



The Economic Burden of Asthma in Greece: A Cross-Sectional Study

Katerina Vellopoulou¹ · Petros Bakakos² · Stelios Loukides³ · Nikos Maniadas⁴ · Georgia Kourlaba¹ 

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Abstract

Background The high prevalence rates of asthma worldwide and the chronic nature of the disease make asthma a major cause of morbidity, imposing a significant socio-economic burden in many countries. Specifically in Greece, the self-reported prevalence of asthma reached 9% in 2017.

Objectives The objective of this study was to estimate the total management cost of asthma in Greece and its potential determinants.

Methods A population-based, random-digit-dialed telephone nationwide survey was conducted to recruit patients with asthma in Greece ($n=353$). A structured questionnaire was used to collect data on demographic and lifestyle characteristics, exacerbations, asthma control, medical resource utilization, and productivity loss during the past 12 months. The total annual direct cost from the societal, payer, and patient perspective as well as the indirect cost was calculated. All costs refer to the year 2017 (€). The significance level was set to $\alpha=0.05$.

Results The mean (95% confidence interval) annual total cost per patient for asthma management from the societal, payer, and patient perspective was €895 (696–1105), €673 (497–861), and €151 (119–188), respectively. The direct medical cost accounted for almost 90% of the total cost, whereas only 4% was attributed to the indirect cost. The direct medical cost was mainly driven by the medication cost (48%). The total annual societal cost was statistically significantly higher in those with not well-controlled asthma ($p=0.014$) and those experiencing exacerbations during the past 12 months ($p<0.001$) than in their counterparts. The total annual economic burden of asthma in Greece was estimated at €727 million and €547 million from the societal and payer perspective, respectively.

Conclusion Our findings indicate that asthma imposes a high economic burden on society and the healthcare system in Greece. Therefore, greater investment in interventions aimed at asthma control and prevention of acute exacerbations may reduce the overall burden of asthma in Greece.

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✉ Georgia Kourlaba
g.kourlaba@evroston.com

¹ EVROSTON LP, Chatzigianni Mexi 5, 115 28, Athens, Greece

² 1st Respiratory Medicine Department, Medical School, National and Kapodistrian University of Athens, Sotiria Chest Diseases Hospital, Athens, Greece

³ 2nd Respiratory Medicine Department, Medical School, National and Kapodistrian University of Athens, Attikon General Hospital, Chaidari, Greece

⁴ Department of Health Services Organization and Management, National School of Public Health, Athens, Greece

Key Points for Decision Makers

The cost of asthma management is significantly higher, almost double, in patients with not well-controlled asthma and those experiencing exacerbations than in their counterparts.

Interventions aiming to control asthma, prevent acute exacerbations, and manage chronic symptoms may reduce the overall burden of the disease in Greece.

1 Introduction

Asthma is a public health problem that affects people all over the world and of all age groups [1–3]. Based on data from the European Respiratory Society (ERS), about

30 million children and adults < 45 years old have asthma in Europe [4]. In Northern and Western Europe, asthma prevalence is more than 10%, whereas some of the highest rates of asthma in the world are in the UK and Ireland [4]. In Greece, based on the most recent data, the self-reported lifetime prevalence of asthma was estimated to be 9% [5].

Despite reductions in asthma mortality rates [6], asthma remains a major cause of disability [3] and its associated high morbidity rates impose a substantial economic burden on society [7]. According to data from the *European Lung Book* [8], the total cost of asthma in Europe was approximately €33.9 billion per annum in 2011. The cost of drugs and oxygen reached €8.0 billion, followed by the cost of outpatient care (primary care, €6.7 billion). Inpatient care played a relatively minor role in the total economic burden since the inpatient cost was estimated to be €4.8 billion. The indirect cost amounted to €14.4 billion taking into account productivity loss due to absenteeism, presenteeism, and early retirement [8]. Globally, the management cost of asthma is closely correlated with co-morbidities, age, and asthma severity [9]. Specifically, older patients and patients with significant co-morbidities or increasing severity have a prolonged length of inpatient stay, leading to increases in hospitalization costs [9]. In particular, the combination of old age and co-morbidities may further exacerbate the disease, resulting in a sharp cost increase associated with their management [9]. Although patients with severe asthma represent less than 10% of asthma population, their costs account for almost 80% of the total economic burden of asthma [10–12].

Despite the high prevalence of asthma in Greece and its substantial impact on patients, healthcare systems, and economies, to the best of our knowledge, available data regarding resource utilization and cost of asthma in Greece are scarce. A recently published study based on data collected from a Delphi panel of leading pulmonologists in Greece showed that the total annual cost for a person with asthma was €2280 (2015 value) from the societal perspective, with direct and indirect cost accounting for 65% and 35% of the total cost, respectively [7]. The authors also found that the asthma management cost increases with progressing asthma exacerbation [7]. However, a cost estimation obtained from a Delphi panel, where only a limited number of physicians report the average resource utilization per patient, is by no means as robust as an estimation obtained from individual data or from population-based studies. Moreover, to the best of our knowledge, there are no studies examining the factors that affect the cost of asthma management in Greece and how these may aid the decision-making process of the involved stakeholders. In this context, the objective of the present study was to estimate the total management cost of asthma per patient in Greece from the societal, payer, and patient perspective and its potential

determinants. Both public and private payments were taken into account when estimating the cost of asthma in Greece.

2 Materials and Methods

2.1 Study Design and Population

The data used to address the objective of the present study came from a population-based, random-digit-dialed (RDD) telephone nationwide survey conducted between November and December 2016. The primary objective of the survey was to estimate the lifetime prevalence of asthma in Greece previously published by Kourlaba et al. in 2018 [5]. In this survey, only subjects aged more than 18 years old were eligible to participate. Responders that fulfilled the criterion of age were then asked to report whether they had been diagnosed with asthma or whether they had regularly used medication to treat asthma (screening question). Among all contacted persons who answered the screening question ($n=3946$), 353 gave a positive response and were interviewed further. We estimated a priori that a sample size of 3946 would be adequate to provide the study, with 80% power to detect a 9% asthma prevalence (the primary objective of the survey) with a precision of 1% at the 95% confidence level. More details on the inclusion and exclusion criteria as well as on the sampling procedure are presented elsewhere [5]. Prior to completion of the survey, participants were asked to give their verbal consent after the interviewers informed them of the purpose of the study, that all data would be kept confidential and anonymous, and that they had the right to terminate the interview at any time.

According to the Greek legislation (Law 2328/1995, Presidential Decree 310/1996, Law 3603/2007, Law 2472/1997, Law 3471/2006), there is no need for ethics approval for telephone surveys such as the one presented here (Association of Opinion Polls and Survey Organizations) [13]. In addition, the survey qualified for institutional review board exemption, as specific regulatory criteria listed elsewhere [14] were met. As such, the study protocol was not submitted to the ethics committee of any institution for approval.

