing, i.e., basic health areas

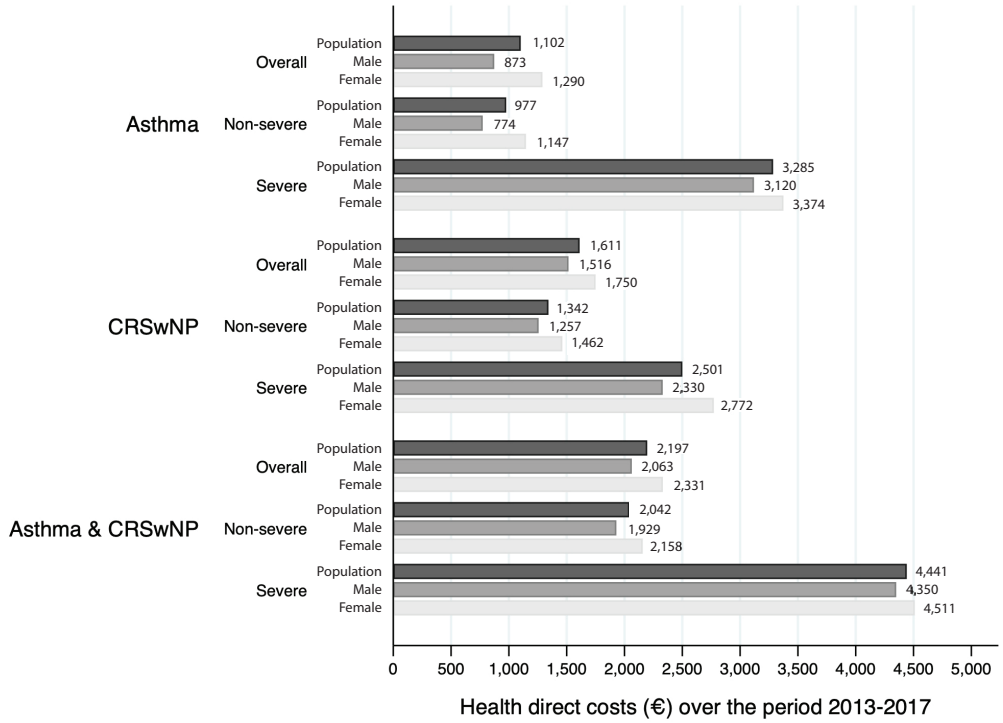

Figure 1. Diagnosis group's average annual health direct costs by severity group and gender. CRSwNP, Chronic rhinosinusitis with nasal polyps.

for the health sectors (abs_i). Models also include error terms ($\varepsilon_{i,t}$). Standard errors were clustered at the abs level because most healthcare decisions and experiences are shared at this aggregate level.

Results

Demographic and clinical characteristics

Table S1 shows the demographic characteristics of the study groups: patients with asthma, patients with CRSwNP, and the control group. Compared to asthma and the control group, a notably higher proportion of CRSwNP patients is within the 10% co-payment category. In comparison, a lower fraction was in the 40% co-payment category for those with CRSwNP. This suggests that the wealth distribution of individuals diagnosed with CRSwNP may be biased to lower-income levels than the control group (Table S1).

Individuals diagnosed with asthma or CRSwNP showed a higher incidence of comorbidities than the control group. For most comorbidities, those diagnosed with CRSwNP showed a higher prevalence of comorbidities than those with asthma. The highest differences in comorbidity prevalence between CRSwNP-diagnosed and control individuals correspond to hypertension and overweight (Table S1).

Healthcare direct costs

In the control group, a higher population density was found to have annual costs below €500-€600 compared with asthma-diagnosed individuals and below €700-€800 compared with CRSwNP-diagnosed individuals (Figures S1A, S1B & S1C). A higher proportion of patients were distributed within the range of €500-€1500 annual costs in both diagnosis groups compared to the control group.

