

BURDEN OF CHILDHOOD ASTHMA IN PORTUGAL

MANUEL JOSÉ FERREIRA DE MAGALHÃES

TESE DE DOUTORAMENTO APRESENTADA
À FACULDADE DE MEDICINA DA UNIVERSIDADE DO PORTO EM
INVESTIGAÇÃO CLÍNICA E EM SERVIÇOS DE SAÚDE

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1. Ferreira-Magalhães M, Sá-Sousa A, Morais-Almeida M, Pité H, Azevedo LF, Azevedo I, Bugalho-Almeida A, Fonseca JA. **Asthma-like symptoms, diagnostic tests, and asthma medication use in children and adolescents: a population-based nationwide survey.** *J Asthma* 2016; 53:269-276.

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2. Ferreira-Magalhães M, Sá-Sousa A, Morais-Almeida M, Azevedo LF, Azevedo I, Pereira AM, Fonseca JA. **High prevalence of hospitalisation for asthma in a population-based paediatric sample.** *Arch Dis Child* 2015; 100:507–508.

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3. Ferreira-Magalhães M, Pereira AM, Sá-Sousa A, Morais-Almeida M, Azevedo I, Azevedo LF, Fonseca JA. **Asthma control in children is associated with nasal symptoms, obesity and health insurance: a nationwide survey.** *Pediatr Allergy Immunol* 2015; 26(5):466-473.

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No âmbito deste projeto de doutoramento:

- participei na análise dos dados pediátricos do Estudo INAsma;
- participei na definição dos objetivos do projeto CASCA e na sua concretização através de apoio em todas as fases do trabalho de campo;
- na definição de hipóteses e análise estatística dos dados de todos os artigos;
- fui responsável pela redação da versão inicial de todos os artigos incluídos nesta dissertação.

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Abreviaturas

ACSS – Portuguese Health Services Central Administration
ADSE - Instituto de Proteção e Assistência na Doença
aOR – adjusted odds ratio
BMI - body mass index
CASCAS – Cost of childhood asthma in Portugal
DALY – disability-adjusted life years
ETS – environmental tobacco smoke
FeNO – exhaled nitric oxide
GARD – Global Alliance against Chronic Respiratory Diseases
GBD – Global Burden of Disease Study
GINA – Global Initiative for Asthma
HRQoL – health-related quality of life
ICS – inhaled steroids
INE – Instituto Nacional de Estatística
ISAAC - International Study of Asthma and Allergies in Childhood
JCR – Journal Citation Reports
LABA – long acting β_2 -agonists
LTRA – leukotriene receptor antagonists
NCA – not-controlled asthma
OR – odds ratio
PFT – pulmonary function tests
QoL – quality of life
SABA – short acting β_2 -agonists
SD – standard deviation
WCA – well-controlled asthma
WHO – World Health Organisation
WoS – Web of Science
95%CI – 95% confidence interval

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ABSTRACT

Background and aims

Asthma is one of the most common chronic diseases in childhood. However, there is a paucity of data on its burden, especially on healthcare services use, level of asthma control and associated costs. Population-based studies and comprehensive analysis are important to assess the whole spectrum of the childhood asthma burden.

The main aim of this research project was to study the burden of asthma in Portuguese children. In order to capture the whole burden of disease, five specific aims were defined: 1) estimate the prevalence of childhood asthma and asthma-like symptoms; 2) assess the proportion of diagnostic tests and medication use in asthma; 3) estimate the proportion of asthma-related healthcare services use; 4) analyse the proportion of controlled asthma and its determinants; 5) determine the cost of illness of asthma and the cost variations with the level of asthma control.

Methods

Data from two primary studies were collected and analysed.

Study 1: the 'Portuguese National Asthma Survey' (INAsma), a nationwide, cross-sectional, population-based telephone survey developed in 2010; pediatric-specific data from first and second phases of INAsma study were analysed. From the 6,003 interviews of Portuguese of all ages, 716 children (0- to 17-years old) were included in the first phase of INAsma, and 98 in the second phase.

Study 2: the 'Asthma in school-aged children: the Guimarães study' (CED2013), a cross-sectional, school-based survey conducted in 2013, used to empower the results of the aim 5) of this research project. From the 2,550 responders between 5 and 12 years old, 110 were included in the cost-of-illness study.

'Lifetime asthma' was defined as a positive answer to "Have you ever had asthma?". 'Current asthma' was defined as 'lifetime asthma' and (1) wheezing, (2) waking with breathlessness, or (3) asthma attack in the previous 12 months, and/or (4) taking asthma medication at the time of the interview. Lifetime hospitalisation was defined as a positive answer to "Have you ever been hospitalised for asthma (inpatient admission >24 hours)?"

only children aged 6- to 17-years old were analysed for lifetime hospitalisations. Asthma control definition was based on GINA criteria, grouping partially controlled and uncontrolled asthma as 'not controlled asthma' (NCA). We used multivariate logistic regression to study factors associated with NCA and with unscheduled medical visits for asthma.

The Cost of Childhood Asthma in Portugal (CASCA Project) was a nationwide, population- and prevalence-based, cost-of-illness study with a societal perspective. Participants in this cost-of-illness study were derived from the INAsma study and CED2013 study. Additional secondary data from several national databases were compiled to inform item values (in euros). Direct costs (healthcare services, diagnostic tests, medication and medical devices) were measured using a bottom-up approach (person-based) and indirect costs (absenteeism, transportation and subsidies) were quantified using the human capital method.

Results

1. Prevalence of childhood asthma and asthma-like symptoms

The prevalence of asthma-like symptoms was 39.4% [95% confidence interval (95%CI), 35.7–43.3]. The most common symptoms were waking with cough (30.9%) and wheezing (19.1%). The prevalence of lifetime asthma was 11.2 (95%CI, 9.1-13.7), and of current asthma was 8.4% (95%CI, 6.6–10.7).

2. Diagnostic tests and medication use in childhood asthma

Among children with current asthma, 79.9% and 52.9% reported prior allergy testing and pulmonary function testing (PFT), respectively. Inhaled medication use in the previous 12 months was reported by 67.6% (reliever inhalers, 40.1%; controller inhalers, 41.5%). Those who only used inhaled reliever medications experienced more asthma attacks [odds ratio (OR), 2.69]. Significantly fewer children with current asthma living in rural areas than those living in urban areas had undergone PFT or used inhaled medication (OR: 0.06 for PFT, 0.20 for medication).

3. Healthcare services use in childhood asthma

In the previous year, 90% (95%CI 84-96%) of children with current asthma had healthcare visits because of asthma: 86% (95%CI 79-93%) had scheduled medical visits, 39% (95%CI 29-

48%) had emergency room visits and 25% (95%CI 16-33%) had at least one unscheduled medical visit to a doctor. The risk of unscheduled medical visits was higher in children with nasal symptoms (aOR 3.63) and in those without health insurance (aOR 2.79), and lower in adolescents (aOR 0.19).

The prevalence of lifetime hospitalisations for asthma in all Portuguese children was 3.9% (95%CI, 2.6–5.7). In children with lifetime asthma, this prevalence was 29.7% (95%CI, 23.6–36.7), and in those with current asthma was 36.5 (95%CI, 28.8-44.9). The presence of any asthma-like symptom in the previous 12 months increased the proportion of lifetime hospitalisations (OR 1.85; 95%CI, 1.16-2.95). Female children had more hospitalisations than males (OR 1.97; 95%CI, 1.22-3.18).

4. Asthma control in children

About half of the children had NCA (49%, 95%CI 39-59%). In the multivariate model, risk factors for NCA were: substantial nasal symptoms (aOR 6.80), overweight/obesity (aOR 3.44) and not having health insurance (aOR 3.78). All the children with NCA had nasal symptoms, and the lack of asthma control was also associated with the increasing number of nasal symptoms ($p < 0.001$).

5. Cost of childhood asthma

The mean annualised costs per child was €929.35 (95%CI, 809.65–1,061.11) for total costs, €698.65 (95%CI, 600.88–798.27) for direct costs, and €230.70 (95%CI, 197.36–263.81) for indirect costs. The extrapolations for the Portuguese children amount to €161,410,007.61 (95%CI, 140,620,769.55–184,293,968.55) for the total costs. Direct costs represent 75.2% and indirect costs 24.8% of the total costs. The costliest domain was the healthcare service use (51.1% of total costs), specifically the scheduled medical visits (20.7% of total costs) and those related to acute asthma care (30% of total costs): emergency department visits (11.7% of total costs), hospitalisations (10.8% of total costs) and non-scheduled medical visits (7.9% of total costs). Children with partly controlled asthma and uncontrolled asthma had higher mean costs per year (adjusted exponential model coefficients: 1.46 [95%CI, 1.12-1.90] and 2.25 [95%CI, 1.56-3.24], respectively).

Conclusions

The results of these studies allowed for a comprehensive estimation of the burden of childhood asthma in Portugal.

Current asthma affects 8.4% (173,681) of Portuguese children. Only half of children with current asthma had ever undergone PFT and even less use controller inhalers. Those who only used reliever inhalers reported more asthma attacks. The results obtained may indicate substandard asthma care, mainly in rural areas. Poor control was observed in half of the Portuguese children with asthma. Nasal symptoms and obesity were found to be important determinants of asthma control and children without health insurance (private or state owned) are at greater risk of poor asthma outcomes; this association was not previously reported in a European country. Also, for the first time, it was described the proportion of asthmatic children hospitalised because of asthma, at least once in their life: more than one third of children with current asthma were hospitalised during their childhood.

The high clinical and healthcare burden of childhood asthma in Portugal is reflected in its costs. The childhood asthma in Portugal costs more than 161 million euros per year, more than 900 € per child with current asthma. Direct costs were ¾ of total costs, mainly related to related to acute asthma care (non-scheduled visits, emergency and hospitalisations). The most important determinants for higher costs were the asthma attacks in the previous 12 months (1.6-fold) and having uncontrolled asthma (2.3-fold). A better asthma control, and a reduction in the acute use of healthcare services, should be the major target for potential reduction of the clinical and economic burden of this disease.

RESUMO

Introdução e objetivos

A asma é uma das doenças crónicas mais comuns em idade pediátrica. No entanto, o conhecimento sobre seu impacto, especialmente no que diz respeito ao uso de serviços de saúde, ao nível de controlo da asma e aos custos associados é escasso. São necessários estudos de base populacional e abrangentes para avaliar todo o espectro do impacto da asma em idade pediátrica.

O principal objetivo deste projeto de investigação foi estudar o impacto da asma em idade pediátrica, em Portugal. Para avaliar o impacto global desta doença foram delineados cinco objetivos específicos: 1) estimar a prevalência de asma e sintomas relacionados; 2) avaliar a proporção de testes de diagnóstico e medicação utilizados na asma; 3) estimar a proporção de utilização de serviços de saúde associados à asma; 4) analisar a proporção de asma controlada e seus determinantes; 5) determinar o custo da doença na asma e as variações dos custos com o nível de controlo.

Métodos

Foram recolhidos e analisados os dados de dois estudos.

Estudo 1: "Inquérito Nacional sobre Asma" (INAsma), um estudo transversal de base populacional nacional desenvolvido em 2010, através da aplicação de entrevista telefónica assistida por computador; foram analisados os dados pediátricos da primeira e segunda fase do estudo INAsma. Das 6.003 entrevistas realizadas a Portugueses de todas as idades, foram incluídas 716 crianças (dos 0 aos 17 anos) na primeira fase e 98 crianças na segunda fase.

Estudo 2: "Asma em crianças em idade escolar; estudo Vimaranesense" (CED2013), um estudo transversal realizado nas escolas básicas do 1º ciclo de Guimarães, em 2013, utilizado para o objetivo 5). Dos 2.550 participantes entre os 5 e 12 anos de idade, foram incluídas 110 crianças para o estudo do custo de doença.

A 'asma ao longo da vida' foi definida como uma resposta positiva a "Alguma vez teve asma?". A 'asma atual' foi definida como 'asma ao longo da vida' e (1) sibilância/pieira, (2) acordar com falta de ar, ou (3) ataque de asma nos 12 meses anteriores, e/ou (4) estar sob medicação para a asma no momento da entrevista. A hospitalização ao longo da vida foi definida como uma resposta positiva à pergunta "Alguma vez já foi hospitalizado por asma (internamento > 24 horas)?" . Foram analisados dados de hospitalizações ao longo da vida entre as idades de 6 a 17 anos. A definição de controlo da asma foi baseada nos critérios do GINA, agrupando a asma parcialmente controlada e mal controlada como "asma não controlada" (NCA). Para estudar os fatores associados à NCA e a visitas médicas não programadas por asma foi efetuado um modelo de regressão logística multivariada.

O Projeto Custo da Asma na Criança em Portugal (Projeto CASCA) foi um estudo de custo de doença a nível nacional, de base populacional, baseado na prevalência da doença e na perspetiva da sociedade. Os participantes neste estudo de custo de doença foram obtidos a partir do estudo INAsma e estudo CED2013. Dados de bases nacionais foram utilizadas para recolha de valores monetários (em euros) dos diferentes domínios analisados. Os custos diretos (serviços de saúde, testes de diagnóstico, medicamentos e dispositivos médicos) foram medidos através de uma abordagem *bottom-up* (baseado no indivíduo) e os custos indiretos (absentismo, transporte e subsídios) foram quantificados utilizando o método de capital humano.

Resultados

1. Prevalência da asma pediátrica e sintomas relacionados com a asma

A prevalência de sintomas associados à asma foi de 39,4% [intervalo de confiança de 95% (95%CI), 35,7-43,3]. Os sintomas mais comuns foram acordar com tosse (30,9%) e sibilância (19,1%). A prevalência de asma ao longo da vida foi de 11,2 (95%CI, 9,1-13,7), e da asma atual foi de 8,4% (95%CI, 6,6-10,7).

2. Utilização de testes diagnóstico e medicação em crianças asmáticas

Entre as crianças com asma atual, 79,9% e 52,9% reportaram história prévia de realização de teste de alergia e testes de função pulmonar (PFT), respetivamente. O uso de medicação inalada nos 12 meses anteriores foi de 67,6% (inaladores de alívio rápido, 40,1%; inaladores de controlo, 41,5%). Os que só usaram inaladores de alívio rápido tiveram mais

crises de asma [razão de odds (OR), 2,69]. As crianças com asma atual que habitavam em áreas rurais realizaram um número significativamente menor de PFTs ou medicação inalada, quando comparados com as que viviam em áreas urbanas (OR: 0,06 para PFT, 0,20 de medicação).

3. Utilização de serviços de saúde por crianças asmáticas

Nos 12 meses anteriores, 90% (IC 95% 84-96%) das crianças com asma atual realizaram consultas médicas devido à sua asma: 86% (95%CI 79-93%) tiveram consultas agendadas, 39% (95%CI 29-48%) foram a um serviço de urgência e 25% (95%CI 16-33%) tiveram, pelo menos, uma consulta não programada. O risco de necessitarem de consultas médicas não programadas foi maior em crianças com sintomas nasais (aOR 3.63) e nas que não tinham seguro de saúde (aOR 2,79), tendo sido menor em adolescentes (aOR 0,19).

A prevalência de hospitalizações alguma vez na vida devido a asma foi de 3,9% (95%CI, 2,6-5,7). Em crianças com asma ao longo da vida essa prevalência foi de 29,7% (95%CI, 23,6-36,7), e naquelas com asma atual foi de 36,5 (95%CI, 28,8-44,9). A presença de qualquer sintoma associado à asma nos 12 meses anteriores aumentou a proporção de hospitalizações alguma vez na vida (OR 1,85; 95%CI, 1,16-2,95). Crianças do sexo feminino tiveram mais internamentos do que as do sexo masculino (OR 1,97; 95%CI, 1,22-3,18).

4. Controlo da asma em crianças

Cerca de metade das crianças tinham NCA (49%, 95%CI 39-59%). No modelo multivariado, os fatores de risco para NCA foram: sintomas nasais substanciais (aOR 6.80), sobrepeso/obesidade (aOR 3.44) e não ter seguro de saúde (aOR 3,78). Todas as crianças com NCA tinham pelo menos um sintoma nasal, e a falta de controlo da asma também foi associada com um maior número de sintomas nasais diferentes ($p < 0,001$).

5. Custo da asma em crianças

A média dos custos totais anuais por criança foi de 929,35€ (95%CI, 809,65–1.061,11), dos quais 698,65€ (95%CI, 600,88–798,27) para custos diretos e 230.70€ (95%CI, 197,36–263,81) para os custos indiretos. O valor absoluto para as crianças portuguesas foi de 161.410.007,61€ (95%CI, 140.620.769,55–184.293.968,55) para os custos totais. Os custos diretos representaram 75,2% e os custos indiretos 24,8% dos custos totais. O domínio com custos mais elevados foi a utilização de serviços de saúde (51,1% dos custos totais),

especificamente as consultas médicas agendadas (20,7% dos custos totais) e os cuidados agudos de asma (30% dos custos totais): idas ao serviço de urgência (11,7% dos custos totais), internamentos (10,8% dos custos totais) e consultas médicas não agendadas (7,9% dos custos totais). As crianças com asma não controlada e asma parcialmente controlada tiveram maiores custos médios por ano (coeficientes do modelo exponencial ajustado: 1,46 [95%CI, 1,12-1,90] e 2,25 e [95%CI, 1,56-3,24], respetivamente).

Conclusões

Os resultados destes estudos permitiram a obtenção de estimativas abrangentes sobre o impacto da asma em idade pediátrica, em Portugal.

A asma atual afeta 8,4% (173.681) das crianças portuguesas. Apenas metade das crianças com asma atual tinha realizado uma PFT alguma vez na vida e mais da metade não usava inaladores de controlo. As crianças que só usavam inaladores de alívio reportaram mais crises de asma. Os resultados obtidos podem indicar cuidados inadequados, principalmente em meios rurais. A falta de controlo foi observada em metade das crianças Portuguesas com asma. Os sintomas nasais e a obesidade foram identificados como determinantes importantes no controlo da asma. Além disso, as crianças sem seguro de saúde (privado ou estatal) estão em maior risco de pior controlo da asma; esta associação não tinha sido previamente documentada em nenhum país europeu. Também, pela primeira vez, foi descrita a proporção de crianças asmáticas que necessitaram de algum internamento por asma durante a sua vida: mais de um terço das crianças com asma atual foram internadas por asma durante a infância e adolescência.

O elevado impacto clínico e no sistema de saúde da asma pediátrica é refletido nos custos associados. A asma pediátrica em Portugal custa mais de 161 milhões de euros por ano, correspondendo a mais de 900€ por criança com asma atual. Os custos diretos representaram ¾ do total dos custos, especialmente relacionados com a utilização serviços de saúde em contexto de exacerbações. Os fatores mais importantes para a custos mais elevados são as crises de asma nos últimos 12 meses (1,6 vezes) e asma não controlada (2,3 vezes). Um melhor controlo da asma, assim como uma redução da utilização de serviços de saúde devido a exacerbações, devem ser os principais alvos para reduzir o impacto clínico e económico da asma pediátrica.

1.INTRODUCTION

1.1 From pathophysiology to clinical presentation

Asthma is a disease with variable presentation caused by a composite interaction of genetic and environmental factors, leading to multiple immunological and histological changes ¹. The crosstalk between impaired innate immunity and environmental susceptibility is responsible for the epithelial cell damage and adaptive immune response that causes inflammation ². The cellular and humoral changes lead to the classical bronchial hyper-reactivity with smooth muscle cells contraction, mucus overproduction, airway wall remodelling and airway narrowing ³. Impaired immunity in asthma is complex and may vary between patients, being typically classified as a T_H2 disorder with eosinophilic inflammation or a T_H17 disorder with neutrophilic inflammation. However, overlap between these immune disorders are often present, as well as changes in other immunologic pathways ¹. Environmental triggers are also major players in asthma pathophysiology; viruses, exercise, cold, irritant or allergen exposure and other well-known factors interact to promote disease development, maintenance, and exacerbation.

Because of this close interaction, several models of asthma definition and classification were successively proposed. These models tend to rely on biological markers or in functional parameters. As so, the definition of endotypes and phenotypes is a major advance in what concerns therapeutic targeting, diagnosis and severity classification ^{4,5}. However, these models have several pitfalls and uncertainty is still present when diagnosing asthma in clinical and epidemiological grounds.

The Global Initiative for Asthma (GINA) is a taskforce that intends to compile and disseminate scientific evidence on asthma, in order to create worldwide consensus in diagnosis and management of asthma ⁶. GINA defines asthma as “a heterogeneous disease, usually characterized by chronic airway inflammation; it is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation”.

Defining asthma during childhood presents additional challenges. Asthma is one of the most common chronic diseases in childhood, but the lack of suitable objective measures for younger ages, or the difficulty of having accurate symptom description throughout childhood, are major limitations when diagnosing asthma in clinical practice and in surveys. Asthma symptoms usually begin during childhood and evolve differently as children grow ⁷. Viral infections and atopy play a major role in developing wheezing disorders and possible asthma development in latter childhood and adulthood ^{8,9}.

In preschool children, asthma diagnosis must be based on symptomatic patterns ⁶. In older children, diagnosis should be based on symptomatic patterns and in objective variable expiratory airflow limitation. The most common signs/symptoms observed in asthma are:

- Wheeze - an expiratory continuous high-pitched sound with musical quality. Is the most distinctive asthma symptom and is generally present when the child is exposed to a trigger. However, since it is the result of intrathoracic airway narrowing and expiratory flow limitation, there are several mechanisms and reasons for a child to wheeze, from anatomical abnormalities of the airways to cystic fibrosis ¹⁰;
- Recurrent or persistent non-productive cough – a physiological mechanism that is usually present in children with asthma. It is caused by the release of pro-inflammatory mediators by airway mucosa, leading to activation of the afferent neurons of the cough reflex. Cough in asthma also typically appears during an episode of exacerbation, but it is commonly associated to an insidious and recurrent presentation, specifically, during exercise or at night ¹¹;
- Breathlessness and chest tightness – these are more specific symptoms that tend to appear mostly during moderate to severe exacerbations. These symptoms are the patient's perception of the difficulty in breathing due to narrowing of the airways and turbulent airflow;
- Activity limitation – a defence mechanism that is present when children with asthma have some degree of ventilation/oxygenation impairment. Younger children usually remain quiet and avoid playing; older children tend to avoid exercise and daily activities;
- Asthma attacks – rapid worsening episodes that usually present with a constellation of symptoms and that require prompt reliever medication.

1.2 Burden of asthma

The burden of asthma has long been an important field of research, aiming to improve asthma care management and outcomes. In 1993, Costa Pereira A. had already developed studies in the community aiming to understand the impact asthma, specifically, the prevalence of asthma and asthma-like symptoms, the use of healthcare services or the assessment of control of symptoms ¹². At the present, asthma is recognized as one of the most common noncommunicable chronic diseases in the world ¹³. The Global Burden of Disease (GBD) study is a worldwide comprehensive cross-sectional study that aggregates data on mortality and morbidity from more than 300 diseases and injuries in 188 countries ¹⁴. The Institute for Health Metrics and Evaluation publishes GBD results periodically since 1990, observing trends in prevalence or risk factors across ages and among populations, aiming to inform decision-makers towards an improvement in health outcomes. According to the estimates from the GBD study 2015, approximately 358 million people of all ages have asthma worldwide ¹⁵. This study also pointed asthma as one of the leading disabling conditions (ranked 23rd), being responsible for more than 26 million disability-adjusted life years (DALYs)/year and more than 397,000 deaths/year in the world ^{16,17}. In children, chronic respiratory diseases were the 4th noncommunicable group of diseases with the highest DALYs (>500 DALYs/100,000 inhabitants) and asthma was one of the diseases with the highest DALYs (ranked in the top 10 worldwide and in the top 5 in Portugal when compared with other single noncommunicable diseases) (Table 1) ¹⁸. Deaths because of asthma in children can be high in developing countries (Table 2), but in Portugal there were only 5 deaths between the year 2000 and 2010 ¹⁹.

Table 1 Disability-adjusted life years from asthma by age, and corresponding ranking when compared with other single noncommunicable diseases (data from Global Disease Burden Study; level 4 ranking) ¹⁶.

Age (years)	Global		Europe		Portugal	
	DALYs*	Rank#	DALYs*	Rank#	DALYs*	Rank#
Under 5	257.54	5	116.39	11	177.25	4
5-9	461.15	1	367.97	1	496.75	1
10-14	383.37	2	369.49	4	477.60	2
15-19	297.09	8	319.22	7	451.26	5

*Disability-adjusted Life Years per 100,000 inhabitants; # Ranking when compared with other single noncommunicable diseases

Table 2 Deaths from asthma by age, and corresponding ranking when compared with other single noncommunicable diseases (data from Global Disease Burden Study; level 4 ranking) ¹⁷.

Age (years)	Global		Europe		Portugal	
	Deaths*	Rank#	Deaths*	Rank#	Deaths*	Rank#
Under 5	9,483.23	16	57.82	27	0.24	29
5-9	2,751.77	12	29.10	19	0.09	33
10-14	3,638.71	10	43.81	15	0.18	27
15-19	3,970.09	11	59.65	24	0.33	32

*Number of deaths per year; #Ranking when compared with other single noncommunicable diseases

The World Health Organization (WHO) Global Alliance against Chronic Respiratory Diseases (GARD) framework identified the worldwide needs in chronic respiratory diseases (specially asthma) data and action plans, including the ones of developed countries ²⁰. Specifically, the GARD advocates that population-based studies are required for the assessment of disease epidemiologic estimates and burden, and that it should be implemented in different countries and settings. Innes Asher and Neil Pearce have recently stated the importance of continuously monitoring childhood asthma prevalence and burden in order to reduce the impact of this disease, with a particular focus on the need for economic studies on asthma ²¹.

Taking into account these needs on the research field of asthma burden, it is also crucial to aggregate comprehensive, precise, generalizable and quality data to inform health policy-makers. Indeed, in the era of widespread information, it is important that health policies can be perfectly fitted to the needs of the populations. Healthcare services resources and interventions should be allocated adequately, after assessing several disease estimates. These types of estimates are part of a burden of disease study and are important to measure population health outcomes. A stepwise approach of the burden of childhood asthma should go from prevalence estimates, to diagnostic tests, medication, healthcare services use, level of asthma control and economic impact.

1.3 Epidemiology of childhood asthma

The clinical presentation of asthma is characterized by a great symptomatic heterogeneity. In order to identify the broad clinical spectrum of the disease, composite measures for asthma definition are increasingly necessary, aiming to obtain more accurate epidemiological prevalence estimates ²². Epidemiological studies with simple and direct questionnaires are essential to obtain good quality data. Prevalence surveys are the first step for a full assessment of a disease burden and their main goals are: to know the number of affected patients in a population; to compare the prevalence of disease in different populations; to examine trends in disease prevalence or severity over time; and to assess the need for health resources allocation.

The results of the 25-year International Study of Asthma and Allergies in Childhood (ISAAC) have changed the global knowledge about the prevalence of asthma and related symptoms, with the implementation of straightforward methodologies and simple ready to use tools in high, medium and lower income countries ²³. A total of 306 centres in 105 countries were included during the 3 phases of ISAAC and children between 6-7 years old and 13-14 years old were selected. The ISAAC survey included 5 Portuguese cities: Porto, Lisboa, Coimbra, Portimão and Funchal. However, as most other studies on the prevalence of asthma or asthma-like symptoms in childhood, it was limited to specific ages and settings. Also, most of the studies that used the ISAAC questionnaire were mainly based on wheeze ²⁴, with little or no focus on other asthma-like symptoms, an approach that has been recently questioned ²².

Prevalence of asthma-like symptoms

According to ISAAC, the prevalence of asthma symptoms in children may reach higher than 35% in some settings, and the global burden is still increasing ²⁵. The global prevalence of current (i.e., reported in the previous 12 months) wheeze in the 6- to 7-year-old group varied from 37.6% in Costa Rica to 2.4% in India, and in the 13- to 14-year-old group from 32.6% in New Zealand to 0.8% in China. In Western Europe, prevalence of current wheeze and cough was, respectively, 9.7% and 20.7% in the 6- to 7-year-old group, and 15.2% and 29.3% in the 13- to 14-year-old group.

Wheeze is the most studied asthma-like symptom in children. A great variability can be observed in the prevalence of current wheeze depending on the countries, settings and pediatric age groups (from 1% to 38% in ISAAC) ²⁵. A recent Portuguese nationwide study on pre-schoolers estimated a current wheeze prevalence of 24.5% ²⁶. There are no other nationwide Portuguese studies in older children, however Phase III ISAAC estimates for current wheeze was 12.9% in the 6- to 7-year-old group, and 10.4% in the 13- to 14-year-old group, in 2002 ²⁷.

Nocturnal cough is a well-known frequent asthma-like symptom; however, it is difficult to find data on this symptom, specifically on the proportion of nocturnal cough in asthmatic children. Mvula et al. found that 27.3% of children aged 5 to 18 years had cough at night, apart from cold or chest infection, but nothing was said about the proportion of asthmatic children that had cough ²⁸. Also, the prevalence of asthma attacks is seldom reported. The United States National Center for Health Statistics reported a 5.4% prevalence of asthma attacks in the previous 12 months among children aged 0 to 17 years ²⁹.

Knowing these pitfalls in data of childhood asthma burden, a comprehensive nationwide Portuguese study on the prevalence of different asthma-like symptoms across all pediatric ages stands out as a decisive step for understanding the patterns of asthma-like symptoms in Portuguese children, specifically in those with asthma.

Asthma Prevalence

Epidemiologic definition of asthma is not consensual, leading to hardly comparable data in reported prevalence estimates that greatly depend on the definition used ^{22,30}. First, asthma estimates depend on the time of diagnosis or the occurrence of asthma-like symptoms included in the definition: 1) it can be based on a known diagnosis of asthma ever in life ('ever had asthma' or 'lifetime asthma' or 'doctor diagnose asthma'); 2) it can be based on active asthma ('current asthma', usually with the presence of one or more asthma symptoms in the previous 12 months). Second, asthma estimates can vary greatly with the type and number of asthma-like symptoms included in the definition. In fact, despite asthma being considered a heterogeneous disease with multiple presenting symptoms, epidemiological childhood asthma definitions and clinical asthma phenotypes are excessively based on wheezing ^{31,32}. Skytt et al. ³³, with data from the Copenhagen Prospective Study on Asthma in Childhood, addressed the lack of validity of wheezing for

asthma diagnosis in children aged 0 to 3 years. They argued for a global description of asthma symptoms to reduce the risk of misclassification of asthma in children. Wheezing-based asthma definitions are also limited by differences in the concept and perception of wheeze ³⁴. Fernandes et al. reported a lack of perception of the term “wheezing” among Portuguese parents and health professionals ³⁵.

The ISAAC used two asthma prevalence approaches: 1) a doctor diagnosis of asthma ever in the lifetime (“ever had asthma”); and 2) “ever had asthma” plus “current wheeze”. The estimates of the first definition were the most disseminated. In Western Europe, the ISAAC estimates for the 6- to 7-year-old group were 9.1% for “ever had asthma” and 4.5% for “ever had asthma plus current wheeze”; for the 13- to 14-year-old group, the estimates were 16.3% for “ever had asthma” and 7.7% for “ever had asthma plus current wheeze”. In Portugal, the prevalence of “ever had asthma” was 9.8% in the 6- to 7-year-old group and 13.2% in the 13- to 14-year-old group ²⁷. Many other studies have been conducted in Portugal, mainly school-based or primary care-based, in selected regions and selected pediatric ages, leading to different prevalence estimates ^{36–42}. The Portuguese Study of Allergic Diseases in Childhood (PAC), performed in Madeira, Cape Verde and Macau, showed a prevalence around 10% in children between 6-10 years old in Madeira ³⁸. In pre-schoolers, two recent Portuguese studies had also reported estimates of physician asthma diagnosis of 4.6% ^{26,43}. These studies brought important data, however, neither the ISAAC nor the other studies estimated the prevalence of asthma across all pediatric ages (<18 years old) or among a representative nationwide sample in Portugal ^{37–39,42}. In fact, few studies worldwide have estimated the nationwide prevalence of asthma in children. Schmitz et al. ⁴⁴ reported a 4.7% prevalence of a doctor-diagnosed lifetime asthma in the German population of 0- to 17-year-old using data from the 2003-2006 German Health Interview and Examination Survey for Children and Adolescents (KiGGS). Data from the 2010 United States National Health Interview Survey for children under the age of 18 years reported an estimated doctor-diagnosed lifetime asthma prevalence of 13.6% and current asthma prevalence of 9.5% ^{45,46}.

1.4 Diagnostic tests and medication use in childhood asthma

Diagnostic tests use in childhood asthma

Asthma diagnosis and management is much based on symptoms ⁶. However, diagnostic tests are also important for diagnosis and assessment of disease. Pulmonary function tests (PFT), especially spirometry with bronchodilation test, are recommended for every child with asthma suspicion above 5 years of age ⁶. Also, allergy tests, namely skin prick tests or serum specific immunoglobulin E to aeroallergens, are important for the assessment of atopic status and optimization of asthma management. Airway inflammation assessment, with exhaled nitric oxide (FeNO) testing, is a recent tool that became clinically feasible in the last years and may be useful in clinical practice ⁴⁷. Moreover, other blood workouts or chest x-rays are often performed in asthmatic patients, depending on the occasion and setting ⁴⁸. Blood workout can be performed to assess atopic status, but it can be also used, more widely, in acute severe exacerbations (i.e. blood gases). Chest x-rays are rarely useful and should not be used routinely; however, it should be reserved for children with other clinical features that may point to other diagnoses and for severe presentations.

Despite GINA recommendations for diagnostic test use in children with asthma, there is a paucity of data regarding the real-life use of diagnostic tests in asthma. Data from the USA showed that only 21% of the family physicians/pediatricians used spirometry for all guideline-recommended clinical situations ⁴⁹. In Portugal, and to the best of our knowledge, there were no published data about the proportion of diagnostic test use in childhood asthma.

Medication use in childhood asthma

Pharmacological treatment is an important part of asthma management and should be adjusted in a continuous control-based cycle ⁶. There are 3 main categories of asthma-specific medications: 1) controller medications; 2) reliever medications; 3) add-on therapies for severe asthma. GINA advocates a stepwise approach to the treatment of asthma in children. At Step 1, the initial option can be short-acting β_2 -agonist (SABA) relievers for symptom relief (especially for children under 6 years of age), or low-dose inhaled corticosteroids (ICS); at Step 2, treatment with low-dose ICS or leukotriene receptor antagonists (LTRA), with as-needed SABA, is preferred; at steps 3–4, different options can be made, such as doubling the dose of ICS, adding ICS and LTRA, or initiating the association

ICS and long-acting β 2-agonist (LABA); at step 5, add-on treatment for severe asthma should be considered.

In the USA, a study based on a prescription database estimated that more than 60% of asthmatic children between 6 and 18 years of age were prescribed with, at least, one drug; SABA was the most frequent medication (52.7% in non-severe asthma and 91.9% in severe asthma), followed by oral steroids (23.0% in non-severe asthma and 63.6% in severe asthma) or ICS (15.3% in non-severe asthma and 79.8% in severe asthma), LTRA (16.6% in non-severe asthma and 48.7% in severe asthma), and association ICS/LABA (10.1% in non-severe asthma and 21.8% in severe asthma) ⁵⁰. In Europe, Dahlen et al reported that 82% of asthmatic Swedish adolescents used asthma medicines in the previous 12 months ⁵¹.

To understand the burden of childhood asthma in Portugal, data on use of asthma medication should be collected at community level and within all pediatric ages.

1.5 Healthcare services use in childhood asthma

One of the major aims of a disease burden study is to inform and help policymakers, especially in the field of healthcare services management. Knowing the patterns of use of different healthcare services is crucial to advocate future action plans, in order to improve management and control of the disease. In childhood asthma, data on healthcare services use is scarce. In a recent state of art manuscript on disease burden of childhood asthma written by the ISAAC main authors, they didn't present data or comment anything about healthcare services use in asthmatic children ²¹; however, they stated that emergency/unplanned medical visits, hospital admissions and medication (controller and reliever), are important components of costs in childhood asthma.

It is known that a higher use of healthcare visits and/or asthma medication is associated with worse asthma control in children ^{52–54}. Also, literature on asthma disease burden in all ages showed that asthma has a higher burden in pediatric ages and that hospitalisations and medications are the most important drivers of direct costs ⁵⁵.

Hospitalisations, emergency and medical visits in childhood asthma

Physician medical visits are pivotal in asthma management. Ideally, asthmatic children should be managed with regular scheduled medical visits, with no need for unscheduled medical visits, emergency department admissions or hospitalisations.

Data on medical visits on childhood asthma are infrequently reported in the literature, difficult to find and have high variability in ages and settings covered by the different studies. There are data on asthma hospitalisation rates in specific years and populations, mainly based in hospital admission databases ^{19,56,57}. In the USA, asthma was responsible for 2.3% of overall hospitalisations in children in the first decade of this century and, in 2009, the rate of hospitalisations for childhood asthma was 18.4 per 10,000 person-years ⁵⁶. In Portugal, the most recent study on asthma hospitalizations, with national data from Health Services Central Administration (ACSS) from 2000-2010, showed a mean global, all-age, rate of annual hospitalisations of 28.1 per 100,000 inhabitants, and 66.6 per 100,000 inhabitants in those aged 0 to 18 years ¹⁹. However, there is a lack of knowledge about the prevalence of hospitalisations for asthma among the overall pediatric population and, specifically, among those with a known asthma diagnosis. Also, the proportion of children with asthma that is

hospitalised because of asthma during their lifetime is still unknown, i.e., no studies have ever been published on the prevalence of lifetime hospitalisations of children with asthma. This means that the proportion of asthmatic pediatric population with, at least, one hospital inpatient admission during childhood is not known.