2.2 Data Collection

Telephone interviews were conducted (average duration 20 min) using a structured questionnaire (see Electronic Supplementary Material), which was developed in collaboration with two local experts (pulmonologists at public hospitals in Athens). The questionnaire concerned the 12 months prior to its completion, unless otherwise specified. It included questions on socio-demographic (age, sex, geographic area, smoking habits) and anthropometric characteristics (weight and height) and co-morbidities. With respect

to the latter, participants were asked to report whether they had experienced any of the following: chronic obstructive pulmonary disease (COPD), hypertension, diabetes mellitus, myocardial infarction, heart failure, allergic rhinitis, or other. Asthma control during the past 4 weeks was also assessed using the Asthma Control Test™ (ACT) [15]. If $ACT \leq 19$, asthma was classified as not well-controlled (NWC), whereas with $ACT > 19$, asthma was considered well-controlled (WC) [15]. Asthma exacerbation was defined as the occurrence of any of the following: (1) antibiotic use for an asthma-associated condition; (2) oral corticosteroid use for worsening asthma; (3) emergency visit due to asthma; or (4) overnight hospitalization due to asthma. These criteria have been employed in previous studies [16] and were validated by experts. Patients were also asked to report the year they were diagnosed with asthma, how many years had passed since the date of asthma diagnosis, and if they had active symptoms of asthma, such as coughing, wheezing, shortness of breath, and chest pressure during the past 12 months.

In addition, in closed-ended questions, the participants had to mention how many times during the past year they underwent asthma-related consultations (private physician visits), hospitalizations, emergency room (ER) visits, pulmonary function tests, such as spirometry or oximetry, and other diagnostic/laboratory tests. Also, information on medication use during the previous 12 months was assessed. Specifically, patients had to choose amongst a pre-specified list of drugs that were used on a regular basis. Local experts reviewed the questionnaire and also confirmed the medical resources and exacerbation criteria.

Finally, productivity loss related to absenteeism and presenteeism was also measured. The productivity loss related to absenteeism was assessed with the following questions

- “In the past year, how many days of work have you missed due to asthma?”
- “In the past year, how many days of work has a family member missed to take care of you?”

Productivity loss due to presenteeism was measured with the questions:

- “In the past year, how many days of work did your health problem affect your ability to produce work output in a high-quality or timely manner?”
- “How much has your average productivity during these days been affected?” (Select a number from 0 to 9, 0: it was not affected, 9: it was affected.)

2.3 Cost Estimation

As already mentioned, the cost was calculated from the societal, payer, and patient perspective. The societal perspective

takes into account all relevant costs, both direct and indirect, and can better inform the decision makers. The cost per payer perspective reflects the reimbursed cost from the third-party payer in Greece, the National Organization for the Provision of Health Services (EOPYY). The cost from the patient perspective or otherwise the out-of-pocket (OOP) cost is the amount paid by the patients, as a co-payment, after deduction of the reimbursed amount. The patient perspective is of relevance to the current study since patients with asthma are subject to co-payment [17]. According to Greek legislation, the level of co-payment in this patient population is equal to 25% for drugs and 15% for diagnostic/laboratory tests, on an outpatient basis [17]. Of note, it was out of scope to ask the participants whether the OOP payments took place at a public or private hospital. Moreover, it should be mentioned that based on current Greek legislation there is no patient co-payment for hospitalizations in public hospitals. More details on how each cost item was calculated, from each perspective, are presented in Sects. 2.3.1 and 2.3.2.

All unit costs are given in euros (€) in 2017 values. No inflation took place in costs coming from official national sources, such as costs of diagnostic/laboratory tests [18] or of hospitalization [19], as the published prices are used until any future adaptation.

2.3.1 Direct Medical and Non-medical Cost Estimation

Direct medical costs reflect and encapsulate all the resource consumption incurred for the care of patients within the healthcare system. Hence, they include items such as private physician visits, laboratory and imaging diagnostic examinations, equipment, medications, and hospitalizations.

To estimate the cost of private physician visits and diagnostic/laboratory tests from the payer perspective, the reimbursed unit cost of private physician visits and laboratory and diagnostic tests (spirometry, oximetry, complete blood count [CBC], allergy tests, blood gas) was multiplied with the number of visits or tests conducted during the past 12 months [18]. The unit costs from the payer perspective of these medical resources along with the cost of equipment (nebulizer) are presented in the Electronic Supplementary Material (Table S1). Patients were also asked to report the total OOP amount spent on these medical resources during the same period. The societal cost of these resources was calculated by summing the corresponding costs from the payer and the patient perspective.

To estimate patient-level medication costs, drugs used on a regular basis, such as inhaled corticosteroids (ICS), long-acting β_2 antagonists (LABA), short-acting β_2 antagonists (SABA), and leukotriene receptor antagonists (Leukotriene Receptor Antagonists (LTRA)), as indicated by the responders, and the corresponding mean daily dose, as obtained from local clinical experts, were combined with the corresponding daily reimbursed

drug cost. The annual drug cost was calculated taking into account an adherence level of 100%. The daily reimbursed drug cost was calculated on the grounds of the reimbursed drug price per pack, as published in the price list bulletin of April 2017 issued by the Greek Ministry of Health [20]. The OOP cost for medication and long-term oxygen therapy was obtained from patients by asking them to report the total amount of money they had paid over the previous 12 months for drugs. Similarly, the societal perspective was the sum of the payer and patient perspective.

To estimate the reimbursed hospitalization cost, the Diagnosis Related Group (DRG) A29 M (Bronchitis and asthma with comorbidities and/or complications) [19] was used as it corresponds to the median length of stay (LOS) resulting from the participants' responses. The hospitalization cost for Bronchitis and asthma with comorbidities and/or complications is €792 with a LOS equal to 4 days [19]. The choice of this DRG was also validated by the experts. However, since the DRG tariffs do not include operational costs of hospitals or staff salaries, the reimbursed costs were assumed to increase by 50% in order to estimate the unit cost of hospitalization from a societal perspective [21, 22]. The cost of visits to the emergency department was set to zero, given that the associated resource use was not assessed [18].

Finally, we estimated the total annual direct medical cost from the patient, payer, and societal perspective by summing the corresponding cost estimations for all types of resources (physician visits, laboratory and diagnostic tests, equipment, medication, and hospitalizations).

Non-medical resource use comprised transportation and home care. Since these resources are not reimbursed by the payer in Greece, their annual direct non-medical cost per patient from the societal perspective is equal to that from the patient perspective (OOP cost).

2.3.2 Indirect Cost

The indirect cost consists of absenteeism and presenteeism costs. Participants were asked to report if they were currently employed and, if the answer was affirmative, they were further asked to report if their employment was full-time or part-time. The absenteeism cost was conservatively estimated by multiplying the total number of workdays lost the previous 12 months, both by patients and caregivers, as reported by the participants, with the mean daily earnings. Mean daily earnings were calculated as the estimated gross domestic product (GDP) per capita in 2017 (€16,811) [23] divided by the number of working days of that year (260.25) and was equal to €65 (see also Table S1, Electronic Supplementary Material). The presenteeism cost was estimated by multiplying the total number of workdays with reduced productivity with the percentage of reduction, both

as reported by the participants, and the mean daily earnings. The percentage reduction was calculated using participants' answer at the question: "How much has your average productivity during these days been affected?" with 1–9 indicating 10–90% reduction [24].