Mean annual costs per patient were higher for individuals with asthma (€1,102.4) or CRSwNP (€1,611.5) compared to the control group (€825.5). Figure 1 shows each diagnosis group's average annual health direct costs by severity group and gender. After stratifying by sex and age range, we observed some heterogeneity in mean costs. These differences were statistically significant. In asthma-diagnosed patients, higher costs were observed for women (€1,289.79) than men (€872.95). The highest mean annual cost was observed in individuals aged >60 when stratifying by age. Similar results were observed in patients with CRSwNP, with higher mean annual costs for all stratified groups (except for the 0-18 range) than the asthma group. These results were corroborated by considering the median values (Tables S2a & S2b). We also calculated the mean annual costs per patient for individuals with both conditions (Table S2c), those figures being significantly higher than those with only one disease (€2,196.8). Furthermore, we calculated the average mean annual costs for those with severe conditions. Disease severity was defined following previous publications [3, 4]. Explicitly, Explicitly, for asthma: 1) high dose intake of inhaled corticosteroids (ICS) for at least six months over the last year or at least 12 months over the last two years (consecutive or not); or 2) treatment with biologics over the last two years; or 3) intake of systemic corticosteroids (SCS) for more than six months over the

last year or more than 12 months over the last two years. Finally, for CRSwNP: 1) SCS intake over the last two years above the annual minimum dose calculated threshold for each SCS in any of the two years; or 2) endoscopic sinus surgery over the period for which we have information (2010-2017). These figures were consistently higher (€4,441.3) than averages obtained without conditioning by severity (€2,041.7) or compared to those with one comorbidity.

Econometric results

Table S3 shows the results of estimating cost differences using the alternative estimation procedures with or without utilising our selection of instruments, as shown in equations (1) and (2). The best-fitting model was obtained with the two-part model and the FMM estimation when accounting for only positive costs. Although the two-part model outperformed the other econometric approaches, results were quite similar between the models, and Instrumental Variables (IV) estimations were not far from OLS estimates. In fact, in individuals diagnosed with CRSwNP, IV and OLS estimates were the same, given the very low probability of being diagnosed with this condition. Our results indicate that individuals with asthma showed annual health direct costs €162 higher than the control group. These higher costs were confirmed after accounting for only positive costs through the FMM procedure, although results were higher (€274) for the best model. Annual health direct costs were significantly higher (€481) and extremely higher (€1,257) at the extreme part of the distribution (heavy users of public healthcare resources) in individuals diagnosed with CRSwNP than in the control group. Akaike information criteria showed that the two-part model was the best estimation procedure.

Table S4 show, and the outputs of models estimating the cost differences by age and gender for asthma and CRSwNP using a two-part model. Within the asthma population, individuals from 0 to 18 years of age had the highest public healthcare resource consumption and the highest cost differences (€293.77) compared to the overall differential found in previously discussed models (€162.04). Differences in costs relative to the control group tend to decrease as age increases, although it reaches €187.60 for individuals 60+ years of age. Cost differences for patients with CRSwNP are much higher and increase by age, with the heaviest users of healthcare resources being in the 50-60 age range (€547.54) compared to the previous overall differential (€481.00).

Discussion

This population-based study revealed that asthma and CRSwNP are costly diseases for healthcare systems, accounting for €1,102 and €1,611 mean annual direct costs per patient, respectively. According to our estimations, these expenses represent €162 increased costs for asthma and €481 increased costs for CRSwNP compared to the control group. In a descriptive sense, individuals with asthma (€1,102.4) or CRSwNP (€1,611.5) showed much higher health direct costs compared to the control group (€825.5). Besides, these figures were consistently higher when both diseases were associated (€2,196.8) and in their severe condition (€4,441.3).

Asthma and CRSwNP are two chronic conditions with an increasing prevalence that pose a substantial socioeconomic burden to healthcare systems [21]. Assessing the direct costs linked to these diseases can help identify areas within diagnosis and treatment that could be improved to manage healthcare resources [5]. However, cost estimations are also subject to critical methodological limitations. They have limited generalizability because estimates are based on reduced sample sizes or do not use the appropriate control group [22]. As costs are tightly influenced by different geographic and sociodemographic factors [5], these estimations cannot be extrapolated to other countries. Moreover, some studies on costs employ restrictive selection criteria that reduce the external validity of the results. However, cost analyses based on real-world data remain useful tools [23].