Kattan et al.⁵⁸ studied an inner-city population of asthmatic children aged 4 to 9 years and concluded that the proportion of hospitalisations in one year was 17% and that of unscheduled medical visits (to emergency department or clinics) was 66%. Different estimates were reported for 7- to 8-year old children from New York City: 26.7% had urgent medical visits for asthma in the previous 12 months⁵⁹. In a Polish study, asthmatic children between 6 and 16 years old were characterized according to several healthcare services utilizations in the previous 12 months: 5.4% needed hospitalisation, 44.1% were seen by a physician and 35.5% performed asthma-related diagnostic tests.

Healthcare access in asthma

In many health systems, health insurance status plays an important role in the access to healthcare services, including for asthmatic children: uninsured children are more likely to have restricted medical care and impaired access to healthcare services^{60,61}. Data on the 2007-2009 US recession has shown that children that experienced a gap on health insurance coverage had poorer asthma control.⁶² In Europe there are different healthcare systems and financing modalities among and within countries, but no study evaluated the influence of the children's health insurance status on asthma outcomes in European countries.

The Portuguese Health System has universal coverage with mixed public-private payers. It is financed by taxes and by health insurances, complemented by out-of-pocket expenses. Health insurances are not only private, but also state-owned, paid by state employees (e.g. ADSE - *Instituto de Proteção e Assistência na Doença*). All Portuguese citizens have access to medical care services in public primary care and hospital units. The public care access is primarily based on visits to primary care physicians that can refer patients to hospital specialities; this is limited by the waiting time and geographic referral areas that prevent the patients from choosing the place where they will be cared for. Private practice/hospital access is dependent on the patient's will to attend these institutions or by health insurance plans. As out-of-pocket expenses can be significant, access is better for those with complementary health insurance coverage. Therefore, citizens with healthcare insurance

may easily choose the site of medical care that they perceive as the best, with easier access to medical specialties and lower waiting time for medical observations and diagnostic tests. As state-owned insurance is available for all state employees (if wanted by them) and some private companies provide health insurance to all their employees, the socioeconomic status is probably only partially related to having health insurance. Regarding medication, prices are the same for every Portuguese child, regardless of health insurance status. Medicines commercialized in Portugal are partly paid by the public health system with a fixed percentage for every drug; the remaining value is supported by citizens, without any payment by health insurance companies.

1.6 Asthma control in children

The main goal of asthma management is to achieve disease control, meaning, good control of symptoms, normal activity levels, normal sleep, no exacerbations, no fixed airflow limitation and no medication side-effects ⁶. A good control of asthma symptoms is the main goal, not only in treating asthma, but also in reducing asthma burden. In children, the proportion of poor asthma control varies widely, from 15% to 90%, depending on the age groups included, countries, settings and control definition ^{52,63–68}. In the USA (2008), the proportion of uncontrolled asthma in 4- to 17-year-old children with asthma who visited a pediatric health care provider was 46% ⁶⁶. Dahlen et al showed a proportion of 47% of uncontrolled asthma in Swedish adolescents (2013) ⁵¹. In Dutch (2007) 6- to 16-year-old asthmatic children with a follow-up in outpatient clinic, the proportion of poor control was 55% ⁶⁸. In French pre-schoolers (2006), uncontrolled asthma based on frequent occurring symptoms was present in 42% ⁶⁷. In Portugal, there were no published data on the prevalence of childhood asthma control.

Several factors have been associated with lack of asthma control in children, such as rhinitis ⁶⁹, eczema ⁶⁵, obesity ⁷⁰, lower socioeconomic status ⁷¹, or parents' impaired perception of asthma control ⁶⁸. Specifically, the strong link between upper and lower airway disease is recognized ^{26,72}. In Dutch asthmatics aged 5 to 18 years, the prevalence of nasal symptoms was 76% and there was an association with poorer asthma control in children in those with untreated nasal symptoms ⁶⁹. Other studies identified that underdiagnosis and undertreatment of rhinitis in asthmatic children was associated with lack of parental recognition and poorer asthma control ^{73,74}. Also, recently published data showed that increased body mass index (BMI) was associated to lack of asthma control ⁶³, to a higher use of inhaled β -agonists or oral corticosteroids,⁷⁰ and to worse asthma control in children with higher airway inflammation ⁷⁵.

Children with uncontrolled asthma need to use more asthma medication and are more likely to use healthcare services for asthma, especially unscheduled medical visits and hospital admissions ^{53,76}. This points towards a higher burden of the disease in children with uncontrolled asthma. Improving knowledge on asthma control, including its prevalence

and related factors, is needed to assess the extent of the asthma-related burden and to inform policymakers, aiming to achieve better results in health.

1.7 Quality of life in childhood asthma

The quality of life (QoL) is a multidimensional concept that encompasses the well-being of a population in several aspects of life (e.g. health, education, finances), as perceived by the individuals, and according to their socio-cultural environment ⁷⁷. QoL can be measured and health is one major determinant of this assessment. Health-related quality of life (HRQoL) was defined by Patrick and Erickson as *'the value assigned to duration of life as modified by the impairments, functional states, perceptions and social opportunities that are influenced by disease, injury, treatment or policy'* ⁷⁸.

Asthma affects the well-being of the patients. One Australian report showed that asthma was associated to significantly lower scores in all the domains of the 8-Item Short Form Health Survey (SF-8), when compare with healthy people ⁷⁹. Also, after mental illnesses, asthma was one of the second conditions that had major impact on QoL, including in the domains of 'Physical functioning', 'Role physical', 'Bodily pain', 'General Health' and 'Vitality'.

In childhood asthma, there are several tools for the evaluation of quality of life, namely, Pediatric Asthma Quality of Life Questionnaire (PAQLQ), Life Activities Questionnaire for Childhood Asthma, Pediatric Quality of Life Asthma Module 4.0 (PedsQL™4.0) or The Living with Asthma Questionnaire (LWAQ) ⁸⁰. One recent meta-analysis in QoL in childhood asthma reported lower scores of QoL in 'Physical functioning', 'Social functioning' and 'Psychological functioning' when considering children's perception, but only found differences in 'Physical functioning' when considering parents' perception ⁸¹. In fact, it is not well established the utility of these QoL tools in childhood asthma because of the lack of validity or reproducibility between children and/or caregivers ^{82,83}. Moreover, the quality of life in asthma patients, namely in children, is known to be closely linked to asthma control or seek for medical attention ⁷⁶. In Brazil, children with controlled or partly controlled asthma showed a significant increased in all the domains of PAQLQ (activities limitation, symptoms and emotional function) when compared with children with uncontrolled asthma ⁸⁴. In the same direction, in Portugal, a study on asthmatic children followed in referral hospitals, using a global QoL tool (DISABKIDS-37), showed that children's perspectives and parents' perspectives differed in several domains and that children with uncontrolled asthma had lower scores in HRQoL ⁸⁵.

1.8 Cost of asthma

Health-related costs are an important part of a disease burden assessment. Health economics analysis is highly relevant because of rising healthcare costs and the consequent threat to the sustainability of healthcare systems around the world ⁸⁶. Therefore, health economics studies are needed to support local decision-makers in defining health priorities ⁸⁷. As governmental health policies become more cost restrictive, it is important to know where is possible to act in order to reduce costs while maintaining or enhancing healthcare quality. In Portugal, health-related costs represented 9,9% of the gross domestic product in 2010 ⁸⁸, highlighting the importance of being thoughtful with healthcare resource allocation. Cost-of-illness studies are the foundation of health economics, informing posterior studies aiming to measure preferences and interventions ^{89,90}.

In childhood asthma, important direct costs (diagnostic tests, medications, medical visits, hospitalisations or emergency department admissions) and indirect costs (mainly caregivers' loss of work days and transportation to healthcare services) are relevant and can be high, especially in severe disease ⁹¹. Having a comprehensive picture of childhood asthma burden, including costs, will allow physicians and policymakers to analyse susceptible points that can be managed in order to have gains in the efficiency of asthma management.

In 2002, Druss et al have coted asthma as the 13th most expensive medical condition in USA ⁹². In 2011, Barnett and Nurmagambetov estimated, by a regression-based method, \$56 billion (in 2009 dollars) of incremental costs of asthma in all-age asthmatic USA population, representing a value of \$3,259 by person/year ⁹³. In the same year, Bravo et al published an estimated cost of asthma in 0- to 15-years-old children, in Spain, of €532 million, meaning a cost of €1,149 person/year ⁹¹. In this study, the authors also analysed the costs within each category of asthma severity, ranging from €403 for the mildest to €5,930 for the severest (costs person/year). Many other economic studies were conducted in asthma all-over the world, with different methodologies, different variables, and different age ranges. However, there are few population-based and comprehensive pediatric studies ⁵⁵.

2.AIMS

The main objective of this research project was to study the burden of asthma in Portuguese children.

As specific aims, we intended to estimate:

1. The prevalence of asthma and asthma-like symptoms in Portuguese children (Paper 1)
2. The number of hospitalisations for asthma in Portuguese children with asthma (Paper 2)
3. The proportion of asthma-related ambulatory healthcare services and medication use in Portuguese children with asthma (Paper 3)
4. The proportion of asthma control and the determinants of control in Portuguese children with asthma (Paper 3)
5. The cost of illness of asthma in Portuguese children and to assess cost variations with level of asthma control (Paper 4)

3. PhD STUDIES

The studies from the present PhD thesis were designed to perform a comprehensive assessment of childhood asthma burden in Portugal. Data from two studies were collected and analysed:

- 1) Portuguese National Asthma Survey (INAsma), a nationwide study developed in two phases:
 - a. Portuguese National Asthma Prevalence Survey (INPA), aimed to estimate asthma and asthma-like symptoms prevalence, as well as cost of childhood asthma, in Portuguese population;
 - b. Portuguese National Asthma Control Survey (INCA), aimed to estimate proportion of asthma control and cost of childhood asthma in Portuguese population;
- 2) Asthma in school-aged children: the Guimarães study (CED2013), designed for empower the results on cost of asthma in school-aged children using a questionnaire and objective assessment.

Data from INAsma, CED2013 and, also, secondary data from specific national databases on healthcare resources costs (healthcare services, diagnostic tests and medication) and occupational costs were compiled in order to study the cost of childhood asthma in Portugal (CASCA Project). The next diagram (Figure 1) shows the studies from the Ph.D. thesis:

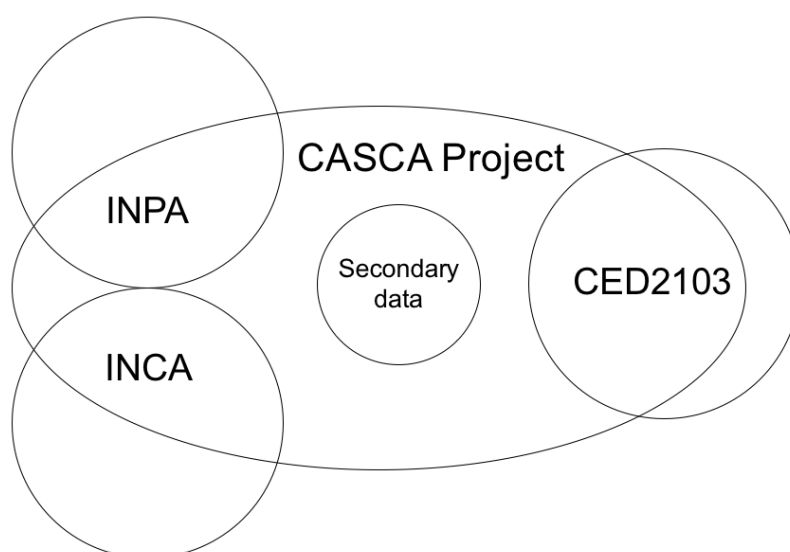


Figure 1

Venn diagram of the different studies of the Ph.D.

Support and Funding

INAsma study was supported by Sociedade Portuguesa de Alergologia e Imunologia Clínica, Sociedade Portuguesa de Pneumologia and Fundação Ciência e Tecnologia – Harvard Medical School Portugal (HMSPIDSIM/SIM/0018/2009).

Data collection of the **CED2013 study** was developed with the support of Guimarães, European Capital of Sports 2013 and Tempo Livre - Centro Comunitário de Desporto e Tempos Livres.

CASCA Project was financed by a Calouste Gulbenkian Foundation competitive grant (P-125964).

4.PAPERS

4.1 Paper 1

Ferreira-Magalhães M, Sá-Sousa A, Morais-Almeida M, Pité H, Azevedo LF, Azevedo I, Bugalho-Almeida A, Fonseca JA.

Asthma-like symptoms, diagnostic tests, and asthma medication use in children and adolescents: a population-based nationwide survey

J Asthma 2016; 53:269-276

ABSTRACT

Objective: This study aimed to estimate the prevalence of asthma-like symptoms, current asthma, asthma diagnostic tests, and inhaled medication use in a nationwide pediatric population (<18 years).

Methods: Pediatric-specific data from a cross-sectional, population-based telephone survey (INAsma study) in Portugal were analysed. current asthma was defined as lifetime asthma and (1) wheezing, (2) waking with breathlessness, or (3) asthma attack in the previous 12 months, and/or (4) taking asthma medication at the time of the interview.

Results: In total, 716 children were included. The prevalence of asthma-like symptoms was 39.4% [95% confidence interval (95%CI), 35.7–43.3]. The most common symptoms were waking with cough (30.9%) and wheezing (19.1%). The prevalence of current asthma was 8.4% (95%CI, 6.6–10.7). Among children with current asthma, 79.9% and 52.9% reported prior allergy testing and pulmonary function testing (PFT), respectively. Inhaled medication use in the previous 12 months was reported by 67.6% (reliever inhalers, 40.1%; controller inhalers, 41.5%). Those who only used inhaled reliever medications experienced more asthma attacks [odds ratio (OR), 2.69]. Significantly fewer children with current asthma living in rural areas than those living in urban areas had undergone PFT or used inhaled medication (OR: 0.06 for PFT, 0.20 for medication).

Conclusions: The prevalence of current asthma in the Portuguese pediatric population was 8.4%. Only half of children with current asthma had ever undergone PFT; more than half did not use controller inhalers, and those who only used reliever inhalers reported more asthma attacks. These findings suggest that asthma management has been substandard, mainly in rural areas.

AIMS

In 2010, we conducted the first Portuguese National Asthma Survey (INAsma) ⁹⁴. In the present paper, we focus on the results obtained from the INAsma pediatric population. Specifically, our primary aim was to estimate the prevalence of asthma-like symptoms and current asthma in the Portuguese pediatric population (<18 years). Our secondary aims were to describe the differences in current asthma prevalence estimates according to different definitions to allow for comparisons with other studies and to assess the proportion of the use of diagnostic tests and inhaled medication among children with current asthma.

METHODS

Study design and setting

The INAsma was a population-based, nationwide, cross-sectional survey applied by telephone interview in Portugal, in 2010. The study methodology has been previously described ⁹⁴.

This study was reviewed and approved by the Ethics Committee of Centro Hospitalar de São João, Porto, Portugal. Informed consent was obtained from the parent(s) or legal guardian(s) of the children included in this study. We followed the STROBE statement for reporting observational studies ⁹⁵.

In this study, we included all the individuals aged <18 years old (henceforth referred to as "children" for simplification).

Sample size

The study sample size was calculated for the total Portuguese population and was based on confidence intervals of proportions. Thus, for the general all-age population, for an estimated *a priori* asthma prevalence of 6% and narrow error margin of 0.015, a sample of 1067 individuals was required. However, the sample size of this study was calculated considering the two phases of the research project. In the first phase, we aimed to estimate the current asthma prevalence in the Portuguese population. In the second phase, we aimed to estimate the proportion of patients with controlled asthma symptoms. Thus, in the second phase of the project, to estimate the proportion of patients with controlled asthma with a 3% margin of error and 95% confidence level, and assuming a proportion of 20% of patients with uncontrolled asthma in the population, we required a sample of at least 554 patients with asthma identified in the first phase of the project. Assuming a 20% loss to follow-up, we required at least 665 patients with asthma during the first phase. Within these premises, and assuming a prevalence of 6% in the Portuguese population and a margin of error of 0.65%, we required a sample of at least 6000 persons from the general, all-age, Portuguese population willing to participate in the first phase of the project.

Households were then randomly selected from the 2010 residential White Pages telephone directory. Four different lists of telephone numbers were randomly selected for each

municipality to allow for substitution of nonresidential telephone numbers. In total, 24,412 telephone numbers were retrieved. One participant (the last person to have had a birthday) was randomly selected from each household.

The inclusion of 716 children allowed us to estimate the current asthma prevalence with an error margin of 0.02 and a 95% confidence level.

Participants

The INAsma target population was the Portuguese general population, and the available population included citizens of all ages living in households with a landline telephone (sampling frame). A cluster sampling design was used to obtain a representative sample of the population. All municipalities were used as natural strata, and a sample of households was then selected with a probability proportional to the municipality population as estimated in the 2001 National Census.

First, all municipalities were used as natural strata; in each municipality, a sample of households with a landline telephone number was selected with a probability proportional to the municipality population as estimated in the 2001 National Census. The target number of households was set at 6,103. The sample of households was derived from the directory listed in the residential White Pages from 2010. A list of all telephone numbers in a specific municipality was compiled to draw a sample of telephone numbers within that municipality. A sample of household telephone numbers was randomly selected from the whole list in each municipality. Because part of the selected telephone numbers were from companies or were not allocated, four lists were randomly selected for each municipality to allow for substitution of non-residential telephone numbers. In total, 24 412 telephone numbers were retrieved.

After the selection and identification of a residential number, one participant was randomly selected from each household. After identification of all residents in the household, the selected participant in each household was the last person to have had a birthday. When the selected individual was younger than 15 years, the respondent was the usual caregiver. Individuals were excluded if they did not understand spoken Portuguese or had cognitive or physical conditions that could hamper the interview. In the final 20% of the sample, an oversampling strategy of male adults and younger adults was used to correct the common overrepresentation of female and older participants observed in the interim analysis.

Instruments and data collection

The instrument for data collection was the Portuguese version of the questionnaire used in the GA²LEN survey, which includes the European Community Respiratory Health Survey questions on asthma symptoms ⁹. Several questions were added regarding socio-educational variables, medications, and diagnostic test use for asthma.

An experienced private company administered the questionnaire through computer-assisted telephone interviews performed by trained and experienced interviewers. Interviews were conducted from March to May of 2010, mostly from 17:00 to 22:00 h on weekdays and 11:00 to 22:00 h on weekends and holidays. No telephone number was abandoned until a minimum of 10 attempts had been made on different occasions. The interviews had a mean duration of 15 min.

To minimize other potential biases in data collection, several quality assurance measures were followed: interviewers were selected based on their previous experience with health-related data collection; each question was discussed in training sessions held between researchers and all interviewers; a research assistant was present during the setup, training, and daily work of the interviewers, motivating and checking compliance with standardized operational procedures; data validity was periodically verified soon after being collected, and custom statistic algorithms were used to detect extreme, illogical, and missing values; and the clarity of the questionnaire and its telephonic administration were assessed in a pilot study involving 25 individuals before starting the data collection.

Variables

Asthma definition variables were defined based on previous studies ^{22,25}. The outcomes were defined as follows:

lifetime asthma: positive answer to “Have you ever had asthma?”.

current asthma: lifetime asthma plus at least one of the following four features: 1) wheezing, 2) waking with breathlessness or 3) having an asthma attack in the last 12 months, or 4) taking asthma medication at the time of the interview.

Nocturnal symptoms: at least one of three symptoms in the last 12 months: waking with breathlessness, waking with chest tightness, or waking with coughing.

Asthma-like symptoms: at least one of three symptoms in the last 12 months: wheezing, nocturnal symptoms, or asthma attacks (wheezing was further described as wheezing with breathlessness or wheezing without a cold).

PFT: positive answer to “Have you ever undergone any test to assess your lung function?” (the interviewer further explained that “it refers to an exam that assesses the breathing capacity, i.e., spirometry, or blowing harder into a machine, or breathing inside a glass box, other than blowing quickly to a plastic tube or peak flow meter”).

Skin prick tests: positive answer to “Have you ever undergone any skin test to assess your allergies?”.

Blood allergy tests: positive answer to “Have you ever undergone any blood test to assess your allergies?”.

Any asthma medication at present: positive answer to “Are you currently taking medication (inhaled, nebulized or oral) for asthma/breathlessness?”.

Inhaled therapy in the last 12 months: positive answer to “In the last 12 months, did you take any inhaled medication for asthma/breathlessness?”. Further characterization of inhaled medication was based on the auto-reported medication name.

Allergic rhinitis: Positive answer to “Do you have any nasal allergies, including hay fever?”.

Atopic dermatitis/eczema: Positive answer to “Have you ever had eczema or skin allergy?”.

Food allergy: Positive answer to “Have you been diagnosed with food allergy by a doctor?”.

Environmental tobacco smoke (ETS): Positive answer to “Does anyone smoke inside your home?”.

Municipality was classified as urban if the residence was located in a municipality with at least one city (cities must have at least 8000 citizens), according to Portuguese legislation ⁹⁷.

Statistical analysis

The sample estimates were weighted according to the 2001 National Census aiming for generalization to the target population ⁹⁸, with the exception of the participants' characteristics description, which was performed without weighting procedures. Statistical

analyses were weighted for the Portuguese pediatric population and performed using the complex samples tool of SPSS version 21 (SPSS IBM, New York, NY, USA).

A sequential simple random sampling method without replacement was used to select a random sample of households with a landline telephone within each stratum (municipality) and then one random eligible household resident. Two types of weights were used: 1) prestratification weights to adjust for the sampling design and 2) poststratification weights to adjust for the true sex and age distribution of the target population, thus partially correcting for nonresponse and noncoverage bias.

Categorical variables were described using absolute and relative frequencies with 95% confidence intervals (95%CI); comparisons were performed with Pearson's chi-squared test. Univariate logistic regression models for outcomes were developed using independent variables as risk/predictive factors. Multivariate logistic regression models were developed to adjust for possible confounders. Results of multivariate logistic regression models were presented as odds ratios (ORs) with 95% CIs. A p-value of <0.05 was considered statistically significant.

RESULTS

Participants

The corrected response rate of the INAsma was 50%. Of the 6,003 participants in the INAsma survey, 716 (11.9%) were children. A flowchart of all participants is shown in Figure 2. One-fifth (21.4%) of the children were younger than 6 years of age, and 39% were 13 to 17 years old; most (80.6%) were from urban areas. The children's characteristics are summarized in Table 3.

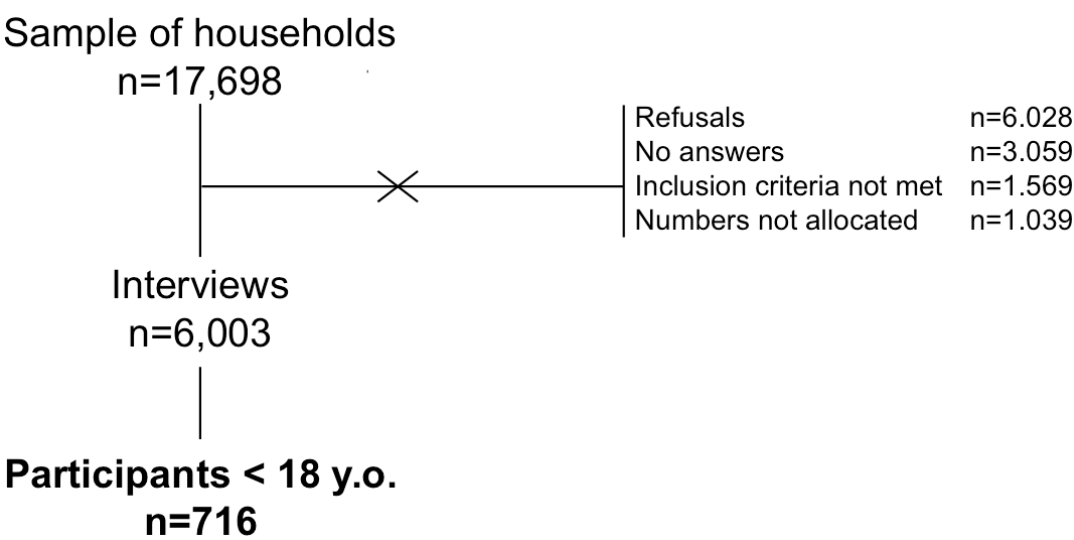


Figure 2 Participants' flowchart.

Table 3 Participants' characteristics in a pediatric sample. Weighted proportion and odds ratio (95% confidence intervals) of current asthma according to sociodemographic and clinical variables.

	Total participants, n (%)	Current asthma, % (95%CI)	Odds Ratio ^a (95%CI)
All Pediatric Population	716 (100.0)	8.4 (6.6-10.7)	
Gender			
Female	270 (37.7)	6.7 (4.3-10.1)	1.00 (Ref)
Male	446 (62.3)	10.1 (7.5-13.4)	1.59 (0.92-2.75)
Age groups			
0-5 years	153 (21.4)	6.5 (3.5-11.6)	1.00 (Ref)
6-12 years	284 (39.7)	9.7 (6.8-13.8)	1.53 (0.73-3.23)
13-17 years	279 (39.0)	8.7 (5.9-12.5)	1.36 (0.64-2.90)
National Region			
North	284 (39.7)	7.2 (4.6-11.1)	1.00 (Ref)
Centre and Islands	179 (25.0)	9.7 (6.3-14.7)	1.35 (0.67-2.74)
South	253 (35.3)	8.7 (5.7-12.9)	1.21 (0.61-2.38)
Municipality^c			
Urban	577 (80.6)	8.0 (5.9-10.8)	1.00 (Ref)
Rural	139 (19.4)	9.8 (6.6-14.3)	1.12 (0.59-2.11)
ETS^b			
No	454 (63.4)	8.2 (5.9-11.3)	1.00 (Ref)
Yes	262 (36.6)	8.8 (6.1-12.6)	1.06 (0.61-1.84)
Allergic rhinitis			
No	558 (77.9)	5.0 (3.4-7.4)	1.00 (Ref)
Yes	158 (22.1)	22.3 (16.6-29.2)	5.15 (3.02-8.78)*
Eczema			
No	517 (72.2)	5.0 (3.4-7.4)	1.00 (Ref)
Yes	199 (27.8)	18.3 (13.6-24.2)	4.08 (2.35-7.08)*
Food allergy			
No	676 (94.4)	8.3 (6.4-10.8)	1.00 (Ref)
Yes	40 (5.6)	9.6 (5.4-16.4)	0.94 (0.45-1.95)

^aAdjusted odds ratio for gender, age, region, municipality and ETS; ^bEnvironmental tobacco smoke. ^cMunicipality was classified as urban if residence was located in municipalities with at least one city (cities must have at least 8000 citizens) according to Portuguese law.

*Statistically significant

Prevalence of asthma-like symptoms

The prevalence of asthma-like symptoms among Portuguese children was 39.4% (95%CI, 35.7–43.3) (Table 4). Asthma-like symptoms were highest in children aged <6 years (47.9%; 95%CI, 40.0–56.0) and lowest in those aged 13 to 17 years (31.8%; 95%CI, 26.3–37.8; $p = 0.005$) (Table 3). Waking during the night with cough was the most prevalent symptom (30.9%; 95%CI, 27.5–34.5), followed by wheezing (19.1%; 95%CI, 16.4–22.1).

Table 4 Weighted prevalence of asthma-like symptoms in the previous 12 months in the Portuguese pediatric population.

	Total population % (95%CI)	Current asthma	
		Yes % (n=66)	No % (n=750)
Any symptom^a	39.4 (35.7-43.3)	91.4 (82.4-96.1)	34.7 (30.9-38.6)
Wheezing	19.1 (16.4-22.1)	76.5 (65.4-84.9)	13.8 (11.4-16.6)
Wheeze w/o cold	8.2 (6.5-10.4)	49.2 (37.2-61.3)	4.5 (3.1-6.3)
Nocturnal symptoms	34.7 (31.1-38.5)	79.2 (68.0-87.3)	30.7 (27.0-34.6)
Waking with breathlessness	5.0 (3.6-7.1)	24.7 (16.1-35.9)	3.2 (2.0-5.3)
Waking with chest tightness	6.7 (5.1-8.8)	27.4 (17.8-39.6)	4.8 (3.4-6.8)
Waking with cough	30.9 (27.5-34.5)	68.7 (56.6-78.7)	27.4 (24.0-31.2)
Asthma attack	3.7 (2.6-5.4)	44.4 (32.6-56.9)	0.0 (0.0-0.0)

^aWheezing or waking with breathlessness or waking with chest tightness or waking with cough or asthma attacks

The prevalence of nocturnal symptoms was higher in children aged <6 years (39.8%; 95%CI, 32.1–48.1) than in those aged 13 to 17 years (OR, 0.61; 95%CI, 0.40–0.94), although the prevalence was not significantly different from that of children aged 6 to 12 years (OR, 0.84; 95%CI, 0.55–1.28). The prevalence of wheezing was highest in children aged <6 years (31.0%; 95%CI, 24.4–38.5) and significantly decreased with age (OR, 0.46; 95%CI, 0.30–0.70 in the 6- to 12-year-old age group; and OR, 0.24; 95%CI, 0.15–0.40 in the 13- to 17-year-old age group) (Figure 3). Among children who reported wheezing in the last 12 months, the symptoms of wheezing without a cold and wheezing with breathlessness were higher in children aged 6 to 12 years than in those aged <6 years ($p < 0.001$) (Figure 4).

The presence of rhinitis and eczema were associated with a higher prevalence of having any asthma-like symptom (OR, 3.67; 95%CI, 2.52–5.39 for rhinitis; and OR, 2.11; 95%CI, 1.51–2.94 for eczema). Supplementary information on asthma-like symptoms is presented in Tables 5 and 6

Table 5 Weighted proportion of asthma-like symptoms and corresponding odds ratio in the Portuguese paediatric population in the previous 12 months according to sociodemographic variables.

	Any symptom ^a		Wheezing			Nocturnal symptoms		Asthma attack	
	% (95%CI)	Odds Ratio ^b (95%CI)	% (95%CI)	Odds Ratio ^b (95%CI)		% (95%CI)	Odds Ratio ^b (95%CI)	% (95%CI)	Odds Ratio ^b (95%CI)
Sex									
Female	36.3 (30.6-42.3)	1.00 (Ref)	14.0 (10.6-18.4)	1.00 (Ref)	] p<0.001	32.6 (27.1-38.6)	1.00 (Ref)	3.3 (1.8-5.9)	1.00 (Ref)
Male	42.5 (37.9-47.2)	1.29 (0.94-1.79)	23.9 (20.1-28.2)	1.96 (1.30-2.97)*		36.8 (32.3-41.6)	1.20 (0.86-1.68)	4.2 (2.7-6.5)	1.29 (0.60-2.78)
Age									
0-5 years	47.9 (40.0-56.0)	1.00 (Ref)	31.0 (24.4-38.5)	1.00 (Ref)	] p<0.001	39.8 (32.1-48.1)	1.00 (Ref)	2.8 (1.2-6.8)	1.00 (Ref)
6-12 years	39.2 (33.5-45.2)	0.70 (0.47-1.05)	17.3 (13.7-21.5)	0.46 (0.30-0.70)*		35.7 (30.3-41.6)	0.84 (0.55-1.28)	5.5 (3.4-8.9)	2.00 (0.71-5.65)
13-17 years	31.8 (26.3-37.8)	0.51 (0.33-0.77)*	9.9 (7.0-13.9)	0.24 (0.15-0.40)*		28.8 (23.5-34.7)	0.61 (0.40-0.94)*	2.5 (1.3-4.6)	0.88 (0.29-2.63)
National region									
North	38.2 (32.3-44.5)	1.00 (Ref)	20.5 (16.0-26.0)	1.00 (Ref)		33.3 (27.7-39.5)	1.00 (Ref)	3.1 (1.7-5.9)	1.00 (Ref)
Center and Islands	43.3 (36.0-50.9)	1.25 (0.84-1.86)	17.4 (13.0-22.9)	0.81 (0.51-1.29)		38.6 (31.6-46.1)	1.26 (0.84-1.89)	2.8 (1.2-6.3)	0.88 (0.30-2.59)
South	37.6 (31.6-44.1)	0.96 (0.66-1.41)	18.8 (14.4-24.0)	0.87 (0.55-1.36)		33.2 (27.3-39.6)	0.99 (0.67-1.46)	5.2 (3.0-8.7)	1.68 (0.71-3.97)
Municipality^c									
Urban	40.5 (36.1-45.0)	1.00 (Ref)	19.3 (16.1-23.0)	1.00 (Ref)		36.0 (31.7-40.5)	1.00 (Ref)	3.4 (2.1-5.3)	1.00 (Ref)
Rural	35.4 (29.6-41.7)	0.81 (0.58-1.12)	18.0 (14.5-22.2)	0.91 (0.63-1.33)		29.9 (24.3-36.1)	0.76 (0.54-1.07)	5.2 (2.9-9.1)	0.90 (0.53-1.52)
ETS^d									
No	38.2 (33.7-43.0)	1.00 (Ref)	19.7 (16.3-23.5)	1.00 (Ref)		32.9 (28.5-37.7)	1.00 (Ref)	3.7 (2.2-6.1)	1.00 (Ref)
Yes	41.6 (35.2-48.3)	1.16 (0.82-1.63)	18.0 (13.8-23.2)	0.89 (0.59-1.33)		37.8 (31.7-44.4)	1.24 (0.88-1.75)	3.9 (2.3-6.3)	1.06 (0.50-2.23)

^aWheezing or waking with breathlessness or waking with chest tightness or waking with cough or asthma attacks. ^bAdjusted odds ratio for gender and age. ^cMunicipality was classified as urban if residence was located in municipalities with at least one city (cities must have at least 8000 citizens) according to Portuguese law. ^dEnvironmental tobacco smoke.

*statistically significant

Table 6 Weighted proportion of asthma-like symptoms and corresponding odds ratio in the Portuguese paediatric population in the previous 12 months according to associated comorbidities.

	Any symptom ^a			Wheezing			Nocturnal symptoms			Asthma attack	
	% (95%CI)	Odds ratio ^b (95%CI)		% (95%CI)	Odds Ratio ^b (95%CI)		% (95%CI)	Odds Ratio ^b (95%CI)		% (95%CI)	Odds Ratio ^b (95%CI)
Rhinitis											
No	34.1 (30.1-38.5)	1.00 (Ref)	] p<0.001	14.3 (11.6-17.6)	1.00 (Ref)	] p<0.001	29.8 (25.9-34.0)	1.00 (Ref)	] p<0.001	2.6 (1.5-4.5)	1.00 (Ref)
Yes	61.2 (53.2-68.7)	3.67 (2.52-5.39)*		38.5 (31.1-46.4)	6.01 (3.82-9.46)*		55.1 (47.1-62.8)	3.36 (2.31-4.89)*		8.3 (5.4-12.7)	3.48 (1.69-7.17)*
Eczema											
No	35.0 (30.8-39.5)	1.00 (Ref)	] p<0.001	15.0 (12.3-18.3)	1.00 (Ref)	] p<0.001	31.0 (26.9-35.3)	1.00 (Ref)	] p<0.001	2.0 (1.1-3.6)	1.00 (Ref)
Yes	52.4 (45.6-59.2)	2.11 (1.51-2.94)*		30.8 (24.8-37.6)	2.77 (1.85-4.15)*		45.8 (38.9-52.9)	1.92 (1.36-2.71)*		8.8 (5.6-13.7)	4.74 (2.16-10.39)*
Food allergy											
No	39.0 (35.1-42.9)	1.00 (Ref)		18.9 (16.1-22.0)	1.00 (Ref)		34.4 (30.7-38.4)	1.00 (Ref)		3.7 (2.5-5.4)	1.00 (Ref)
Yes	48.3 (34.4-62.5)	1.58 (0.87-2.88)		22.8 (13.2-36.6)	1.52 (0.78-2.98)		40.0 (27.1-44.5)	1.35 (0.72-2.50)		4.9 (2.1-11.0)	1.35 (0.53-3.44)

^aWheezing or waking with breathlessness or waking with chest tightness or waking with cough or asthma attacks. ^bAdjusted odds ratio for gender and age. *Statistically significant

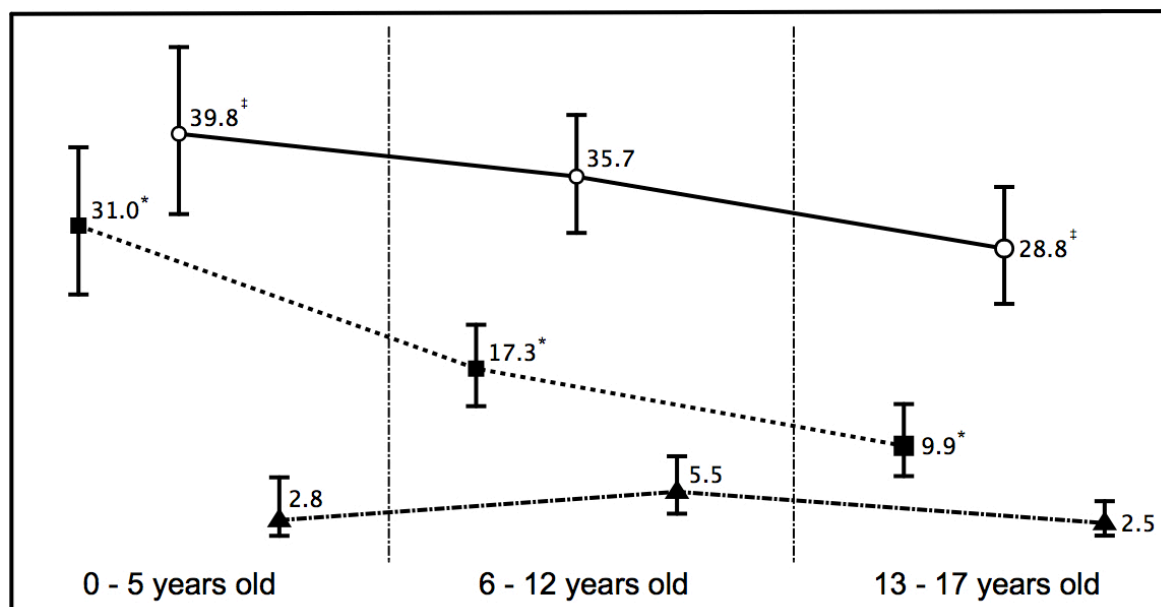


Figure 3 Weighted prevalence of asthma-like symptoms within the previous 12 months, according to age group (%; 95%CI).