Finally, the total annual cost from the societal perspective was the sum of the direct medical and non-medical cost from the societal perspective and the indirect cost.

2.4 Calculation of the Economic Burden of the Disease

To estimate the total economic burden of lifetime asthma, the annual cost per patient as calculated in the present study was multiplied by the total number of patients with lifetime asthma in Greece. The total number of patients with lifetime asthma was obtained by multiplying the lifetime prevalence of asthma, 9% (95% confidence interval [CI] 8–10) [5], with the total adult population in Greece, based on the 2011 census [25]. The total economic burden of asthmatic patients with active symptoms during the past 12 months was also calculated, based on the percentage of patients with active symptoms during the past 12 months in our study. To control for uncertainty, the upper and lower boundaries of the CIs of the total cost were multiplied with the number of patients with lifetime asthma or active symptoms during the past 12 months, as obtained after applying the upper and lower boundaries of the prevalence to the total adult population of Greece. The results represented the minimum and maximum total economic burden.

2.5 Statistical Analysis

Categorical data were summarized as absolute (n) and relative frequencies (%), and continuous data, except for the cost, were summarized as median (interquartile range [IQR]) or mean $\pm$ standard deviation, when appropriate. Cost data were truncated at zero as they do not follow normal distribution. Therefore, they are presented as the mean and 95% CI using the 95% percentile bootstrap CI (i.e., 2.5% and 97.5% quantiles of the bootstrap distribution) [26], as obtained from 5000 non-parametric bootstrapped resamples.

The Chi-squared test without correction of continuity was used to evaluate the associations between categorical variables. The Student's t test or Mann–Whitney test was used to assess the association between a continuous variable and a binary variable (i.e., WC vs. NWC asthma), when appropriate. The significance level was set to $\alpha = 0.05$. Statistical analysis was performed using STATA[®] (version 13.0, STATA Corp, College Station, TX, USA) and IBM SPSS[®] Statistics software (version 20.0, IBM Corp., Armonk, NY, USA).

A generalized linear model (GLM) with gamma family and log link, as supported by the Box–Cox test and modified Park test, was applied to determine factors associated with the total annual cost per patient and lifetime asthma from the societal perspective [27]. Of note, the zero costs were replaced with the value of 0.1. Baseline demographic, lifestyle, anthropometric, and clinical characteristics of patients were considered as potential independent factors. Simple models were used to identify subjects' characteristics associated with the total annual cost from the societal perspective at a univariate level. Thereinafter, the factors identified to be significantly related to the total cost were entered in a multiple GLM to identify those independently associated with the total societal cost. The results are presented as β -coefficients and 95% CIs.

3 Results

3.1 Baseline Characteristics

The baseline characteristics of our sample are presented in Table 1. The majority of patients had WC asthma with a mean ACT score of 20.34, whereas acute exacerbations over the past 12 months were detected in slightly less than half of the participants. Moreover, of the three smoking status categories (Table 1), non-smokers were the most frequently reported (42%). About 24% of patients reported that they were free of co-morbidities, with hypertension being the most frequent co-morbidity (29%). Lastly, 78% of the participants had active symptoms of asthma during the past 12 months.

3.2 Resource Utilization in the Overall Sample and in Well-Controlled (WC) or Not Well-Controlled (NWC) Asthma

Table 2 summarizes the annual medical resource utilization as reported by the participants. Overall, CBC tests and physicians' consultations were the most frequently used medical resources during the past year, followed by spirometry. Only 6% of participants were hospitalized at least once during the previous year with a mean LOS of hospitalization of 4 days. Regarding medication, the three most commonly used drug classes were ICS/LABA (57%), oral corticosteroids (33%), and antibiotics (31%).

Overall, the use of medical resources was significantly higher in subjects with NWC asthma than in those with WC asthma ($p < 0.001$), especially concerning treatment medication, whereas the mean number of hospitalizations did not differ significantly between the two subject groups.

Table 1 Baseline characteristics of patients with lifetime asthma in Greece ($n = 353$)

Characteristics	<i>n</i>	%
Sex		
Male	127	36
Female	226	64
Age (years)		
18–29	48	14
30–39	58	16
40–49	62	18
50–59	59	17
60–69	54	15
70 +	72	20
Obesity status		
Normal weight (BMI < 25 kg/m ²)	120	35
Overweight (BMI 25–30 kg/m ²)	156	44
Obese (BMI > 30 kg/m ²)	77	21
Geographic area		
Urban area (> 10,000 residents)	247	70
Semi-urban area (2,000–10,000 residents)	45	13
Rural area (< 2,000 residents)	61	17
Co-morbidities		
Any co-morbidity	268	76
No co-morbidity	85	24
Patients with active symptoms in the previous 12 months		
No	78	22
Yes	275	78
Years passed since asthma diagnosis		
≤ 5.0	54	15
5.1–10.0	71	20
> 10	227	64
Acute exacerbations		
No	188	53
Yes	165	47
Smoking status		
Current smoker	110	31
Ex-smoker	94	27
Non-smoker	149	42
Passive smoker		
No	217	61
Yes	136	39

BMI body mass index

3.3 Total Cost of Lifetime Asthma Per Patient

The mean (95% CI) annual total cost per patient with lifetime asthma from the societal perspective was €895 (696–1,105), with the direct medical cost accounting for almost 90% of the total cost, while only 6% of the total cost was attributed to the direct non-medical cost and just 4% to the indirect

Table 2 Annual resource utilization per patient with asthma and by asthma control during the past 12 months in Greece ($n=353$)

Resource utilization	Total sample	Not controlled	Controlled	<i>p</i> value
Private physician visits				
Mean (SD)	1.3 (2.8)	1.8 (3.1)	0.9 (1.7)	0.008
% of patients with at least one visit	46	54	41	0.023
Visits to hospital/health center outpatient clinic				
Mean (SD)	0.6 (1.6)	1.01 (2.4)	0.4 (0.8)	0.001
% of patients with at least one visit	28	35.54	20.64	0.003
Visits to hospital emergency department				
Mean (SD)	0.2 (0.7)	0.4 (0.7)	0.1 (0.6)	<0.001
% of patients with at least one visit	13	25.8	5.1	<0.001
Hospitalizations				
Number of hospitalization [mean (SD)]	1.6 (1.4)	1.5 (1.3)	1.8 (1.6)	0.435
% of patients with at least one hospitalization	6	12	3	0.001
Length of hospitalization [mean (SD)]	4.2 (2.1)	3.5 (1.8)	6.2 (1.5)	0.006
Equipment				
% of patients using nebulizer ^a	16	32	8	<0.001
Medication				
Antibiotics (%)	31	45	23	<0.001
Oral corticosteroids (%)	33	52	23	<0.001
ICS/LABA (%)	57	62	54	0.176
SABA (%)	25	22	26	0.440
Leuko-RA (%)	16	24	11	0.003
Laboratory/diagnostic tests				
Peak flow meter [mean (SD)]	0.5 (2.9)	1.02 (4.8)	0.2 (0.7)	<0.001
% of patients with at least one peak flow meter	22	39	13	<0.001
Spirometry [mean (SD)]	0.5 (0.9)	0.8 (1.3)	0.3 (0.6)	<0.001
% of patients with at least one spirometry	39	56	30	<0.001