This is one of the most extensive studies analysing the direct costs of asthma and CRSwNP in Spain, with data from 450,402 patients with asthma, 28,958 with CRSwNP and 1,221,184 patients without asthma or CRSwNP. Previous clinical studies on asthma costs conducted in Spain included 303 and 627 patients [8, 24], whereas no other research assessing the costs of CRSwNP in Spain has been carried out. Of remarkable importance is that patients with CRSwNP showed a higher prevalence of comorbidities than those with asthma, except for allergy, depression, and COPD. This is an essential factor to consider as comorbidities have been closely associated with increased costs in asthma [25] and CRSwNP [26].

Mean annual direct costs were higher in patients with asthma (€1,102) and CRSwNP (€1,611) than in the control group (€825). Many studies estimated annual costs for asthma, whereas data on CRSwNP is scarce. Our estimated yearly costs for asthma are similar to those reported in a prospective study conducted in Spain, which shows a societal cost of €1,726 per patient annually [8]. These results slightly differ from a retrospective study for 627 patients in patients with severe asthma, which reported an annual direct cost of €1,533 [8]. A systematic review found the most crucial direct cost drivers in asthma were hospitalisations and medications, whereas work and school losses were the main indirect contributing factors [27]. It is essential to highlight that expenses associated with hospitalisations vary widely between countries and that higher costs have been identified in private vs public hospitals in some studies [28, 29]. In this context, Spain's public healthcare system guarantees universal coverage for all residents. Comparing cost estimations for CRSwNP is harder since no other study has been performed in Spain. Our results are similar to those obtained in a cross-sectional study reporting

a total cost of €1,501 per patient/year in Europe [18]. The main cost drivers in CRS identified in previous studies are ambulatory expenses, followed by prescription and in-hospital costs [30].

In our estimations, mean annual direct costs were higher for women than men with asthma and CRSwNP diagnoses. Three high-quality studies previously found higher direct costs for women vs men [31, 32]. Some authors interpret these findings as an indication that women might use acute care facilities more because of poor medication compliance or because they are more concerned about the disease and seek more medical care than men [25]. Our database found the highest costs for people >60 years old, which confirms and the results in [25], which showed that the cost of asthma was strongly correlated with age. This study also showed that mean annual costs were significantly higher per patient for individuals with both conditions (€2,196.8) than for those with only one disease. Our results are similar to those found in the existing literature for the U.S., where costs are also higher for patients with both conditions than for those with one [17, 33].

Econometric results showed that individuals with asthma required €162-€274 higher annual direct costs than the control group. For individuals with CRSwNP, direct yearly costs were even higher (€481 compared to the reference population), reaching €1,257 increased direct costs for heavy users of public health resources. These results confirm that asthma and CRSwNP are two costly diseases, reinforcing the need to optimise diagnosis and treatment strategies to allocate healthcare resources better.

The study's main limitations are i) that we did not consider the effect of indirect and outpatient costs in our analysis; and ii) that costs were based on public healthcare use without considering private use. Besides, the indication of biologics for severe CRSwNP since the middle of 2019, in addition to the previous indication in severe eosinophilic asthma, could modify this data in both directions by increasing the costs of medication and decreasing the costs of the use of rescue medication (oral corticosteroids) and endoscopic sinus surgery as well as the costs of their adverse events and complications, respectively. However, this analysis was not one objective of our analysis ending in 2017. Despite these limitations, this study is the first to compare the direct annual costs of asthma and CRSwNP using a large database from Catalonia. From a policy perspective, these results may be helpful when planning healthcare budgets and identifying areas that require better optimisation of healthcare resource use.

Conclusion

This population-based study revealed that asthma and CRSwNP are associated with great economic burdens for healthcare systems. The economic burdens appear higher for individuals with both conditions than those with one condition and the control group.