Symbols represent prevalence of: ○nocturnal symptoms (waking with breathlessness or waking with chest tightness or waking with cough); ■ wheezing; ▲ asthma attack.

*Difference between age groups with $p < 0.001$; [‡]Difference between age groups with $p < 0.001$.

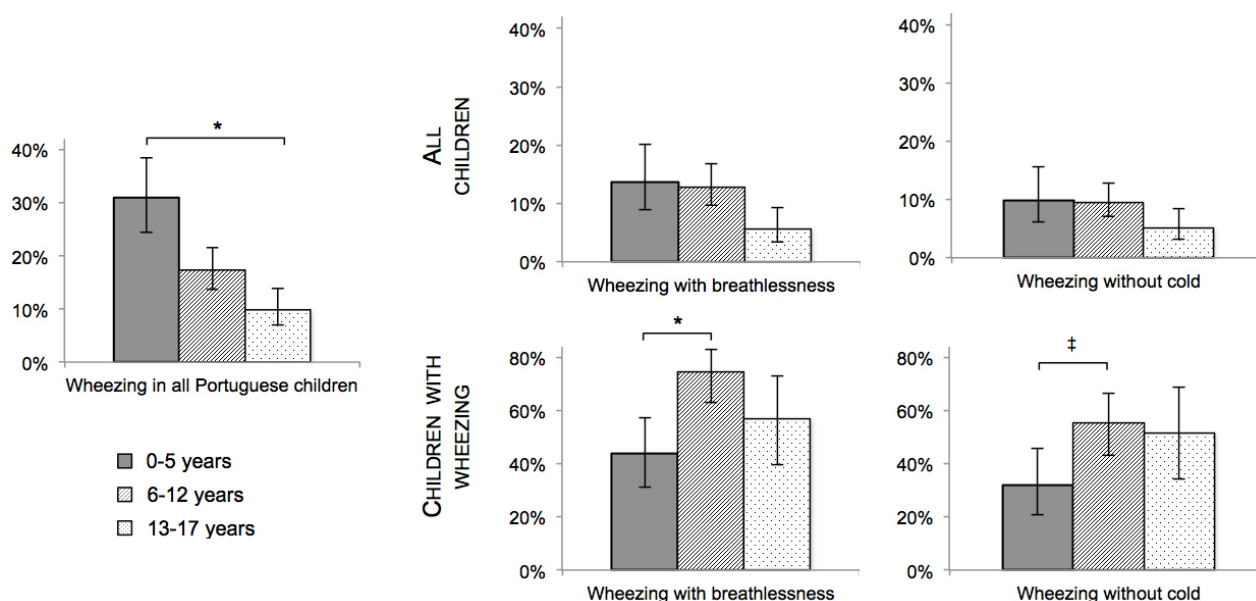


Figure 4 Weighted prevalence of wheezing with breathlessness and wheezing without a cold in the Portuguese pediatric population. * $p < 0.001$, † $p = 0.03$.

Prevalence of wheezing in all Portuguese children: 31.0% in 0- to 5-year age group (OR, 1.00); 17.3% in 6- to 12-year age group (OR, 0.46; 95%CI, 0.30–0.72); 9.9% in 13- to 17-year age group (OR, 0.25; 95%CI, 0.15–0.41). Prevalence of wheezing with breathlessness in all Portuguese children: 13.6% in 0- to 5-year age group; 12.8% in 6- to 12-year age group; 5.7% in 13- to 17-year age group. Prevalence of wheezing without a cold in all Portuguese children: 9.9% in 0- to 5-year age group; 9.5% in 6- to 12-year age group; 5.1% in 13- to 17-year age group. Prevalence of wheezing with breathlessness among all children who wheezed: 43.7% in 0- to 5-year age group (OR, 1.00); 74.4% in 6- to 12-year age group (OR, 3.73; 95%CI, 1.79–7.78); 57.0% in 13- to 17-year age group (OR, 1.71; 95%CI, 0.83–3.50). Prevalence of wheezing without a cold among all children who wheezed: 31.9% in 0- to 5-year age group (OR, 1.00); 55.2% in 6- to 12-year age group (OR, 2.64; 95%CI, 1.27–5.48); 51.7% in 13- to 17-year age group (OR, 2.28; 95%CI, 0.96–5.43).

Asthma prevalence

The prevalence of lifetime asthma was 11.2% (95%CI, 9.1–13.7), and that of current asthma was 8.4% (95%CI, 6.6–10.7). No statistically significant differences were found in the prevalence of current asthma according to region or other sociodemographic variables (Table 3). A higher risk for current asthma was found in children with rhinitis and eczema (OR, 5.20; 95%CI, 3.05–8.85 for rhinitis; and OR, 4.17; 95%CI, 2.41–7.19 for eczema). Table 7 shows an overview of different asthma definitions according to the inclusion of different proxies of asthma prevalence.

Table 7 Mean changes in serum myeloperoxidase per unit of several general and cardiovascular risk variables, in the normal weight and overweight/obesity groups.

	Population % (95%CI)	Total weighted population (2,066,953)
Lifetime asthma	11.2 (9.1-13.7)	230,886
Current asthma		
(with symptoms in the previous 12 months)		
Wheezing w/o cold	8.2 (6.5-10.4)	169,991
Lifetime asthma + wheezing	6.4 (4.8-8.6)	132,848
Lifetime asthma + wheezing OR waking with breathlessness	7.0 (5.3-9.1)	143,958
Lifetime asthma + wheezing OR asthma attack OR waking with breathlessness	7.2 (5.5-9.4)	149,199
Lifetime asthma + wheezing OR waking with breathlessness OR waking chest tightness OR waking cough	8.3 (6.5-10.6)	171,829
Lifetime asthma + wheezing OR asthma attack OR waking with breathlessness OR current asthma medication ^a	8.4 (6.6-10.7)	173,681
Lifetime asthma + wheezing OR asthma attack OR waking with breathlessness / chest tightness / cough	8.4 (6.6-10.7)	173,963
Lifetime asthma + wheezing OR asthma attack OR current asthma medication OR waking with breathlessness / chest tightness / cough	9.1 (7.2-11.5)	188,819

^a Definition used as *current asthma*

Diagnostic tests and medication for asthma

PFT and allergy tests (skin prick tests and/or blood allergy tests) were performed in 12.6% (95%CI, 10.3–15.2) and 28.3% (95%CI, 24.9–31.9) of children, respectively. About half of children with current asthma aged ≥ 6 years had undergone PFT (52.9%; 95%CI, 46.0–59.8), and this prevalence did not change if they have had an asthma attack in the previous 12 months. Children with current asthma who lived in rural areas were less likely to report diagnostic testing than those from urban areas (OR, 0.06; 95%CI, 0.04–0.09 for PFT; and OR, 0.39; 95%CI, 0.22–0.69 for allergy tests) (Table 8).

Among children with current asthma, the frequency of any asthma medication at the time of the interview was 76.4% (95%CI, 64.4–85.3). Inhaled reliever and controller therapy were used in the previous 12 months by 40.1% (95%CI, 28.5–53.0) and 41.5% (95%CI, 29.6–54.5) of children with current asthma, respectively (Table 9). Children who reported using only inhaled reliever medication in the previous year, without any inhaled controllers, were more likely to experience an asthma attack in the same time period (OR, 2.69; 95%CI, 1.24–5.84). Children with current asthma from rural areas were less likely to report using any inhaled therapy in the previous 12 months (OR, 0.20; 95%CI, 0.09–0.43).

Table 8 Weighted proportions (95% confidence interval) of pulmonary function tests, allergy tests (skin or blood), and inhaled medication use in Portuguese children with current asthma. Bold values are statistically significant differences between row subgroups.

	PFT^a ever % (95%CI)	Allergy tests^b ever % (95%CI)	Inhaled meds^c in the last 12 months % (95%CI)
All	45.7 (33.8-58.1)	79.9 (67.9-88.2)	67.6 (58.4-75.7)
Gender			
Female	36.9 (26.0-49.3)	87.0 (67.5-95.5)	74.9 (70.7-79.3)
Male	51.4 (41.3-61.4)	75.3 (70.2-79.8)	62.9 (49.1-74.9)
Age groups			
0-5 years old	21.9 (13.5-33.6)	48.4 (27.1-70.3)	72.1 (38.7-91.4)
6-12 years old	46.4 (40.2-52.7)	97.1 (96.8-97.5)	72.5 (64.8-79.1)
13-17 years old	61.5 (47.4-73.9)	79.4 (69.0-87.0)	58.1 (47.4-68.1)
National region			
North	44.0 (29.6-59.4)	93.3 (82.4-97.7)	57.9 (36.5-76.8)
Centre and Islands	38.6 (29.5-48.5)	75.6 (75.2-75.9)	69.8 (69.3-70.2)
South	53.9 (41.0-66.2)	71.3 (56.2-82.7)	74.7 (61.2-84.7)
Municipality^d			
Urban	57.6 (46.9-67.7)	83.9 (74.8-90.1)	76.4 (63.4-85.9)
Rural	7.3 (7.2-7.3)*	67.0 (66.6-67.5)*	39.2 (29.5-49.9)*
Allergic rhinitis			
No	43.8 (33.8-54.4)	71.4 (59.5-81.0)	67.6 (51.8-80.1)
Yes	47.4 (38.9-56.1)	87.7 (84.0-90.7)	67.7 (59.5-74.9)
Food allergy			
No	46.2 (38.4-54.2)	78.6 (72.0-84.0)	67.6 (57.8-76.1)
Yes	37.6 (37.6-37.6)	100.0 (n/a)	67.8 (67.8-67.8)

^aPFT: pulmonary function tests. ^bAllergy tests: blood and/or skin tests. ^cInhaled meds: inhaled medication use. n/a: not applicable; ^dMunicipality was classified as urban if residence was located in municipalities with at least one city (cities must have at least 8000 citizens) according to Portuguese law. *statistically significant.

Table 9 Weighted proportion of medication use in children with lifetime asthma or current asthma.

	Lifetime asthma % (95%CI)	Current asthma % (95%CI)
Pulmonary function tests	41.4 (31.6-51.9)	45.7 (33.8-58.1)
Allergy tests (skin and/or blood)	72.1 (62.1-80.3)	79.9 (67.9-88.2)
Any asthma medication at the time of survey^a	57.5 (47.3-67.1)	76.4 (64.4-85.3)
Inhaled therapy in previous 12 months	48.1 (38.1-58.3)	67.6 (55.5-77.8)
Reliever inhaled meds in previous 12 months	30.2 (21.1-41.1)	40.1 (28.5-53.0)
SABA ^b	23.7 (15.6-34.3)	31.5 (21.0-44.4)
Anticholinergics	6.4 (2.6-15.2)	8.6 (3.4-19.8)
Controller inhaled meds in previous 12 months	31.2 (22.0-42.3)	41.5 (29.6-54.5)
LABA ^c	4.8 (1.6-13.8)	6.4 (2.1-17.9)
Fluticasone	11.2 (5.7-20.9)	14.9 (7.6-27.1)
Budesonide	4.9 (2.1-10.6)	6.5 (2.8-14.0)
Budesonide/Formoterol	5.1 (2.3-11.1)	6.8 (3.0-14.7)
Fluticasone/Salmeterol	9.9 (4.6-19.8)	13.1 (6.2-25.6)
ONLY Reliever inhaled therapy in previous 12 months^d	17.9 (10.9-27.9)	23.8 (14.6-36.3)

^aReference to any asthma medication (inhaled, nebulized, or oral); ^bSABA: short-acting β -agonist; ^cLABA: long-acting β -agonist; ^dWithout use of inhaled controller therapy (no specific information on oral control therapy was available)

CONCLUSION

A high prevalence of asthma-like symptoms was found in the Portuguese pediatric population (39.4%; 95%CI, 35.7–43.3), and the prevalence of current asthma was 8.4% (95%CI, 6.6–10.7). This study showed that less than half of children with current asthma had been on inhaled controller medication in the previous 12 months and that only 52.9% of those aged ≥ 6 years had undergone PFT.

Asthma-like symptoms were present in more than one-third of Portuguese children, and the prevalence of current asthma was 8.4%. Age influenced asthma-like symptoms patterns, and asthma prevalence varied according to different definitions. Therefore, using composite measures and reporting different operational estimates is advisable. Fewer than half of the children with current asthma had used inhaled controller medications in the previous year, and those who used inhaled relievers alone had experienced twice more asthma attacks. PFT were underused among asthmatic children. Also, the findings on low inhaled controller medication and PFT use were more prevalent in children living in rural areas.

4.2 Paper 2

Ferreira-Magalhães M, Sá-Sousa A, Morais-Almeida M, Azevedo LF, Azevedo I, Pereira AM, Fonseca.

High prevalence of hospitalisation for asthma in a population-based paediatric sample

Arch Dis Child 2015; 100:507–508

AIMS

In 2010, we conducted the first Portuguese National Asthma Survey (INAsma) ⁹⁴. In the present paper, we focus on the results obtained from the INAsma pediatric population. In this paper, our aim was to report the proportion of lifetime hospitalisations for asthma in Portuguese children and adolescents aged 6- to 17-years-old (hereafter referred as “children”).

METHODS

Study design and setting

INAsma was a cross-sectional, population-based, all-age, nationwide telephone survey conducted in 2010 to estimate asthma prevalence and control in Portugal. Details on the first phase of INAsma methods are described above (see “Methods” section from “Paper 1”).

This study was reviewed and approved by the Ethics Committee of Centro Hospitalar de São João, Porto, Portugal. Informed consent was obtained from the parent(s) or legal guardian(s) of the children included in this study.

Participants and sample size

INAsma's first phase population was described above (see “Methods” section from “Paper 1”). The INAsma target population was the Portuguese general population, and the available population included citizens of all ages living in households with a landline telephone. A cluster sampling design was used to obtain a representative sample of the population. Briefly, all municipalities were used as natural strata, and a sample of households was then selected with a probability proportional to the municipality population as estimated in the 2001 National Census. Households were randomly selected from the 2010 residential White Pages telephone directory. Four different lists of telephone numbers were randomly selected for each municipality to allow for substitution of nonresidential telephone numbers. In total, 24 412 telephone numbers were retrieved. One participant (the last person to have had a birthday) was randomly selected from each household. In this study, we considered all included individuals aged <18 years old (henceforth referred to as “children” for simplification).

For this specific paper, we included all the INAsma participants aged 6- to 17-years-old (n=563); this sample was representative of the Portuguese children ⁹⁸. This sample size allowed us to estimate the prevalence of lifetime hospitalisations with a margin of error of 0.1, considering a 95% confidence level.

Instruments and data collection

Instruments and data collection were the ones described above for the first phase of INASma (see “Methods” section from “Paper 1”).

The instrument for data collection was the Portuguese version of the questionnaire used in the GA²LEN survey, which includes the European Community Respiratory Health Survey questions on asthma symptoms ⁹⁶. Several questions were added regarding socio-educational variables, medications, diagnostic test, and healthcare services use for asthma. Data were collected by computer-assisted telephone interviews from March to May 2010. Selected participants directly answered the questionnaire. However, in accordance with Portuguese legislation, when the selected individual was younger than 15 years old, the respondent was the usual and most knowledgeable caregiver. To minimize potential bias in data collection, several quality-assurance measures were followed (for details, see “Methods” section from “Paper 1”).

Variables

The main variables and outcomes were defined as follows:

Lifetime hospitalisations was defined as a positive answer to “Have you ever been hospitalised for asthma (inpatient admission >24 hours)?”.

Lifetime asthma was defined as a positive answer to “Have you ever had asthma?”.

current asthma was defined as lifetime asthma plus, at least, one of the following in the previous 12 months: wheezing, waking with breathlessness, asthma attack; or currently taking asthma medication.

The other variables were described above (see “Methods” section from “Paper 1”).

Statistical analysis

The sample estimates were weighted according to the 2001 National Census aiming for generalization to the target population ⁹⁸. Statistical analyses were performed using the complex samples tool of SPSS version 21 (SPSS IBM, New York, NY, USA).

Categorical variables were described using relative frequencies with 95%CI; comparisons were performed with Pearson's chi-squared test. Univariate logistic regression models for

outcomes were developed using independent variables as risk/predictive factors. Multivariate logistic regression models were developed to adjust for possible confounders. Results of multivariate logistic regression models were presented as odds ratios (ORs) with 95% CIs. A p-value of <0.05 was considered statistically significant.

RESULTS

The prevalence of lifetime hospitalisations for asthma in Portuguese children was 3.9% (95%CI, 2.6–5.7). In children with lifetime asthma, this prevalence was 29.7% (95%CI, 23.6–36.7) (Table 10). Children with current asthma had a higher prevalence of hospitalisations (36.5; 95%CI, 28.8–44.9) than children with history of lifetime asthma but without current asthma (prevalence, 13.4; 95%CI, 11.5–15.6) (OR, 3.70; 95%CI, 2.64–5.20). The presence of any asthma-like symptom in the previous 12 months increased the proportion of lifetime hospitalisations (OR 1.85; 95%CI, 1.16–2.95). Female children had more hospitalisations than males (OR 1.97; 95%CI, 1.22–3.18). No differences in the prevalence of lifetime hospitalisations were observed with socioeconomic status or in children with rhinitis, sinusitis, or food or drug allergies.

Table 10 Proportion and odds ratio (95%CI) for lifetime hospitalisations for asthma in Portuguese children aged 6- to 17-years-old with lifetime asthma. Bold values are statistically significant.

	Lifetime hospitalisations % (95%CI)	Odds Ratio for lifetime hospitalisations (95%CI)
Overall	29.7 (23.6-36.7)	
Sex		
Male	24.1 (18.0-31.5)	1.00 (Ref)
Female	38.5 (28.8-49.2)	1.97 (1.22-3.18)
Age groups		
6-12 years old	33.0 (24.2-43.1)	1.00 (Ref)
13-17 years old	26.4 (19.0-35.5)	0.73 (0.40-1.34)
Regions		
North	26.1 (20.0-33.2)	1.00 (Ref)
Centre and Islands	46.8 (33.8-60.3)	2.10 (1.31-4.76)
South	14.5 (6.2-30.2)	0.48 (0.18-1.31)
Municipality		
Urban	27.3 (19.1-37.4)	1.00 (Ref)
Rural	35.9 (35.9-35.9)	1.49 (0.94-2.37)
Socioeconomic status[‡]		
Low	34.1 (25.3-44.3)	1.00 (Ref)
Medium	19.7 (11.3-32.1)	0.47 (0.19-1.19)
High	23.5 (3.4-73.1)	0.59 (0.06-5.47)
ETS^{‡‡}		
No	34.4 (24.5-45.7)	1.00 (Ref)
Yes	24.0 (17.9-31.3)	0.60 (0.31-1.17)
'Wheezing'		
No	18.8 (15.2-23.0)	1.00 (Ref)
Yes	41.1 (32.7-50.1)	3.03 (2.15-4.26)
'Nocturnal symptoms'[*]		
No	21.8 (11.8-36.7)	1.00 (Ref)
Yes	34.6 (27.6-42.4)	1.90 (0.85-4.25)
'Asthma attack'		
No	23.4 (17.0-31.3)	1.00 (Ref)
Yes	43.5 (33.0-54.5)	2.52 (1.46-4.34)
'Asthma-like symptoms'^{††}		
No	21.2 (15.4-28.5)	1.00 (Ref)
Yes	33.2 (25.9-41.5)	1.85 (1.16-2.95)
'Current asthma'		
No	13.4 (11.5-15.6)	1.00 (Ref)
Yes	36.5 (28.8-44.9)	3.70 (2.64-5.20)

[‡]Socioeconomic status was categorized based on occupation and school education of the person who contributed most to the household income. ^{‡‡}Environmental tobacco smoke. ^{*} "Nocturnal symptoms" in the last 12 months: waking with breathlessness or waking with cough or waking with chest tightness. [†] "Asthma-like symptoms" in the last 12 months: wheezing or nocturnal symptoms or asthma attacks.

CONCLUSION

For the first time, the proportion of lifetime hospitalisations for asthma was reported for a national population-based paediatric sample. In the present study, a high number of hospitalisations for asthma were observed, with more than 55,000 Portuguese children aged 6- to 17-years-old hospitalised for asthma during their lifetime. Moreover, of the children with current asthma more than one third had been hospitalised for asthma, at least once in their lifetime. Our results should contribute to improve knowledge on asthma-related hospitalisations in children, leading to the development of healthcare programs aiming to reduce their frequency.

4.3 Paper 3

Ferreira-Magalhães M, Pereira AM, Sá-Sousa A, Morais-Almeida M, Azevedo I, Azevedo LF, Fonseca JA.

Asthma control in children is associated with nasal symptoms, obesity and health insurance: a nationwide survey

Pediatr Allergy Immunol 2015; 26(5):466-473.

ABSTRACT

Background: This study aimed to estimate the prevalence of asthma control and determinants of poor control in the Portuguese pediatric population (<18 years); secondarily, we described asthma-related healthcare services and medication use.

Methods: Data of 98 children with current asthma, from the second phase of a nationwide population-based telephone survey (INAsma study), were analysed. Asthma control definition was based on GINA criteria, grouping partially controlled and uncontrolled asthma as 'not-controlled asthma' (NCA). We used multivariate logistic regression to study factors associated with NCA and with unscheduled medical visits for asthma.

Results: About half of the children had NCA (49%, 95%CI 39-59%). In the multivariate model, risk factors for NCA were: substantial nasal symptoms (aOR 6.80), overweight/obesity (aOR 3.44) and not having health insurance (aOR 3.78). All the children with NCA had nasal symptoms, and the lack of asthma control was also associated with the increasing number of nasal symptoms ($p<0.001$).

In the previous year, 90% (95%CI 84-96%) of children with current asthma had healthcare visits and 67% (95%CI 58-77%) used medication for asthma. The risk of unscheduled medical visits was higher in children with nasal symptoms (aOR 3.63) and in those without health insurance (aOR 2.79), and lower in adolescents (aOR 0.19).

Conclusions: Half of the children with asthma were poorly controlled. Nasal symptoms and obesity are important determinants of asthma control. Children without health insurance are at greater risk of poor asthma outcomes; this association is reported for the first time in a European country.

AIMS

In 2010, we conducted the first Portuguese National Asthma Survey (INAsma), a two-phase nationwide study aiming to estimate asthma prevalence and control.⁹⁴ In the present paper, we report data from children and adolescents included in the second phase of the study. Our aims were to estimate the prevalence of asthma control and determinants of poor control in the Portuguese pediatric population (<18 years old). Secondary aims were to describe asthma-related healthcare services and medication use.

METHODS

Study design and setting

INAsma was a nationwide survey from the general population applied by telephone interview to individuals living in Portugal in 2010.

This study was approved by the Ethics Committee of *Centro Hospitalar de São João*, Porto, Portugal. Oral informed consent was obtained from parent(s) or legal guardian(s). We followed the STROBE statement for reporting observational studies ⁹⁵.

Sample size

The sample size calculation was based on confidence intervals for proportions. The sample size for this study was calculated considering the two phases of the INAsma research project. In the first phase, we aimed to estimate the current asthma prevalence in the Portuguese population. In the second phase, we aimed to estimate the proportion of patients with controlled asthma symptoms. Thus, in the second phase of the project, to estimate the proportion of patients with controlled asthma with a 3% margin of error and 95% confidence level, and assuming a proportion of 20% of patients with uncontrolled asthma in the population, we required a sample of at least 554 patients with asthma identified in the first phase of the project. Assuming a 20% loss to follow-up, we required at least 665 patients with asthma during the first phase. Within these premises, and assuming a prevalence of 6% in the Portuguese population and a margin of error of 0.65%, we required a sample of at least 6,000 persons from the general Portuguese population willing to participate in the first phase of the project.

Participants

The target population was the Portuguese general population. The available population included all individuals living in Portugal in households with a landline telephone (sampling frame). To obtain a representative sample of the population, a stratified cluster sampling design was used.

In the first phase of INAsma, all municipalities were used as natural strata; in each municipality, a sample of households with a landline telephone number was selected with a probability proportional to the municipality population as estimated in the 2001 National

Census. The target number of households was set at 6,103. The sample of households was derived from the directory listed in the residential White Pages from 2010. A list of all telephone numbers in a specific municipality was compiled to draw a sample of telephone numbers within that municipality. A sample of household telephone numbers was randomly selected from the whole list in each municipality. Because part of the selected telephone numbers were from companies or were not allocated, four lists were randomly selected for each municipality to allow for substitution of non-residential telephone numbers. In total, 24,412 telephone numbers were retrieved.

After the selection and identification of a residential number, one participant was randomly selected from each household. After identification of all residents in the household, the selected participant in each household was the last person to have had a birthday. When the selected individual was younger than 15 years, the respondent was the usual caregiver. Individuals were excluded if they did not understand spoken Portuguese or had cognitive or physical conditions that could hamper the interview. In the final 20% of the sample, an oversampling strategy of male adults and younger adults subjects was used to correct the common overrepresentation of female and older participants observed in the interim analysis.

In the second phase of INAsma, all the participants that were identified as having current asthma in this first phase of the INAsma study were eligible for participation in the second phase. Additional asthmatics identified in the participant households were also contacted. Individuals identified as having rhinitis only or as healthy that agreed to participate in the second phase of the study were re-contacted and used for comparison purposes (not used for this paper purposes).

Instruments and data collection

The instrument for data collection in the second phase of INAsma was based on the Portuguese version of the GA²LEN survey questionnaire ⁹⁶; it also included the Control of Allergic Rhinitis and Asthma Test (CARAT)⁹⁹ and questions on socio-educational factors and use of healthcare resources.

An experienced private company administered the questionnaire, using computer-assisted telephone interviews performed by trained and experienced interviewers. In the first phase,

interviews were conducted from March to May of 2010. In the second phase, interviews were conducted from June to October of 2010.

Interviews were conducted mostly from 17:00 to 22:00 h on weekdays and 11:00 to 22:00 h on weekends and holidays. No telephone number was abandoned until a minimum of 10 attempts had been made on different occasions. To minimize other potential biases in data collection, several quality assurance measures were followed: interviewers were selected based on their previous experience with health-related data collection; each question was discussed in training sessions held between researchers and all interviewers; a research assistant was present during the setup, training, and daily work of the interviewers, motivating and checking compliance with standardized operational procedures; data validity was periodically verified soon after being collected, and custom statistic algorithms were used to detect extreme, illogical, and missing values; and the clarity of the questionnaire and its telephonic administration were assessed in a pilot study involving 25 individuals before starting the data collection.

Variables and outcomes definition

Current asthma was defined as children with lifetime asthma plus at least one of the following: wheezing, awakening with breathlessness or having an asthma attack in the last 12 months, or taking asthma medication at the time of the interview.

Asthma control definition was based on GINA criteria for asthma symptom control ¹⁰⁰: 'Well-controlled asthma' (WCA) corresponds to "well controlled" from GINA guidelines; and partially controlled and uncontrolled were grouped as 'Not controlled asthma' (NCA).

Unscheduled medical visits for asthma was defined as having at least one emergency department and/or any unscheduled medical attendance because of asthma worsening/exacerbation in the previous 12 months.

Nasal symptoms were classified as 'mild/absent' or 'substantial' based on the daily frequency of 4 isolated symptoms - runny nose, stuffy nose, itchy nose or sneeze in the previous 4 weeks. Each symptom was scored as: 0, if present "almost every day"; 1, if "≥ 2 days a week"; 2, if "1 or 2 days a week"; or 3, if "never". When the sum of all symptoms was > 7, nasal symptoms were classified as 'mild/absent'; when ≤ 7 they were considered 'substantial'.

Overweight/obesity was defined as a z-score >1 for body-mass index (BMI), using WHO Growth reference 2007 macros.¹⁰¹

Having health insurance was defined as a positive answer to “Do you/your child have/has any healthcare insurance?”.

Previous medical diagnosis of rhinitis was defined as a positive answer to “Have you been diagnose as having rhinitis by a doctor?”.

Night awakening with symptoms was defined as at least one of 3 symptoms in the last 12 months: waking with breathlessness, waking with chest tightness or waking with coughing.

Controller medication was defined as use of any inhaled steroid, inhaled long-acting β -agonist, inhaled association of steroid and β -agonist or leukotriene receptor antagonist.

Reliever medication: use of any inhaled/nebulized short-acting β -agonist or anticholinergic, oral short-acting β -agonist or oral steroid.

Other medication was defined as use of any antihistamine or cough medication for asthma-like symptoms.

Any asthma medication was defined as use of any controller, reliever or other medication for asthma-like symptoms.

Municipality was classified as urban, if residence was located in municipality with at least one city (cities must have at least 8000 citizens), according to Portuguese law ⁹⁷.

Socioeconomic Status was categorized based on family income, occupation and school education of the person who contributes more for the household income.

ETS: was defined as a positive answer to “Does anyone smoke inside your home?”.

Study sample and statistical analysis

The sample size was calculated considering the two phases of the INAsma study ⁹⁴. The proportion of not controlled asthma was estimated with a margin of error of 0.098, considering a 95% confidence level (95%CI). Statistical analyses were performed using SPSS version 22 (SPSS IBM, New York, NY, USA). Categorical variables were described using frequencies and compared with Pearson's chi-squared test. We used multivariate logistic

regression analysis to evaluate which variables were associated with 1) NCA and with 2) asthma-related unscheduled medical visits. For each outcome, we used a data-driven backward approach, with *a priori* inclusion of predictive variables with p-value <0.20 in univariate analysis. The two final multivariate models included the statistically significant variables. Results from the logistic regressions were presented as adjusted odds ratio (aOR) with 95%CI. A p-value <0.05 was considered statistically significant. Hosmer-Lemeshow test and percentage of correctly predicted cases were used to assess goodness-of-fit for logistic regression models.

RESULTS

Overall, 716 children completed the first phase of the INAsma study (Figure 2); all the participants identified as having current asthma were eligible for participation in the second phase. Additional asthmatics identified in the participants' households were also contacted. The flowchart (Figure 6) summarizes the children included in INAsma study. The participant's characteristics are summarized in Table 11.

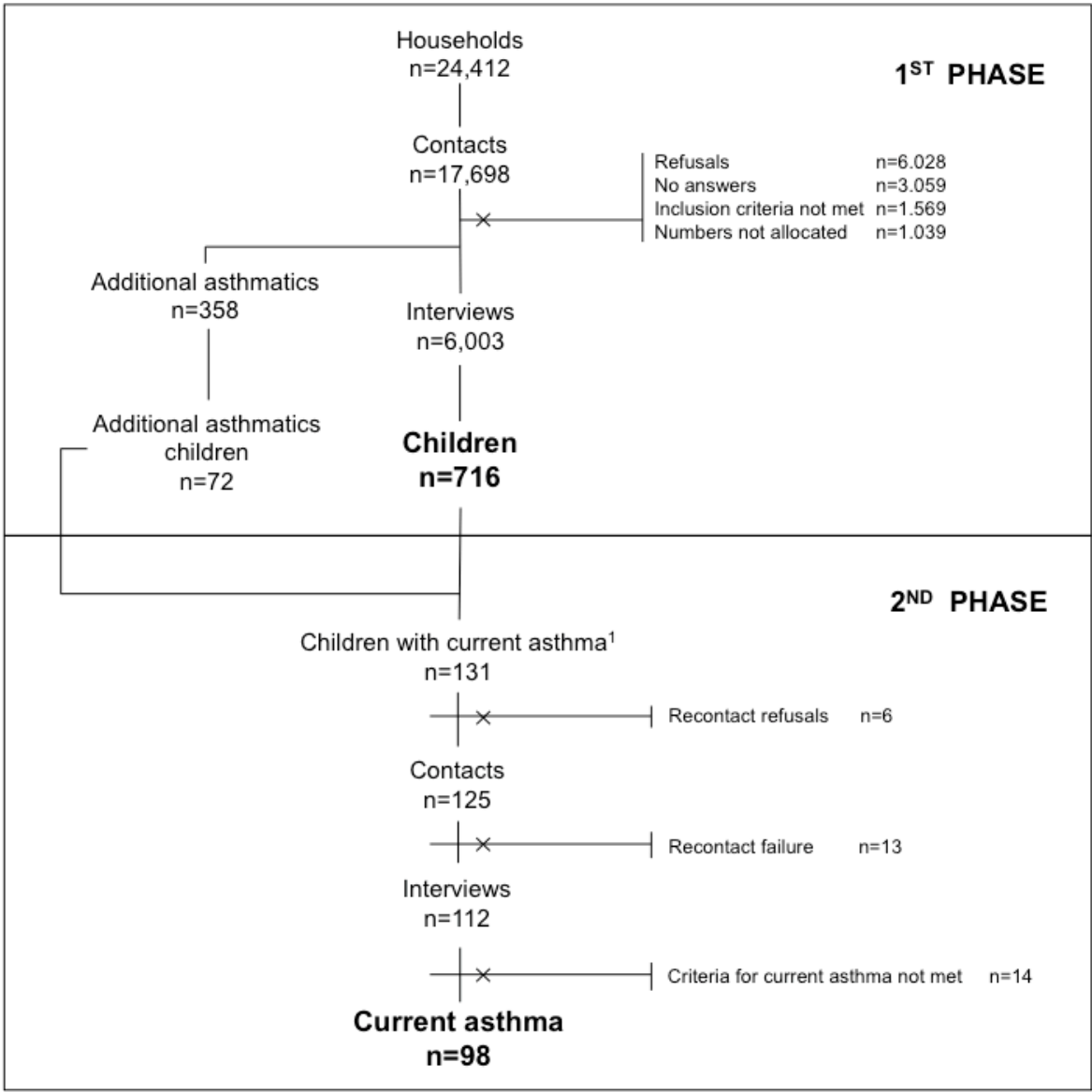


Figure 6 Participants' flowchart.

¹Current asthma - Lifetime asthma + (wheezing OR asthma attack OR awakening with breathlessness OR current asthma medication).

Table 11 Participants characteristics - n(%). There are not statistical differences between diagnostic groups. Statistically significant differences in asthma control are presented in bold.

	Current asthma (n=98)	Asthma Control	
		Well Controlled (n=48)	Not controlled (n=46)
Gender			
Female	33 (33%)	14 (45%)	17 (55%)
Male	65 (66%)	34 (54%)	29 (46%)
Age groups			
0-5 years old	18 (18%)	11 (65%)	6 (35%)
6-12 years old	46 (47%)	22 (50%)	22 (50%)
13-17 years old	34 (35%)	15 (46%)	18 (55%)
Region			
North	46 (47%)	21 (49%)	22 (51%)
Centre/Islands	22 (22%)	9 (41%)	13 (59%)
South	30 (30.6)	18 (62%)	11 (38%)
Municipality[†]			
Rural	24 (25%)	10 (44%)	13 (57%)
Urban	74 (76%)	38 (54%)	33 (47%)
SES[#]			
High	15 (15%)	11 (73%)	4 (27%)
Medium	33 (34%)	18 (60%)	12 (40%)
Low	50 (51%)	19 (39%)	30 (61%)
Health insurance			
Yes	47 (50%)	30 (68%)	14 (32%)
No	47 (50%)	17 (36%)	30 (64%)
Body mass index			
Thinness	3 (3%)	1 (33%)	2 (67%)
Normal	57 (60%)	33 (62%)	20 (38%)
Overweight/Obesity	35 (37%)	11 (31%)	24 (69%)
ETS[‡]			
Yes	40 (41%)	23 (59%)	16 (41%)
No	58 (59%)	25 (46%)	30 (55%)

[†]Municipality was classified as urban if residence was located in municipalities with at least one city (cities must have at least 8000 citizens) according to Portuguese law; [#]Socioeconomic Status, categorized based on family income, occupation and school education of the person who contributes more for the household income. [‡]Environmental Tobacco Smoke. *p=0.03. **p=0.002. ***p=0.005.

About half of the children with current asthma had NCA (49%, 95%CI 39-59%; Table 11). Nasal symptoms in the previous 4 weeks were present in 89% (95%CI 83-95%) of children with current asthma (Table 12). Nevertheless, previous medical diagnosis of rhinitis was made in only 45% (95%CI 35-55%) of children with current asthma. All asthma-like and nasal symptoms were more frequent in children with NCA (p<0.001; Figure 7 and Table 13), when compared with WCA. In children with a parent/self-report of good asthma control, only 52% fulfilled the criteria for WCA.

Table 12 Rhinitis diagnosis ever and nasal symptoms in the previous 4 weeks, in children with current asthma, % (95%CI); and level of asthma control within children with rhinitis diagnosis ever and nasal symptoms in the previous 4 weeks, % (95%CI).