ICS/LABA inhaled corticosteroids/long-acting β_2 antagonists, *Leuko-RA* leukotriene receptor antagonists, *SABA* short-acting β_2 antagonists, *SD* standard deviation

^aOccasional or systematic use of nebulizer

Values in bold indicate the statistically significant results

cost. About half of the total annual direct medical cost was driven by the medication cost, followed by the cost of laboratory tests (Table 3). The mean (95% CI) annual total cost per patient from the payer perspective (EOPYY) reached €673 (496–861), whereas the respective amount paid by the patients reached €151 (119–188) (Table 3).

3.4 Total Cost of Asthma Per Patient with Active Symptoms

The total annual cost per patient from the societal, payer, and OOP perspective was statistically significantly higher when symptoms of asthma were present than in their counterparts ($p < 0.001$). In particular, the total mean (95% CI) annual cost per patient with active symptoms of asthma was estimated to be €1031 (818–1317) from the societal perspective, €763 (591–1006) from the payer perspective, and €178 (142–226) from the patient perspective (Table S2, Electronic Supplementary Material). In addition, as shown in Table S2, the mean (95% CI) cost per patient with active symptoms is even

higher in case of NWC asthma, where the cost reached €1331 (1026–1853) from the societal perspective. The respective cost in WC asthma was €737 per patient ($p < 0.001$).

3.5 Annual Cost Per Patient with WC and NWC Asthma

The total annual cost, as well as the direct medical cost from the payer, patient, and societal perspective of patients with NWC asthma, was found to be almost double that of patients with WC asthma ($p \leq 0.001$) (Table 3). The breakdown of the total annual cost from the societal perspective for both groups of patients is presented in Fig. 1. It should be noted that medication use, which accounts for the largest part of the total annual cost in both groups, did not vary a lot between the two groups. However, the hospitalization and laboratory costs accounted for a much higher proportion of the total annual cost in patients with NWC asthma than in those with WC asthma (hospitalizations: 16% vs. 9%; laboratory costs: 37% vs. 26%).

Table 3 Annual total, direct and indirect cost per patient with asthma in Greece, for the overall sample and for patients with well-controlled and not well-controlled asthma (€; 2017 values)

Cost	Total sample [mean (95% CI ^a)]	NWC [mean (95% CI ^a)]	WC [mean (95% CI ^a)]	<i>p</i> value
Total cost societal perspective	895 (696–1105)	1285 (918–1699)	637 (439–863)	< 0.001
Total cost payer perspective (EOPYY)	673(497–861)	962 (648–1306)	478 (306–650)	< 0.001
Total cost OOP	151 (119–188)	195 (156–232)	119 (78–172)	< 0.001
Direct medical cost—societal perspective	855 (676–1085)	1215 (911–1619)	614 (437–838)	< 0.001
Private physician visits	44 (33–59)	52 (39–67)	30 (22–39)	0.001
Hospitalizations	111 (57–175)	207 (85–344)	59 (11–129)	0.001
Medication	389 (306–496)	541 (360–789)	264 (229–305)	< 0.001
Laboratory tests	267 (140–413)	336 (103–631)	235 (86–406)	< 0.001
Equipment	45 (33–59)	78 (61–103)	26 (15–49)	0.001
Direct non-medical cost—societal perspective	6 (2–11)	11 (5–22)	3(0.4–10)	0.014
Indirect cost	34 (21–49)	59 (32–98)	19 (7–34)	< 0.001
Absenteeism	22 (12–33)	30 (15–49)	15 (5–29)	0.023
Presenteeism	13 (6–22)	29 (11–55)	4 (1–8)	0.001
Direct medical cost—payer perspective (EOPYY)	673 (503–868)	962 (652–1354)	478 (322–670)	< 0.001
Direct non-medical cost—payer perspective (EOPYY)	0	0	0	
Direct medical cost—OOP	145 (117–181)	184 (150–227)	116 (82–173)	< 0.001
Direct non-medical cost—OOP	6 (2–11)	11 (5–22)	3(0.4–10)	0.014
Transportation	5 (1–9)	7 (1–17)	3 (0.3–9)	0.018
Homecare and support	1 (0.1–2.5)	3 (0.2–71)	0 (0–0)	0.007

CI confidence interval, EOPYY National Organization for the Provision of Health Services, NWC not well-controlled, OOP out of pocket, WC well-controlled

^aCI derived using the percentile bootstrap method

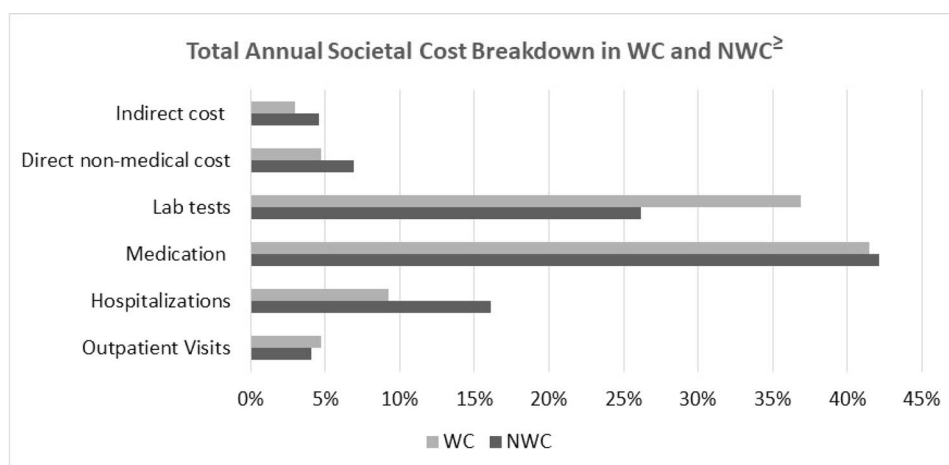
Values in bold indicate the statistically significant results

3.6 Annual Cost Per Patient With and Without Exacerbations During the Past 12 Months

Similarly, the total annual cost from the societal, payer, and patient perspective was statistically significantly higher in patients who experienced exacerbations during

the previous year than in patients not reporting any exacerbations (Table 4). In particular, the mean (95% CI) total annual cost was estimated at €1388 (1030–1775) and €462 (319–642) for patients with and without exacerbations, respectively (Table 4).