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Authors' contributions

TM performed the database analysis. TM analysed the results and wrote the manuscript. IS-C developed the cost database. IS-C, AV, JM, PR, and RM-C collaborated to develop and correct the manuscript.

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Conflicts of interest

There are no patents, products in development or marketed products to declare. The authors of this manuscript have no relevant financial or other relationships to disclose. JM is or has been a member of national and international scientific advisory boards, consulting received fees for lectures, and grants for research projects or clinical trials from AstraZeneca, Genentech-Roche, GSK, LETI, Lilly, Menarini, MSD, Mitsubishi-Tanabe, NOUCOR/Uriach, Novartis, OPTINOSE, Proctor & Gamble, Regeneron Pharmaceuticals Inc., Sanofi-Genzyme, UCB Pharma, and Viatris/MEDA Pharma.

Data availability

None to declare.

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Assocociate Editor:
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This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL

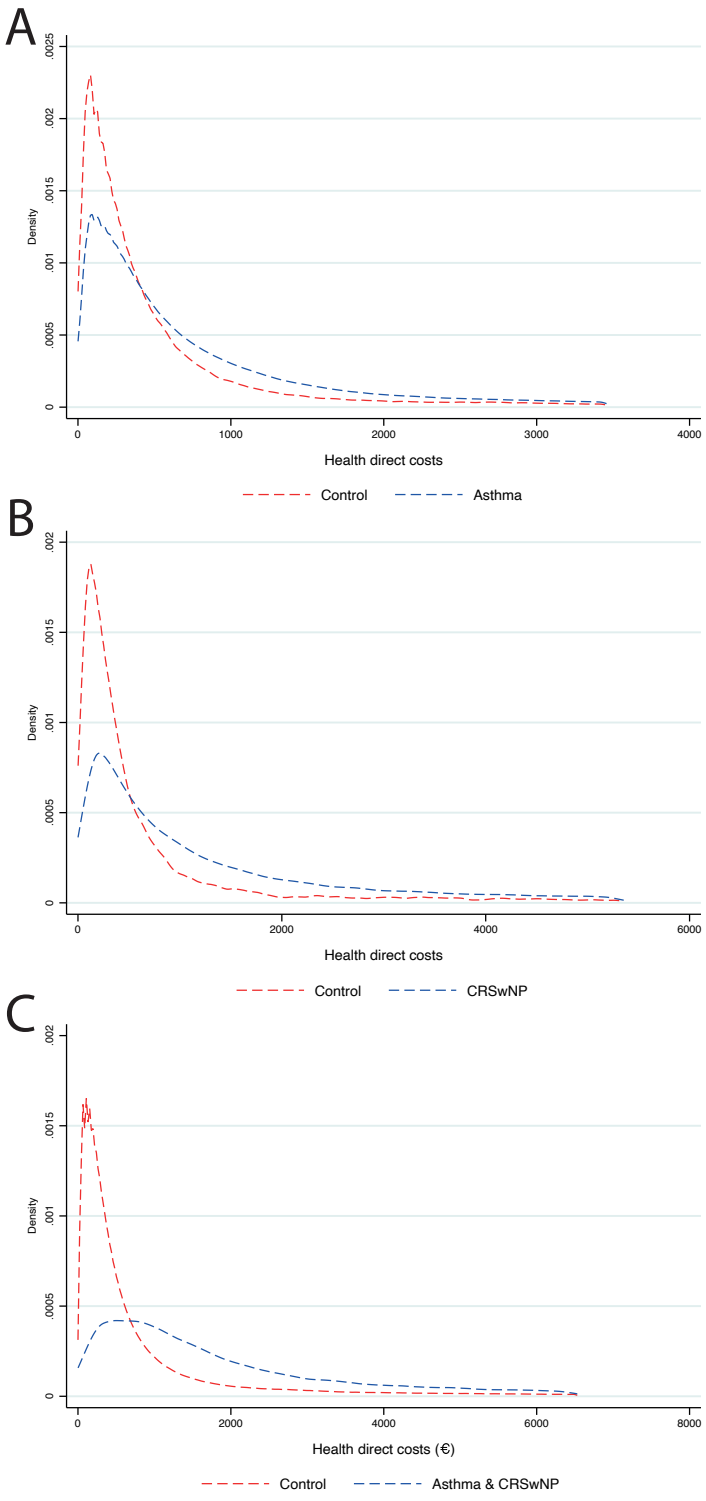

Figure S1. Annual health direct costs. Kernel density distribution for asthma (A), CRSwNP (B) and asthma with CRSwNP (C). Values below the 90th percentile were plotted. Total costs include visits (to general practitioners, hospitalisations, and emergency department visits), drug consumption and healthcare procedures. Density refers to the density of point features around each output raster cell. CRSwNP, Chronic rhinosinusitis with nasal polyps.

Table S1. Socioeconomic characteristics in patients with asthma or chronic rhinosinusitis with nasal polyps and the control group.