	Current asthma children	Asthma Control		p
		Well controlled	Not controlled	
Doctor diagnosis of rhinitis				
No	55% (45-65)	49% (33-65)	51% (35-68)	0.42
Yes	45% (35-55)	53% (40-66)	47% (34-60)	
Any nasal symptom*				
No	11% (5-17)	100% (n/a)	0% (n/a)	0.001
Yes	89% (83-95)	45% (34-55)	55% (45-66)	
Itchy nose				
No	34% (25-42)	77% (63-92)	23% (8-37)	<0.001
Yes	66% (57-75)	38% (26-50)	62% (50-74)	
Sneeze				
No	33% (23-42)	67% (50-84)	33% (16-50)	0.04
Yes	67% (58-77)	44% (32-56)	56% (44-69)	
Runny nose				
No	56% (46-66)	64% (52-77)	36% (23-48)	0.004
Yes	44% (34-54)	33% (19-48)	67% (52-82)	
Stuffy nose				
No	48% (38-58)	73% (60-86)	27% (14-41)	<0.001
Yes	52% (42-62)	31% (18-44)	69% (57-82)	
Number of nasal symptoms				
0	11% (5-17)	100% (n/a)	0% (n.a.)	<0.001
1	10% (4-15)	100% (n/a)	0% (n.a.)	
2	37% (27-46)	50% (33-67)	50% (33-69)	
3	24% (16-33)	32% (12-51)	68% (49-88)	
4	19% (11-27)	22% (3-41)	78% (59-97)	

*'Any nasal symptom': runny nose or stuffy nose or itchy nose or sneeze. n/a: not applicable.

Table 13 Proportion (%) of children with asthma-like symptoms, nasal symptoms and life impairment by asthma-like/nasal symptoms in the previous 4 weeks (never, ≤ 2 days/week or >2 days/week), according to asthma control.

	Well Controlled			Not controlled		
	Never	≤ 2	>2	Never	≤ 2	>2
Any asthma like-symptom*	83%	17%	0%	13%	33%	54%
Wheezing	88%	13%	0%	44%	24%	31%
Breathlessness	92%	8%	0%	52%	27%	21%
Chest tightness during exercise	100%	0%	0%	42%	29%	29%
Any nasal symptom*	23%	29%	48%	0%	11%	89%
Runny nose	73%	15%	13%	44%	22%	35%
Stuffy nose	48%	28%	24%	26%	35%	39%
Itchy nose	50%	13%	38%	15%	22%	63%
Sneeze	42%	27%	31%	22%	20%	59%
Any daily limitation*	100%	0%	0%	28%	26%	46%
Night wakening w/ symptoms [‡]	100%	0%	0%	52%	17%	30%
Daily activities limitation [‡]	100%	0%	0%	50%	20%	30%

* $p < 0.001$ between WCA and NCA. [‡] because of asthma-like or nasal symptoms

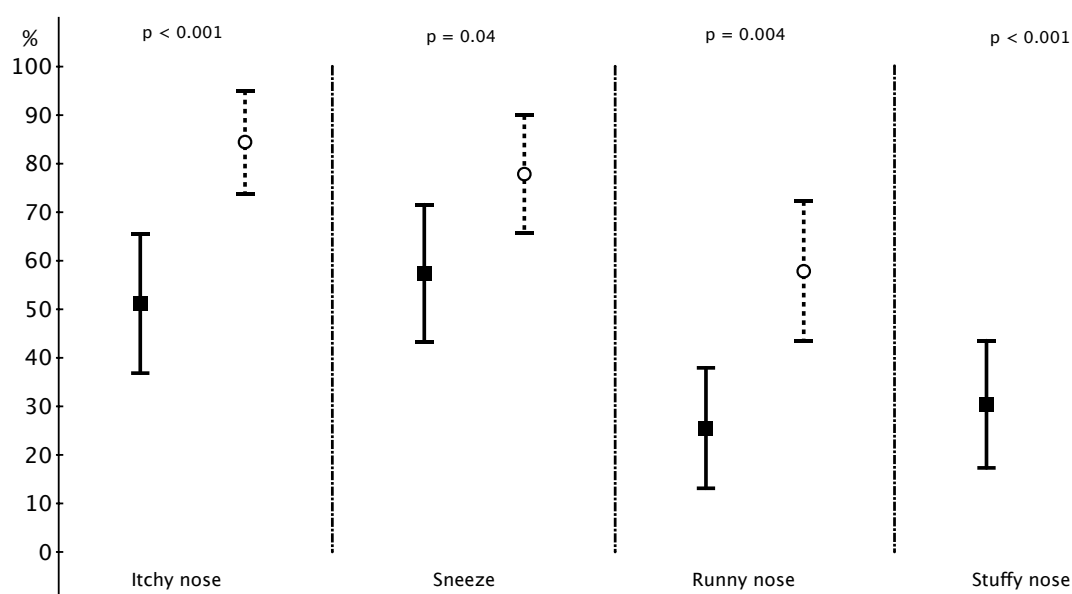


Figure 7 Prevalence of isolated nasal symptoms in asthmatic children, stratified by asthma control (prevalence and 95%CI).

Full line – controlled asthma; Dotted line – not controlled asthma.

Determinants of poor asthma control

Control of asthma was significantly worse in children with substantial nasal symptoms, overweight/obesity, lower socioeconomic status, unscheduled medical attendance for asthma or in those without health insurance coverage, in univariate analysis (Table 14).

Children with any nasal symptom had significantly more NCA ($p=0.001$; Table 13). Moreover, as the number of nasal symptoms increased, the proportion of children with NCA also increased (Figure 8): none of the children with 0 or 1 nasal symptom had NCA, while 50% of those with 2 symptoms, 68% of those with 3 symptoms and 78% of those with 4 different nasal symptoms had NCA.

In the final multivariate model, the risk factors for NCA were: having substantial nasal symptoms (aOR 6.80, 95%CI 2.34-19.80), overweight/obesity (aOR 3.60, 95%CI 1.46-10.13) and not having health insurance (aOR 3.78, 95%CI 1.36-10.92).

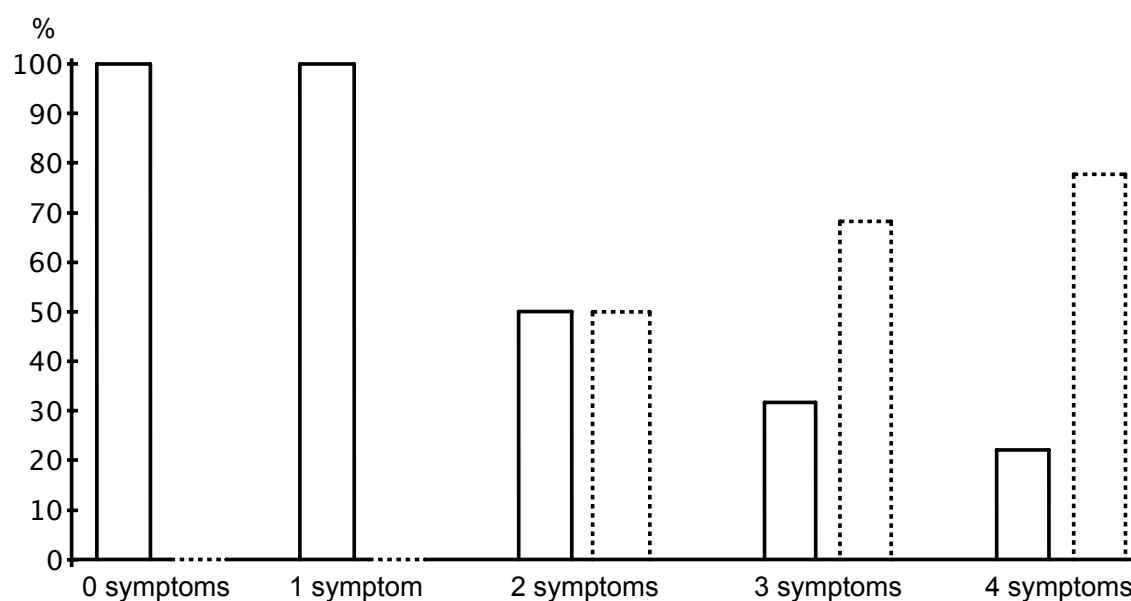


Figure 8 Frequency of number of nasal symptoms in asthmatic children, according to asthma control.

Full line – well-controlled asthma; Dotted line – not controlled asthma.

Table 14 Crude and adjusted odds ratio for not controlled asthma and unscheduled medical visits.

	Not controlled asthma		Unscheduled visits	
	Crude odds ratio (95%CI)	Adjusted odds ratio (95%CI)	Crude odds ratio (95%CI)	Adjusted odds ratio (95%CI)
Gender				
Female	1.00 (ref)	n.i.	1.00 (ref)	n.i.
Male	0.70 (0.30-1.67)		1.54 (0.66-3.61)	
Age				
0-5 years old	1.00 (ref)	n.i.	1.00 (ref)	1.00 (ref)
6-12 years old	1.83 (0.58-5.83)		1.16 (0.38-3.53)	0.72 (0.21-2.43)
13-17 years old	2.20 (0.66-7.36)		0.37 (0.11-1.24)	0.19 (0.05-0.78)
Body mass index				
Normal	1.00 (ref)	1.00 (ref)	1.00 (ref)	n.i.
Overweight/Obese	3.60 (1.46-8.89)	3.44 (1.17-10.13)	0.74 (0.32-1.73)	
Nasal symptoms				
Absent/mild	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Substantial	4.42 (1.85-10.56)	6.80 (2.34-19.80)	2.82 (1.22-6.53)	3.63 (1.39-9.51)
Municipality[†]				
Rural	1.00 (ref)	n.i.	1.00 (ref)	n.i.
Urban	0.67 (0.26-1.72)		0.66 (0.26-1.67)	
SES[#]				
High	1.00 (ref)		1.00 (ref)	
Medium	1.83 (0.47-7.13)		2.08 (0.54-8.01)	
Low	4.34 (1.21-15.63)	n.i.	2.71 (0.75-9.80)	n.i.
Health insurance				
Yes	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
No	3.78 (1.59-9.02)	3.85 (1.36-10.92)	2.10 (0.92-4.81)	2.79 (1.08-7.21)
Local of asthma care				
Public	1.00 (ref)	n.i.	1.00 (ref)	n.i.
Private	0.71 (0.31-1.60)		0.68 (0.30-1.53)	
Scheduled medical visits				
Yes	1.00 (ref)		1.00 (ref)	
No	0.30 (0.08-1.20)	n.i.	0.30 (0.08-1.17)	n.i.
Unscheduled medical visits				
Yes	1.00 (ref)		-	-
No	0.44 (0.19-0.99)	n.i.	-	-
Asthma control				
Controlled	-	-	1.00 (ref)	n.i.
Not controlled	-	-	2.29 (1.01-5.28)	

Bold values show statistical significant differences. n.i.: not included in the model (non-significant variables)

[†]Municipality was classified as urban if residence was located in municipalities with at least one city (cities must have at least 8000 citizens) according to Portuguese law; [#]Socioeconomic Status, categorized based on family income, occupation and school education of the person who contributes more for the household income.

Asthma control model: Hosmer-Lemeshow test = 0.37 and 75% of correctly predicted cases.

Unscheduled visits model: Hosmer-Lemeshow test = 0.95 and 67% of correctly predicted cases.

Healthcare visits and medication use by children with current asthma

Healthcare medical visits for asthma are discriminated in Table 15. In the previous 12 months, 90% (95%CI 84-96%) of children with current asthma had at least one asthma-related visit to healthcare services (Table 15): 86% (95%CI 79-93%) had scheduled medical visits, 39% (95%CI 29-48%) had emergency room visits and 25% (95%CI 16-33%) had at least one unscheduled medical visit to a doctor. All the pre-schoolers had asthma-related healthcare visits (scheduled or unscheduled) in the last year, compared to 94% (95%CI 86-100%) of school age children and 79% (95%CI 66-93%) of adolescents ($p=0.04$). The determinants of unscheduled medical visits, in the multivariate model, were substantial nasal symptoms (aOR 3.63, 95%CI 1.39-9.51), not having health insurance (aOR 2.79, 95%CI 1.08-7.21) and age 13- to 17-years-old (aOR 0.19, 95%CI 0.05-0.78; Table 14). Children with NCA had significant more unscheduled medical visits and hospitalisations.

In children with current asthma, 67% (95%CI 58-77%) used asthma medication in the previous 4 weeks (Table 16): controller medication was used by 58% (95%CI 48-68%) and reliever medication by 31% (95%CI 22-40%). Children with NCA had a non-significant higher frequency of any medication use (76%, 95%CI 64-88%) when compared with those with WCA (58%, 95%CI 44-72%); no statistically significant differences were seen in the use of controller or reliever medication. Over-the-counter medications (e.g.: antihistamines and cough medication) were used more frequently by children with NCA ($p<0.02$; Table 17). School-aged children used more asthma medication ($p=0.03$), comparing with pre-schoolers and adolescents (Table 16).

Table 15 Healthcare medical visits for asthma in the previous 12 months, % (95%CI). Statistically significant differences in asthma control are presented in bold.

	Healthcare medical visits	Scheduled	Unscheduled	Emergency Department	Hospitalisations
Overall	90% (84-96)	86% (79-93)	25% (16-33)	39% (29-48)	5% (1-10)
Gender					
Female	91% (81-100)	87% (81-94)	18% (10-25)	33% (23-42)	0% (n.a.)
Male	89% (82-97)	85% (78-92)	29% (19-38)	42% (32-52)	7% (2-13)
Age groups					
0-5 years old	100% (n/a)*	88% (82-95)	23% (15-32)	47% (37-57)	11% (4-17)
6-12 years old	93% (86-100)*	91% (85-96)	32% (23-42)	46% (36-56)	4% (0-8)
13-17 years old	79% (66-93)*	78% (69-86)	15% (8-22)	25% (16-33)	3% (0-6)
Region					
North	93% (86-100)	84% (77-92)	26% (17-35)	37% (27-46)	0% (n.a.)
Centre/Islands	86% (72-100)	90% (84-96)	33% (23-42)	52% (42-62)	19% (11-26)
South	87% (75-99)	86% (79-93)	17% (9-24)	34% (25-44)	3% (0-7)
Municipality					
Rural	83% (68-98)	75% (58-92)	21% (5-37)	50% (30-70)	5% (0-14)
Urban	92% (86-98)	89% (81-96)	26% (16-36)	35% (24-46)	5% (0-10)
SES†					
High	86% (67-100)	73% (51-95)	14% (7-21)	21% (1-42)	7% (0-20)
Medium	88% (77-99)	82% (69-95)	24% (9-39)	36% (20-52)	0% (n.a.)
Low	92% (85-100)	92% (85-99)	28% (16-40)	45% (31-59)	8% (1-16)
Health insurance					
No	94% (86-100)	84% (76-91)	27% (18-36)	51% (41-61)	9% (3-14)
Yes	89% (81-98)	91% (86-97)	25% (16-34)	31% (22-41)	2% (0-5)
ETS‡					
No	90% (80-99)	88% (83-95)	24% (16-33)	39% (29-48)	4% (0-7)
Yes	90% (82-98)	83% (74-90)	26% (18-34)	39% (29-48)	8% (2-12)
Asthma control					
Controlled	87% (78-97)	81% (70-92)	15% (5-25)	30% (17-43)	0% (n.a.)
Not controlled	96% (90-100)	94% (87-100)	35% (21-49)#	46% (32-60)	11% (2-20)#

‡Environmental Tobacco Smoke. †Socioeconomic Status, categorized in high (A social class), medium (B and C social classes) and low (D social class) based on occupation and school education of the person who contributes more for the household income. *p=0.04. #p=0.03

Table 16 Medication use for asthma in the previous 4 weeks, in children with current asthma, % (95%CI). Statistically significant differences in asthma control are presented in bold.

	Any asthma medication	Controller medication	Reliever medication
All children with current asthma	67% (58-77)	58% (48-68)	31% (22-40)
Gender			
Female	76% (61-90)	67% (51-83)	36% (20-53)
Male	63% (51-75)	54% (42-66)	28% (17-39)
Age groups			
0-5 years old	56% (33-79)	50% (27-73)	22% (3-41)
6-12 years old	80% (69-92)[#]	67% (54-81)	37% (23-51)
13-17 years old	56% (39-73)	50% (33-67)	27% (12-41)
Region			
North	72% (59-85)	67% (54-81)	28% (15-41)
Centre/Islands	68% (49-88)	46% (25-66)	41% (20-61)
South	60% (43-78)	53% (36-71)	27% (11-43)
Municipality[†]			
Rural	58% (39-78)	46% (26-66)	29% (11-47)
Urban	70% (60-81)	62% (51-73)	31% (21-42)
SES[#]			
High	73% (51-96)	60% (35-85)	47% (22-72)
Medium	67% (51-83)	67% (51-83)	21% (7-35)
Low	66% (53-79)	52% (38-66)	32% (19-45)
Health insurance			
Yes	62% (48-76)	57% (43-72)	28% (15-41)
No	72% (60-85)	57% (43-72)	36% (23-50)
ETS[‡]			
Yes	65% (50-80)	48% (32-63)	38% (23-53)
No	69% (57-81)	66% (53-78)	26% (15-37)
Asthma control			
Controlled	58% (44-72)	52% (38-66)	25% (13-37)
Not controlled	76% (64-88)	63% (49-77)	39% (25-53)

[†]Municipality was classified as urban if residence was located in municipalities with at least one city (cities must have at least 8000 citizens) according to Portuguese law. [#]Socioeconomic Status, categorized based on family income, occupation and school education of the person who contributes more for the household income.

[‡]Environmental Tobacco Smoke. n/a: not applicable. [#]p=0.03

Table 17 Asthma medication use in the previous 4 weeks, in children with current asthma, % (95%CI). Statistically significant differences in asthma control are presented in bold.

	Asthmatics	Asthma Control		p-value
		Well controlled	Not controlled	
Any asthma meds	67% (58-77)	58% (44-72)	76% (64-88)	0.07
Rescue meds[†]	31% (22-40)	25% (13-37)	39% (25-53)	0.14
SABA inh/nbz	30% (21-39)	25% (13-37)	37% (23-51)	0.21
Ipatrop inh/nbz	10% (4-16)	10% (2-19)	11% (2-20)	0.94
Oral SABA	1% (0-3)	0% (n/a)	2% (0-6)	0.49
Oral steroids	1% (0-3)	0% (n/a)	2% (0-6)	0.49
Control meds[‡]	58% (48-68)	52% (38-66)	63% (49-77)	0.28
ICS inh alone	24% (15-32)	19% (8-30)	28% (15-41)	0.28
ICS + LABA inh	21% (13-30)	19% (8-30)	24% (12-36)	0.54
LABA inh alone	98% (95-100)	100% (n/a)	96% (90-100)	0.24
LTRA	30% (21-39)	29% (16-42)	26% (13-39)	0.74
Other meds	32% (23-41)	21% (9-32)	43% (29-58)	0.02
Antihistamine	29% (20-38)	21% (9-32)	39% (25-53)	0.05
Cough meds	2% (0-5)	0% (n/a)	4% (0-10)	0.24

SABA: short-acting β -agonist. Inh: inhaled. nbz: nebulized. ICS: inhaled corticosteroids. LABA: long-acting β -agonist. LTRA: leukotriene receptor antagonist (LTRA). n/a: not applicable.

[†]SABA or ipratropium or oral steroids. [‡]ICS alone or LABA alone or ICS + LABA or LTRA

Healthcare insurance and healthcare services access

The frequency of children with health insurance coverage followed in private practice/hospital for their asthma was significantly higher than those followed in public settings ($p<0.001$; Table 18).

Table 18 Proportion of healthcare insurance coverage, n (%). Statistically significant differences in asthma control are presented in bold.

	Healthcare insurance	
	No (n=47)	Yes (n=47)
Region		
North	20 (44%)	25 (56%)
Centre/Islands	15 (71%)	6 (29%)
South	12 (43%)	16 (57%)
Municipality[†]		
Urban	32 (45%)	39 (55%)
Rural	15 (65%)	8 (35%)
SES[#]		
Low	37 (77%)	11 (23%)
Medium	8 (26%)	23 (74%)
High	2 (13%)	13 (87%)
Local of asthma care		
<u>Public</u>	34 (72%)	13 (28%)
Primary care	12 (80%)	3 (20%)
Hospital	22 (69%)	10 (31%)
<u>Private</u>	12 (27%)	33 (73%)
Practice	12 (28%)	31 (72%)
Hospital	0 (0%)	2 (100%)
Scheduled medical visits		
No	8 (67%)	4 (33%)
Yes	39 (48%)	43 (52%)
Unscheduled medical visits		
No	20 (42%)	28 (58%)
Yes	17 (60%)	18 (40%)

[†]Municipality was classified as urban if residence was located in municipalities with at least one city (cities must have at least 8000 citizens) according to Portuguese law; [#]Socioeconomic Status, categorized based on family income, occupation and school education of the person who contributes more for the household income.

* $p<0.001$

CONCLUSION

Only half of children with asthma were controlled in this nationwide study. Determinants for not controlled asthma were the presence of substantial nasal symptoms, overweight/obesity and not having healthcare insurance. Our results support the importance of modifiable factors, namely nasal symptoms and obesity, as determinants of asthma control in children. Healthcare insurance status was related to asthma control; in our healthcare system, this association may be related to parents' options in choosing the site of medical asthma care for their children. More studies are needed to understand the effect on asthma control of the access to different types of asthma care services and of being able to choose where the child is cared for asthma.

4.4 Paper 4

Ferreira-Magalhães M, Pereira AM, Sá-Sousa A, Azevedo I, Azevedo LF, Fonseca JA.

Cost of asthma in children: a nationwide, population-based, cost-of-illness study

Submitted

ABSTRACT

Background: This study aimed to estimate the cost of asthma in Portuguese children; furthermore, we studied the factors associated with cost of asthma and the costs per level of asthma control.

Methods: A nationwide, population- and prevalence-based cost-of-illness study with a societal perspective was conducted. We measured direct and indirect costs using a bottom-up approach and a human capital method, respectively, for 208 children (<18 years), from two national repositories. Generalised linear modelling for analysis of asthma costs' determinants and sensitivity analysis to assess uncertainty were performed.

Results: The mean annualised asthma cost per child was €929.35 (95%CI, 809.65–1,061.11): €698.65 (95%CI, 600.88–798.27) for direct costs, and €230.70 (95%CI, 197.36–263.81) for indirect costs. Extrapolations for the Portuguese children amounted to €161,410,007.61 (95%CI, 140,620,769.55–184,293,968.55) for total costs. Direct costs represent 75.2% with the costliest domain (51.1% of total costs) being the healthcare service use: 20.7% for scheduled medical visits and 30.4% for acute asthma care – non-scheduled medical visits (7.9%, €12,766,203.20), emergency department visits (11.7%, €18,932,464.80) and hospitalisations (10.8%, €17,406,946.00).

Children with partly controlled and uncontrolled asthma had higher mean costs per year (adjusted coefficients: 1.46 [95%CI, 1.12-1.90] and 2.25 [95%CI, 1.56-3.24], respectively).

Conclusions: Costs of childhood asthma are high (0.9% of the healthcare expenditures in Portugal). Direct costs represented 3/4 of total costs, mainly related to the use of healthcare services for acute asthma care. Policies and interventions to improve asthma control and reduce acute use of healthcare services have the potential to reduce asthma costs.

AIMS

This study aimed to estimate the cost of childhood asthma in Portugal. Secondary aims were:

- 1) to describe direct and indirect costs, 2) to determine factors associated with costs, and
- 3) to assess the variance of costs with the level of asthma control.

METHODS

Study design and setting

The Cost of Childhood Asthma in Portugal (CASCA project) was a Portuguese, nationwide, population- and prevalence-based, cost-of-illness study with a societal perspective. This project was reviewed and approved by the Ethics Committee of *Centro Hospitalar de São João*, Porto, Portugal. Informed consent was obtained from parent(s) or legal guardian(s).

This project was approved and granted by Calouste Gulbenkian Foundation (P-125964).

Participants

Data from participants of two studies (INAsma and CED2013) was analysed. The flowchart (Figure 9) summarizes the children included in the CASCA project.

INAsma was a nationwide survey, from the general population, applied by telephone interview to individuals living in Portugal in 2010. The study methodology has been previously described^{102,103}. Briefly, to obtain a representative sample of the general population, a two-stage cluster and stratified sampling design was performed, using municipality as stratum and randomly selecting participants from households. When the selected individual had <15 years old, the respondent was the usual and most knowledgeable caregiver. Overall, 716 children (0- to 17-years-old) completed the first phase of the INAsma study; all the participants identified as having current asthma were eligible for participation in the second phase. Additional asthmatics identified in the participants' households were also contacted in the second phase.

To increase the sample size in school-aged children, data from a survey on childhood asthma conducted in the city of Guimarães (CED2013 study) was used. CED2013 study was a population-based survey applied to children attending primary public schools in a Portuguese city (Guimarães), in 2013. In order to obtain a representative sample from the population, we performed a two-stage randomization based on the city council's official database of schools and students: 1) randomization of schools and 2) randomization of children within each included school. From an approximated universe of 6,000 children attending primary public schools in Guimarães, 4,300 written self-administered

questionnaires were distributed to caregivers. At the end of the CED2013 study, questionnaires of 2,550 children (5- to 12-years-old) were available for analysis.

For the cost-of-illness analysis we included 208 children with current asthma: 98 (0- to 17-years old) from the second phase of INAsma Study, and 110 school-aged children (5- to 12-years old) from the CED2013 Study (Figure 9).

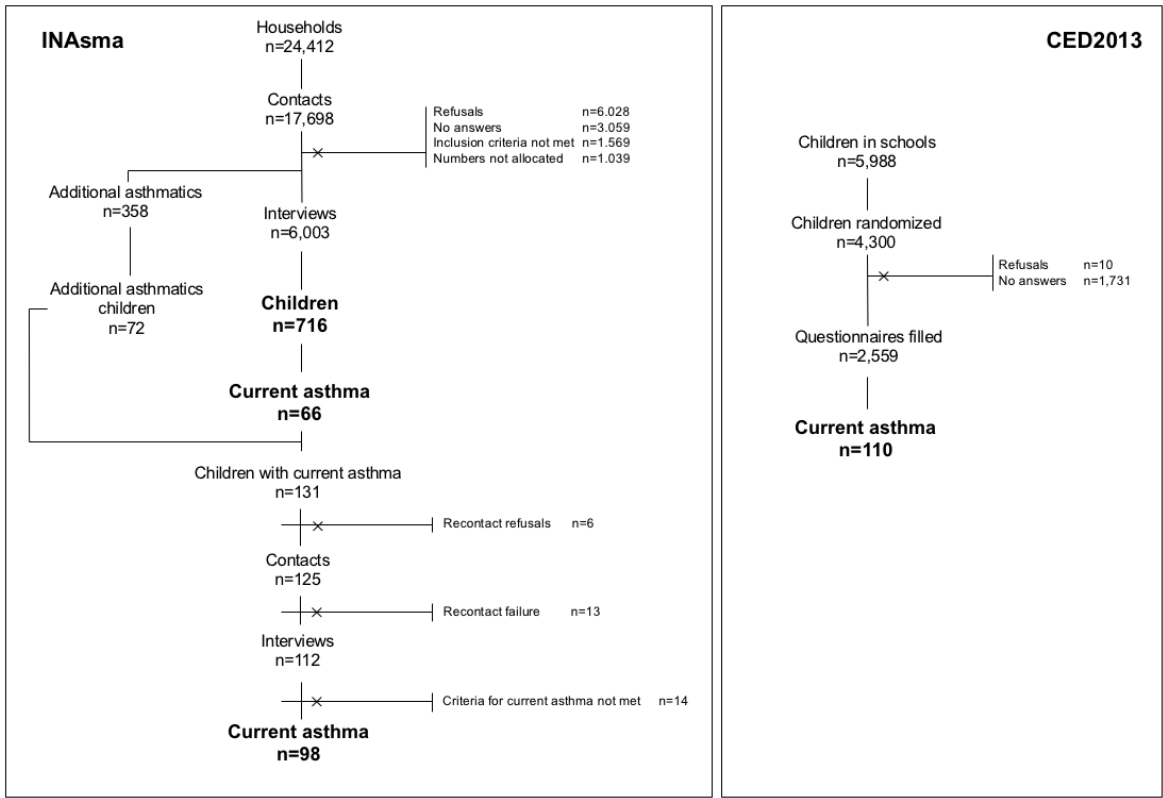


Figure 9 Participants' flowchart of children included in the cost-if-illness analysis.

¹*Current asthma* - Lifetime asthma + (wheezing OR asthma attack OR awakening with breathlessness OR current asthma medication).

Instruments and data collection

The instrument for data collection on asthma prevalence, associated factors and cost domains were similar in INAsma study and CED2013 study. The questionnaire was design in 6 parts: 1) questions on socio-educational factors; 2) questions on asthma-like symptoms in the previous 12 months; 3) questions on use of healthcare resources because of asthma in the previous 12 months; 4) question on asthma medication in the previous 12 months; 5) questions on asthma control; and 6) questions on asthma associated comorbidities. Questions on diagnostic tests performed in the previous 12 months, type and number, were only included in the CED2013 study.

In INAsma study, the questionnaire was administered using computer-assisted telephone interviews performed by trained and experienced interviewers. In the first phase of INAsma study, interviews were conducted from March to May of 2010. In the second phase, interviews were conducted from June to October of 2010. Interviews were conducted mostly from 17:00 to 22:00 h on weekdays and 11:00 to 22:00 h on weekends and holidays. No telephone number was abandoned until a minimum of 10 attempts had been made on different occasions. To minimize other potential biases in data collection, several quality assurance measures were followed: interviewers were selected based on their previous experience with health-related data collection; each question was discussed in training sessions held between researchers and all interviewers; a research assistant was present during the setup, training, and daily work of the interviewers, motivating and checking compliance with standardized operational procedures; data validity was periodically verified soon after being collected, and custom statistic algorithms were used to detect extreme, illogical, and missing values; and the clarity of the questionnaire and its telephonic administration were assessed in a pilot study involving 25 individuals before starting the data collection.

In CED2013 study, a written self-administered questionnaire was given to the usual and most knowledgeable caregiver. First, the CED2013 study coordinator had meetings with school delegates and teachers from each school included. In the meetings, the study procedures were explained and the questionnaires / parental informed consents were distributed. Then, each teacher distributed the questionnaire and informed consent to each randomized

child. The questionnaires and informed consents were taken home by the children and, in case of consent, brought back to the teacher after the parents completed them. Then the questionnaires were collected by the study coordinator. Data collection was conducted from November 2013 to February 2014. To minimize potential biases in data collection, several quality assurance measures were followed: each procedure was discussed during the meeting with school delegates and teachers; periodic phone calls to the school delegates were made in order to assess the ongoing data collection; data validity and randomization numbers were double checked during the electronic reading of the questionnaires.

Data collection of prices of healthcare services, diagnostic tests, medication, holding chambers, absenteeism, transportation and subsidies were performed in different sources and databases as described below.

Cost estimation methods

Direct healthcare costs of childhood asthma were estimated using a bottom-up approach (person-based). The cost domains included in direct costs were: 1) healthcare services; 2) diagnostic tests; and 3) treatment.

1) Healthcare services (scheduled medical visits, non-scheduled medical visits, emergency department visits and hospitalisations) costs were based on the national values defined by Portuguese Central Administration of Health system (ACSS) in 2010⁸⁸. For INAsma sample, the unitary costs were those from the healthcare services of their own catchment area. If no official values existed for one catchment area (in our sample there was a lack of tariffs for five hospitals), average market prices were used. For CED2013 sample, the unitary costs used were the mean prices from INAsma estimates (for each healthcare service), in order to maintain the National mean estimates and avoiding being biased from one particular catchment area.

2) Diagnostic tests (blood workout, skin prick test, spirometry and chest x-ray) costs were based on national values for 2010 defined by the Ministry of Health¹⁰⁴.

Treatment included costs with asthma-specific medication, other asthma-related medication and holding chambers. Costs of medication (asthma-specific and other

asthma-related medication) were based on national values defined by National Authority of Medicines and Health Products (INFARMED) and published in Infomed – Medical products database ¹⁰⁵. The cost of one dose of each pharmacologic group was calculated by the arithmetic mean cost for each group (using all the medications available in each pharmacologic group). Table 19 shows the dosage and mean cost for each pharmacological group of asthma-specific medication. For determination of the number of doses needed by a child per year, and per asthma exacerbation, a consensus was achieved by two allergologists and two pediatricians, in accordance to international guidelines and based on a conservative estimation of adherence ⁶; the mean use was the scenario considered for cost calculation; minimum and maximum usage scenarios were used for sensitivity analysis (Table 20). The use of reliever medication was considered if: 1) use was reported in the previous 12 months; 2) use was reported in the previous 4 weeks; 3) an asthma attack was reported in the previous 12 months. The use of controller medication was considered based on parent/self-reported use in the previous 12 months. The value of one year of allergen immunotherapy was set by consensus by two pediatricians and two allergologists, after consulting the market prices of the mostly used specific immunotherapies for childhood asthma in Portugal. The price was established as 400€ and 200€/year for sublingual and subcutaneous administration, respectively. For assessing the prices of the holding chambers, the average of three market prices, from three different companies, was used.

Table 19 Prices of asthma-specific medication available in Portugal used in this cost-of-illness study.

Pharmacological group	Dose*	Mean price per dose
Inhaled steroids		
Fluticasone	125µg	0.1957 €
Fluticasone	250µg	0.3447 €
Fluticasone	500µg	0.6660 €
Budesonide	200µg	0.1034 €
Budesonide	400µg	0.2079 €
Budesonide	800µg	0.4198 €
Inhaled steroids plus LABA		
Fluticasone/Salmeterol	125/25µg	0.7752 €
Fluticasone/Salmeterol	250/50µg	0.4931 €
Fluticasone/Salmeterol	500/100µg	0.9862 €
Budesonide/Formoterol	80/4.5µg	0.3557 €
Budesonide/Formoterol	160/4.5µg	0.4135 €
Budesonide/Formoterol	320/9µg	0.8182 €
LTRA		
Montelukaste	4mg	0.8109 €
Montelukaste	5mg	0.8296 €
Montelukaste	10mg	0.6232 €
SABA		
Salbutamol	200µg	0.0626 €
Oral steroid		
Betamethasone/Deflazacort (oral solution)	Equivalent to 1mg of prednisone	0.0305 €
Prednisolone/Deflazacort (oral pill)	Equivalent to 1mg of prednisone	0.0324 €

*Assumed used dose per day as described in Table 20.

LABA: long-acting β_2 -agonist; LTRA: leukotriene-receptor antagonist; SABA: short-acting β_2 -agonist.

Table 20 Estimation of the mean number of doses of asthma medication use. For reliever medication, the mean, minimum and maximum use are referred to each asthma exacerbation. For controller medication, the mean, minimum and maximum use are referred to the use in one year.

	Type of use	Description
RELIEVER MEDICATION	Mean use per exacerbation	
	SABA	200µg, 3id, 5 days
	Inhaled steroid step-up	125µg fluticasone or 200µg budesonide, 1id, 2 weeks
	Oral steroid	1mg/Kg/day of prednisone equivalent, 5 days
	Minimum use per exacerbation	
	SABA	200µg, 3id, 2 days
	Inhaled steroid step-up	125µg fluticasone or 200µg budesonide, 1id, 1 week
	Oral steroid	1mg/Kg/day of prednisone equivalent, 3 days
	Maximum use per exacerbation	
CONTROLLER MEDICATION	SABA	200µg, 3id, 10 days
	Inhaled steroid step-up	125µg fluticasone or 200µg budesonide, 1id, 4 weeks
	Oral steroid	1mg/Kg/day of prednisone equivalent, 7 days
	Mean use per year	
	Inhaled steroid	125µg fluticasone or 200µg budesonide, bid, 6 months
	Inhaled steroid / LABA	125µg fluticasone or 160µg budesonide, bid, 6 months
	LTRA	1 pill, 1id, 6 months
	Minimum use per year	
	Inhaled steroid	125µg fluticasone or 200µg budesonide, 1id, 2 months
	Inhaled steroid / LABA	125µg fluticasone or 80µg budesonide, 1id, 2 months
	LTRA	1 pill, 1id, 2 months
	Maximum use per year	
	Inhaled steroid	250µg fluticasone or 400µg budesonide, bid, 12 months
	Inhaled steroid / LABA	250µg fluticasone or 160µg budesonide, bid, 12 months
	LTRA	1 pill, 1id, 12 months

LABA: long-acting β_2 -agonist; LTRA: leukotriene-receptor antagonist; SABA: short-acting β_2 -agonist.

Indirect healthcare costs of childhood asthma were estimated using the human capital method. The cost domains included in indirect costs were: 1) absenteeism; 2) transportation and 3) subsidies because of asthma.

- 1) Reported professions of the caregiver were categorized according to the Portuguese Classification of Occupations 2010 from the National Statistics Institute (INE) ¹⁰⁶. The monthly income was based on the national reports from the Ministry of Social Security and matched to each professional category ¹⁰⁷. The daily income was achieved by dividing the monthly income by 22 workdays in a month. Costs related to absenteeism of parents or legal guardians were then calculated by multiplying the daily income for the number of reported absent days.

- 2) Costs with transportation for medical visits were estimated using the road distances between postal code of the participants and the respective referral public hospital as assessed by Google maps®. The value used for 1 kilometre was 0.36€, based on the price defined by the Portuguese government.
- 3) The subsidy value per child with asthma was that established by the Portuguese government for 2010 ¹⁰⁸ and was considered if reported in the questionnaire.

Each cost item was calculated for each participant by multiplying the parent/self-reported amount of resources used by the unitary costs of the resources. The total cost was then calculated for each participant by adding direct and indirect costs. Mean cost per patient was achieved by the sum of the total cost of each participant, dividing for the total number of asthmatic children in our sample. Costs were indexed to 2010 Portuguese prices in euros.