Fig. 1 Breakdown of the total annual cost from the societal perspective for both well-controlled and not well-controlled patients



WC: well controlled asthma, NWC: Not well controlled asthma

≥ The repartition of each cost parameter sums up to 100% in both groups (WC, NWC)

3.7 Factors Related to the Total Annual Societal Cost for the Management of Asthma

The simple GLM revealed that among the nine variables considered as independent factors, only patients' body mass index (BMI) status, depression, asthma control, and the experience of exacerbations during the past 12 months were found to be significantly associated with the total annual cost per patient with lifetime asthma from the societal perspective. Insertion of these factors in a multivariate GLM model revealed that all of them were significantly associated with the total cost per patient. More specifically, it was found that the total annual societal cost was statistically significantly higher by 80% among overweight ($p < 0.001$) and 100% among obese patients ($p = 0.003$) than in individuals with normal weight. Moreover, the annual societal cost was found to be three times higher among patients with depression ($p = 0.018$) and those who were experiencing exacerbations ($p < 0.001$) during the past 12 months than in their counterparts. On the other hand, the annual societal cost of patients with WC asthma was found to be almost 40% lower than in those with NWC asthma ($p = 0.014$) (Table 5). The annual societal cost (95% CI) from the multivariate analysis was estimated at €909 (671–1146).

3.8 National Economic Burden of Asthma

The resulting number (95% CI) of adults with lifetime asthma in Greece was 812,281 (726,590–887,260). Using the total

mean (95% CI) annual cost per patient from the societal perspective, i.e., €895 (696–1105) (see Table 3), the annual societal burden of asthma in Greece was estimated to be €727 million (506 million–980 million). The total (95% CI) annual economic burden for EOPPY was estimated to be €547 million (361 million–764 million). Taking into account only patients with active symptoms during the past 12 months, the economic burden was estimated to be €567 million (394 million–765 million) and €426 million (282 million–596 million) from the societal and payer perspective, respectively.

4 Discussion

To the best of our knowledge, this is the first study in Greece aiming to estimate the resource utilization and cost of asthma in the adult population using individual data, providing useful insights.

With respect to resource utilization, CBC tests and physician visits were the most frequently used medical resources in a 12-month timespan, followed by spirometry and oximetry tests. Regarding medication use, the drug class of ICS/LABA was most frequently used, followed by antibiotics. On the other hand, in the REcognise Asthma and LInk to Symptoms and Experience (REALISE) survey, conducted in 11 European countries, antibiotics were used by the vast majority of responders (62%) followed by corticosteroids (44%) [28]. Also, in our study, the proportion of patients having at

Table 4 Annual total, direct, and indirect cost per patient with asthma in Greece, with and without exacerbations during the past 12 months, from the payer, patient, and societal perspective (€; 2017 values)

Cost	Exacerbations during the past 12 months		<i>p</i> value
	No [mean (95% CI) ^a]	Yes [mean (95% CI) ^a]	
Total cost societal perspective	462 (319–643)	1,388 (1031–1775)	≤ 0.001
Total cost payer perspective (EOPYY)	347 (210–509)	1044 (736–1341)	≤ 0.001
Total cost OOP	94 (67–126)	215 (159–285)	≤ 0.001
Direct medical cost—societal perspective	441 (308–623)	1327 (962–1663)	≤ 0.001
Private physician visits	23 (18–30)	67 (45–102)	≤ 0.001
Hospitalizations	0	238 (122–371)	≤ 0.001
Medications	226 (188–268)	574 (398–804)	≤ 0.001
Laboratory tests	174 (51–337)	373 (154–620)	≤ 0.001
Equipment	18 (8–27)	75 (55–105)	≤ 0.001
Direct non-medical cost—societal perspective	2 (0–2.6)	17 (4–22)	≤ 0.001
Indirect cost	20 (6–39)	50 (27–77)	0.007
Absenteeism	10 (2–21)	35 (19–54)	< 0.005
Presenteeism	11 (2–23)	15 (6–28)	0.101
Direct medical cost—payer perspective (EOPYY)	347 (210–509)	1044 (736–1341)	≤ 0.001
Direct medical cost—OOP	93 (68–126)	203 (155–269)	≤ 0.001

CI confidence interval, EOPYY National Organization for the Provision of Health Services, OOP out of pocket

^aCI derived using the percentile bootstrap method

Values in bold indicate the statistically significant results

Table 5 Association between baseline socio-demographic and clinical characteristics and total annual cost of asthma per patient from societal perspective; results from generalized linear model

Characteristic	Univariate [β -coefficient (95% CI)]	Multivariate ^a [β -coefficient (95% CI)]
Sex		
Men	Reference	
Women	0.390 (− 0.117 to 0.897)	
Age (years)	0.012 (0.000 to 0.024)	0.004 (− 0.008 to 0.015)
Smoking status		
Current smokers	Reference	
Ex-smoker	0.002 (− 0.548 to 0.553)	
Non-smokers	− 0.381 (− 0.929 to 1.673)	
BMI (kg/m ²)		
Underweight/normal weight	Reference	Reference
Overweight	0.589 (0.085 to 1.094)	0.679 (0.282 to 1.075)
Obese	0.704 (0.151 to 1.257)	0.685 (0.202 to 1.168)
Depression		
No	Reference	Reference
Yes	1.069 (0.429 to 1.708)	0.785 (− 0.174 to 1.743)
Years passed since asthma diagnosis		
< 5	Reference	
5–10	0.685 (− 0.085 to 1.455)	
> 10	0.496 (− 0.114 to 1.106)	
Geographic area		
Urban	Reference	
Semi-urban/rural	− 0.029 (− 0.550 to 0.492)	
Asthma control		
NWC	Reference	Reference
WC	− 0.702 (− 1.177 to 0.228)	− 0.489 (− 0.888 to − 0.089)
Exacerbations		
No	Reference	Reference
Yes	1.099 (0.658 to 1.541)	1.004 (0.561 to 1.446)

BMI body mass index, CI confidence interval, NWC not well-controlled, WC well-controlled

^aAkaike information criterion: 15.06035, Bayesian information criterion: − 1281.923

Values in bold indicate the statistically significant results

least one ER visit or hospitalization was much lower than in other European countries (ER: 13% vs. 24%; hospitalizations: 6% vs. 12%) [28]. This difference may be explained by the high proportion of visits to general practitioners (GPs), as a result of which hospitalizations are avoided. Our percentage of hospitalizations (6%) was much closer to that reported in Sweden (7%); the lowest was reported in REALISE [28], with the highest being reported in Norway (22%) [29]. As expected, our study revealed that resource consumption was higher in patients with NWC asthma.

The total cost from the societal, payer, and patient perspective was assessed. The results demonstrated a substantial economic burden imposed by asthma on the healthcare system and society in Greece. Overall, the mean total annual cost per patient with lifetime asthma from the societal perspective was estimated at €895. The direct medical cost was the main cost component of the total cost of asthma (~90%),

consistent with the findings of other studies [30–34]. A recently conducted Greek study [7] based on a Delphi panel, estimated that the total annual cost of asthma per patient was €2282, with direct costs accounting for 65% of this and pharmaceutical cost being the key cost component, consistent with the findings of our study [7]. Even though similar cost items were considered in both studies and the same sources were used for the cost calculation, the great variation in the results may stem from the differences in study design. The study of Souliotis et al. [7] was based on the estimates of seven pulmonologists, whereas GPs were not included in the Delphi panel. Estimations of pulmonologists can be based on patients with increased medical resource use compared with patients who consult with GPs. On the other hand, our study is subject to recall bias and to self-reported information, which may lead to underestimation of costs.