	Asthma population (N= 450,402)	CRSwNP population (N= 28,956)	Population with asthma & CRSwNP (N= 11,564)	Population without asthma and CRSwNP (N= 753,390)
Average age, years, mean (SD)	41.27 (23.85)	53.96 (16.88)	54.96 (15.83)	33.86 (25.83)
Female	55.03 (0.50)	40.84 (0.49)	49.78 (0.50)	56.04 (0.50)
Spanish	91.27 (0.28)	90.04 (0.30)	92.87 (0.26)	84.60 (0.36)
Exempted, mean (SD)	4.52 (0.21)	3.26 (0.18)	3.36 (0.18)	4.86 (0.21)
10% co-payment	26.07 (0.44)	37.71 (0.48)	38.38 (0.49)	21.48 (0.41)
40% co-payment	45.96 (0.50)	35.30 (0.48)	33.37 (0.47)	50.17 (0.50)
50% co-payment	22.04 (0.41)	22.36 (0.42)	23.41 (0.42)	22.34 (0.42)
60% co-payment	0.61 (0.08)	0.66 (0.08)	0.79 (0.09)	0.44 (0.07)
Excluded from co-payment	0.80 (0.09)	0.70 (0.08)	0.69 (0.08)	0.71 (0.08)
Asthma (%), mean (SD)	100.00 (0.00)	39.94 (0.49)	100.00	0.00
CRSwNP (%), mean (SD)	2.57 (0.16)	100.00 (0.00)	100.00	0.00
Non-specific allergy, mean (SD)	5.84 (0.23)	4.99 (0.22)	6.02 (0.24)	4.45 (0.21)
Hypertension	20.80 (0.41)	30.87 (0.46)	30.61 (0.46)	16.26 (0.37)
Diabetes	7.67 (0.27)	9.83 (0.30)	9.05 (0.29)	6.20 (0.24)
Dyslipidaemia	7.34 (0.26)	9.44 (0.29)	10.39 (0.31)	5.67 (0.23)
Anxiety	17.29 (0.38)	17.57 (0.38)	18.57 (0.39)	13.20 (0.34)
Ischemic disease	2.41 (0.15)	3.18 (0.18)	2.61 (0.16)	1.71 (0.13)
Overweight condition	18.85 (0.39)	19.52 (0.40)	20.56 (0.40)	13.13 (0.34)
Depression	4.29 (0.20)	4.45 (0.21)	5.02 (0.22)	2.64 (0.16)
Alcohol-related diseases	0.05 (0.02)	2.71 (0.16)	2.01 (0.14)	0.00 (0.03)
COPD	2.48 (0.16)	2.38 (0.15)	3.59 (0.19)	0.00 (0.02)

Note: standard deviation in parenthesis. All figures correspond to percentages except average age. Abbreviations: CRSwNP, Chronic rhinosinusitis with nasal polyps; COPD, Chronic obstructive coronary disease; SD, standard deviation.