Definitions

Current asthma was defined as children with 'ever had asthma' plus at least one of the following: wheezing, awakening with breathlessness or having an asthma attack in the previous 12 months, or taking asthma medication at the time of the interview.

Nocturnal symptoms: at least one of three symptoms in the previous 12 months: waking with breathlessness, waking with chest tightness, or waking with coughing.

Asthma control definition was based on GINA criteria for asthma symptom control ¹⁰⁰, and categorized as 'controlled', 'partially controlled' and 'uncontrolled'.

Scheduled medical visits for asthma: having at least one routine appointment because of asthma routine follow-up, in the previous 12 months.

Unscheduled medical visits for asthma: having at least one unscheduled medical attendance (not in an emergency department) because of asthma worsening/exacerbation, in the previous 12 months.

Emergency department visits for asthma: having at least one emergency department visit because of asthma worsening/exacerbation, in the previous 12 months.

Hospitalisation for asthma: having at least one hospital inpatient admission for more than 24 hours because of asthma worsening/exacerbation, in the previous 12 months.

Blood workout: having performed blood workout for asthma in the previous 12 months. Blood workout was assumed to include complete blood count, quantification of total immunoglobulin E and Phadiatop®.

Chest x-ray: having performed chest x-ray because of asthma in the previous 12 months.

Skin prick tests: having performed skin prick tests because of asthma or allergies ever in life. The cost of skin prick test per child, per year, was achieved by dividing the price of the skin prick test by the number of years of asthma diagnosis.

Pulmonary function tests: having performed pulmonary function tests because of asthma in the previous 12 months. It was assumed that *pulmonary function tests* included a spirometry with bronchodilation test.

Controller medication: use of any inhaled steroid, inhaled long-acting β -agonist, inhaled association of steroid and β -agonist or leukotriene receptor antagonist in the previous 12 months.

Reliever medication: use of any inhaled/nebulized short-acting β -agonist or oral steroid in the previous 12 months.

Immunotherapy: use of any kind of "anti-allergic vaccines" (allergy specific or non-specific), oral or subcutaneous, in the previous 12 months (CED2013 participants), or ever in life (INAsma participants). For INAsma participants, the cost of immunotherapy per child, per year, was achieved by dividing the price of the immunotherapy by the number of years of asthma diagnosis. It was assumed by consensus the following distribution within the positive responders: in the 0- to 6-year old group, 40% performed sublingual specific immunotherapy and 60% non-specific immunotherapy; in the 7- to 17-year old group, 40% performed subcutaneous specific immunotherapy, 30% sublingual specific immunotherapy and 20% non-specific immunotherapy.

Antihistamine: was assumed by consensus that 66% of asthmatic children with nasal symptoms, and 10% of those without nasal symptoms, took one dose of antihistamine for 120 days, in a 12-month period.

Antibiotic: was assumed by consensus that antibiotic was used in half of asthma exacerbations.

Flu vaccine: was assumed by consensus that 10% of children with asthma took flu shot in the previous 12 months, in 2010.

Missed schooldays: number of days missed by the child to the school because of asthma in the previous 12 months.

Missed workdays: number of days missed by the caregiver to the work because of the child's asthma in the previous 12 months.

Subsidy: been granted with a monetary subsidy because of asthma in the previous 12 months. This monthly grant given by Portuguese Social Security can be granted to a family of an asthmatic child after the parents and the physician sign and submit official form.

Holding chambers: every participant who used inhaler medication was assumed to ever had a spacer, until a maximum of three spacers. The number of spacers used was dependent of the age of the child and the age of the first asthma diagnosis: if 0- to 1-year-old, one spacer used; if 2- to 5-year-old, one or two spacers (depending on the time of diagnosis); if ≥ 6 years-old, one to three spacers used (depending on the time of diagnosis). Then the value of the spacers was divided by the years since asthma diagnosis, in order to obtain the price per year.

Statistical analysis

Statistical analysis was performed using SPSS version 23 (SPSS IBM, New York, NY, USA). General characteristics of the included participants were described using absolute and relative frequencies.

Cost variables were all annualised and presented as mean and standard deviation (SD) or 95% confidence interval (95%CI), calculated using bootstrap methods because of their

skewed distributions ^{109,110}. For each cost item and domain, extrapolated estimates for the Portuguese population were calculated. Extrapolation estimates were based on a prevalence estimate of current asthma from INAsma Study (8.4% [95%CI, 6.6-10.7]), corresponding to a total weighted population of 173,681 Portuguese children with current asthma ¹⁰². The factors associated with costs of childhood asthma were assessed using mixed Poisson-gamma models. We analysed crude and adjusted associations; for the final model of adjusted coefficients we included the variables with a p-value <0.05 and age groups (not statistically significant) because of the potential overrepresentation of school-aged children. Cost differences in levels of asthma control were also analysed using mixed Poisson-gamma models. A p-value of <0.05 was considered statistically significant.

We additionally used decision analytic modelling to perform univariate and multivariate deterministic sensitivity analysis, in order to evaluate how the uncertainty would impact the estimates of national annualised costs of childhood asthma in Portugal. Univariate deterministic sensitivity analysis was performed with the 95%CI of the proportion estimates of occurrence of each item in Portuguese population. The multivariate deterministic sensitivity analysis was set with two case scenarios. The best-/worst-case scenario were set, respectively, with: the lower/upper limit of the 95%CI of current asthma prevalence in Portuguese children; scenario of minimum/maximum use of asthma medications; and the lower/upper limit of the 95%CI for the proportion of occurrence of each item in Portuguese population.

RESULTS

Characteristics of the children included in cost-of-illness analysis are summarized in Table 21. Differences between the mean annualised costs of the two studied populations are shown in Table 22; differences were only seen in the 'Treatment' domain and total costs were not significantly different.

Estimates of mean annualised costs for each cost domain are presented in Table 23. The mean annualised total costs per child were €929.35 (95%CI, 809.65–1,061.11), with €698.65 (95%CI, 600.88–798.27) for direct costs, and €230.70 (95%CI, 197.36–263.81) for indirect costs. The extrapolations for Portuguese children amount to absolute total costs of €161,410,007.61 (95%CI, 140,620,769.55–184,293,968.55), with direct costs of €121,341,498.02 (95%CI, 104,362,186.11–138,645,096.07) and indirect costs of €40,068,509.59 (95%CI, 34,276,935.33–45,819,027.76).

Direct costs represent 75% and indirect costs 25% of the total costs. The most expensive domain was healthcare services use (€82,519,684.10; 51% of total costs), specifically scheduled medical visits (€33,414,070.10; 21% of total costs) and those related to acute asthma care (€49,105,614.06; 30% of total costs): non-scheduled medical visits (€12,766,203.20), emergency department visits (€18,932,464.80) and hospitalisations (€17,406,946.00).

Table 21 Participants characteristics - n(%).

	Children with current asthma		TOTAL (n=208)
	INCA (n=98)	CASCA (n=110)	
Gender			
Female	33 (33%)	43 (39%)	76 (37%)
Male	65 (66%)	67 (61%)	132 (63%)
Age groups			
0- 5 years old	18 (18%)	3 (3%)	21 (10%)
6-12 years old	46 (47%)	107 (97%)	153 (74%)
13-17 years old	34 (35%)	0 (0%)	34 (16%)
Caregiver education			
No education	15 (16%)	0 (0%)	15 (7%)
0-4 years (basic 1 st cycle)	33 (34%)	6 (6%)	39 (19%)
5-9 years (basic 2 nd and 3 rd cycle))	42 (43%)	27 (25%)	69 (34%)
10-12 years (secondary)	7 (7%)	27 (25%)	34 (17%)
>12 years (higher)	0 (0%)	47 (44%)	47 (23%)
Mensual income of caregiver			
< 650.00 €	18 (19%)	34 (32%)	52 (26%)
650.00 – 749.99 €	36 (38%)	21 (20%)	57 (28%)
750.00 – 1,199.99€	11 (12%)	21 (20%)	32 (16%)
>= 1,200.00 €	31 (32%)	30 (28%)	61 (30%)
Asthma-like symptoms			
Wheezing	77 (79%)	95 (88%)	172 (84%)
Nocturnal symptoms	70 (71%)	84 (78%)	154 (74%)
Asthma attacks	44 (46%)	73 (68%)	127 (61%)
Healthcare use			
Scheduled medical visits	84 (86%)	91 (83%)	175 (83%)
Unscheduled medical visits	24 (25%)	51 (46%)	75 (36%)
Emergency department visits	37 (39%)	49 (45%)	86 (41%)
Hospitalisation	5 (5%)	5 (5%)	10 (5%)
Diagnostic tests			
Blood workout	-	28 (26%)	-
Chest x-ray	-	32 (30%)	-
Spirometry	-	34 (32%)	-
Skin prick tests (ever)	71 (72%)	87 (79%)	156 (73%)
Medication			
Controller medication	68 (69%)	84 (76%)	152 (73%)
Reliever medication	52 (53%)	85 (77%)	137 (66%)
Allergen-specific immunotherapy	-	35 (32%)	-
Absenteeism			
Missed schooldays	32 (33%)	65 (59%)	97 (47%)
Missed workdays	-	50 (46%)	-
Subsidy			
Yes	16 (17%)	-	-
No	80 (83%)	-	-
Asthma control			
Well controlled	48 (51%)	66 (68%)	114 (60%)
Partly controlled	37 (40%)	21 (22%)	58 (31%)
Uncontrolled	8 (9%)	10 (10%)	18 (9%)

Table 22 Mean costs per child, per year, in the two primary studies.

	Mean cost per patient (euros)		p
	INAsma	CED2013	
TOTAL COSTS	875.99	976.88	0.443
DIRECT COSTS	637.03	753.54	0.326
Healthcare services use	440.93	505.59	0.558
Scheduled medical visits	193.67	191.25	0.926
Acute asthma care	247.26	314.34	0.500
Non-scheduled medical visits	52.79	91.96	0.059
Emergency department visits	122.54	96.95	0.552
Hospitalisation	71.93	125.43	0.408
Diagnostic tests	55.41	50.02	0.511
Blood workout	15.80	13.12	0.401
Chest x-ray	5.50	4.54	0.324
Pulmonary function tests	29.23	26.66	0.639
Skin prick tests	4.87	5.71	0.308
Treatment	140.70	197.93	<0.001*
Asthma-specific medication	90.48	93.65	0.779
Controller medication	83.75	85.77	0.856
Reliever medication	6.73	7.88	0.239
Other asthma medication	35.19	86.12	<0.001*
Immunotherapy	17.88	64.68	<0.001*
Antihistamines	11.74	9.06	<0.001*
Antibiotics	4.99	11.80	<0.001*
Flu vaccine	0.59	0.59	1.00
Holding chamber	15.02	18.17	0.024
INDIRECT COSTS	238.96	223.34	0.660
Parental absenteeism	77.75	79.78	0.915
Transportation	21.42	23.72	0.553
Subsidies	139.80	119.84	0.496

*statistically significant differences between the two studies.

Table 23 Annualised costs (in euros) of childhood asthma in Portugal: total costs, mean cost per child with current asthma and percentage of total costs for each domain/variable.

	Total costs in Portuguese children* (95%CI#)	Mean cost per patient† (95%CI#)	Percentage of total costs
TOTAL COSTS	161,410,007.61 (142,367,218.84 - 181,369,857.87)	929.35 (819.71 - 1,044.27)	100%
DIRECT COSTS	121,341,498.02 (104,319,912.15 - 139,851,241.14)	698.65 (600.64 - 805.22)	75.2%
Healthcare services use	82,519,684.10 (67,027,110.46 - 99,248,305.38)	475.12 (385.92 - 571.46)	51.1%
Scheduled medical visits	33,414,070.10 (29,192,806.15 - 38,204,470.63)	192.39 (168.08 - 219.97)	20.7%
Acute asthma care	49,105,614.06 (35,070,014.88 - 64,089,678.45)	282.73 (201.92 - 369.01)	30.4%
Non-scheduled medical visits	12,766,203.20 (9,809,363.94 - 15,874,252.35)	73.50 (56.48 - 91.40)	7.9%
Emergency department visits	18,932,464.80 (13,136,536.12 - 26,300,288.04)	109.01 (75.64 - 151.43)	11.7%
Hospitalisation	17,406,946.00 (6,189,712.95 - 30,072,795.68)	100.22 (35.64 - 173.15)	10.8%
Diagnostic tests	9,128,914.10 (7,988,735.48 - 10,293,812.35)	52.56 (46.00 - 59.27)	5.7%
Blood workout	2,498,121.71 (2,056,174.62 - 3,027,259.83)	14.38 (11.84 - 17.43)	1.5%
Chest x-ray	867,148.15 (726,594.46 - 1,012,508.13)	4.99 (4.18 - 5.83)	0.5%
Pulmonary function tests	4,840,864.14 (4,047,079.93 - 5,594,160.80)	27.87 (23.30 - 32.21)	3.0%
Skin prick tests	922,780.11 (787,921.22 - 1,060,409.35)	5.31 (4.54 - 6.11)	0.6%
Treatment	29,692,899.78 (26,638,427.58 - 32,734,734.89)	170.96 (153.38 - 188.48)	18.4%
Asthma-specific medication	16,005,602.20 (14,170,511.21 - 16,552,789.28)	92.16 (81.59 - 102.71)	9.9%
Controller medication	14,731,639.10 (12,945,695.43 - 16,516,489.95)	84.82 (74.54 - 95.31)	9.1%
Reliever medication	1,273,963.08 (1,122,865.03 - 1,433,510.87)	7.34 (6.47 - 8.25)	0.8%
Other asthma medication	10,789,280.82 (8,948,166.70 - 12,786,638.37)	62.12 (51.52 - 73.62)	6.7%
Immunotherapy	7,403,386.43 (5,663,424.78 - 9,313,209.42)	42.63 (32.61 - 53.62)	4.6%
Antihistamines	1,792,454.72 (1,663,308.20 - 1,910,421.53)	10.32 (9.58 - 11.00)	1.1%
Antibiotics	1,491,836.29 (1,264,692.94 - 1,736,306.33)	8.59 (7.28 - 10.00)	0.9%
Flu vaccine	101,603.39 (n.a.)	0.59 (n.a.)	0.1%
Holding chamber	2,898,016.76 (2,659,281.90 - 3,159,830.54)	16.69 (15.31 - 18.19)	1.8%
INDIRECT COSTS	40,068,509.59 (34,117,635.12 - 46,811,024.16)	230.70 (196.44 - 269.52)	24.8%
Parental absenteeism	13,689,797.60 (10,775,047.66 - 16,906,907.47)	78.82 (62.04 - 97.34)	8.5%
Transportation	3,931,536.64 (3,397,478.25 - 4,553,290.57)	22.64 (19.56 - 26.22)	2.4%
Subsidies	22,447,175.39 (17,551,402.93 - 27,735,327.31)	129.24 (101.06 - 159.69)	13.9%

Each cost item was calculated for each participant by multiplying the parent/self-reported amount of resources used by the unitary costs of the resources. Costs were indexed to 2010 Portuguese prices in euros.

*Total costs were extrapolated to total Portuguese children with current asthma (n=173,681)(9);#Bootstrapped 95%CI; n.a., not applicable; †Mean cost per patient: sum of the total cost of each participant, dividing for the total number of asthmatic children in our sample

Factors associated with costs of childhood asthma

We observed significant crude associations between total annualised costs of childhood asthma and nocturnal symptoms, asthma attacks and level of asthma control (Table 24). However, only asthma attacks and level of asthma control had significant and independent associations with total annualised costs of childhood asthma in the final multivariate model adjusted for age.

Children with asthma attacks in the previous 12 months had higher costs than those without asthma attacks (adjusted exponential model coefficients: 1.57 [95%CI, 1.22-2.02]). Children with partly controlled asthma and uncontrolled asthma had higher mean costs per year with adjusted exponential model coefficients of 1.46 [95%CI, 1.12-1.90] and 2.25 [95%CI, 1.56-3.24], respectively. The mean annualised costs per asthmatic child were €747.63 in those with controlled asthma, €1,120.50 in partly controlled and 1,758.44 in uncontrolled ($p<0.001$) (Figure 10; Table 25). Total costs and direct costs, specifically healthcare services use by acute asthma care and diagnostic tests domains were significantly higher in children with uncontrolled asthma (Figure 11; Table 25). Scheduled medical visits, treatment or indirect costs were not different between asthma control groups.

Table 24 Factors associated with annualised total costs of childhood asthma in Portugal.

	Mean cost (SD)	Factors associated with childhood		
		Crude association (95%CI)	Adjusted association* (95%CI)	
Gender				
Female	999.44 (1,155.01)	1.00 (ref)	n.i.	
Male	888.99 (806.34)	0.89 (0.67-1.18)	n.i.	
Age groups				
0- 5 years old	1,035.91 (1,146.11)	1.00 (ref)	1.00 (ref)	
6-12 years old	969.84 (974.54)	0.94 (0.60-1.46)	0.86 (0.59 -1.26)	
13-17 years old	681.33 (618.04)	0.66 (0.39-1.14)	0.64 (0.40-1.03)	
Caregiver education				
No education	1,190.65 (1,311.41)	1.00 (ref)	n.i.	
0-4 years (basic 1 st cycle)	1,011.55 (1,151.59)	0.85 (0.49-1.47)	n.i.	
5-9 years (basic 2 nd and 3 rd cycle)	1,010.83 (1,136.31)	0.85 (0.51-1.42)	n.i.	
10-12 years (secondary)	669.32 (442.65)	0.56 (0.32-1.01)	n.i.	
>12 years (higher)	840.07 (477.72)	0.71 (0.41-1.21)	n.i.	
Mensual income of caregiver				
< 650.00 €	1,064.76 (1,187.16)	1.00 (ref)	n.i.	
650.00 – 749.99 €	1,009.69 (909.77)	0.95 (0.67-1.35)	n.i.	
750.00 – 1,199.99€	839.60 (972.68)	0.79 (0.52-1.21)	n.i.	
>= 1,200.00 €	755.10 (550.96)	0.71 (0.50-1.02)	n.i.	
Wheezing				
No	776.19 (746.83)	1.00 (ref)	n.i.	
Yes	964.25 (985.50)	1.24 (0.84-1.83)	n.i.	
Nocturnal symptoms				
No	685.41 (588.66)	1.00 (ref)	n.i.	
Yes	1,014.00 (1,034.80)	1.48 (1.07-2.05)	n.i.	
Asthma attacks				
No	677.58 (713.02)	1.00 (ref)	1.00 (ref)	
Yes	1,136.82 (1,058.60)	1.68 (1.27-2.22)	1.57 (1.22-2.02)	
Asthma control				
Controlled	747.63 (562.79)	1.00 (ref)	1.00 (ref)	
Partly controlled	1,120.50 (1,135.96)	1.50 (1.14-1.98)	1.46 (1.12-1.90)	
Uncontrolled	1,758.44 (1,795.65)	2.35 (1.60-3.47)	2.25 (1.56-3.24)	

Bold values show statistical significant differences. n.i.: not included in the model (non-significant variables)

*Adjusted coefficients were calculated using multivariate mixed Poisson-gamma (Tweedie distribution family) generalised linear models. Goodness-of-fit statistics for the multivariate regression model: scaled deviance (D = 214.8; df = 174); scaled Pearson chi-square (χ^2 = 258.7; df = 174); AIC = 2,818.9; consistent AIC = 2,865.3)

Table 25 Variations of annualised costs (in euros) of childhood asthma in Portugal with level of asthma control.

	Costs in Portuguese childhood asthma, Mean per patient (Total)	Costs by level of asthma control, Mean per patient (Total)			p
		Controlled	Partly controlled	Uncontrolled	
TOTAL COSTS	929.35 (161,410,007.61)	747.63 (71,167,055.27)	1,120.50 (54,266,054.08)	1,758.44 (26,429,556.38)	<0.001
DIRECT COSTS	698.65 (121,341,498.02)	530.33 (50,482,832.36)	867.49 (42,012,844.31)	1,440.75 (21,654,576.11)	<0.001
Healthcare services use	475.12 (82,519,684.10)	319.57 (30,419,891.60)	623.39 (30,190,811.20)	1,165.13 (17,511,979.70)	<0.001
Scheduled medical visits	192.39 (33,414,070.10)	181.15 (17,244,101.80)	206.10 (9,981,647.47)	217.53 (3,269,427.92)	0.568
Acute asthma care	282.73 (49,105,614.06)	138.41 (13,175,789.78)	417.29 (20,209,163.72)	947.60 (14,242,551.75)	<0.001
Non-scheduled medical visits	73.50 (12,766,203.20)	44.87 (4,271,498.91)	110.45 (5,349,124.30)	151.77 (2,281,183.03)	0.001
Emergency department visits	109.01 (18,932,464.80)	66.65 (6,344,166.13)	132.43 (6,413,529.98)	370.00 (5,561,056.87)	<0.001
Hospitalisation	100.22 (17,406,946.00)	26.89 (2,560,124.74)	174.41 (8,446,509.44)	425.83 (6,400,311.85)	0.012
Diagnostic tests	52.56 (9,128,914.10)	37.18 (3,539,650.55)	72.98 (3,534,604.54)	100.31 (1,507,731.49)	<0.001
Blood workout	14.38 (2,498,121.71)	8.49 (808,204.49)	23.06 (1,116,640.16)	31.52 (473,725.95)	<0.001
Chest x-ray	4.99 (867,148.15)	3.08 (293,310.97)	8.45 (409,391.50)	8.09 (121,576.70)	<0.001
Pulmonary function tests	27.87 (4,840,864.14)	20.29 (1,931,110.53)	35.42 (1,715,577.41)	57.44 (863,394.97)	<0.001
Skin prick tests	5.31 (922,780.11)	5.33 (507,024.56)	6.05 (292,995.46)	3.26 (49,033.87)	0.147
Treatment	170.96 (29,692,899.78)	173.58 (16,523,290.25)	171.12 (8,287,428.60)	175.31 (2,634,864.95)	0.989
Asthma-specific medication	92.16 (16,005,602.20)	89.83 (8,550,662.78)	98.12 (4,751,962.26)	97.30 (1,462,487.33)	0.799
Controller medication	84.82 (14,731,639.10)	82.86 (7,887,138.11)	89.57 (4,337,774.83)	88.93 (1,336,583.85)	0.859
Reliever medication	7.34 (1,273,963.08)	6.97 (663,524.67)	8.55 (414,187.43)	8.38 (125,903.49)	0.375
Other asthma medication	62.12 (10,789,280.82)	67.06 (6,383,728.66)	54.77 (2,652,576.47)	64.94 (976,087.22)	0.607
Immunotherapy	42.63 (7,403,386.43)	48.46 (4,612,917.26)	33.33 (1,614,131.09)	42.50 (638,787.03)	0.433
Antihistamines	10.32 (1,792,454.72)	9.81 (933,602.18)	11.12 (538,544.70)	11.30 (169,773.18)	0.189
Antibiotics	8.59 (1,491,836.29)	8.21 (781,522.75)	9.74 (471,568.97)	10.56 (158,734.41)	0.560
Flu vaccine	0.59 (101,603.39)	0.59 (85,686)	0.59 (28,331.71)	0.59 (8,792.60)	1.00
Holding chamber	16.69 (2,898,016.76)	16.69 (1,588,898.81)	18.23 (882,889.86)	13.06 (196,290.39)	0.119
INDIRECT COSTS	230.70 (40,068,509.59)	217.29 (20,684,222.92)	253.01 (12,253,209.76)	317.69 (4,774,980.26)	0.322
Parental absenteeism	78.82 (13,689,797.60)	85.73 (8,161,146.46)	69.27 (3,354,538.48)	86.63 (1,302,125.13)	0.749
Transportation	22.64 (3,931,536.64)	20.03 (1,907,125.93)	26.04 (1,261,007.56)	34.53 (518,942.13)	0.106
Subsidies	129.24 (22,447,175.39)	111.52 (10,615,950.52)	157.70 (7,637,663.73)	196.53 (2,953,913.01)	0.237

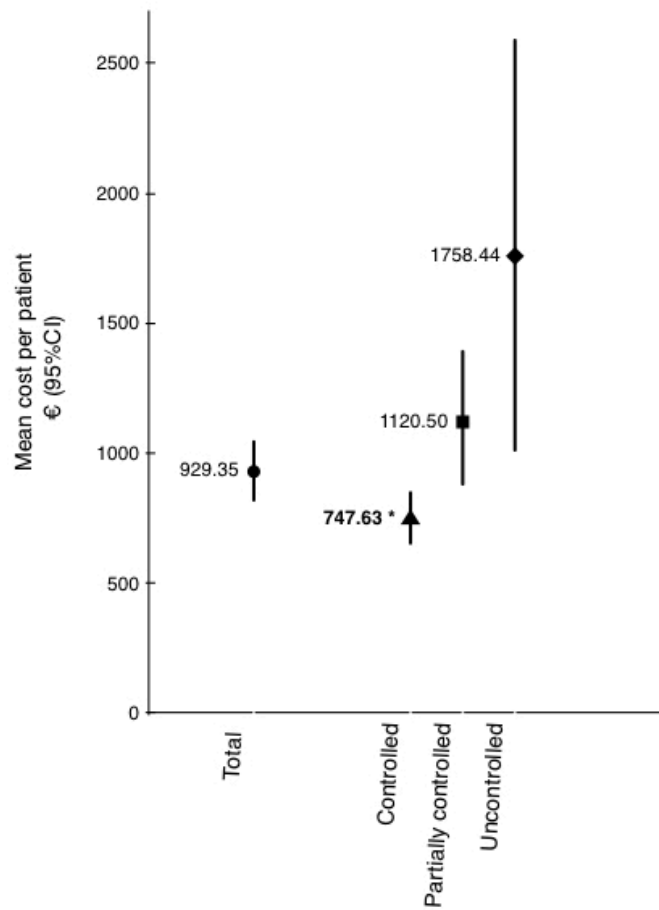


Figure 10 Mean cost per child with current asthma, per year; mean cost variation according to the level of asthma control. Mean costs are marked in euros and the lines represent 95%CI. * $p < 0.001$ between groups of asthma control.

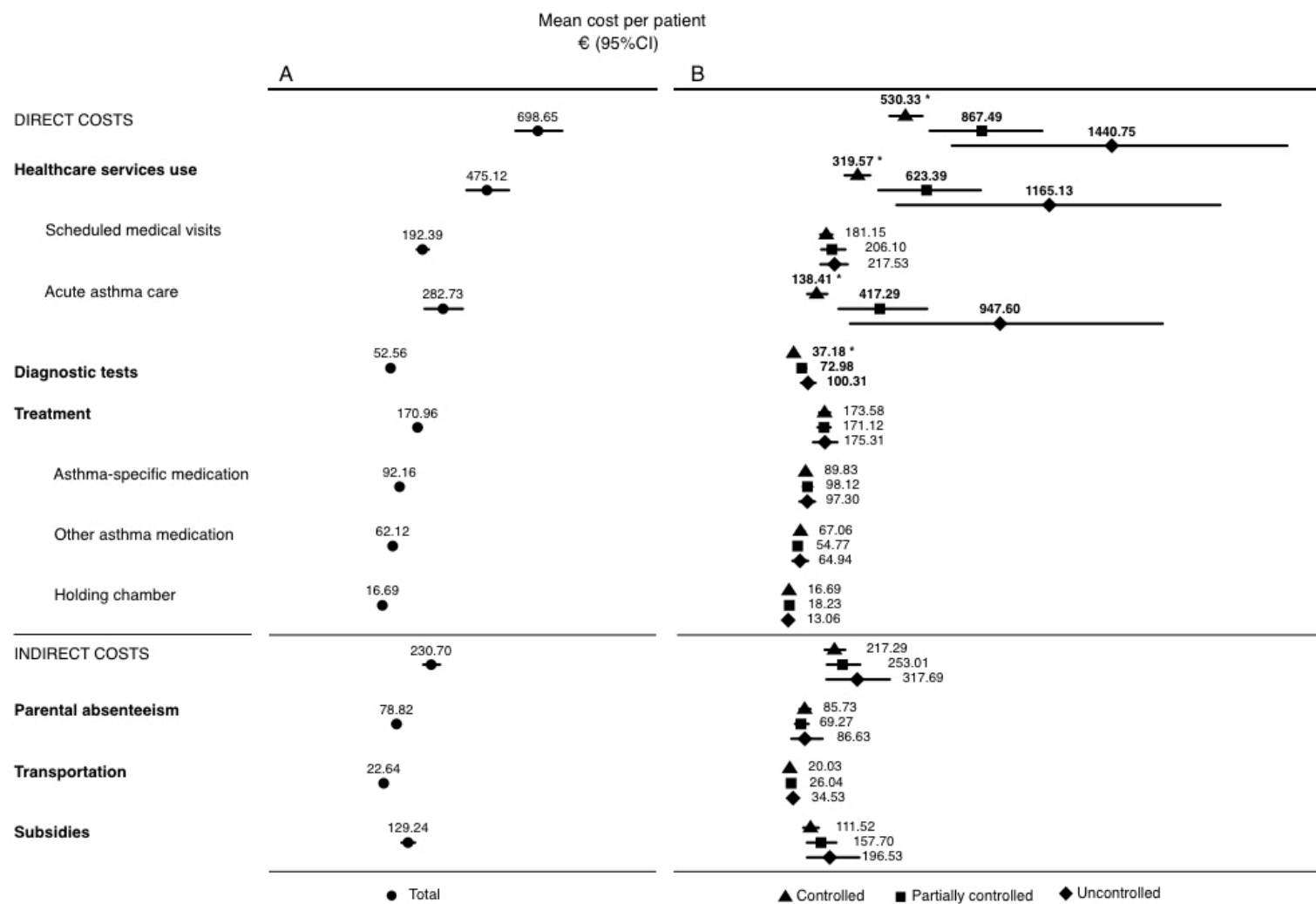


Figure 11 Mean cost per child with current asthma, per year, in each domain. Panel A: total costs. Panel B: cost variation according to the level of asthma control. * $p < 0.001$ between groups of asthma control. thesis.

Sensitivity analysis

In univariate deterministic sensitivity analysis (Table 26), each lower and upper limit was estimated by using the 95%CI of the proportion of occurrence in Portuguese population for each variable, as estimated previously ¹⁰². The adjusted estimates for the mean of annualised costs per child with asthma varied between €657.79 and €1,223.99 in total costs: between €497.24 and €915.53 in direct costs, and €160.55 and €308.45 in indirect costs. The extrapolations of the total annualised costs for the Portuguese children varied between €114,245,801.21 and €212,583,389.35 in total costs: between €86,360,787.25 and €159,010,961.96 in direct costs, and €27,885,013.95 and €53,572,427.39 in indirect costs.

In multivariate deterministic sensitivity analysis (Table 27), the adjusted estimates for the mean of annualised costs per child with asthma varied between €606.99 and €1,424.38 in total costs: between €446.44 and €1,140.07 in direct costs, and €160.55 and €284.31 in indirect costs. The extrapolations of the total annualised costs for the Portuguese children varied between €79,585,960.00 and €308,018,952.55 in total costs: between €58,535,047.13 and €246,538,052.49 in direct costs, and €21,050,912.88 and €61,480,900.06 in indirect costs.

The adjusted estimates for the mean of annualised costs per child with asthma in total costs varied between -35% and +53%, in direct costs between -36 and +63%, and in indirect costs between -30 and +23%.

Table 26 Univariate deterministic sensitivity analysis – Annualised total costs extrapolated to total Portuguese children with current asthma and mean costs per patient.

	Costs in Portuguese childhood asthma Total (mean per patient)	Univariate deterministic sensitivity analysis* Total (mean per patient)	
		Lower limit*	Upper limit*
TOTAL COSTS	161,410,007.61 (929.35)	114,245,801.21 (657.79)	212,583,389.35 (1,223.99)
DIRECT COSTS	121,341,498.02 (698.65)	86,360,787.25 (497.24)	159,010,961.96 (915.53)
Healthcare services use	82,519,684.14 (475.12)	56,424,066.12 (324.87)	111,100,595.44 (639.68)
Scheduled medical visits	33,414,070.09 (192.39)	30,694,320.20 (176.73)	36,133,819.98 (208.05)
Acute asthma care	49,105,614.06 (282.73)	25,729,745.92 (148.14)	74,966,775.46 (431.63)
Non-scheduled medical visits	12,766,203.22 (73.50)	8,170,370.06 (47.04)	16,851,388.25 (97.02)
Emergency department visits	18,932,464.81 (109.01)	14,077,986.65 (81.06)	23,301,495.15 (134.16)
Hospitalisation	17,406,946.03 (100.22)	3,481,389.21 (20.04)	34,813,892.06 (200.45)
Diagnostic tests	9,128,914.10 (52.56)	6,623,276.28 (38.13)	11,634,551.94 (66.99)
Blood workout	2,498,121.71 (14.38)	1,729,468.88 (9.96)	3,266,774.54 (18.81)
Chest x-ray	867,148.15 (4.99)	607,003.71 (3.49)	1,127,292.60 (6.49)
Pulmonary function tests	4,840,864.14 (27.87)	3,479,371.10 (20.03)	6,202,357.18 (35.71)
Skin prick tests	922,780.11 (5.31)	807,432.60 (4.65)	1,038,127.62 (5.98)
Treatment	29,692,899.78 (170.96)	23,313,444.86 (134.23)	36,275,814.58 (208.86)
Asthma-specific medication	16,005,602.20 (92.16)	13,095,804.16 (75.40)	18,915,400.20 (108.91)
Controller medication	14,731,639.10 (84.82)	12,191,701.32 (70.20)	17,271,576.88 (99.44)
Reliever medication	1,273,963.08 (7.34)	904,102.83 (5.21)	1,643,823.33 (9.46)
Other asthma medication	10,789,280.82 (62.12)	7,708,909.77 (44.39)	14,029,857.80 (80.78)
Immunotherapy	7,403,386.43 (42.63)	5,321,184.00 (30.64)	9,485,588.86 (54.62)
Antihistamines	1,792,454.72 (10.32)	1,493,712.27 (8.60)	2,091,197.17 (12.04)
Antibiotics	1,491,836.29 (8.59)	843,211.82 (4.85)	2,270,185.66 (13.07)
Flu vaccine	101,603.39 (0.59)	50,801.70 (0.29)	182,886.10 (1.05)
Holding chamber	2,898,016.76 (16.69)	2,508,730.93 (14.44)	3,330,556.57 (19.18)
INDIRECT COSTS	40,068,509.59 (230.70)	27,885,013.95 (160.55)	53,572,427.39 (308.45)
Parental absenteeism	13,689,797.60 (78.82)	11,011,358.94 (63.40)	16,368,236.26 (94.24)
Transportation	3,931,536.64 (22.64)	3,669,434.20 (21.13)	4,193,639.08 (24.15)
Subsidies	22,447,175.39 (129.24)	12,500,522.82 (71.97)	32,393,827.96 (186.51)

*Each upper and lower limit was estimated by using the 95%CI of the proportion of occurrence in Portuguese population for each item.

Table 27 Multivariate deterministic sensitivity analysis – Annualised total costs extrapolated to total Portuguese children with current asthma and mean costs per patient.

	Costs in Portuguese childhood asthma	Multivariate sensitivity analysis	
		Best-case scenario*	Worst-case scenario#
TOTAL COSTS	161,410,007.61 (929.35)	79,585,960.00 (606.99)	308,018,952.55 (1,424.38)
DIRECT COSTS	121,341,498.02 (698.65)	58,535,047.13 (446.44)	246,538,052.49 (1,140.07)
Healthcare services use	82,519,684.10 (475.12)	42,595,571.35 (324.87)	138,329,936.99 (639.68)
Scheduled medical visits	33,414,070.10 (192.39)	23,171,710.16 (176.73)	44,989,758.82 (208.05)
Acute asthma care	49,105,614.00 (282.73)	19,423,861.19 (148.14)	93,340,178.17 (431.63)
Non-scheduled medical visits	12,766,203.20 (73.50)	6,167,963.51 (47.04)	20,981,450.09 (97.02)
Emergency department visits	18,932,464.80 (109.01)	10,627,732.56 (81.06)	29,012,394.70 (134.16)
Hospitalisation	17,406,946.00 (100.22)	2,628,165.12 (20.04)	43,346,333.38 (200.45)
Diagnostic tests	9,128,914.10 (52.56)	5,000,033.78 (38.13)	14,486,032.35 (66.99)
Blood workout	2,498,121.71 (14.38)	1,305,608.05 (9.96)	4,067,419.36 (18.81)
Chest x-ray	867,148.15 (4.99)	458,238.33 (3.49)	1,403,577.64 (6.49)
Pulmonary function tests	4,840,864.14 (27.87)	2,626,641.61 (20.03)	7,722,475.88 (35.71)
Skin prick tests	922,780.11 (5.31)	609,545.80 (4.65)	1,292,559.47 (5.98)
Treatment	29,692,899.78 (170.96)	10,939,442.00 (83.43)	93,722,083.15 (433.40)
Asthma-specific medication	16,005,602.20 (92.16)	3,225,956.01 (24.60)	67,162,295.84 (310.58)
Controller medication	14,731,639.10 (84.82)	2,883,526.64 (21.99)	63,387,483.49 (293.12)
Reliever medication	1,273,963.08 (7.34)	342,429.37 (2.61)	3,774,812.35 (17.46)
Other asthma medication	10,789,280.82 (62.12)	5,819,598.60 (44.39)	22,412,953.76 (103.64)
Immunotherapy	7,403,386.43 (42.63)	4,017,060.24 (30.64)	16,754,942.43 (77.48)
Antihistamines	1,792,454.72 (10.32)	1,127,631.03 (8.60)	2,603,722.95 (12.04)
Antibiotics	1,491,836.29 (8.59)	636,556.20 (4.85)	2,826,579.23 (13.07)
Flu vaccine	101,603.39 (0.59)	38,351.14 (0.29)	227,709.14 (1.05)
Holding chamber	2,898,016.76 (16.69)	1,893,887.38 (14.44)	4,146,833.55 (19.18)
INDIRECT COSTS	40,068,509.59 (230.70)	21,050,912.88 (160.55)	61,480,900.06 (284.31)
Parental absenteeism	13,689,797.60 (78.82)	8,312,678.55 (63.40)	20,379,882.34 (94.24)
Transportation	3,931,536.64 (22.64)	2,770,123.76 (21.13)	5,221,446.58 (24.15)
Subsidies	22,447,175.39 (129.24)	9,968,110.57 (76.03)	41,101,017.72 (190.06)

*Best-case scenario was set with: the lower limit of the 95%CI of CA prevalence in Portuguese children; scenario of minimum use of asthma medications; and the lower limit of the 95%CI for the proportion of occurrence of each variable in Portuguese population. #Worst-case scenario was set with: the upper limit of the 95%CI of CA prevalence in Portuguese children; scenario of maximum use of asthma medications; and the upper limit of the 95%CI for the proportion of occurrence of each variable in Portuguese population.