Interestingly, in contrast to other studies [4, 7, 35] showing that indirect cost makes up most of the total cost, in our study it only accounted for 4% of the total cost. This difference can be attributed to the differences in the methods used to collect data or to estimate the cost, as well as to the differences in the study populations. For example, indirect costs were quite high in the pediatric asthmatic population [4, 36], a population that was not included in our study. Moreover, in our study the long recall period (1 year) might have led to underreporting of the number of workdays lost. More specifically, there was a big difference in our indirect cost estimation and that reported in another Greek study, possibly due to the difference in how workdays loss was assessed between the two studies. In the study of Souliotis et al. [7], the number of lost workdays due to asthma was derived from the sick leave prescribed by physicians (10.5 days), whereas in our study it was derived from the participants' reports (4.5 days).

Asthma costs closely correlated with NWC asthma and exacerbations in other European studies [7, 37, 38]. However, in Greece there were no previous population-based sampling studies assessing the relation of the management cost of asthma with control of asthma. Similarly to our findings, where the cost per patient with NWC asthma was two times higher than that of patients with WC, the aforementioned European survey revealed that the mean total societal cost per patient ranged from €509 in patients with WC asthma to €2281 in patients with uncontrolled disease [35]. Regarding the cost of exacerbations, we found that patients reporting exacerbations had a three times higher cost than patients without exacerbations. Similar results were also found in an Italian study, where the cost of asthma was more than double (€2284) in patients with more than five exacerbations than that of patients with no exacerbations (€900) [37]. In addition, a study conducted in Switzerland showed that the relative proportions of cost categories, and especially that of medication cost, differed greatly between those with and without exacerbations (70% vs. 28%) [38], which was not the case in our study, since medication cost was already high (about 45%) in patients without exacerbations.

Comparing the total annual societal cost per patient with asthma with the corresponding costs incurred in other chronic diseases in Greece, it was found out that the mean societal annual cost for asthma patients is much lower than that imposed by diabetes [39], coronary artery disease, cerebrovascular disease, or peripheral artery disease [40].

There are several major limitations of the present study. First is the recall bias, as the 1-year recall period may be considered too long to recall medication or other resource use. Additionally, a timespan of 12 months can be considered too large for accurate reporting of presenteeism or absenteeism. However, the limited timespan of 7 days typically used in Work Productivity and Activity Impairment

(WPAI) Questionnaire would be inadequate to depict disease exposure and costs. Work loss in the past 7 days would not be an appropriate measure when considering chronic diseases such as asthma. In addition, asthma severity was not recorded, and hence was not incorporated in the analysis. Last but not least, our sample may not be representative of the patients with asthma since the sample was selected in order to be representative of the general population to address the primary objective of the study.

Regarding limitations of the cost calculations, both direct and indirect costs are expected to be underestimated, mainly due to the recall bias, resulting from the long 12-month timespan and the self-reporting of information. On the other hand, the assumption of a 100% adherence level may have led to an overestimation of the drug cost. Finally, as there were no accurate estimations of the hospitalization cost from the societal perspective, an increase of 50% was applied to the DRG tariff [21]. However, double counting is not likely to occur, since resource use during hospitalization is not reimbursed in any other way. It is important to note that the estimated DRGs in Greece tend to be underestimated compared with the actual costs (personal communication with an expert in health economics in Greece).

5 Conclusion

Despite the limitations that may occur due to the sampling procedure of an epidemiologic study, the findings of the present study indicate that asthma results in a high economic burden of asthma on the Greek society. In particular, it was found that the total annual burden of asthma in Greece reaches €772 million, with the direct medical cost accounting for 90% of the total cost. Moreover, the present study provides unique data regarding the great impact of asthma on patients if asthma is NWC. Greater investment in interventions aimed at achieving asthma control in particular phenotypes, preventing acute exacerbations, and managing chronic symptoms may reduce the overall burden of asthma in Greece.

Author Contributions K.V. conducted part of the data analysis and wrote the manuscript. G.K. designed the study, conducted part of the analysis, interpreted the results, and wrote part of the manuscript. She also reviewed the manuscript. N.M., P.B., and S.L. contributed in the study design, questionnaire development, results interpretation, and manuscript writing.

Compliance with Ethical Standards

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Conflict of Interest The authors, Katerina Vellopoulou, Petros Bakakos, Stelios Loukides, Nikos Maniadakis, and Georgia Kourlaba declare that they have no conflicts of interest related to the content of this study.

Data Availability Statement The dataset, along with the software code, will be provided upon request.

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Electronic Supplementary material: Appendix I

Journal: Applied Health Economics and Health Policy

Title: The economic burden of asthma in Greece: a cross-sectional study

Authors: Katerina Vellopoulou, Petros Bakakos, Stelios Loukides, Nikos Maniadas, Georgia Kourlaba

Corresponding Author

Dr. Kourlaba Georgia

EVROSTON LP

Chatzigianni Mexi 5, 115 28, Athens, Greece

Tel: +30 216 900 1701 Fax: +30 216 900 1702

e-mail: g.kourlaba@evroston.com

Symptoms & Effects (Clinical and Financial) of Asthma

RESEARCH QUESTIONNAIRE – SEPTEMBER 2016

Good morning/good evening. My name is and I work in MRB, which is an independent research company and is currently conducting a survey regarding the health issues.

1. Initially, I would like to ask if there are any people older than 18 years old in your household?

Yes ☐ No ☐ I do not reply ☐

If «NO» or «NOT REPLY» ->SAY THANK YOU AND HANG UP

If «YES» ->ASK TO TALK TO THE PERSON WITH THE LATEST BIRTHDAY (last-birthday method) and read the information statement.

If this person is not present or willing to talk ->SAY THANK YOU AND HANG UP

PLEASE READ: We would like to assure you that all the provided information will remain confidential, without the possibility of identification of specific responder. Our practices are legal and attuned with the principles and provisions of the Data Protection Authority, and each of your answers will be presented together with the replies of the other respondents. The duration of the overall survey will not exceed the **15 minutes**.

Considering all we have mentioned; would you like to participate in this survey?

Thank you in advance for your participation.

In case of patient's inability to be interviewed (e.g., old, etc)

Could we ask some questions to a person who is responsible for the patient's care?