Table S2a. Annual direct costs (€) in patients with asthma.

	Total cost Mean (SD)	Total cost Median (95% CI)	Non-severe cost Mean (SD)	Severe cost Mean (SD)
Population	1,102.35 (1,964.65)	412.18 (411.30 - 413.08)	977.33 (1,799.75)	3,285.25 (3,108.15)
Male	872.95 (1,699.64)	316.21 (314.89 - 317.62)	773.97 (1,539.65)	3,119.87 (3,063.20)
Female	1,289.79 (2,138.96)	508.56 (507.07 - 510.16)	1,147.35 (1,975.30)	3,374.40 (3,128.50)
Age range				
0-5 years	1,265.96 (2,015.38)	607.57 (600.54 - 614.26)	1,242.7 (1,982.5)	2,169.86 (2,887.44)
6-11 years	759.07 (1,298.27)	392.02 (389.85 - 394.44)	745.79 (1,267.3)	2,845.17 (3,129.62)
12-15 years	607.1 (1,066.24)	327.05 (325.44 - 328.27)	594.72 (1,027.75)	3,366.48 (3,386.41)
16-17 years	542.55 (1,066.76)	255.99 (253.69 - 259.08)	527.88 (1,028.77)	3,288.85 (2,911.09)
18-29 years	507.04 (1,222.06)	185.41 (184.15 - 186.60)	496.9 (1,200.33)	2,540.35 (2,810.13)
30-39 years	704.69 (1,614.66)	223.34 (221.69 - 224.79)	689.65 (1,592.64)	2,353.1 (2,758.29)
40-49 years	779.5 (1,574.46)	301.77 (300.15 - 303.41)	739.78 (1,514.92)	2,463.5 (2,715.42)
50-59 years	1,106.28 (1,853.58)	496.80 (493.74 - 499.81)	1,007.12 (1,735.85)	2,703.92 (2,744.73)
>60 years	2,154.43 (2,664.92)	1,186.22 (1,181.74 - 1,190.59)	1,889.32 (2,468.23)	3,512.53 (3,173.26)

Note: Outliers (costs above the 95th percentile) were excluded; SD, standard deviation.

Table S2b. Annual direct costs (€) in patients with CRSwNP.

	Total cost Mean (SD)	Total cost Median (95% CI)	Non-severe cost Mean (SD)	Severe cost Mean (SD)
Population	1,611.49 (2,391.02)	654.80 (648.57 – 661.21)	1,342.01 (2,083.44)	2,500.77 (3,037.81)
Male	1,515.90 (2,357.63)	569.35 (561.80 - 576.69)	1,256.79 (2,035.06)	2,330.19 (3,022.87)
Female	1,749.95 (2,431.93)	786.96 (776.66 - 798.36)	1,462.02 (2,144.01)	2,772.17 (3,041.91)
Age range				
0-18 years	755.42 (1,437.80)	300.10 (290.10 - 316.99)	626.43 (1,098.61)	1,838.92 (2,828.82)
18-29 years	828.28 (1,753.37)	237.83 (228.37 - 244.16)	696.52 (1,507.4)	1,689.35 (2,732.57)
30-39 years	1,042.46 (1,980.30)	299.23 (291.80 - 307.36)	851.92 (1,671.21)	1,819.72 (2,788.49)
40-49 years	1,174.66 (2,042.72)	396.37 (386.62 - 407.22)	919.07 (1,673.16)	1,976.26 (2,762.78)
50-59 years	1,417.12 (2,165.76)	586.03 (574.52 - 598.69)	1,123.27 (1,765.46)	2,245.62 (2,863.25)
>60 years	2,249.63 (2,712.28)	1,213.12 (1,195.85 - 1,229.29)	1,964.15 (2,461.31)	3,127.99 (3,214.00)

Note: Outliers (costs above the 95th percentile) were excluded; SD, standard deviation.

Table S2c. Annual direct costs (€) in patients with asthma and CRSwNP.