CONCLUSION

Childhood asthma in Portugal costs €161,410,007.61 per year, corresponding to €929.35 per child with current asthma. The total cost estimate of childhood asthma corresponds to 0.91% of the Portuguese expenses in health in 2010. Direct costs were 3/4 of total costs, mainly related to acute asthma care (non-scheduled visits, emergency and hospitalisations). The most important factors determining higher costs were asthma attacks in the previous 12 months (1.6-fold) and uncontrolled asthma (2.3-fold). A better asthma control, with a consequent reduction in the acute use of healthcare services, should be the major target for potential savings in this disease.

5. DISCUSSION

In the present dissertation, the aim was to assess the burden of childhood asthma in Portugal.

For this purpose, five main domains were covered:

- 1) childhood asthma **prevalence**;
- 2) **diagnostic tests and medication** in childhood asthma;
- 3) **healthcare services use** in childhood asthma;
- 4) childhood asthma **control**;
- 5) childhood asthma **costs**.

The PhD project was designed to describe the childhood asthma burden in Portugal in a comprehensive manner. The main study was a cross-sectional, nationwide, all-age study, designed to study several asthma domains in the Portuguese general population (INAsma study). A post-hoc analysis of pediatric population (0- to 17-years old, inclusive) was performed. For the strengthening of the cost analysis, a cross-sectional study on asthma was conducted in children from primary schools of a Portuguese city. Additionally, secondary data on direct costs were used.

Asthma prevalence and burden are high among children. However, there is a paucity of data on this topic. This PhD project brought some important and comprehensive data on Portuguese childhood asthma.

5.1 Major findings

A high prevalence of asthma-like symptoms was found in the Portuguese pediatric population (39.4%; 95%CI, 35.7–43.3). The prevalence of lifetime asthma was 11.2 (95%CI, 9.1–13.7) and current asthma was 8.4% (95%CI, 6.6–10.7). Less than half of children with current asthma had been on inhaled controller medication in the previous 12 months and only 52.9% of those at or above the age of 6 years had undergone PFT.

A high proportion of healthcare services use for asthma, in the previous 12 months, was observed: 86% (95%CI, 79–93%) had scheduled medical visits, 25% (95%CI, 16–33%) had unscheduled medical visits, 39% (95%CI, 29–48%) had emergency department visits and 5% (95%CI, 1–10%) were hospitalised. Importantly, more than one third of children with asthma, or over 55,000 Portuguese children, aged 6 to 17 years were hospitalised for asthma during their lifetime.

Half of children with current asthma were not controlled (49%, 95%CI 39–59%). Determinants for 'not controlled asthma' were the presence of substantial nasal symptoms (aOR 6.8, 95%CI 2.34–19.80), overweight/obesity (aOR 3.60, 95%CI 1.46–10.13) and not having health insurance (aOR 3.78, 95%CI 1.36–10.92). The presence of a higher number of nasal symptoms was associated with poorer asthma control, in a cumulative way. Moreover, children with substantial nasal symptoms and without health insurance needed more unscheduled medical services, while adolescents needed less.

Childhood asthma in Portugal costs €161,410,007 per year, corresponding to €929.35 per child with current asthma. Direct costs were the majority of costs (75.2% of total costs), especially healthcare services use (51.1% of total costs). The most important factors for higher costs were asthma attacks in the previous 12 months (1.6-fold) and uncontrolled asthma (2.3-fold).

5.2 Strengths and limitations

Strengths

The major strength of this PhD thesis is the generalisability of the results for the Portuguese population. The core study was a Portuguese cross-sectional nationwide study (INAsma) and the participants were randomly recruited from the general Portuguese population. Also, overall, our sample followed the same distribution of the Portuguese national pediatric population assessed by the INE ⁹⁸.

The study on asthma prevalence (Paper 1) was the first population-based nationwide epidemiological study aiming to estimate the asthma prevalence in Portugal. It included a large representative sample of the Portuguese population, among all municipalities and pediatric ages, allowing us to estimate the prevalence of asthma-like symptoms, current asthma, diagnostic tests, and medication use in asthmatic children. Nationwide studies on the prevalence of asthma across the entire pediatric population have only been previously performed in Germany and the United States ⁴⁴⁻⁴⁶; no previous study has reported the prevalence of asthma-like symptoms across all pediatric ages.

For the first time, the proportion of lifetime hospitalisations for asthma was reported for a national population-based paediatric sample (Paper 2). In our country, about one-third of asthmatic children were hospitalised for asthma at least once in their lifetime.

The study on asthma control (Paper 3) was the first study assessing childhood asthma control in Portugal and, for the first time, we reported the effect of health insurance coverage on asthma control in a European country.

The cost of illness study (Paper 4) was the first Portuguese nationwide, population-based study on costs of childhood asthma. The cost domains analysed allowed us to create a comprehensive picture of childhood asthma costs in Portugal, as did the prevalence-based analysis and societal perspective. We performed a univariate and multivariate deterministic sensitivity analysis, aiming to understand different variations according to uncertainty. Sensitivity analysis is crucial to highlight variability, to make comparisons with other data, and is recommended in economic studies ^{111,112}, but this was the first cost-of-illness study on childhood asthma to report a sensitivity analysis.

Limitations

This PhD thesis on childhood asthma burden has limitations that need to be considered for an adequate interpretation of its results. The first limitation is the absence of a study on the quality of life in Portuguese childhood asthma. The assessment of this domain is important to understand the impact of the disease in children and caregivers' lives. However, the utility of the available tools in the assessment of quality of life in asthma is not well established because of the lack of validity or reproducibility between children and/or caregivers ^{82,83}. Moreover, the quality of life in asthmatic children is known to be closely linked to asthma control or seeking medical attention ^{76,85}. We do have data on asthma control, healthcare services use and also on school absenteeism that can be an objective proxy of the impact on the quality of life due to asthma among these children.

Also, each specific study has some limitations. The INAsma survey was designed for the overall Portuguese population; however, the questions included in the questionnaire and the definitions used are similar to others used in international and Portuguese pediatric studies ^{113–115}. The use of the 2001 National Census for sampling could not account for the reduction in the number of births that occurred since then; however, it was the most recently available data at the time of data collection (2010). Also, the study's pediatric sample follows the characteristics of the Portuguese pediatric population ⁹⁸. The use of landline telephones excludes households without residential telephones; nevertheless, it allowed us to guarantee a stratified cluster sample by region, and it was a method previously used in similar studies assessing asthma control in children ⁶⁴. Answers were given by the main caregiver for participants under 15 years of age and by the adolescent when the participant was ≥15 years old, as imposed by Portuguese law. This may limit comparisons between these age groups; however, changes from parent-reported to self-reported outcomes are recommended between school-age and adolescence ¹¹⁶, and other studies on asthma prevalence in pediatric ages had similar methodology ⁴⁴. Finally, we could not obtain a clinical confirmation of the diagnosis; therefore, participants' misclassification can be expected, as in any similar survey.

In the study of asthma control (Paper 3), the sample size may have limited the precision of our estimates in subgroup analysis but we were able to construct logistic regression models with good fit for the main outcomes. Physician assessment could not be included in this type of study. Yet, we used an internationally recommended measure for asthma control – the

GINA guidelines – which are frequently used in epidemiological studies with similar methodology ¹¹⁷. Also, parents' recall of doctor's diagnosis, e.g. rhinitis, may lead to underestimation of concomitant diseases.

In the cost of childhood asthma study (Paper 4) there were some limitations regarding the participants and the reported outcomes used for cost estimations. Participants were derived from INAsma and CED2013; school-age children may be overrepresented in our sample, nevertheless, this is the age group with the higher prevalence of asthma in our country ¹⁰². Also, differences in cost estimations between the two studies were only seen in the domain of 'Treatment' and total costs were not significantly different (Table 22). Data on diagnostic tests use and immunotherapy were only available in the CED2013 study and then extrapolated for the entire sample. The assumptions made in the treatment domain may also have masked higher cost differences between asthma control groups. Specifically, medication costs were based on the reported medicines used in the previous year, but we were unable to assess the number of doses taken by each participant; we used a clinical consensus approach for the number of doses of controller and reliever medication, based on GINA guidelines and on conservative estimations of adherence. In transportation, we used an official Portuguese price by kilometre, however we could not assess how many of the patients used public transports or ambulances. The absenteeism costs were based on a mean Portuguese daily income according to the parents' professional occupation, not with a reported income; this could possibly underestimate the costs of absenteeism. Also, we could not assess parents' presenteeism because of child's asthma.

5.3 Epidemiology of childhood asthma

Childhood asthma-like symptoms

In our study, the prevalence of asthma-like symptoms among Portuguese children was 39.4%. A multinational study of children aged 1 to 5 years showed that approximately one-third had wheezing, coughing, or breathlessness¹¹³, which was lower than our observation in children aged <6 years old (47.9%). However, the time period considered in that study was only 6 months, while the time period in our study was 12 months. Two recent Portuguese studies reported estimates of wheezing in preschoolers (24.5% and 27.5%)^{43,118}, similar to our results. Mvula et al.²⁸ found that 27.3% of children aged 5 to 18 had cough at night, apart from cold or chest infection. Our question did not distinguish different causes of cough and association to colds; however, our prevalence among children aged 0- to 17-years old (30.9%) was similar to that reported by Mvula et al.²⁸.

The United States National Center for Health Statistics reported a 5.4% prevalence of asthma attacks among children aged 0- to 17-years old²⁹. The slightly lower prevalence among Portuguese children (3.7%) may be related to differences in the definition of asthma attacks in the two populations.

The prevalence of wheezing and nocturnal symptoms decreased with age (Figure 3). However, after the age of 5 years, most children with wheezing exhibited wheezing without a cold and wheezing with breathlessness (Figure 4). These results suggest that age influences asthma-like symptom patterns. These findings are in agreement with previous studies suggesting that wheezing in younger children is more closely related to immature airways and viral respiratory illnesses⁸, whereas older children tend to exhibit wheezing even without respiratory infections.

Childhood asthma prevalence

There is no consensus on the epidemiologic definition of current asthma, which leads to hardly comparable differences in reported prevalence estimates, depending on the definition used^{22,30}. Wheezing-based asthma definitions are limited by differences in the concept and perception of wheezing. Fernandes et al.³⁵ reported a lack of perception of the term "wheezing" among Portuguese parents and health professionals. To account for this problem, we used several synonyms of wheezing in Portuguese in wheezing-related

questions. Additionally, the presence of wheezing was not mandatory in our definition of current asthma. Therefore, we presented estimates using different combinations of asthma proxies (Table 7). The definition we chose includes the less frequent nocturnal symptom, 'waking with breathlessness'; the term 'asthma attack' to improve specificity; and 'asthma medication', because children with asthma may not experience symptoms when controlled with medication, and medication is a known valid proxy for asthma prevalence ^{119,120}. By using several definitions of asthma used in different studies, our prevalence estimates varied from 6.4% (lifetime asthma *plus* wheezing in the last year) and 9.1% (lifetime asthma *plus* any asthma-like symptom in the last year or current asthma medication). These differences highlight the importance of setting standardized definitions to allow for comparisons between studies.

Our estimate of lifetime asthma was based on the same question of ISAAC. Our estimate in the 6- to 12-year-old group (12.3%) was higher than that in the 6- to 7-year-old group in the Portuguese ISAAC survey (9.8%) ²⁷, while our estimate for the 13- to 17-year-old group (13.9%) was similar to that in the 13- to 14-year-old group in the ISAAC survey (13.8%). In preschoolers, two recent Portuguese studies had also reported estimates of physician asthma diagnosis similar to ours: 4.6% in both studies ^{43,118}.

Schmitz et al. ⁴⁴ reported a 4.7% prevalence of a doctor-diagnosed lifetime asthma in the German population of 0- to 17-year-old using data from the 2003-2006 German Health Interview and Examination Survey for Children and Adolescents (KiGGS). This prevalence was much lower than ours and is in agreement with the estimated prevalence of lifetime asthma among German children reported in the ISAAC, which was also much lower than that in Portugal (in Germany, 4.3% in 6- to 7-year-old children and 7.5% in 13- to 14-year-old children) ²⁵. Data from the 2010 United States National Health Interview Survey for children under the age of 18 years reported an estimated doctor-diagnosed lifetime asthma prevalence of 13.6% and current asthma prevalence of 9.5% ^{45,46}, which were similar to our estimations.

There was an expected higher prevalence of current asthma in children with allergic rhinitis (OR 5.15) or eczema (OR 4.08). The impact of allergic rhinitis on asthma has long been recognized, ¹²¹ and a recent Portuguese study had also report an association between wheezing and rhinitis in pre-schoolers (OR 4.0)²⁶. In a German study, similar results on rhinitis were found in school-aged children and adolescents (OR 4.51 and 5.99, respectively), but

the association with atopic dermatitis seemed to be lower (OR 1.30 and 1.50, in school-aged children and adolescents, respectively); however, methodology on data collection could have hampered these results, namely on the diagnosis of atopic dermatitis (ICD-10 diagnosis recorded in computer systems used in the practices of resident physicians)¹²².

We found no significant differences in asthma prevalence between regions, municipality (urban vs. rural) or exposure to environmental tobacco smoke. Higher prevalence of childhood asthma is reported in the literature ^{123,124}, and causes for a this higher prevalence are discussed ¹²⁵. However other works also found no significant differences between municipality areas ¹²⁶. Differences in definition of rural and urban areas may play a role in the outcomes ¹²⁷, as the degree of urbanisation / density of population can be related to these differences ¹²⁸. In our studies, municipality was defined based on Portuguese legislation ⁹⁷; though this definition may not clearly differentiate rural and urban environments in Portugal. In what concerns environmental tobacco smoke, question on household exposure for tobacco may not be sufficient to identify differences in current asthma/asthma-like symptoms prevalence, as there are several forms of environmental tobacco smoke inside and outside households.

5.4 Diagnostic tests and medication use in childhood asthma

In spite of the recommendations to perform spirometry as part of asthma management ⁶, only about half of the Portuguese children with current asthma at or over the age of 6 years had undergone PFT. Similarly, fewer than half of Portuguese children with current asthma had used inhaled controller medications within the previous 12 months, even considering a current asthma definition based on several symptoms occurring in the last 12 months, like the one used in our study. Moreover, those who only used reliever inhaled medication in the previous year, without any controller inhalers, were twice as likely to have experienced an asthma attack in the same time period. Similar results were found in Canada where only 45% of children with asthma used inhalers on a regular basis ¹²⁹. In Denmark, Moth et al showed that children who performed PFT and those medicated with controller medication experienced less hospitalisations ¹³⁰. Our results in this domain of diagnostic tests and medication use are worrisome and shows how the burden of childhood asthma could be affected by these factors.

As told previously, no differences in the prevalence of asthma or asthma-like symptoms were found between urban and rural municipalities; however, children living in rural areas were much less likely to have undergone PFT or allergy tests or used inhaled medication. In agreement with our data, a Greek study with school-aged children also showed that the prevalence of asthma diagnosis was the same between rural and urban areas despite findings on the narrowing of small airways in urban environments ¹³¹. Disparities in health care for rural-dwelling patients with asthma have been reported, indicating that those with asthma who live in rural areas receive substandard care for asthma; however, there are limited direct data on these findings ¹³². Taken together, our results and those of previous studies on diagnostic tests and medication use may be related to differences in healthcare access and may suggest substandard asthma care in Portuguese children, especially in less urbanized areas.

5.5 Healthcare services use in childhood asthma

To the best of our knowledge, there are no nationwide Portuguese data on prevalence of healthcare medical visits because of asthma in childhood. Our results showed high proportion of scheduled medical visits (86%) in the previous 12 months; however, one-fourth had also had unscheduled medical visits because of asthma, 40% had emergency visits and 5% were hospitalised. Interestingly, we observed a significant progressive decrease of overall asthma medical visits, in the older age groups. In USA, Kattan et al reported proportions of healthcare utilization in the previous year, in 1997: unscheduled/emergency medical visits (65%) and hospitalisation (17%)⁵⁸. These results were higher than ours, but we must acknowledge that this study was done in 90's and the recruitment was made in emergency department and clinics, incurring in selection bias with possible overrepresentation of severer cases of asthma. A more recent study (2007), from National USA databases, had reported healthcare services utilization rates per 100 children with asthma: total ambulatory visits (87.2), emergency visits (9.9) and hospitalisations (1.6)²⁹. Differences to our results may be related with healthcare access differences between Portugal and the USA, as well as follow-up strategies of acute asthma in outpatient clinic vs. emergency department.

We found a high number of hospitalisations for asthma throughout childhood, with more than 55,000 Portuguese children aged 6 to 17 years hospitalised for asthma during their lifetime. Moreover, of the children with current asthma more than one third had been hospitalised for asthma ever in life. We observed a trend towards a higher proportion of hospitalisations among children from lower socioeconomic status. This is a high number of hospitalisations, especially among the younger, and more studies with comparable data from other countries and settings are needed. Surprisingly, this measure of societal burden of pediatric asthma has never been described for any pediatric population. Our results should contribute to improve knowledge on asthma-related hospitalisations in children, leading to the development of healthcare programs aiming to reduce their frequency. These results on lifetime hospitalisations is limited by the lack of diagnosis/lifetime hospitalisations confirmation by physician, as other epidemiological studies. So, we excluded participants aged 0 to 5 years from the analysis to avoid misclassification of hospital admissions for bronchiolitis and/or viral-induced wheezing. To our knowledge, only one other study reported the prevalence of lifetime hospitalisations in children¹³³; however,

it included only children aged 6 to 7 years from one Italian city, and the proportion on children with asthma that had lifetime hospitalisations was not reported.

5.6 Asthma control in children

High frequency of not controlled asthma

The proportion of Portuguese children with controlled asthma (51%) was similar to that found in 6- to 17-year-old children in the USA (46%)⁶⁶, in Dutch 6- to 16-year-old children (55%)⁶⁸ or in French pre-schoolers (42%)⁶⁷; however, estimates on the prevalence of uncontrolled asthma in children are highly variable (15-90%) depending on the studies^{52,63}. In our report, only half of the children that were considered controlled by their caregivers had, in fact, controlled asthma. Carroll et al have shown that parents usually overestimate asthma control¹³⁴. Others reported a poorer asthma control⁶⁸, or medication underuse among parents that failed to correctly estimate control⁶⁴.

The prevalence of nasal symptoms in children with current asthma (79%) was similar to that found in Dutch asthmatic aged 5- to 18-years-old (76%)⁶⁹. Despite the majority of our children with asthma having nasal symptoms, less than half of these (45%) reported a past medical diagnosis of rhinitis. Underdiagnosis and undertreatment of rhinitis in asthmatic children was associated with lack of parental recognition and poorer asthma control.^{73,74}

In our study, the increasing number of nasal symptoms was associated with a decrease in asthma control (Figure 8). We could not find previous papers assessing the association of the cumulative number of nasal symptoms with the lack of asthma control in children, nevertheless, previous studies supported a strong link between upper and lower airway disease^{26,72}.

Worse asthma control in children with obesity, nasal symptoms and absence of health insurance

Determinants for not controlled asthma were the presence of substantial nasal symptoms, overweight/obesity and not having health insurance (Table 14). Rhinitis is a known co-morbidity associated with poorer asthma control in children, especially in those with untreated nasal symptoms.⁶⁹ Our results are in line with these findings, as substantial nasal symptoms were associated to a six-fold higher probability of NCA. Recently published data also showed that increased BMI was associated to more asthma symptoms, activity limitation¹³⁵, lack of asthma control⁶³, higher use of inhaled β -agonists or oral corticosteroids

⁷⁰, and to worst asthma control in children with higher airway inflammation ⁷⁵. In our study, overweight/obesity was associated with a three-fold higher probability of NCA.

As explained previously in Introduction, the Portuguese Health System is a mixed universal healthcare system. It is financed by taxes and by health insurances, both private and public (for state employees), complemented by out-of-pocket expenses. All Portuguese citizens have access to medical care services in public primary care and hospital units. The public care access is primarily based on visits to primary care physician that can refer to hospital specialities; this is limited by the waiting time and referral geographical areas that prevent the patients from fully choosing the place where they will be followed. Private practices/hospitals access is only dependent on patient will to attend these institutions; however, due to significant out-of-pocket expenses, access is easier for those with complementary health insurance coverage. In fact, citizens with healthcare insurance, regardless of the socioeconomic status, may easily choose the site of medical care that they perceive as the best, with easier access to medical specialities and lower waiting time for medical observations. Regarding medication, prices are the same for every Portuguese child, independently of health insurance status.

In our model, not having health insurance was associated with a three-fold higher probability of NCA. Also, on exploratory univariate analysis, the frequency of children with health insurance coverage followed in private practice/hospital for their asthma was significantly higher than those followed in public settings ($p < 0.001$; Table 18). Taking these results altogether, we may speculate that these relations between asthma control and health insurance status may address differences in types of asthma care that can be influenced by parents' options in choosing the site of medical asthma care for their children (either public or private providers).

Healthcare visits and medication use differences in asthma control

We showed a trend towards more healthcare visits and medication use in children with NCA. Previous studies had already shown the association between healthcare visits and/or medication with uncontrolled asthma ^{52,53}. Children with NCA used more antihistamines and cough medication than those with WCA; this association of NCA with a higher use of over-the-counter medication was already observed in asthma patients ¹³⁶, and it may point to a worse asthma care plan in children with NCA.

Unscheduled medical visits for asthma worsening/exacerbation were more frequent in children with substantial nasal symptoms and without health insurance, and less frequent in adolescents. This model on urgent medical care, which was also used as a proxy for poor asthma control, corroborates that uninsured children, as well as those with substantial nasal symptoms, were at a higher risk of uncontrolled asthma and use of urgent medical care.

5.7 Cost of childhood asthma

Health economics studies are needed to support local decision-makers in defining priorities for public health programs ⁸⁷. As governmental health policies become more cost-aware, it is important to know where is possible to act in order to reduce costs while maintaining or enhancing healthcare quality. In Portugal, health-related costs represented 9,9% of the gross domestic product in 2010 ⁸⁸, highlighting the importance of being cautious with healthcare resource allocation. As one of the most common chronic diseases in childhood, asthma should have good economic data available. Many economic studies were conducted in asthma all-over the world with different methodologies, different variables, and different age ranges. However, there are few population-based and comprehensive pediatric studies ⁵⁵.

We conducted a cost-of-illness analysis on Portuguese childhood asthma, with a prevalence-based, societal perspective, that allowed a broad economic analysis of the disease. We adopted a societal perspective, the most comprehensive approach, because it uses the direct and indirect costs for all members of the society ¹³⁷. From a societal perspective, the childhood asthma in Portugal costs over €150 million per year, corresponding to more than €900 per child with CA. Childhood asthma costs correspond to 0.91% of the Portuguese expenses in health in 2010. These expenditures are undertaken together by the patients, by the Portuguese state and by health insurance companies, depending on the type of healthcare services used. Direct costs were 3/4 of the costs, with the most being related to healthcare services use and specially to acute asthma care. The most important factors for higher costs were uncontrolled asthma (2.3-fold) and asthma attacks in the previous 12 months (1.6-fold).

Total, direct and indirect costs of childhood asthma

The cost estimates for childhood asthma in Portugal were slightly lower than the Spanish estimates in 2008 (€1,149 child/year) ⁹¹. Otherwise, USA estimates for 2008 prices of 5- to 17-years old asthmatics were lower than ours: \$791 child/year (direct costs, \$401 child/year; indirect costs, \$390 child/year) ¹³⁸. In that study, the authors analysed data from the 1996 Medical Expenditure Panel Survey and the type of asthma-related expenditures used in

direct costs were not clear. In Turkey, a study performed in 2006, in pediatric allergy and asthma referral centres, reported medical and non-medical costs of \$1,597 per child/year (medical, \$775; non-medical, \$821), however, no formal indirect costs were reported ¹³⁹. The definition of medical costs was similar to our definition of direct costs, and the results were also similar (assuming 1.23 exchange rate of dollar to euro, in 2006). Non-medical costs included transportation (not absenteeism), but were mainly driven by non-allergic household measures (\$710) like air filters, special vacuum cleaners or anti-allergic bed covers, that we did not assess in our study, as the current guidelines do not recommend them ⁶.

Direct costs were the majority of costs in our study (75% of total costs), especially healthcare services use (51% of total costs). Previously published studies reported proportions of direct costs between 61-88% ⁵⁵. Healthcare services use in the context of asthma worsening (non-scheduled medical visits, emergency and hospitalisations) were, altogether, 30% of the total costs of childhood asthma in Portugal. Reducing acute asthma care costs, should be one of the major targets for potential savings. Also, by reducing it other domains (e. g., indirect costs) could also be lowered.

Indirect costs were one-fourth of the costs in childhood asthma. Other studies showed that indirect costs can be as high as 50% ⁵⁵. The lack of assessment of costs related to presenteeism and lower salaries in Portugal may justify our proportion of indirect costs. Nevertheless, more than 13 million euros were spent yearly with parental absenteeism because of childhood asthma. This value can represent a potential higher burden to society, as loss of parental work can further impact the overall economy.

Determinants of cost variation in childhood asthma

The most important determinants for higher costs were the asthma attacks in the previous 12 months (1.6-fold) and having uncontrolled asthma (2.3-fold). This reinforce the need for a higher control in asthmatic children, in order to reduce the associated costs. Also in the Spanish study, costs variations within each category of asthma severity ranged from €403 for mild asthma to €5.930 for severe asthma (costs child/year) ⁹¹.

Direct costs were significantly higher in children with uncontrolled asthma, specifically healthcare services use and diagnostic test use. Interestingly, there were no significant differences in costs of scheduled medical visits and treatment for controlled vs. uncontrolled children. The domains with the higher cost raises from children with controlled vs. uncontrolled asthma were 'non-scheduled visits' (€45 to €152 child/year) and, mostly, 'emergency department visits' (€67 to €370 child/year) and 'hospitalisations' (€27 to €426 child/year) (Table 25). Indirect costs were also higher in uncontrolled asthmatics, although without a significant increase; absenteeism seems to be similar in the different levels of asthma control.

Considering a hypothetical scenario (data not shown) in which all Portuguese children with asthma were controlled, the savings would be more than 30,000,000 € per year (20% reduction). As previously reported, children with not controlled asthma had significantly more unscheduled medical visits and hospitalisations ^{103,140}; knowing that uncontrolled asthma is, also, the major determinant for higher costs, effective policies should be directed to improve asthma control and reduce acute care medical visits.

5.8 Future directions

In children, epidemiological asthma definitions and clinical asthma phenotypes are primarily based upon wheezing ³¹. However, Skytt et al. ³³, based on data from the Copenhagen Prospective Study on Asthma in Childhood, addressed the lack of validity of wheezing for asthma diagnosis in children aged 0 to 3 years. They argued for a global description of asthma symptoms to reduce the risk of misclassification of asthma in children. We suggest that questionnaires directed at children and adolescents should include different measures to comprehensively assess asthma characteristics (previous diagnosis, several symptoms, and medication), thus aiming to obtain precise estimates of asthma prevalence, especially in younger children. In any case, standardization of epidemiologic asthma definitions and their clinical validation are needed ²².

Also, it is important to create awareness to the importance of a good asthma control in children. The lack of control was, definitely, the major driver of high burden in childhood asthma. If the proportion of good asthma control increased, one can speculate that it will decrease the burden of this disease by lowering all the adverse outcomes. Good asthma control is associated to lower healthcare services use because of asthma worsening. Also, healthcare services use is the domain with the highest increase in costs in children with uncontrolled asthma. Previous studies have reported economic savings with outreach asthma programs for children ¹⁴¹, however, cost-effectiveness studies on asthma interventions directed to improving control and reducing costs will be of major interest for patients, parents, healthcare providers and policy-makers.

Future studies should be designed to have multinational cost-of-illness data, aiming to understand differences between asthma care and to compare outcomes. Quality-of-life assessment in childhood asthma should also be improved and be part of a burden of disease analysis. A nationwide quality-of-life study on childhood asthma should be designed to assess the social impact of this disease. This type of approach will further characterize the disease burden in Portugal, helping in defining policies in local healthcare services or schools.

6. CONCLUSION

This PhD thesis brought comprehensive estimates on the burden of childhood asthma in Portugal.

Current asthma affects 8.4% of Portuguese children (173,681 Portuguese children with asthma) and 11.2% had lifetime asthma. Different asthma definitions lead to different prevalence estimates (from 6.3% to 9.1%). Our results showed that only half of children with current asthma had ever undergone pulmonary function tests and that management has been substandard, mainly in rural areas. Also, more than half of the children with current asthma did not use controller inhalers, and those who only used reliever inhalers reported more asthma attacks.

Children with asthma had a high proportion of scheduled medical visits (86%) in the previous 12 months. However, one-fourth had also unscheduled medical visits because of asthma, 40% had emergency visits and 5% were hospitalised. Children with lack of asthma control had more unscheduled medical visits and hospitalisations. For the first time, it was described the proportion of asthmatic children hospitalised because of asthma, at least once, in their life: more than one third of Portuguese children with current asthma were hospitalised during their childhood. Our results should contribute to improve knowledge on asthma-related hospitalisations in children, leading to the development of healthcare programs aiming to reduce their frequency.

The abovementioned facts can contribute, to the lack of control observed in half of the Portuguese children with asthma. Nasal symptoms and obesity were found to be important determinants of asthma control. Also, children without health insurance (private or state owned) are at greater risk of poor asthma outcomes; this association was not previously reported in a European country.

The high clinical and healthcare burden of childhood asthma is reflected in the associated costs. The total cost estimate of childhood asthma corresponds to 0.91 % of the Portuguese expenses in health in 2010. The childhood asthma in Portugal costs €161,410,007 per year, corresponding to €929.35 per child with current asthma. Direct costs were the majority of costs (75% of total costs), especially healthcare services use (51% of total costs). The most

important factors for higher costs are asthma attacks in the previous 12 months (1.6-fold) and uncontrolled asthma (2.3-fold).

The lack of control was the major driver of the high burden of childhood asthma. A poor asthma control in children was associated with: 1) more asthma-like symptoms, 2) more nasal symptoms, 3) more healthcare services use, 4) more asthma medication use, and 5) higher costs for the society.

The burden of childhood asthma in Portugal is high and, altogether, these findings point towards the need for a better asthma control in Portuguese children to reduce the burden of childhood asthma for families, healthcare system and society in general. Policymakers, clinicians and the ones responsible for children's care should define priorities and implement procedures towards the achievement of a better asthma control and reduction in the need of acute asthma care, aiming to reduce the high burden of this disease in Portugal.

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8.APPENDICES

8.1 PhD Tasks

1) PhD Planning and Setup

Dates: January 2012 - October 2015

Work completed:

- a) Regular meetings with supervisor and co-supervisor;
 - b) Definition of PhD project tasks;
 - c) Strategies of dissemination of results;
 - d) Presentation of PhD project in a scientific meeting (PhD output 7);
 - e) Progression report of PhD project.
-

2) Bibliographic review

Dates: January 2012 - December 2012

Work completed:

- a) Bibliographic review of relevant published evidence in children focused on:
 - i. Asthma-like symptoms
 - ii. Asthma prevalence
 - iii. Asthma control
 - iv. Asthma medication use
 - v. Healthcare services use for asthma
 - vi. Burden of asthma
 - vii. Cost of asthma
-

3a) INAsma Study: Analysis of pediatric-specific data

Dates: May 2012 - April 2013

Work completed:

- a) Estimates on asthma-like symptoms prevalence;
- b) Estimates on asthma prevalence;
- c) Estimates on use of asthma medication;
- d) Estimates on healthcare services use for asthma;
- e) Estimates on level of asthma control;
- f) Determinants of asthma control.

3b) INAsma Study: Dissemination of pediatric-specific results

Dates: May 2013 - June 2015

Work completed:

- a) Presentation of preliminary results of INAsma Study in congresses (PhD output 5 and 6);
- b) Writing of manuscript drafts;
- c) Publication of PhD output 2;
- d) Publication of PhD output 3;
- e) Publication of PhD output 1.

Work to be completed:

- a) Dissemination (paper publication) of the results within the aims of CASCA project (in submission).
-

4a) CED2013 Study: Setup

Dates: January 2013 - March 2014

Work completed:

- a) Meetings with the researchers team of CED2013 Study;
- b) Completion of the final questionnaire;
- c) Completion of standard operational procedures;
- d) Submission to the Ethical Committee of University of Porto;
- e) Submission to Comissão Nacional de Proteção de Dados;
- f) Randomization of participants;
- g) Preparation of data collection of phase 1 and 2;
- h) Hiring of one researcher collaborator.

4b) CED2013 Study: Data collection

Dates: November 2013 - June 2014

Work completed:

- a) Data collection of phase 1;
- b) Data collection of phase 2.

4c) CED2013 Study: Data analysis and Dissemination

Dates: July 2014 - October 2015

Work completed:

- a) Organisation of database;
- b) Preliminary analysis;
- c) Public presentation of preliminary results (PhD outputs 8, 9 and 10);
- d) Elaboration of an individual report of pulmonary function tests for each child assessed.

Work to be completed:

- b) Dissemination (paper publication) of the results within the aims of CASCA project (in submission).
-

5a) CASCA Project: Setup

Dates: May 2012 – December 2013

Work completed:

- a) Meetings with the researchers' team of CASCA Project;
- b) Definition of study methodology;
- c) Definition of relevant direct and indirect costs;
- d) Submission to Gulbenkian Foundation Grant;
- e) Elaboration of CASCA project website.

5b) CASCA Project: Data collection of secondary data

Dates: July 2014 - December 2015

Work completed:

- a) Data collection of ICAR;
- b) Data collection of CED2013;
- c) Asthma hospitalisations from databases from ACSS;
- d) Medication names, brands, doses and process from Infomed®;
- e) Professional activities classification and salaries from INE;
- f) Organisation of databases.

5c) CASCA Project: Data analysis and Dissemination

Dates: January 2015 - December 2015

Work completed:

- a) Cost-of-illness analysis of asthma in Portuguese children (PhD output 4);
- b) Public presentation of preliminary results (PhD output 9 and 10).

Work to be completed:

- a) Dissemination (paper publication) of the results within the aims of CASCA project (in submission).
-

6) PhD thesis completion

Dates: January 2016 – July 2017

Work completed:

- a) Draft of the final thesis of PhD;

Work to be completed:

- a) Public presentation and discussion of PhD thesis.

8.2 PhD Outputs

PEER-REVIEW SCIENTIFIC PUBLICATIONS

1

["Asthma-like symptoms, diagnostic tests and asthma medication use in children and adolescents: a population-based nationwide survey"](#)

Full-paper published in *Journal of Asthma* [Impact factor 1.85 from JCR®, ISI WoS; 75th percentile of 'Respiratory System' (journal n. 39th/58)]

Ferreira-Magalhães M, Sá-Sousa A, Morais-Almeida M, Pité H, Azevedo LF, Azevedo I, Bugalho-Almeida A, Fonseca JA. **Asthma-like symptoms, diagnostic tests, and asthma medication use in children and adolescents: a population-based nationwide survey.** *J Asthma* 2016; 53:269-276.

2

["High prevalence of hospitalisation for asthma in a population-based paediatric sample"](#)

Original research letter published in *Archives of Disease in Childhood* [Impact factor 1.85 from JCR®, ISI WoS; 15th percentile of 'Pediatrics' (journal n. 13th/120)]

Ferreira-Magalhães M, Sá-Sousa A, Morais-Almeida M, Azevedo LF, Azevedo I, Pereira AM, Fonseca JA. **High prevalence of hospitalisation for asthma in a population-based paediatric sample.** *Arch Dis Child* 2015; 100:507–508.

3

["Asthma control in children is associated with nasal symptoms, obesity and health insurance: a nationwide survey"](#)

Full-paper published in *Pediatric Allergy and Immunology* [Impact factor 3.95 from JCR®, ISI WoS; 5th percentile of 'Pediatrics' (journal n. 5th/120)]

Ferreira-Magalhães M, Pereira AM, Sá-Sousa A, Morais-Almeida M, Azevedo I, Azevedo LF, Fonseca JA. **Asthma control in children is associated with nasal symptoms, obesity and health insurance: a nationwide survey.** *Pediatr Allergy Immunol* 2015; 26(5):466-473.