- ☐ Yes (CONTINUE)
- ☐ No (Say "Thank you" and end the interview)

A. DEMOGRAPHICS	
A1. Gender of the patient	Male ☐ Female ☐
A2. Age of the patient (NOTE THE EXACT AGE HERE) _____	☐ 18 – 29 ☐ 30 – 39 ☐ 40 – 49 ☐ 50 – 59 ☐ 60 – 69 ☐ 70+
A3. In which from the following regions belongs the location of your household based on the distribution of population?	☐ Athens ☐ Thessaloniki ☐ URBAN AREA (OVER 10.000 RESIDENTS) ☐ SEMI- URBAN AREAS (2.000 – 10.000 RESIDENTS) ☐ RURAL AREA (UP TO 2.000 RESIDENTS)
A4. Weight	 (in Kg)
A5. Height	 (in m)
B. CLINICAL HISTORY	
B1. Have you been diagnosed or do you regularly use medication for Asthma;	Yes ☐ No ☐ Do not reply ☐
<i>IF the answer is “I DON’T REPLY”: SAY THANK YOU AND HANG UP (NOT COUNT IN THE DENOMINATOR FOR PREVALENCE)</i> <i>If the answer is “No”: SAY “THANK YOU” AND HANG UP (COUNT IN THE DENOMINATOR)</i> <i>If the answer is “Yes”: Move on to the rest of the questionnaire (COUNT IN CONTACTS)</i>	
B2a. Which year have you been diagnosed with Asthma?	
B2b. If she/he doesn’t remember the exact year of diagnosis, we ask how many years have passed since the date of the diagnosis.	☐ ≤ 1 year ☐ 1,1-5 years ☐ 5,1-10 years ☐ >10 years
B2c. During the past 12 months, did you have any asthma symptoms (e.g. coughing, wheezing, shortness of breath, and chest pressure)?	Yes ☐ No ☐
B3a. Have you been diagnosed or do you regularly use medication for the following diseases?	☐ COPD ☐ Hypertension ☐ Diabetes ☐ Myocardial Infarction ☐ Heart Failure ☐ Allergic Rhinitis

	☐ Rhinitis ☐ Cancer ☐ Rheumatoid Arthritis ☐ gastroesophageal reflux disease ☐ Depression ☐ Obesity ☐ Skin allergies or diseases
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C. SMOKING HABITS	
C1. In which of the following categories do you belong based on your smoking habits?	☐ Current smoker (presently smoking cigarettes/cigars/pipe at least once a day) ☐ Former smoker (not currently smoking, but had smoked at least 100 cigarettes in their lifetime and at some point smoked on a daily basis) ☐ Non-smoker (smoked fewer than 100 cigarettes in their lifetime or never smoked at all)
«Note: If the answer is “Current smoker, go to question C2 & then to question C4a. If the answer is “Former smoker” go to question C3 and then to question C4a.	
C2. How many cigarettes do you smoke on average every day?	 cigarettes/day
C3. How much time has passed since smoking cessation?	
C4. Do you live or/and work in a space with current smokers? (passive smoker)	Yes ☐ No ☐
C5. Do you live or/and work in a space with environmental smoke/dust or fumes exposures?	Yes ☐ No ☐

D. Control of Asthma (ACT)	
The following five questions aim to appraise to what extent your asthma is under control.	
D1. In the <u>past 4 weeks</u>, how much of the time did your asthma keep you from getting as much done at work, school or at home.	1. All of the time 2. Most of the time 3. Some of the time 4. A little of time 5. None of the time
D2. During the past 4 weeks, how often have you had shortness of breath?	1. More than once a day 2. Once a day 3. 3-6 times a week 4. Once or twice a week 5. Not at all
D3. During the <u>past 4 weeks</u>, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at	1. 4 or more nights a week 2. 2 or 3 nights a week 3. Once a week

night or earlier than usual in the morning?	4. Once or twice 5. Not at all
D4. During the <u>past 4 weeks</u>, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?	1. 3 or more times per day 2. 1 or 2 times per day 3. 2 or 3 times per week 4. Once a week 5. Not at all
D5. How would you rate your asthma control during the <u>past 4 weeks</u>?	1. Not controlled at all 2. Poorly controlled 3. Somewhat controlled 4. Well controlled 5. Completely controlled

E.IMPACT ON THE DAILY LIFE ACTIVITIES

The following questions concern the impact of asthma on your daily activities the past 4 weeks. Οι επόμενες ερωτήσεις ρωτούν πως το άσθμα σας έχει επηρεάσει τις καθημερινές δραστηριότητες κατά τις 4 τελευταίες εβδομάδες:

E3. During the past 4 weeks, how often did asthma interfere with your social life?	Not at all ☐ A little ☐ Somewhat ☐ A great deal ☐
E5. During the past 4 weeks, how often were you restricted in the sports, hobbies, or other recreations you engaged in because of your asthma?	Not at all ☐ A little ☐ Somewhat ☐ A great deal ☐

TH. PSYCHOLOGICAL BURDEN

The following questions concern the extent to which asthma affects your psychological condition.

TH1. During the past 4 weeks, how often were you limited in going certain places because you were afraid of getting an asthma attack and not being able to get help?	Not at all ☐ A little ☐ Somewhat ☐ A great deal ☐
TH2. During the past 4 weeks, how often were you worried about your present or future life because of asthma?	Not at all ☐ A little ☐ Somewhat ☐ A great deal ☐
TH3. During the past 4 weeks, how often did you worry about asthma shortening your life?	Not at all ☐ A little ☐ Somewhat ☐ A great deal ☐
TH4. During the past 4 weeks, how often did you feel dependent on your asthma sprays?	Not at all ☐ A little ☐ Somewhat ☐ A great deal ☐

I. TREATMENT ADHERENCE

The following question is about adherence to your asthma medication.

I1. Which of the following statements best describes how often you take your asthma	☐ I take it everyday
--	---

medication?

- ☐ I take it sometimes
- ☐ I used to, but I do not take it anymore
- ☐ I take it only on symptoms
- ☐ I have never taken

J. EVALUATION OF YOUR HEALTH STATUS (EQ-5D)

Which one from the following statements describes better your health status?

J1. Mobility	☐ I have no problems in walking about ☐ I have some problems in walking about ☐ I am confined to bed
J2. Self-Care	☐ I have no problems with self-care ☐ I have some problems washing or dressing myself ☐ I am unable to wash or dress myself
J3. Usual Activities (<i>e.g. work, study, housework, family or leisure activities</i>)	☐ I have no problems with performing my usual activities ☐ I have some problems with performing my usual activities ☐ I am unable to perform my usual activities
J4. Pain/Discomfort	☐ I have no pain or discomfort ☐ I have moderate pain or discomfort ☐ I have extreme pain or discomfort
J5. Anxiety/Depression	☐ I am not anxious or depressed ☐ I am moderately anxious or depressed ☐ I am extremely anxious or depressed

L. EVALUATION OF WORKING ABILITY & EXPENDITURE

The following questions aim to explore the impact of your health status on the ability to work and on your expenses:

L1. Are you currently employed (working for pay)?

Yes ☐ No ☐

L2. Define whether you were working full or part time, the past 6 months.

☐ Fulltime

☐ Part time

«**NOTE:** If the answer is NO, go to the question ... »

During the last 12 months:

L3a. Did you miss any days of work due to asthma?