	Total cost Mean (SD)	Total cost Median (95% CI)	Non-severe cost Mean (SD)	Severe cost Mean (SD)
Population	2,196.75 (2,584.86)	1,275.53 (1,260.83 – 1,288.63)	2,041.74 (2,455.92)	4,441.29 (3,272.60)
Male	2,063.30 (2,542.32)	1,153.06 (1,133.22 – 1,169.18)	1,929.07 (2,423.96)	4,349.80 (3,308.82)
Female	2,331.35 (2,620.23)	1,402.16 (1,379.31 – 1,423.94)	2,157.65 (2,483.08)	4,510.60 (3,243.95)
Age range				
0-18 years	1,071.84 (1,521.02)	592.22 (523.68 - 644.96)	1,031.66 (1,396.7)	6,897.35 (5,082.91)
18-29 years	1,200.21 (2,072.75)	427.61 (402.51 - 451.65)	1,150.54 (1,972.26)	5,752.92 (4,615.19)
30-39 years	1,483.08 (2,258.96)	646.72 (623.90 - 669.50)	1,446.75 (2,224.29)	3,440 (3,108.06)
40-49 years	1,611.42 (2,173.57)	879.16 (857.49 - 902.69)	1,526.7 (2,071.43)	3,653.72 (3,294.72)
50-59 years	1,933.04 (2,327.35)	1,138.96 (1,113.25 – 1,159.56)	1,806.52 (2,222.91)	3,772.86 (2,952.95)
>60 years	2,961.89 (2,841.49)	1,987.07 (1,957.42 - 2,021.44)	2,757.52 (2,712.07)	4,868.09 (3,280.13)

Note: Outliers (costs above 95th percentile) were excluded; SD, standard deviation; CRSwNP, Chronic rhinosinusitis with nasal polyps

Table S3. Differential annual costs (€) from alternative estimations for asthma.

	IV estimation
Propensity score matching	143.09 (3.67)***
Two-part model	162.04 (3.37)***
FMM 2 latent class (matched units) for positive costs	
Class 1	182.12 (2.18)***
Class 2	53.17 (0.80)***
FMM 3 latent class (matched units) for positive costs	
Class 1	222.05 (0.24)***
Class 2	274.36 (0.71)***
Class 3	274.52 (0.37)***

Note: *, ** and *** denote statistical significance levels 10%, 5% and 1%, respectively. The sample size was 6,105,920 (propensity score matching & two-part models) and 5,416,821 (FMM). Standard errors are in parenthesis. Standard errors for FMM estimations were based on mean differences across predictions for both classes. Class 1 refers to regular healthcare users, whereas Class 2 identify heavy healthcare users after dropping those individuals with extreme costs. All regressions include as controls: age (non-linearly), gender, nationality, the considered comorbidities (non-specific allergy, hypertension, diabetes, dyslipidaemia, anxiety, ischemic disease, overweight condition, depression, alcohol diseases related, and chronic obstructive pulmonary disease), co-payment levels plus pharmacy limits and basic health areas fixed effects. FMM, finite mixture model; IV, Instrumental Variables.

Table S4. Differential annual costs from alternative estimations for CRSwNP

	IV estimation
Propensity score matching	409.75 (25.85)***
Two-part model	481.00 (10.56)***
FMM 2 latent class (matched units) for positive costs	
Class 1	439.75 (0.35)***
Class 2	1,256.92 (0.50)***
FMM 3 latent class (matched units) for positive costs	
Class 1	217.03 (0.25)***
Class 2	1,530.70 (0.56)***
Class 3	995.21 (0.41)***

Note: *, ** and *** denote statistical significance levels 10%, 5% and 1%, respectively. The sample size was 6,101,775 (propensity score matching & two-part model) and 5,416,821 (FMM). Standard errors are in parenthesis. Standard errors for FMM estimations are based on mean differences across predictions for both classes. Class 1 refers to regular healthcare users, whereas Class 2 identify heavy healthcare users after dropping those individuals with extreme costs. All regressions include as controls: age (non-linearly), gender, nationality, the considered comorbidities (non-specific allergy, hypertension, diabetes, dyslipidaemia, anxiety, ischemic disease, overweight condition, depression, alcohol diseases related, and chronic obstructive pulmonary disease), co-payment levels plus pharmacy limits and basic health areas fixed effects. FMM, finite mixture model; IV, Instrumental Variables; CRSwNP, Chronic rhinosinusitis with nasal polyps.