4

["Cost of asthma in children: a nationwide, population-based, cost-of-illness study"](#)

Full-paper submitted

Ferreira-Magalhães M, Amaral R, Pereira AM, Sá-Sousa A, Azevedo I, Azevedo LF, Fonseca JA. **Cost of asthma in children: a nationwide, population-based, cost-of-illness study.**

ORAL PRESENTATIONS AND POSTERS

5

"Prevalence and control of current asthma in Portuguese paediatric population"

Poster presented at European Respiratory Society Congress, Amsterdam 2011

Abstract published in *European Respiratory Journal* [7.13]

Ferreira-Magalhães M, Sá-Sousa A, Morais-Almeida M, Azevedo L, Bugalho-Almeida A, Fonseca JA. **Prevalence and control of current asthma in Portuguese paediatric population.** *Eur Resp J* 2011; 38(55): 781S(p4254).

6

"Prevalência e controlo da asma na população pediátrica Portuguesa – Inquérito Nacional da Asma"

Oral presentation at Congresso Nacional de Pediatria, Albufeira, 2011

Abstract published in *Acta Pediátrica Portuguesa*

Ferreira-Magalhães M, Sá-Sousa A, Morais-Almeida A, Azevedo LF, Bugalho-Almeida A, Fonseca JA. **Prevalência e controlo de asma na população pediátrica portuguesa – Inquérito Nacional da Asma.** *Acta Pediatr Portuguesa* 2011; 42(5):S21 (Sup. I).

7

"Diagnóstico, controlo e impacto da asma na criança"

Oral presentation at Encontro Hispano-Luso de Internos de Pediatria, 2012

8

"Asma em crianças Vimeirense do 1º ciclo: sintomas, medicação e utilização de serviços de saúde"

Oral presentation at 35º Reunião Anual da Sociedade Portuguesa de Alergologia e Imunologia Clínica, Porto, 2014

Ferreira-Magalhães M, Amaral R, Guimarães J, Moreira A, Vaz R, Moreira P, Fonseca J. **Asma em crianças Vimeirense do 1º ciclo: sintomas, medicação e utilização de serviços de saúde.** *Revista Portuguesa de Imunoalergologia* 2014;XXII:18.

DISSEMINATION ACTIVITIES TO THE COMMUNITY

9

“Asma em crianças Vimeirense do 1º ciclo: sintomas, medicação e utilização de serviços de saúde”

Public open session in school for presentation of the results from the study performed in partnership with the European Capital of Sports 2013 (Guimarães - CED2013), Guimarães, 2015

10

“Asma tira milhares de crianças à escola”

Newspaper article published in *Diário do Minho* on 7th of May of 2015.

11

“Custo da asma na criança em Portugal”

Press release on Worldwide Asthma Day 2016 about the preliminary results from cost of illness study of childhood asthma in Portugal.

Several news were disseminated by newspaper (e.g. Público, Diário de Notícias, Jornal de Notícias) and televisions (RTP).

8.3 Awards / Distinctions

1

2nd place for the best oral presentation of the session, SPAIC 2015

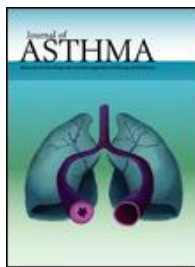
The oral presentation "Asma em crianças Vimaraneses do 1º ciclo: sintomas, medicação e utilização de serviços de saúde" presented at the 35º Reunião Anual da Sociedade Portuguesa de Alergologia e Imunologia Clínica won the 2nd place for the best oral presentation of the session.

2

Editor's Choice Series, Pediatric Allergy and Immunology, August 2015

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Asthma-like symptoms, diagnostic tests, and asthma medication use in children and adolescents: a population-based nationwide survey

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ADOLESCENT

Asthma-like symptoms, diagnostic tests, and asthma medication use in children and adolescents: a population-based nationwide survey

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Abstract

Objective: This study aimed to estimate the prevalence of asthma-like symptoms, current asthma (CA), asthma diagnostic tests, and inhaled medication use in a nationwide pediatric population (<18 years). **Methods:** Pediatric-specific data from a cross-sectional, population-based telephone survey (INASMA study) in Portugal were analyzed. CA was defined as lifetime asthma and (1) wheezing, (2) waking with breathlessness, or (3) asthma attack in the previous 12 months, and/or (4) taking asthma medication at the time of the interview. **Results:** In total, 716 children were included. The prevalence of asthma-like symptoms was 39.4% [95% confidence interval (95% CI): 35.7–43.3]. The most common symptoms were waking with cough (30.9%) and wheezing (19.1%). The prevalence of CA was 8.4% (95% CI: 6.6–10.7). Among children with CA, 79.9% and 52.9% reported prior allergy testing and pulmonary function testing (PFT), respectively. Inhaled medication use in the previous 12 months was reported by 67.6% (reliever inhalers, 40.1%; controller inhalers, 41.5%). Those who only used inhaled reliever medications experienced more asthma attacks [odds ratio (OR): 2.69]. Significantly fewer children with CA living in rural areas than those living in urban areas had undergone PFT or used inhaled medication (OR: 0.06 for PFT, 0.20 for medication). **Conclusions:** The prevalence of CA in the Portuguese pediatric population was 8.4%. Only half of children with CA had ever undergone PFT; more than half did not use controller inhalers, and those who only used reliever inhalers reported more asthma attacks. These findings suggest that asthma management has been substandard, mainly in rural areas.

Keywords

Cough, epidemiology, pediatrics, prevalence, respiratory function tests, treatment, wheezing

History

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Introduction

Asthma is one of the most common chronic diseases in children [1]. According to the Global Initiative for Asthma, asthma is a heterogeneous disease characterized by variable symptoms [2]. Composite measures to define asthma are increasingly necessary to obtain more accurate epidemiological prevalence estimates [3], and population-based studies are important for the assessment of these estimates [4].

The results of the 20-year International Study of Asthma and Allergies in Childhood (ISAAC) have changed our

knowledge about the worldwide prevalence of asthma and related symptoms [5]. The ISAAC included some Portuguese cities [6], but neither the ISAAC nor other studies estimated the prevalence of asthma across all pediatric ages (<18 years) or among a representative nationwide sample in Portugal [7–10]. In fact, to the best of our knowledge, very few studies have estimated the prevalence of asthma in this age range using nationwide samples [11–13]. Moreover, different asthma definitions are presented in the literature, making it difficult to accurately compare estimates between studies [3,14]. The patterns of asthma-like symptoms may also differ among various pediatric ages. However, no data have been published on the prevalence of specific asthma symptoms, other than wheezing, in all pediatric ages.

A diagnosis of asthma is based on symptoms and confirmation of variable expiratory flow limitation, making pulmonary function testing (PFT) an important tool. A

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stepwise approach for asthma management takes the previous two features and medication, primarily inhaler use, into account [2]. Epidemiological assessment of asthma should also focus on data from the above-mentioned asthma features closely linked to diagnosis and management.

In 2010, we conducted the First Portuguese National Asthma Survey (INAsma) [15]. In the present paper, we focus on the results obtained from the INAsma pediatric population. Specifically, our primary aim was to estimate the prevalence of asthma-like symptoms and current asthma (CA) in the Portuguese pediatric population (<18 years). Our secondary aims were to describe the differences in CA prevalence estimates according to different definitions to allow for comparisons with other studies and to assess the proportion of the use of diagnostic tests and inhaled medication among children with CA.

Materials and methods

Study design and participants

The INAsma was a population-based, nationwide, cross-sectional survey applied by telephone interview in Portugal in 2010. The study methodology has been previously described [15,16]. The INAsma target population was the Portuguese general population, and the available population included citizens of all ages living in households with a landline telephone. A cluster sampling design was used to obtain a representative sample of the population (detailed in the Supplementary file). Briefly, all municipalities were used as natural strata, and a sample of households was then selected with a probability proportional to the municipality population as estimated in the 2001 National Census. Households were randomly selected from the 2010 residential White Pages telephone directory. Four different lists of telephone numbers were randomly selected for each municipality to allow for substitution of nonresidential telephone numbers. In total, 24 412 telephone numbers were retrieved. One participant (the last person to have had a birthday) was randomly selected from each household. In this study, we considered all included individuals aged <18 years (henceforth referred to as “children” for simplification).

This study was reviewed and approved by the Ethics Committee of Centro Hospitalar de São João, Porto, Portugal. Informed consent was obtained from the parent(s) or legal guardian(s) of the children included in this study. We followed the STROBE statement for reporting observational studies [17].

Instruments and data collection

The instrument for data collection was the Portuguese version of the questionnaire used in the GA²LEN survey, which includes the European Community Respiratory Health Survey questions on asthma symptoms [18]. Several questions were added regarding socio-educational variables, medications, and diagnostic test use for asthma. Data were collected by computer-assisted telephone interviews from March to May 2010. Selected participants directly answered the questionnaire. However, in accordance with Portuguese legislation, when the selected individual was younger than 15 years old,

the respondent was the usual and most knowledgeable caregiver. To minimize potential bias in data collection, several quality-assurance measures were followed (Supplementary file) [15].

Variables

Asthma definition variables were defined based on previous studies [3,5]. The outcomes were defined as follows: *Lifetime asthma (LA)*: positive answer to “Have you ever had asthma?”; *CA*: LA plus at least one of the following four features: (1) wheezing, (2) waking with breathlessness, (3) having an asthma attack in the last 12 months, or (4) taking asthma medication at the time of the interview; *Nocturnal symptoms*: at least one of the three symptoms in the last 12 months: waking with breathlessness, waking with chest tightness, or waking with coughing; *Asthma-like symptoms*: at least one of the three symptoms in the last 12 months: wheezing, nocturnal symptoms, or asthma attacks (wheezing was further described as wheezing with breathlessness or wheezing without a cold); *PFT*: positive answer to “Have you ever undergone any test to assess your lung function?”; *Skin prick tests*: positive answer to “Have you ever undergone any skin test to assess your allergies?”; *Blood allergy tests*: positive answer to “Have you ever undergone any blood test to assess your allergies?”; *Any asthma medication at present*: positive answer to “Are you currently taking medication (inhaled, nebulized, or oral) for asthma/breathlessness?”; *Inhaled therapy in the last 12 months*: positive answer to “In the last 12 months, did you take any inhaled medication for asthma/breathlessness?” Further characterization of inhaled treatment was based on auto-reported medication: *Allergic rhinitis*: Positive answer to “Do you have any nasal allergies, including hay fever?”; *Atopic dermatitis/eczema*: Positive answer to “Have you ever had eczema or skin allergy?”; *Food allergy*: Positive answer to “Have you been diagnosed with food allergy by a doctor?”; and *Environmental tobacco smoke*: Positive answer to “Does anyone smoke inside your home?”. *Municipality* was classified as urban if the residence was located in a municipality with at least one city (cities must have at least 8000 citizens), according to Portuguese legislation.

Sample size and statistical analysis

The study sample size was calculated for the total Portuguese population and took into account the two phases of the INAsma project [15]. Thus, for the general all-age population, we estimated an *a priori* asthma prevalence of 6% and a proportion of controlled asthma of 20%. Assuming a 20% loss to follow-up, at least 665 patients with asthma were required. Within these premises, and assuming a margin of error of 0.65%, our study required a sample of at least 6000 persons from the general Portuguese population willing to participate in the first phase of the INAsma. The inclusion of 716 children allowed us to estimate CA prevalence with an error margin of 0.02 and a 95% confidence level.

The sample estimates were weighted according to the 2001 National Census aiming for generalization to the target population [19]. A sequential simple random sampling method without replacement was used to select a random

sample of households with a landline telephone within each stratum (municipality) and then one random eligible household resident. Two types of weights were used: (1) prestratification weights to adjust for the sampling design and (2) poststratification weights to adjust for the true sex and age distribution of the target population, thus partially correcting for nonresponse and noncoverage bias.

Statistical analyses were weighted for the Portuguese pediatric population and performed using the complex samples tool of SPSS version 21 (SPSS IBM, New York, NY, USA), with the exception of the participants' characteristics description, which was performed without weighting procedures. Categorical variables were described using absolute and relative frequencies with 95% confidence intervals (95% CIs); comparisons were performed with Pearson's chi-squared test. Univariate logistic regression models for outcomes were developed using independent variables as risk/predictive factors. Multivariate logistic regression models were developed to adjust for possible confounders. Results of multivariate logistic regression models were presented as odds ratios (ORs) with 95% CIs. A *p* value of <0.05 was considered statistically significant.

Results

Participants

The corrected response rate of the INAsma was 50%. Of the 6003 participants in the INAsma survey, 716 (11.9%) were children. A flowchart of all participants is shown in Figure S1. One-fifth (21.4%) of the children were younger than 6 years of age, and 39% were 13–17 years old; most (80.6%) were from urban areas. The children's characteristics are summarized in Table 1.

Prevalence of asthma-like symptoms

The prevalence of asthma-like symptoms among Portuguese children was 39.4% (95% CI, 35.7–43.3) (Table 2). Asthma-like symptoms were highest in children aged <6 years (47.9%; 95% CI, 40.0–56.0) and lowest in those aged 13–17 years (31.8%; 95% CI, 26.3–37.8; *p* = 0.005) (Table S1). Waking during the night with cough was the most prevalent symptom (30.9%; 95% CI, 27.5–34.5), followed by wheezing (19.1%; 95% CI, 16.4–22.1).

The prevalence of nocturnal symptoms was higher in children aged <6 years (39.8%; 95% CI, 32.1–48.1) than in those aged 13–17 years (OR: 0.61; 95% CI, 0.40–0.94), although the prevalence was not significantly different from that of children aged 6–12 years (OR: 0.84; 95% CI: 0.55–1.28). The prevalence of wheezing was highest in children aged <6 years (31.0%; 95% CI: 24.4–38.5) and significantly decreased with age (OR: 0.46; 95% CI: 0.30–0.70 in the 6- to 12-year-old age group; and OR: 0.24; 95% CI: 0.15–0.40 in the 13- to 17-year-old age group) (Figure 1). Among children who reported wheezing in the last 12 months, the symptoms of wheezing without a cold and wheezing with breathlessness were higher in children aged 6–12 years than in those aged <6 years (*p* < 0.001) (Figure 2).

The presence of rhinitis and eczema was associated with a higher prevalence of having any asthma-like symptom (OR: 3.67; 95% CI: 2.52–5.39 for rhinitis; and OR: 2.11; 95% CI:

1.51–2.94 for eczema). Supplementary information on asthma-like symptoms is presented in Tables S1 and S2.

Asthma prevalence

The prevalence of LA was 11.2% (95% CI: 9.1–13.7), and that of CA was 8.4% (95% CI: 6.6–10.7). No statistically significant differences were found in the prevalence of CA according to region or other sociodemographic variables (Table 1). A higher risk of CA was found in children with rhinitis and eczema (OR: 5.20; 95% CI: 3.05–8.85 for rhinitis; and OR: 4.17; 95% CI: 2.41–7.19 for eczema). Table 3 shows an overview of different asthma definitions according to the inclusion of different proxies of asthma prevalence.

Diagnostic tests and medication for asthma

PFT and allergy tests (skin prick tests and/or blood allergy tests) were performed in 12.6% (95% CI: 10.3–15.2) and 28.3% (95% CI: 24.9–31.9) of children, respectively. About half of children with CA aged ≥6 years had undergone PFT (52.9%; 95% CI: 46.0–59.8), and this prevalence did not change if they had had an asthma attack in the previous 12 months. Children with CA who lived in rural areas were less likely to report diagnostic testing than those from urban areas (OR: 0.06; 95% CI: 0.04–0.09 for PFT; and OR: 0.39; 95% CI: 0.22–0.69 for allergy tests) (Table 4).

Among children with CA, the frequency of any asthma medication at the time of the interview was 76.4% (95% CI: 64.4–85.3). Inhaled reliever and controller therapy were used in the previous 12 months by 40.1% (95% CI: 28.5–53.0) and 41.5% (95% CI: 29.6–54.5) of children with CA, respectively (Table S3). Children who reported using only inhaled reliever medication in the previous year, without any inhaled controllers, were more likely to experience an asthma attack in the same time period (OR: 2.69; 95% CI: 1.24–5.84). Children with CA from rural areas were less likely to report using any inhaled therapy in the previous 12 months (OR: 0.20; 95% CI: 0.09–0.43).

Discussion

A high prevalence of asthma-like symptoms was found in the Portuguese pediatric population (39.4%; 95% CI: 35.7–43.3), and the prevalence of CA was 8.4% (95% CI: 6.6–10.7). This study showed that less than half of children with CA had been on inhaled controller medication in the previous 12 months and that only 52.9% of those aged ≥6 years had undergone PFT.

This study was the first population-based nationwide epidemiological study aiming to estimate the asthma prevalence in Portugal among all municipalities and pediatric ages. It included a large representative sample of the Portuguese population, allowing us to estimate the prevalence of asthma-like symptoms, CA, diagnostic tests, and medication use in asthmatic children. Nationwide studies on the prevalence of asthma across the entire pediatric population have only been previously performed in Germany and the United States [11–13]; no previous study has reported the prevalence of asthma-like symptoms across all pediatric ages. A multinational study of children aged 1–5 years showed that

Table 1. Participants' characteristics in a pediatric sample.

	Total participants, n (%)	Current asthma % (95% CI)	Odds ratio ^a (95% CI)
All pediatric Population	716 (100.0)	8.4 (6.6–10.7)	
Gender			
Female	270 (37.7)	6.7 (4.3–10.1)	1.00 (Ref)
Male	446 (62.3)	10.1 (7.5–13.4)	1.59 (0.92–2.75)
Age groups			
0–5 years	153 (21.4)	6.5 (3.5–11.6)	1.00 (Ref)
6–12 years	284 (39.7)	9.7 (6.8–13.8)	1.53 (0.73–3.23)
13–17 years	279 (39.0)	8.7 (5.9–12.5)	1.36 (0.64–2.90)
National region			
North	284 (39.7)	7.2 (4.6–11.1)	1.00 (Ref)
Centre and Islands	179 (25.0)	9.7 (6.3–14.7)	1.35 (0.67–2.74)
South	253 (35.3)	8.7 (5.7–12.9)	1.21 (0.61–2.38)
Municipality			
Urban	577 (80.6)	8.0 (5.9–10.8)	1.00 (Ref)
Rural	139 (19.4)	9.8 (6.6–14.3)	1.12 (0.59–2.11)
ETS ^b			
No	454 (63.4)	8.2 (5.9–11.3)	1.00 (Ref)
Yes	262 (36.6)	8.8 (6.1–12.6)	1.06 (0.61–1.84)
Allergic rhinitis			
No	558 (77.9)	5.0 (3.4–7.4)	1.00 (Ref)
Yes	158 (22.1)	22.3 (16.6–29.2)	5.15 (3.02–8.78)*
Eczema			
No	517 (72.2)	5.0 (3.4–7.4)	1.00 (Ref)
Yes	199 (27.8)	18.3 (13.6–24.2)	4.08 (2.35–7.08)*
Food allergy			
No	676 (94.4)	8.3 (6.4–10.8)	1.00 (Ref)
Yes	40 (5.6)	9.6 (5.4–16.4)	0.94 (0.45–1.95)

Weighted proportion and odds ratio (95% confidence intervals) of current asthma according to sociodemographic and clinical variables.

^aAdjusted odds ratio for gender, age, region, municipality, and ETS.

^bEnvironmental tobacco smoke.

*Statistically significant.

Table 2. Weighted prevalence of asthma-like symptoms in the previous 12 months in the Portuguese pediatric population.

	Total population % (95% CI)	Current asthma	
		Yes % (n = 66)	No % (n = 750)
Any symptom ^a	39.4 (35.7–43.3)	91.4 (82.4–96.1)	34.7 (30.9–38.6)
Wheezing	19.1 (16.4–22.1)	76.5 (65.4–84.9)	13.8 (11.4–16.6)
Wheeze w/o cold	8.2 (6.5–10.4)	49.2 (37.2–61.3)	4.5 (3.1–6.3)
Nocturnal symptoms	34.7 (31.1–38.5)	79.2 (68.0–87.3)	30.7 (27.0–34.6)
Waking with breathlessness	5.0 (3.6–7.1)	24.7 (16.1–35.9)	3.2 (2.0–5.3)
Waking with chest tightness	6.7 (5.1–8.8)	27.4 (17.8–39.6)	4.8 (3.4–6.8)
Waking with cough	30.9 (27.5–34.5)	68.7 (56.6–78.7)	27.4 (24.0–31.2)
Asthma attack	3.7 (2.6–5.4)	44.4 (32.6–56.9)	0.0 (0.0–0.0)

^aWheezing or waking with breathlessness or waking with chest tightness or waking with cough or asthma attacks.

approximately one-third had wheezing, coughing, or breathlessness [20], which is lower than our observation in children aged <6 years (47.9%). However, the time period considered in that study was only 6 months, while the time period in our study was 12 months. Two recent Portuguese studies reported estimates of wheezing in preschoolers (24.5% and 27.5%) [21,22], similar to our results. Mvula et al. [23] found that 27.3% of children aged 5–18 years had cough at night, apart from cold or chest infection. Our question did not distinguish different causes of cough and association to colds; however, our prevalence among children aged 0–17 years (30.9%) is similar to that reported by Mvula et al. [23].

The United States National Center for Health Statistics reported a 5.4% prevalence of asthma attacks among children

aged 0–17 years [24]. The slightly lower prevalence among Portuguese children (3.7%) may be related to differences in the definition of asthma attacks in the two populations.

Differences in asthma-like symptom patterns in various age subgroups

The prevalence of wheezing and nocturnal symptoms decreased with age (Figure 1). However, after the age of 5 years, most children with wheezing exhibited wheezing without a cold and wheezing with breathlessness (Figure 2). These results suggest that age influences asthma-like symptom patterns. These findings are in agreement with previous studies suggesting that wheezing

Figure 1. Weighted prevalence of asthma-like symptoms within the previous 12 months, according to age group (%; 95% CI). Symbols represent prevalence of: ○ nocturnal symptoms (waking with breathlessness or waking with chest tightness or waking with cough); ■ wheezing; ▲ asthma attack. *Difference between age groups with $p < 0.001$; †Difference between age groups with $p < 0.001$.

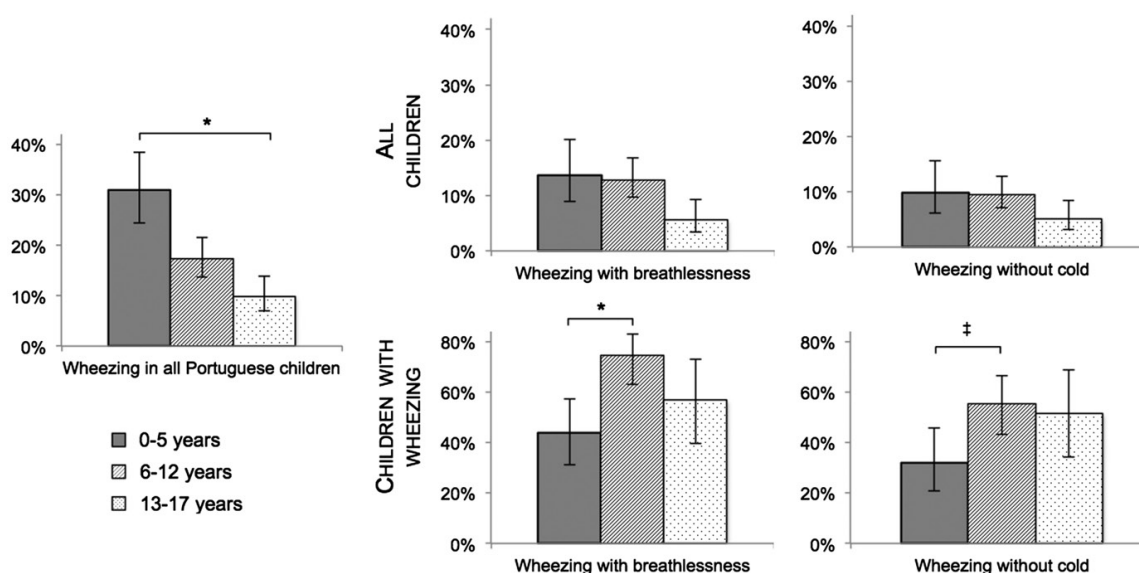
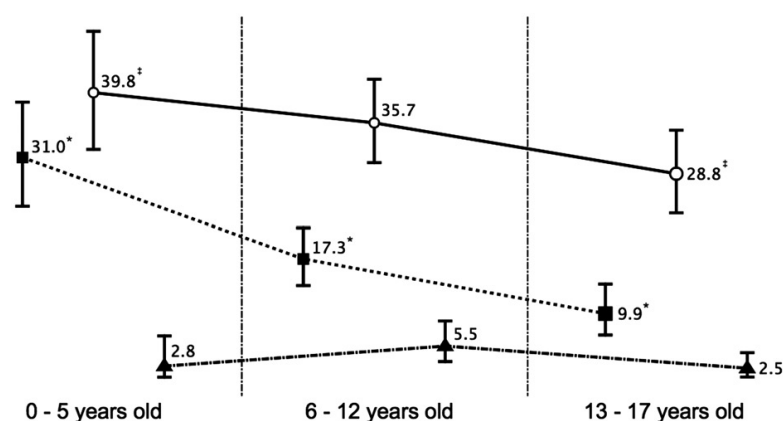


Figure 2. Weighted prevalence of wheezing with breathlessness and wheezing without a cold in the Portuguese pediatric population. * $p < 0.001$, † $p = 0.03$. Prevalence of wheezing in all Portuguese children: 31.0% in 0- to 5-year age group (OR: 1.00); 17.3% in 6- to 12-year age group (OR: 0.46; 95% CI: 0.30–0.72); 9.9% in 13- to 17-year age group (OR: 0.25; 95% CI: 0.15–0.41). Prevalence of wheezing with breathlessness in all Portuguese children: 13.6% in 0- to 5-year age group; 12.8% in 6- to 12-year age group; 5.7% in 13- to 17-year age group. Prevalence of wheezing without a cold in all Portuguese children: 9.9% in 0- to 5-year age group; 9.5% in 6- to 12-year age group; 5.1% in 13- to 17-year age group. Prevalence of wheezing with breathlessness among all children who wheezed: 43.7% in 0- to 5-year age group (OR: 1.00); 74.4% in 6- to 12-year age group (OR: 3.73; 95% CI: 1.79–7.78); 57.0% in 13- to 17-year age group (OR: 1.71; 95% CI: 0.83–3.50). Prevalence of wheezing without a cold among all children who wheezed: 31.9% in 0- to 5-year age group (OR: 1.00); 55.2% in 6- to 12-year age group (OR: 2.64; 95% CI: 1.27–5.48); 51.7% in 13- to 17-year age group (OR: 2.28; 95% CI: 0.96–5.43).

in younger children is more closely related to immature airways and viral respiratory illnesses [25], whereas older children tend to exhibit wheezing even without respiratory infections.

Asthma prevalence

There is no consensus on the epidemiologic definition of CA, which leads to hardly comparable differences in reported prevalence estimates, depending on the definition used [3,14]. Therefore, we presented estimates using different combinations of asthma proxies (Table 3). The definition we chose

includes the less frequent nocturnal symptom, waking with breathlessness; the term asthma attack to improve specificity; and asthma medication, because children with asthma may not experience symptoms when controlled with medication, and medication is a known valid proxy for asthma prevalence [26,27]. By using definitions of prevalence used in different studies, our prevalence estimates varied from 6.3% (LA plus wheezing in the last year) and 9.1% (LA plus any asthma-like symptom in the last year or CA medication). These differences highlight the importance of setting standardized definitions to allow for comparisons between studies.

Table 3. Weighted Asthma prevalence in the Portuguese pediatric population, using different asthma proxies.

	Population % (95% CI)	Total weighted population (2,066,953)
Lifetime asthma	11.2 (9.1–13.7)	230,886
Current asthma (with symptoms in the previous 12 months)		
Wheezing w/o cold	8.2 (6.5–10.4)	169,991
Lifetime asthma + wheezing	6.4 (4.8–8.6)	132,848
Lifetime asthma + wheezing OR waking with breathlessness	7.0 (5.3–9.1)	143,958
Lifetime asthma + wheezing OR asthma attack OR waking with breathlessness	7.2 (5.5–9.4)	149,199
Lifetime asthma + wheezing OR waking with breathlessness OR waking chest tightness OR waking cough	8.3 (6.5–10.6)	171,829
Lifetime asthma + wheezing OR asthma attack OR waking with breathlessness OR current asthma medication ^a	8.4 (6.6–10.7)	173,681
Lifetime asthma + wheezing OR asthma attack OR waking with breathlessness/chest tightness/cough	8.4 (6.6–10.7)	173,963
Lifetime asthma + wheezing OR asthma attack OR current asthma medication OR waking with breathlessness/chest tightness/cough	9.1 (7.2–11.5)	188,819

^aDefinition used as *current asthma*.

Table 4. Weighted proportions (95% confidence interval) of pulmonary function tests, allergy tests (skin or blood), and inhaled medication use in Portuguese children with current asthma.

	PFT ^a ever % (95% CI)	Allergy tests ^b ever % (95% CI)	Inhaled meds ^c in the last 12 months % (95% CI)
All	45.7 (33.8–58.1)	79.9 (67.9–88.2)	67.6 (58.4–75.7)
Gender			
Female	36.9 (26.0–49.3)	87.0 (67.5–95.5)	74.9 (70.7–79.3)
Male	51.4 (41.3–61.4)	75.3 (70.2–79.8)	62.9 (49.1–74.9)
Age groups			
0–5 years old	21.9 (13.5–33.6)	48.4 (27.1–70.3)	72.1 (38.7–91.4)
6–12 years old	46.4 (40.2–52.7)	97.1 (96.8–97.5)	72.5 (64.8–79.1)
13–17 years old	61.5 (47.4–73.9)	79.4 (69.0–87.0)	58.1 (47.4–68.1)
National region			
North	44.0 (29.6–59.4)	93.3 (82.4–97.7)	57.9 (36.5–76.8)
Centre and Islands	38.6 (29.5–48.5)	75.6 (75.2–75.9)	69.8 (69.3–70.2)
South	53.9 (41.0–66.2)	71.3 (56.2–82.7)	74.7 (61.2–84.7)
Municipality			
Urban	57.6 (46.9–67.7)	83.9 (74.8–90.1)	76.4 (63.4–85.9)
Rural	7.3 (7.2–7.3)	67.0 (66.6–67.5)	39.2 (29.5–49.9)
Allergic rhinitis			
No	43.8 (33.8–54.4)	71.4 (59.5–81.0)	67.6 (51.8–80.1)
Yes	47.4 (38.9–56.1)	87.7 (84.0–90.7)	67.7 (59.5–74.9)
Food allergy			
No	46.2 (38.4–54.2)	78.6 (72.0–84.0)	67.6 (57.8–76.1)
Yes	37.6 (37.6–37.6)	100.0 (n/a)	67.8 (67.8–67.8)

^aPFT, pulmonary function tests. ^bAllergy tests: blood and/or skin tests. ^cInhaled medications: inhaled medication use. n/a: not applicable. Bold values are statistically significant differences between row subgroups.

Our estimate of LA is based on the same question of ISAAC. The estimate in the 6- to 12-year-old age group (12.3%) was higher than that in the 6- to 7-year-old age group in the Portuguese ISAAC survey (9.8%) [6], while our estimate for the 13- to 17-year-old age group (13.9%) was similar to that in the 13- to 14-year-old age group in the ISAAC survey (13.8%). In preschoolers, two recent Portuguese studies had also reported estimates of physician asthma diagnosis similar to ours: 4.6% in both studies [21,22].

Schmitz et al. [11] reported a 4.7% prevalence of a doctor diagnose LA in the Germany population of 0- to 17-year-old using data from the 2003–2006 German Health Interview and Examination Survey for Children and Adolescents (KiGGS). This prevalence was much lower than ours and is in agreement with the estimated prevalence of LA among

German children reported in the ISAAC, which was also much lower than that in Portugal (in Germany, 4.3% in 6- to 7-year-old children and 7.5% in 13- to 14-year-old children) [5]. Data from the 2010 United States National Health Interview Survey for children aged <18 years reported an estimated doctor diagnosed LA prevalence of 13.6% and CA prevalence of 9.5% [12,13], which are similar to our estimations.

Asthma symptoms other than wheezing

In children, epidemiological asthma definitions and clinical asthma phenotypes are primarily based upon wheezing [28]. However, Skytt et al. [29], based on data from the Copenhagen Prospective Study on Asthma in Childhood,

addressed the lack of validity of wheezing for asthma diagnosis in children aged 0–3 years. They argued for a global description of asthma symptoms to reduce the risk of misclassification of asthma in children. Wheezing-based asthma definitions are also limited by differences in the concept and perception of wheezing. Fernandes et al. [30] reported a lack of perception of the term “wheezing” among Portuguese parents and health professionals. To account for this problem, we used several synonyms of wheezing in Portuguese in wheezing-related questions. Additionally, the presence of wheezing was not mandatory in our definition of CA.

We suggest that questionnaires directed at children and adolescents should include different measures to comprehensively assess asthma characteristics (previous diagnosis, several symptoms, and medication), thus aiming to obtain precise estimates of asthma prevalence, especially in younger children. In any case, standardization of epidemiologic asthma definitions and their clinical validation are needed [3].

Diagnostic tests and medication for asthma

In spite of the recommendations to perform spirometry as part of asthma management [2], only about half of the Portuguese children with CA aged ≥ 6 years had undergone PFT. Similarly, fewer than half of Portuguese children with CA had used inhaled controller medications within the previous 12 months, even considering a CA definition based on several symptoms occurring in the last 12 months, like the one used in our study. Moreover, those who only used reliever inhaled medication in the previous year, without any controller inhalers, were twice as likely to have experienced an asthma attack in the same time period.

No differences in the prevalence of asthma or asthma-like symptoms were found between urban and rural municipalities; however, children living in rural areas were much less likely to have undergone PFT or allergy tests or used inhaled medication. In agreement with our data, a Greek study with school-aged children also showed that the prevalence of asthma diagnosis was the same between rural and urban areas despite findings on the narrowing of small airways in urban environments [31]. Disparities in health care for rural-dwelling patients with asthma have been reported, indicating that those with asthma who live in rural areas receive substandard care for asthma; however, there are limited direct data on these findings [32]. Taken together, our results and those of previous studies on diagnostic tests and medication use may be related to differences in health-care access and may suggest substandard asthma care in Portuguese children, especially in less urbanized areas.

Limitations

This study has several limitations. The survey was designed for the overall Portuguese population; however, the questions included in the questionnaire and the definitions used are similar to others used in international and Portuguese pediatric studies [33–35]. The use of the 2001 National Census for sampling could not account for the reduction in the number of births that occurred in the last decade; however, it was the most recently available data at the time of data

collection. Also, the study’s pediatric sample follows the characteristics of the Portuguese pediatric population characteristics [19]. The use of landline telephones excludes households without residential telephones; nevertheless, it allowed us to guarantee a stratified cluster sample by region. Answers were given by the main caregiver for participants <15 years old and by the adolescent when the participant was ≥ 15 years old. This may limit comparisons between these age groups; however, changes of parent-reported to auto-reported outcomes are recommended between school age and adolescence [23], and other studies on asthma prevalence in pediatric ages had similar methodology [11]. Finally, we could not obtain a clinical confirmation of the diagnosis; therefore, participants’ misclassification can be expected, as in any similar survey.

Conclusion

Asthma-like symptoms were present in more than one-third of Portuguese children, and the prevalence of CA was 8.4%. Age influenced asthma-like symptoms patterns, and asthma prevalence varied according to different definitions. Therefore, using composite measures and reporting different operational estimates is advisable. Fewer than half of the children with CA had used inhaled controller medications in the previous year, and those who used inhaled relievers alone had experienced twice more asthma attacks. PFT were underused among asthmatic children. Also, the findings on low inhaled controller medication and PFT use were more prevalent in children living in rural areas.

Declaration of interest

The authors report no conflicts of interest. None of the authors received any honorarium, grant, or other form of payment to produce the manuscript. The authors alone are responsible for the content and writing of the paper.

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Supplementary material available online
Supplementary Tables S1 and S2



High prevalence of hospitalisation for asthma in a population-based paediatric sample

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LETTERS

High prevalence of hospitalisation for asthma in a population-based paediatric sample

The asthma prevalence and burden are high among children. However, available data for asthma hospitalisation in children have been mainly reported as annual rates of asthma hospitalisations.¹ The proportion of children with asthma that are hospitalised because of asthma during their lifetime is still unknown.

INASMA was a cross-sectional, population-based, all-age, nationwide telephone survey conducted in 2010 to estimate asthma prevalence and control in Portugal. Details on INASMA methods are described elsewhere.² We report the proportion of lifetime hospitalisation (LH) for asthma in Portuguese children and adolescents aged 6–17 years (hereafter referred to as ‘children’). INASMA included 563 participants in this age group, representative of the Portuguese paediatric population.³ This sample size allowed us to estimate the prevalence of LH with a margin of error of 0.1, considering a 95% confidence level. LH was defined as a positive answer to ‘Have you ever been hospitalised for asthma (inpatient admission >24 h)?’ Lifetime asthma was defined as a positive answer to ‘Have you ever had asthma?’ Current asthma was defined as lifetime asthma plus, at least, one of the following in the previous 12 months: wheezing, waking with breathlessness, asthma attack, or currently taking asthma medication.

The prevalence of LH for asthma in Portuguese children was 3.9% (95% CI 2.6 to 5.7). In children with lifetime asthma, this prevalence was 29.7% (95% CI 23.6 to 36.7) (table 1). Children with current asthma had a higher prevalence of hospitalisations (36.5%; 95% CI 28.8 to 44.9) than children with a history of lifetime asthma but without current asthma (prevalence 13.4%; 95% CI 11.5 to 15.6) (OR 3.70; 95% CI 2.64 to 5.20). The presence of any asthma-like symptom in the previous 12 months increased the proportion of LH (OR 1.85; 95% CI 1.16 to 2.95). Female children had more hospitalisations than male children (OR 1.97; 95% CI 1.22 to 3.18). No differences in the prevalence of LH were observed with socioeconomic status or in children with rhinitis, sinusitis, or food or drug allergies.