Yes ☐ No ☐

L3b. If Yes, how many days?

..... days

L4a Did your health problem affect your ability to produce work output in a high-quality or timely manner? (You were not attentive; you didn't accomplish all your tasks, etc.)

Yes ☐ No ☐

L4b. If Yes, how many days, did you have reduced productivity;

..... days

L4c. How much has your average productivity during these days been affected?

(Select a number from 0 to 9, 0: it was not affected. 9: it was affected)

0	1	2	3	4	5	6	7	8	9
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L5a. Did a family member had to miss any days of work because of your asthma?

Yes ☐ No ☐

L5b. If Yes, how many days?

..... days

L6a. If you are not currently working, please define if this is because of early retirement due to asthma

Yes ☐ No ☐

L6b. In case of early retirement due to asthma, please mention your age of retirement.

..... years

M. EVALUATION OF OTHER EXPENSES (DIRECT NON- MEDICAL)

The following questions aim to estimate the amount of money you spent out-of-pocket for asthma.

M1a. Did you have to spend any money out-of-pocket during the past 12 months as copayment for your asthma medication?	Yes ☐ No ☐
M1b. If yes, how much money (approximately)?	€
M2b. Did you have to spend any money out-of-pocket, during the past 12 months, as copayment to laboratory/ diagnostic tests?	Yes ☐ No ☐
M2b. If yes, how much money (approximately)?	€
M3a. Did you have to spend any money out-of-pocket, during the past 12 months, for physician visits for your asthma?	Yes ☐ No ☐
M3b. If yes, how much money (approximately)?	€
M4a. Did you have to spend any money out of pocket, during the past 12 months for transport because of asthma?	Yes ☐ No ☐
M4b. If yes, how much money (approximately)?	€
M5a. Did you have to spend any money out of pocket, during the past 12 months, for home equipment relative to asthma?	Yes ☐ No ☐
M5b. If yes, how much money (approximately)?	€
M6a. Did you have to spend any money out-of-pocket for home assistance (from healthcare professional or other)?	Yes ☐ No ☐
M6b. If yes, how much money (approximately)?	€

N. HEALTHCARE RESOURCE UTILIZATION		
How many times during the past 12 months you had to (because of asthma):		
N1. Visit the doctor to his/her private office?		
N2. Visit a hospital/health center outpatient clinic?		
N3. Visit a hospital emergency department?		
During the past 12 months:		
N4a. Did you had to be hospitalized because of asthma?	Yes ☐ No ☐	
N4b. If yes, how many times?		
N4c. Length of stay per hospitalization?	 days	
N5. Are you, currently, using nebulizer?	Yes ☐ No ☐	
How many times during the past 12 months did you undergo any of the following Lab/Diagnostic tests?		
N6. Peak flow meter (plastic portable device in which you blow the air)		
N7. Spirometry		
N8. Oximetry		
N10. Blood test		
N11. Test of allergic reaction (skin prick or RAST test)		
N12. Blood gas		
N13. Did you take any antibiotics, during the past 12 months for any condition related asthma?	Yes ☐ No ☐	
N14. Did you take any oral steroids, during the past 12 months for your asthma?	Yes ☐ No ☐	
N15. Finally, could you mention which of the following medicines did you take during the past 12 months for asthma, and how many times per day? (eg: 2 x 2, 2 x 3 etc);		
SPONTANEOUS REPLIES		
		Daily Dose
SYMBICORT	1	
RELVAR	2	
XOLAIR	3	
FOSTER	4	
PULMOTON	5	

SINGULAIR	6	
ASMANEX	7	
SPYRIVA	8	
ROLENIUM	9	
SERETIDE	10	
Άλλο		

THANK YOU FOR YOUR PARTICIPATION

Electronic Supplementary material: Appendix II

Journal: Applied Health Economics and Health Policy

Title: The economic burden of asthma in Greece: a cross-sectional study

Authors: Katerina Vellopoulou, Petros Bakakos, Stelios Loukides, Nikos Maniadakis, Georgia Kourlaba

Corresponding Author

Dr. Kourlaba Georgia

EVROSTON LP

Chatzigianni Mexi 5, 115 28, Athens, Greece

Tel: +30 216 900 1701 Fax: +30 216 900 1702

e-mail: g.kourlaba@evroston.com

Table S1: Unit costs considered in the cost analysis from the payer perspective (€, 2017)

Table S1: Unit costs considered in the cost analysis from the payer perspective (€, 2017)

Resource use	Reimbursed unit cost (€)	Source
Laboratory and diagnostic tests		
Peak flow meter	0	[18]
Oximetry	7.5	[18]
Spirometry	3.5	[18]
CBC	1.7	[18]
Allergy tests	3.6	[18]
Blood gas	9.6	[18]
Outpatient visits		
Hospital outpatient department	0	[18]
Hospital accident and emergency department	0	Assumption
Private physician visits	10	[18], ISA
Equipment		
Nebulizer	250	[18]
Hospitalization		
DRG Tariff	792*	[19]
Productivity loss		
Mean daily earnings	65	Calculation ^{>}

CBC: Complete Blood Count, DRG: Diagnosis Related Group, ISA: Athens Medical Association

[>]Calculation: GDP per capita €16,811 [23] divided by 260.25 (annual working days in Greece)

*Bronchitis and asthma with comorbidities and/or complications (DRG code: A29M)

Table S2: Annual total, direct and indirect cost per patient with active symptoms of asthma in Greece

Table S2: Annual total, direct and indirect cost per patient with active symptoms of asthma in Greece, for the general population and for patients with well-controlled (WC) and not-well controlled (NWC) asthma (€, 2017)

	Total sample (n=275)[‡]	NWC	WC	p-value*
	Mean (95% CI[‡])	Mean (95% CI[‡])	Mean (95% CI[‡])	
Total cost Societal perspective	1,031 (818;1,317)	1,331 (1,026;1,853)	737 (502;1,125)	<0.001
Total cost Payer perspective (EOPYY)	763 (591;1,006)	994 (704;1,503)	532 (354;854)	<0.001
Total cost OOP	178 (142;226)	202 (166.6;253.8)	150 (105;236)	<0.001
Direct medical cost from societal perspective	981 (764; 1,233)	1,258 (920; 1,670)	707 (457; 1,015)	<0.001
Direct non-medical cost from societal perspective	7 (3; 14)	11 (5; 25)	5 (0.8; 16)	<0.001
Indirect cost	42 (27;66)	62 (39;114)	25 (11;59)	0.003
Direct medical cost payer perspective (EOPYY)	763 (539; 965)	995 (671; 1,393)	532 (342; 826)	<0.001
Direct medical OOP cost	171 (136; 212)	191 (153; 230)	145 (97; 218)	<0.001

CI: Confidence Interval, EOPYY: National Organization for the Provision of Health Services, OOP: out of pocket, WC: well-controlled, NWC: not-well controlled

[‡] Patients with active symptoms of asthma from the overall sample

[‡]CI has been derived by using the percentile bootstrap method

*Mann-Whitney test