Table S5a. Differential annual costs (€) for asthma: two-part model.

Overall	162.04 (3.37)***
0-18	293.77 (6.10)***
[18-30[	44.17 (5.66)***
[30-40[	44.93 (5.86)***
[40-50[	101.29 (5.45)***
[50-60[	169.91 (7.25)***
[60-[	187.60 (7.89)***
Male	141.17 (4.11)***
Female	177.27 (4.16)***

Note: *, ** and *** denote statistical significance levels 10%, 5% and 1%, respectively. Standard errors are in parenthesis. All regressions include as controls: age (non-linearly for gender equations), gender, nationality, the considered comorbidities (non-specific allergy, hypertension, diabetes, dyslipidaemia, anxiety, ischemic disease, overweight condition, depression, alcohol diseases related, and chronic obstructive pulmonary disease), co-payment levels plus pharmacy limits and basic health areas fixed effects.

Table S5b. Differential annual costs (€) for CRSwNP: two-part model.

Overall	481.00 (10.56)***
[18-30[	343.36 (33.30)***
[30-40[	428.46 (23.11)***
[40-50[	541.09 (29.18)***
[50-60[	547.54 (22.18)***
[60-[	528.34 (19.60)***
Male	425.21 (13.26)***
Female	563.80 (17.19)***

Note: *, ** and *** denote statistical significance levels 10%, 5% and 1%, respectively. Standard errors are in parenthesis. All regressions include as controls: age (non-linearly for gender equations), gender, nationality, the considered comorbidities (non-specific allergy, hypertension, diabetes, dyslipidaemia, anxiety, ischemic disease, overweight condition, depression, alcohol diseases related, and chronic obstructive pulmonary disease), co-payment levels plus pharmacy limits and basic health areas fixed effects. CRSwNP, Chronic rhinosinusitis with nasal polyps.

STROBE Statement - Checklist of items that should be included in reports of cohort studies

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract; **Abstract**
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found; **Abstract**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported; **Introduction**
Objectives	3	State specific objectives, including any prespecified hypotheses; **Introduction**
Methods		
Study design	4	Present key elements of study design early in the paper; **Data sources and study population**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection; **Data sources and study population**
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up; **Data sources and study population; Assignment of Healthcare Procedure Costs**
		(b) For matched studies, give matching criteria and number of exposed and unexposed; **Data sources and study population**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable; **Econometric methodology**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group; **Econometric methodology**
Bias	9	Describe any efforts to address potential sources of bias; Data sources and study population; **Econometric methodology**
Study size	10	Explain how the study size was arrived at; **Econometric methodology**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why; **Econometric methodology**
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding; **Econometric methodology**
		(b) Describe any methods used to examine subgroups and interactions; **Econometric methodology**
		(c) Explain how missing data were addressed
		(d) If applicable, explain how loss to follow-up was addressed
		(e) Describe any sensitivity analyses; **Econometric methodology**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed; **Demographic and clinical characteristics**
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders; **Demographic and clinical characteristics**
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time; **Healthcare direct costs**
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included; **Econometric results**
		(b) Report category boundaries when continuous variables were categorized; **Demographic and clinical characteristics & Healthcare direct costs**
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses; **Econometric results**

STROBE Statement - Checklist of items that should be included in reports of cohort studies. *Continued.*

	Item No	Recommendation
Discussion		
Key results	18	Summarise key results with reference to study objectives; **Discussion**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias; **Discussion**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence; **Discussion**
Generalisability	21	Discuss the generalisability (external validity) of the study results; **Discussion**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based; **Conflict of interest**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.