In the present study, a high number of hospitalisations for asthma were

observed, with more than 55 000 Portuguese children aged 6–17 years hospitalised for asthma during their lifetime. Moreover, of the children with current asthma, more than one-third had been hospitalised for asthma. Our study is limited by the lack of diagnosis/LH confirmation by a physician, as in other epidemiological studies. We excluded from the analysis participants aged 0–5 years to avoid misclassification of hospital admissions for bronchiolitis and/or viral-induced wheezing. To our knowledge, only one other study reported the prevalence of LH in children⁴; however,

it only included children aged 6–7 years from one Italian city, and the proportion of children with asthma who had LH was not reported. More studies with comparable data from other countries and settings are needed. Our results should contribute to improve knowledge on asthma-related hospitalisations in children, leading to the development of healthcare programmes aiming to reduce their frequency.

For the first time, the proportion of LH for asthma was reported for a national population-based paediatric sample. In Portugal, about one-third of children with

Table 1 Proportion and OR (95% CI) for lifetime hospitalisation (LH) for asthma in Portuguese children aged 6–17 years with lifetime asthma

	LH % (95% CI)	OR for LH (95%CI)
Overall	29.7 (23.6 to 36.7)	
Sex		
Male	24.1 (18.0 to 31.5)	1.00 (Ref)
Female	38.5 (28.8 to 49.2)	1.97 (1.22 to 3.18)
Age groups		
6–12 years old	33.0 (24.2 to 43.1)	1.00 (Ref)
13–17 years old	26.4 (19.0 to 35.5)	0.73 (0.40 to 1.34)
Regions		
North	26.1 (20.0 to 33.2)	1.00 (Ref)
Centre and Islands	46.8 (33.8 to 60.3)	2.10 (1.31 to 4.76)
South	14.5 (6.2 to 30.2)	0.48 (0.18 to 1.31)
Municipality		
Urban	27.3 (19.1 to 37.4)	1.00 (Ref)
Rural	35.9 (35.9 to 35.9)	1.49 (0.94 to 2.37)
Socioeconomic status*		
Low	34.1 (25.3 to 44.3)	1.00 (Ref)
Medium	19.7 (11.3 to 32.1)	0.47 (0.19 to 1.19)
High	23.5 (3.4 to 73.1)	0.59 (0.06 to 5.47)
ETS†		
No	34.4 (24.5 to 45.7)	1.00 (Ref)
Yes	24.0 (17.9 to 31.3)	0.60 (0.31 to 1.17)
‘Wheezing’		
No	18.8 (15.2 to 23.0)	1.00 (Ref)
Yes	41.1 (32.7 to 50.1)	3.03 (2.15 to 4.26)
‘Nocturnal symptoms’‡		
No	21.8 (11.8 to 36.7)	1.00 (Ref)
Yes	34.6 (27.6 to 42.4)	1.90 (0.85 to 4.25)
‘Asthma attack’		
No	23.4 (17.0 to 31.3)	1.00 (Ref)
Yes	43.5 (33.0 to 54.5)	2.52 (1.46 to 4.34)
‘Asthma-like symptoms’§		
No	21.2 (15.4 to 28.5)	1.00 (Ref)
Yes	33.2 (25.9 to 41.5)	1.85 (1.16 to 2.95)
‘Current asthma’		
No	13.4 (11.5 to 15.6)	1.00 (Ref)
Yes	36.5 (28.8 to 44.9)	3.70 (2.64 to 5.20)

Bold values are statistically significant.

*Socioeconomic status was categorised based on occupation and school education of the person who contributed most to the household income.

†Environmental tobacco smoke.

‡‘Nocturnal symptoms’ in the last 12 months: waking with breathlessness or waking with cough or waking with chest tightness.

§‘Asthma-like symptoms’ in the last 12 months: wheezing or nocturnal symptoms or asthma attacks.

PostScript

asthma have been hospitalised for asthma at least once in their lifetime.

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Contributors Manuel Ferreira-Magalhães participated in data analysis, interpretation of results and wrote the manuscript draft. Ana Sá-Sousa participated in data collection, data analysis and reviewed the manuscript. Mário Morais-Almeida participated in study conception and critical review of the manuscript. Filipe Azevedo participated in study design and reviewed the manuscript. Inês Azevedo participated in interpretation of results and critical review of the manuscript. Ana Margarida Pereira participated in data analysis and critical review of the manuscript. João A. Fonseca is responsible for the INASMA study and participated in all stages and tasks.

Competing interests None.

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EDITOR'S CHOICE

The Editor recommends this issue's articles to the reader

Time to symptom improvement using elimination diets in non-IgE-mediated gastrointestinal food allergies

The prevalence of food allergy in the pediatric population has increased in recent decades, and it is recognized as a major public health concern. The most common allergens are cow's milk, soya, egg, and wheat. The clinical presentation of the non-IgE-mediated food allergy is characterized by heterogeneous gastrointestinal symptom manifestations and lack of conclusive tests, with the final diagnosis mainly based on the improvement of symptoms after initiation of exclusion diet.

The majority of the available studies regarding this subject focus on the management options. However, there is paucity of data on time to symptom improvement using elimination diets in these cases, with the recommended length for a diagnostic exclusion diet being based on experts' opinion and varying from 2 to 12 weeks.

In this study, Lozinsky et al. (1) investigated 131 children with suspected diagnosis of non-IgE-mediated food allergy on elimination diet, assessing the time required for symptom improvement with a questionnaire that evaluated the nine most common gastrointestinal symptoms in this disease. The authors showed significant improvement of the symptoms after 4 weeks of elimination diet in more than 98% of the studied children, which highlights the fact that this might be the minimum length necessary to evaluate response. The study also shows that although patients presented with significant symptom improvements, it was clear that some symptoms responded only partially and some did not improve at all. While rectal bleeding improved in 70% of the children, diarrhea, food aversion, and pain fully improved in only 30%. Therefore, clinicians dealing with food allergy should not expect full remission of symptoms with elimination diet in all of the cases, so perhaps the term 'Not IgE', rather than non-IgE-mediated allergy, could be used.



Adriana Chebar Lozinsky

Diagnostic accuracy of patch test in children with food allergy

The most common triggers of food allergy are hen's egg and cow's milk in childhood. Much research has been conducted to find practical methods for diagnosing these allergies. In this context, several studies have investigated atopy patch tests (APT) as a diagnostic tool for food allergies. However, results have not been consistent, both for IgE- and non-IgE-mediated food allergy.

Sozmen et al. (2) analyzed data from 243 children with a suspicion of egg or cow's milk allergy. All children underwent APT, skin prick test (SPT), and oral food challenge (OFC). The study population included both IgE- and non-IgE-mediated food-allergic children. The authors found that a quarter of the group reacted in food challenge and 23% (56) of children had positive APT. Sensitivity, specificity, negative predictive value, and positive predictive value for both egg and cow's milk allergy were all low for APT. There was no significant difference between children with positive APT results and those with negative APT results in age, gender, positive OFC outcome, and symptoms occurring during OFC. APT did not have an additional value to improve diagnostic accuracy of SPT.

The authors concluded that OFC remains the primary mean for identifying children with food allergy. APT is not necessary in daily clinical practice and could not predict the results of OFC. The authors also reviewed the studies in the last 10 years regarding the diagnostic role of APT in diagnosing of food allergy and compared the results and methods of these studies with their findings.



Sule Caglayan Sozmen

Asthma control in children is associated with nasal symptoms, obesity, and health insurance: a nationwide survey

Asthma control has been associated with several factors, such as modifiable medical conditions or social characteristics. Also, children with uncontrolled asthma are more likely to use medication and healthcare services for asthma. Health insurance status may play an important role in modeling healthcare access in asthmatic children. In Europe, there are different healthcare systems and financing modalities among and within countries, but no study has evaluated the influence of the children's health insurance status on asthma outcomes.

Ferreira-Magalhães et al. (3) published the results of a nationwide study that assessed asthma control in children and adolescents (0–18 years of age) randomized from the general population. In this study, half of children did not have their asthma controlled. Having substantial nasal symptoms, being obese, and not having health insurance were the significant determinants of lack of asthma control in children. Moreover, the presence of substantial nasal symptoms and the absence of health insurance were also associated with higher unscheduled medical visits for asthma.

Rhinitis is a known risk factor for uncontrolled asthma, but this study also showed that the presence of a higher number of different nasal symptoms (runny nose, stuffy nose, itchy nose, or sneeze) was associated with a higher prevalence of lack of asthma control.

Children without health insurance were at greater risk of poor asthma outcomes such as uncontrolled asthma and higher use of unscheduled medical attendance. In the mixed Portuguese healthcare system, this may point to the importance of parents' options in choosing the site of medical asthma care for their children.

This population-based study shows that lack of asthma control is high in these children. It also brings important new evidence on determinants of asthma control, not only regarding the classical modifiable factors, such as nasal symptoms and obesity, but also regarding the influence of health insurance status and healthcare access.



Manuel Ferreira-Magalhães

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This logo highlights the Editor's Choice articles in the table of contents and the first page of each of the articles.

Asthma control in children is associated with nasal symptoms, obesity, and health insurance: a nationwide survey

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Keywords

asthma; control; delivery of health care; health insurance; obesity; rhinitis; wheezing

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Abstract

Background: This study aimed to estimate the prevalence of asthma control and determinants of poor control in the Portuguese pediatric population (<18 years); secondarily, we described asthma-related healthcare services and medication use.

Methods: Data of 98 children with current asthma, from the second phase of a nationwide population-based telephone survey (INAsma study), were analyzed. Asthma control definition was based on GINA criteria, grouping partially controlled and uncontrolled asthma as 'not-controlled asthma' (NCA). We used multivariate logistic regression to study factors associated with NCA and with unscheduled medical visits for asthma.

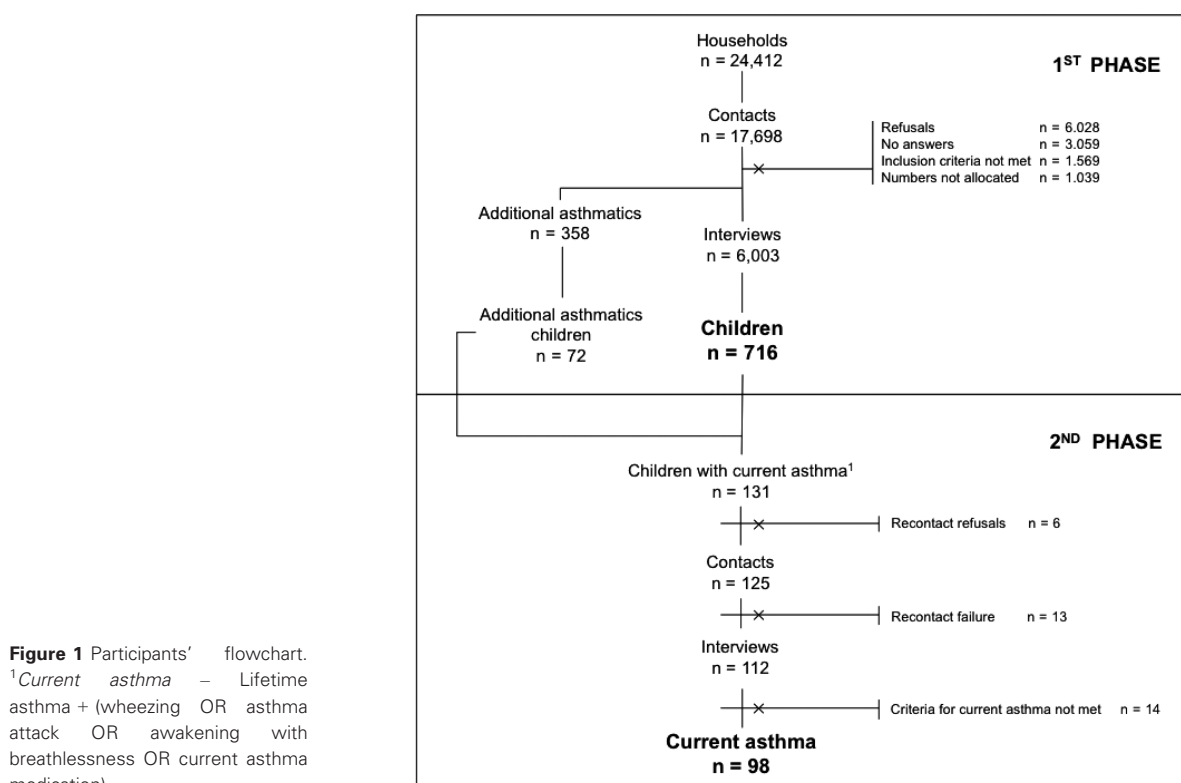
Results: About half of the children had NCA (49%, 95% CI 39–59%). In the multivariate model, risk factors for NCA were as follows: substantial nasal symptoms (aOR 6.80), overweight/obesity (aOR 3.44), and not having health insurance (aOR 3.78). All the children with NCA had nasal symptoms, and the lack of asthma control was also associated with the increasing number of nasal symptoms ($p < 0.001$). In the previous year, 90% (95% CI 84–96%) of children with current asthma had healthcare visits and 67% (95% CI 58–77%) used medication for asthma. The risk of unscheduled medical visits was higher in children with nasal symptoms (aOR 3.63) and in those without health insurance (aOR 2.79), and lower in adolescents (aOR 0.19).

Conclusions: Half of the children with asthma were poorly controlled. Nasal symptoms and obesity are important determinants of asthma control. Children without health insurance are at greater risk of poor asthma outcomes; this association is reported for the first time in a European country.

The main goal of asthma management is to achieve disease control (1). In children, the proportion of poor asthma control varies widely, from 15% to 90%, depending on the age groups included, countries, settings, and control definition (2–8). Children with uncontrolled asthma need to use more asthma medication and are more likely to use healthcare services for asthma, especially unscheduled medical visits (9, 10). Several factors have been associated with lack of asthma control in children, such as rhinitis (11), eczema (4), obesity (12), lower

socioeconomic status (13), or parents' impaired perception of asthma control (7).

Health insurance status plays an important role in healthcare access, namely in asthmatic children: uninsured children are more likely to have restricted medical care and impaired access to healthcare services (14, 15). Data on the 2007–2009 US recession has shown that children that experienced a gap on health insurance coverage had poorer asthma control (16). In Europe,



there are different healthcare systems and financing modalities among and within countries, but no study evaluated the influence of the children's health insurance status on asthma outcomes.

Improving knowledge on asthma control, including its prevalence and related factors, is needed to assess the extent of the asthma-related burden and to inform policymakers, aiming to achieve better results in health.

In 2010, we conducted the first Portuguese National Asthma Survey (INAsma), a two-phase nationwide study aiming to estimate asthma prevalence and control (17). In the present paper, we report data from children and adolescents included in the second phase of the study. Our aims were to estimate the prevalence of asthma control and determinants of poor control in the Portuguese pediatric population (<18 years). Secondary aims were to describe asthma-related healthcare services and medication use.

Methods

Study design and participants

INAsma was a nationwide survey from the general population applied by telephone interview to individuals living in Portugal in 2010. The study methodology has been previously described (17). Briefly, to obtain a representative sample of the general population a two-stage cluster and stratified sampling design was performed, using municipality as stratum and randomly

selecting participants from households. When the selected individual had <15 years old, the respondent was the usual and most knowledgeable caregiver. Methodological details are described in supplementary file.

Overall, 716 children completed the first phase of the INAsma study (Fig. 1); all the participants identified as having current asthma were eligible for participation in the second phase. Additional asthmatics identified in the participants' households were also contacted. The flowchart (Fig. 1) summarizes the children included in INAsma study.

This study was approved by the Ethics Committee of *Centro Hospitalar de São João*, Porto, Portugal. Oral informed consent was obtained from parent(s) or legal guardian(s). We followed the STROBE statement for reporting observational studies (18).

Instruments and data collection

The instrument for data collection in the second phase of INAsma was based on the Portuguese version of the GA²LEN survey questionnaire (19); it also included the Control of Allergic Rhinitis and Asthma Test (CARAT) (20) and questions on socio-educational factors and use of healthcare resources. Trained interviewers performed data collection between June and October 2010, using computer-assisted telephone interview. To minimize potential bias in data collection, the same quality-assurance measures used in the first phase were followed (supplementary file).

Table 1 Participants characteristics – n(%). There are not statistical differences between diagnostic groups. Statistically significant differences in asthma control are presented in bold

	Current asthma (n = 98) (%)	Asthma Control (%)	
		Well Controlled (n = 48)	Not controlled (n = 46)
Gender			
Female	33 (33)	14 (45)	17 (55)
Male	65 (66)	34 (54)	29 (46)
Age groups			
0–5 years old	18 (18)	11 (65)	6 (35)
6–12 years old	46 (47)	22 (50)	22 (50)
13–17 years old	34 (35)	15 (46)	18 (55)
Region			
North	46 (47)	21 (49)	22 (51)
Centre/Islands	22 (22)	9 (41)	13 (59)
South	30 (30.6)	18 (62)	11 (38)
Urbanity†			
Rural	24 (25)	10 (44)	13 (57)
Urban	74 (76)	38 (54)	33 (47)
SES‡			
High	15 (15)	11 (73)	4 (27)*
Medium	33 (34)	18 (60)	12 (40)*
Low	50 (51)	19 (39)	30 (61)*
Health insurance			
Yes	47 (50)	30 (68)	14 (32)**
No	47 (50)	17 (36)	30 (64)**
Body mass index			
Thinness	3 (3)	1 (33)	2 (67)
Normal	57 (60)	33 (62)	20 (38)***
Overweight/Obesity	35 (37)	11 (31)	24 (69)***
ETS§			
Yes	40 (41)	23 (59)	16 (41)
No	58 (59)	25 (46)	30 (55)

†Urbanity was classified as urban if residence was located in municipalities with at least one city (cities must have at least 8000 citizens) according to Portuguese law.

‡Socioeconomic Status, categorized based on family income, occupation, and school education of the person who contributes more for the household income.

§Environmental Tobacco Smoke.

*p = 0.03. **p = 0.002. ***p = 0.005.

Variables and outcomes definition

Current asthma was defined as children with ‘lifetime asthma’ plus at least one of the following: wheezing, awakening with breathlessness or having an asthma attack in the previous 12 months, or taking asthma medication at the time of the interview.

Nasal symptoms were classified as ‘mild/absent’ or ‘substantial’ based on the daily frequency of 4 isolated symptoms – runny nose, stuffy nose, itchy nose, or sneeze in the previous 4 weeks. Each symptom was scored as: 0, if present ‘almost

every day’; 1, if ‘≥2 days a week’; 2, if ‘1 or 2 days a week’; or 3, if ‘never’. When the sum of all symptoms was >7, nasal symptoms were classified as ‘mild/absent’; when ≤7, they were considered ‘substantial’.

Overweight/obesity was defined as a z-score >1 for body mass index (BMI), using WHO Growth reference 2007 macros (21).

Having health insurance was defined as a positive answer to ‘Do you/your child have/has any healthcare insurance?’.

Asthma control definition was based on GINA criteria for asthma symptom control (1): ‘Well-controlled asthma’ (WCA) corresponds to ‘well controlled’ from GINA guidelines; and partially controlled and uncontrolled were grouped as ‘not-controlled asthma’ (NCA). *Unscheduled medical visits for asthma* was defined as having at least one emergency department and/or any unscheduled medical attendance because of asthma worsening/exacerbation in the previous 12 months. Additional definitions are available in supplementary material.

Table 2 Rhinitis diagnosis ever and nasal symptoms in the previous 4 weeks, in children with current asthma, % (95% CI); and level of asthma control within children with rhinitis diagnosis ever and nasal symptoms in the previous 4 weeks, % (95% CI)

	Current asthma children, %	Asthma control, %		p
		Well controlled	Not controlled	
Doctor diagnosis of rhinitis				
No	55 (45–65)	49 (33–65)	51 (35–68)	0.42
Yes	45 (35–55)	53 (40–66)	47 (34–60)	
Any nasal symptom*				
No	11 (5–17)	100 (n/a)	0 (n/a)	0.001
Yes	89 (83–95)	45 (34–55)	55 (45–66)	
Itchy nose				
No	34 (25–42)	77 (63–92)	23 (8–37)	<0.001
Yes	66 (57–75)	38 (26–50)	62 (50–74)	
Sneeze				
No	33 (23–42)	67 (50–84)	33 (16–50)	0.04
Yes	67 (58–77)	44 (32–56)	56 (44–69)	
Runny nose				
No	56 (46–66)	64 (52–77)	36 (23–48)	0.004
Yes	44 (34–54)	33 (19–48)	67 (52–82)	
Stuffy nose				
No	48 (38–58)	73 (60–86)	27 (14–41)	<0.001
Yes	52 (42–62)	31 (18–44)	69 (57–82)	
Number of nasal symptoms				
0	11 (5–17)	100 (n/a)	0 (n.a.)	<0.001
1	10 (4–15)	100 (n/a)	0 (n.a.)	
2	37 (27–46)	50 (33–67)	50 (33–69)	
3	24 (16–33)	32 (12–51)	68 (49–88)	
4	19 (11–27)	22 (3–41)	78 (59–97)	

Bold values show statistical significant differences of asthma control in children, according to the presence of different nasal symptoms. n/a, not applicable.

*‘Any nasal symptom’: runny nose or stuffy nose or itchy nose or sneeze.

Study sample size and statistical analysis

The sample size was calculated considering the two phases of the INAsma study (17). The proportion of not-controlled asthma was estimated with a margin of error of 0.098, considering a 95% confidence level (95% CI). Statistical analyses were performed using SPSS version 22 (SPSS IBM, New York, NY, USA). Categorical variables were described using frequencies and compared with Pearson's chi-squared test. We used multivariate logistic regression analysis to evaluate which variables were associated with (1) NCA and with (2) asthma-related unscheduled medical visits. For each outcome, we used a data-driven backward approach, with *a priori* inclusion of predictive variables with p -value < 0.20 in univariate analysis. The two final multivariate models included the statistically significant variables. Results from the logistic regressions were presented as adjusted odds ratio (aOR) with 95% CI. A p -value < 0.05 was considered statistically significant. Hosmer–Lemeshow test and percentage of correctly predicted cases were used to assess goodness of fit for logistic regression models.

Results

The participant's characteristics are summarized in Table 1.

About half of the children with current asthma had NCA (49%, 95% CI 39–59%; Table 1). Nasal symptoms in the previous 4 weeks were present in 89% (95% CI 83–95%) of children with current asthma (Table 2). Nevertheless, previous medical diagnosis of rhinitis was made in only 45% (95% CI 35–55%) of children with current asthma. All asthma-like and nasal symptoms were more frequent in children with NCA ($p < 0.001$; Fig. 2 and Table S1), when compared with WCA. In children with a parent/self-report of good asthma control, only 52% fulfilled the criteria for WCA.

Determinants of poor asthma control

Control of asthma was significantly worse in children with substantial nasal symptoms, overweight/obesity, lower socioeconomic status, and unscheduled medical attendance for asthma, or in those without health insurance coverage, in univariate analysis (Table 3).

Children with any nasal symptom had significantly more NCA ($p = 0.001$; Table 2). Moreover, as the number of nasal symptoms increased, the proportion of children with NCA also increased (Fig. 3): none of the children with 0 or 1 nasal symptom had NCA, while 50% of those with 2 symptoms, 68% of those with 3 symptoms and 78% of those with 4 different nasal symptoms had NCA.

In the final multivariate model, the risk factors for NCA were as follows: having substantial nasal symptoms (aOR 6.80, 95% CI 2.34–19.80), overweight/obesity (aOR 3.60, 95% CI 1.46–10.13), and not having health insurance (aOR 3.78, 95% CI 1.36–10.92).

Healthcare visits and medication use by children with current asthma

In the previous 12 months, 90% (95% CI 84–96%) of children with current asthma had at least one asthma-related visit to healthcare services (Table S2): 86% (95% CI 79–93%) had scheduled medical visits, 39% (95% CI 29–48%) had emergency room visits, and 25% (95% CI 16–33%) had at least one unscheduled medical visit to a doctor. All the preschoolers had asthma-related healthcare visits (scheduled or unscheduled) in the last year, compared with 94% (95% CI 86–100%) of school age children and 79% (95% CI 66–93%) of adolescents ($p = 0.04$). The determinants of unscheduled medical visits, in the multivariate model, were substantial nasal symptoms (aOR 3.63, 95% CI 1.39–9.51), not having health insurance (aOR

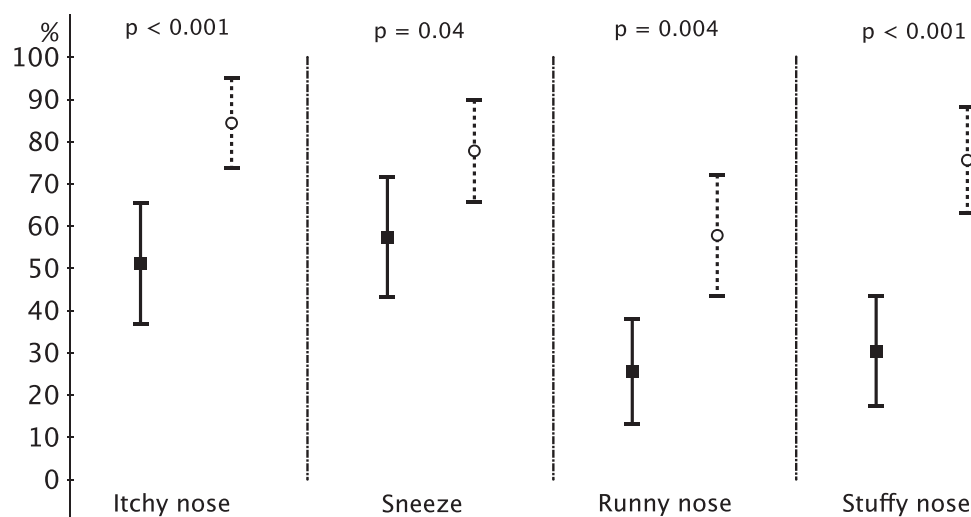


Figure 2 Prevalence of isolated nasal symptoms in asthmatic children, stratified by asthma control (prevalence and 95% CI). Full line – controlled asthma; Dotted line – not-controlled asthma.

Table 3 Crude and adjusted odds ratio for not-controlled asthma and unscheduled medical visits

	Not-controlled asthma		Unscheduled visits	
	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Gender				
Female	1.00 (ref)	n.i.	1.00 (ref)	n.i.
Male	0.70 (0.30–1.67)		1.54 (0.66–3.61)	
Age				
0–5 years old	1.00 (ref)	n.i.	1.00 (ref)	1.00 (ref)
6–12 years old	1.83 (0.58–5.83)		1.16 (0.38–3.53)	0.72 (0.21–2.43)
13–17 years old	2.20 (0.66–7.36)		0.37 (0.11–1.24)	0.19 (0.05–0.78)
Body mass index				
Normal	1.00 (ref)	1.00 (ref)	1.00 (ref)	n.i.
Overweight/Obese	3.60 (1.46–8.89)	3.44 (1.17–10.13)	0.74 (0.32–1.73)	
Nasal symptoms				
Absent/mild	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Substantial	4.42 (1.85–10.56)	6.80 (2.34–19.80)	2.82 (1.22–6.53)	3.63 (1.39–9.51)
Urbanity†				
Rural	1.00 (ref)	n.i.	1.00 (ref)	n.i.
Urban	0.67 (0.26–1.72)		0.66 (0.26–1.67)	
SES‡				
High	1.00 (ref)	n.i.	1.00 (ref)	n.i.
Medium	1.83 (0.47–7.13)		2.08 (0.54–8.01)	
Low	4.34 (1.21–15.63)		2.71 (0.75–9.80)	
Health insurance				
Yes	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
No	3.78 (1.59–9.02)	3.85 (1.36–10.92)	2.10 (0.92–4.81)	2.79 (1.08–7.21)
Local of asthma care				
Public	1.00 (ref)	n.i.	1.00 (ref)	n.i.
Private	0.71 (0.31–1.60)		0.68 (0.30–1.53)	
Scheduled medical visits				
Yes	1.00 (ref)	n.i.	1.00 (ref)	n.i.
No	0.30 (0.08–1.20)		0.30 (0.08–1.17)	
Unscheduled medical visits				
Yes	1.00 (ref)		–	–
No	0.44 (0.19–0.99)	n.i.	–	–
Asthma control				
Controlled	–	–	1.00 (ref)	n.i.
Not controlled	–	–	2.29 (1.01–5.28)	

Bold values show statistical significant differences. n.i.: not included in the model (non-significant variables).

Asthma control model: Hosmer–Lemeshow test = 0.37 and 75% of correctly predicted cases.

Unscheduled visits model: Hosmer–Lemeshow test = 0.95 and 67% of correctly predicted cases.

†Urbanity was classified as urban if residence was located in municipalities with at least one city (cities must have at least 8000 citizens) according to Portuguese law.

‡Socioeconomic Status, categorized based on family income, occupation, and school education of the person who contributes more for the household income.

2.79, 95% CI 1.08–7.21) and age 13–17 (a OR 0.19, 95% CI 0.05–0.78; Table 3).

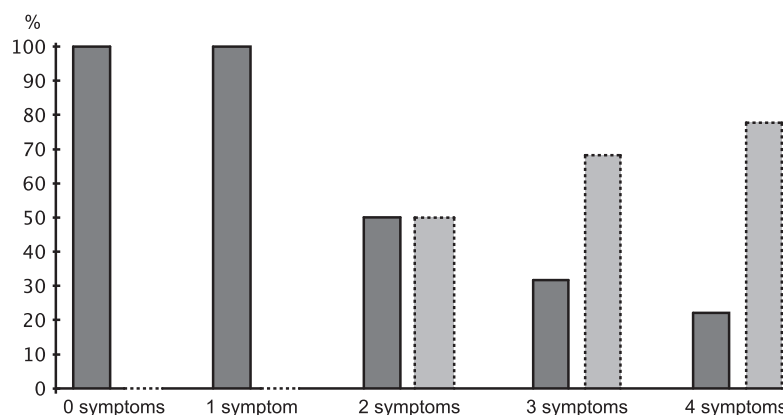
In children with current asthma, 67% (95% CI 58–77%) used asthma medication in the previous 4 weeks (Table S3): controller medication was used by 58% (95% CI 48–68%) and reliever medication by 31% (95% CI 22–40%). Children with NCA had a non-significant higher frequency of any medication use (76%, 95% CI 64–88%) when compared with those with WCA (58%, 95% CI 44–72%); no statistically significant differences were seen in the use of controller or reliever

medication. Over-the-counter medications (e.g.: antihistamines and cough medication) were used more frequently by children with NCA ($p < 0.02$; Table S3). School-aged children used more asthma medication ($p = 0.03$), comparing with pre-schoolers and adolescents (Table S2).

Discussion

In this nationwide study from the general population, only half of children with asthma were controlled. Determinants for not-

Figure 3 Frequency of number of nasal symptoms in asthmatic children, according to asthma control. Full line – well-controlled asthma; Dotted line – not-controlled asthma.



controlled asthma were the presence of substantial nasal symptoms, overweight/obesity, and not having health insurance. The presence of a higher number of nasal symptoms was associated with poorer asthma control. Moreover, children with substantial nasal symptoms and without health insurance needed more unscheduled medical services, while adolescents needed less.

Strengths and limitations

This was the first study assessing childhood asthma control in Portugal, and for the first time, we reported the effect of health insurance coverage on asthma control in a European country. The participants were randomly recruited from the general Portuguese population, and overall, our sample followed the same distribution of our National pediatric population (22).

The sample size may limit the precision of our estimates in subgroup analysis, but we were able to construct logistic regression models with good fit for the main outcomes. The use of a selection strategy based on landline telephone numbers excluded households without residential telephone; nevertheless, it is a widely used method for epidemiological nationwide surveys, and it was already used in similar studies assessing asthma control in children (3). Physician assessment cannot be included in this type of study. Yet, we used an internationally recommended measure for asthma control – the GINA guidelines – which are frequently used in epidemiological studies with similar methodology (23). Also, parents' recall of doctor's diagnosis, for example, rhinitis, may lead to underestimation of concomitant diseases.

High frequency of not-controlled asthma

The proportion of Portuguese children with controlled asthma was similar to that found in USA 6- to 17-year-old children (46%) (5), in Dutch 6- to 16-year-old children (55%) (7), or in French preschoolers (42%) (6); however, estimates on the prevalence of uncontrolled asthma in children are highly variable (15-90%) depending on the studies (2, 8). In our report, only half of the children that were considered controlled by their caregivers had, in fact, controlled asthma. Carroll et al. have shown that

parents usually overestimate asthma control (24). Others reported a poorer asthma control (7), or medication underuse among parents that failed to correctly estimate control (3).

The prevalence of nasal symptoms in children with current asthma (79%) was similar to that found in Dutch asthmatic aged 5–18 (76%) (11). Although the majority of our children with asthma had nasal symptoms, less than half of these (45%) reported a past medical diagnosis of rhinitis. Under-diagnosis and under-treatment of rhinitis in asthmatic children was associated with lack of parental recognition and poorer asthma control (25, 26).

In our study, the increasing number of nasal symptoms was associated with a decrease in asthma control (Fig. 3). We could not find previous papers assessing the association of the number of nasal symptoms with the lack of asthma control in children; nevertheless, previous studies supported a strong link between upper and lower airway disease (27, 28).

Worse asthma control in children with obesity, nasal symptoms, and absence of health insurance

Determinants for not-controlled asthma were the presence of substantial nasal symptoms, overweight/obesity, and not having health insurance (Table 3). Rhinitis is a known comorbidity associated with poorer asthma control in children, especially in those with untreated nasal symptoms (11). Our results are in line with these findings, as substantial nasal symptoms were associated to a six-fold higher probability of NCA. Recently published data also showed that increased BMI was associated to lack of asthma control (2), to a higher use of inhaled β -agonists or oral corticosteroids (12), and to worst asthma control in children with higher airway inflammation (29). In our study, overweight/obesity was associated with a three-fold higher probability of NCA.

The Portuguese Health System is a mixed universal health-care system. It is financed by taxes and by health insurances, both private and public (for state employees), complemented by out-of-pocket expenses. All Portuguese citizens have access to medical care services in public primary care and hospital units. The public care access is primarily based on visits to primary care physician that can refer to hospital specialties;

this is limited by the waiting time and referral geographical areas that prevent the patients from fully choosing the place where they will be followed. Private practices/hospitals access is only dependent on patient's will to attend these institutions; however, due to significant out-of-pocket expenses, the access is easier for those with complementary health insurance coverage. In fact, citizens with healthcare insurance, regardless of the socioeconomic status, may easily choose the site of medical care that they perceive as the best, with easier access to medical specialities and lower waiting time for medical observations. In what concerns medication, prices are the same for every Portuguese children, independently of health insurance status.

In our model, not having health insurance was associated with a three-fold higher probability of NCA. Also, on exploratory univariate analysis, the frequency of children with health insurance coverage followed in private practice/hospital for their asthma was significantly higher than those followed in public settings ($p < 0.001$; Table S4). Taking these results altogether, we may speculate that these relations between asthma control and health insurance status may address differences in types of asthma care that can be influenced by parents' options in choosing the site of medical asthma care for their children (either public or private providers).

Healthcare visits and medication use by children with current asthma

We showed a trend toward more healthcare visits and medication use in children with NCA. Previous studies had

already shown the association between healthcare visits and/or medication with uncontrolled asthma (8, 10). Children with NCA used more antihistamines and cough medication than those with WCA; this association of NCA with a higher use of over-the-counter medication was already observed in asthma patients (30), and it may point to a worst asthma care plan in children with NCA.

Unscheduled medical visits for asthma worsening/exacerbation were more frequent in children with substantial nasal symptoms and without health insurance, and less frequent in adolescents. This model on urgent medical care, which was also used as a proxy for poor asthma control, corroborates that uninsured children, as well as those with substantial nasal symptoms, were at a higher risk of uncontrolled asthma and use of urgent medical care.

In conclusion, only half of children with asthma were controlled in this nationwide study. Determinants for not-controlled asthma were the presence of substantial nasal symptoms, overweight/obesity, and not having healthcare insurance. Our results support the importance of modifiable factors, namely nasal symptoms and obesity, as determinants of asthma control in children. Healthcare insurance status was related to asthma control; in our healthcare system, this association may be related to parents' options in choosing the site of medical asthma care for their children. More studies are needed to understand the effect on asthma control of the access to different types of asthma care services and of being able to choose where the child is cared for asthma.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. INASma study details.

Table S1. Proportion (%) of children with asthma-like symptoms, nasal symptoms and life impairment by asthma-like/nasal symptoms in the previous 4 weeks (never, ≤ 2 days/week or > 2 days/week), according to asthma control.

Table S2. Healthcare use for asthma in the previous 12 months and medication use for asthma in the previous 4 weeks, in children with current asthma, % (95% CI).

Table S3. Asthma medication use in the previous 4 weeks, in children with current asthma, % (95% CI).

Table S4. Proportion of healthcare insurance coverage, n (%).



Cost of asthma in children: a nationwide, population-based, cost-of-illness study

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1 Cost of asthma in children: a nationwide, population-based, cost-of-
2 illness study

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26 **Abstract**

27 **Background:** This study aimed to estimate the cost of asthma in Portuguese children;
28 furthermore, we studied the factors associated with cost of asthma and the costs per level
29 of asthma control.

30 **Methods:** A nationwide, population- and prevalence-based cost-of-illness study with a
31 societal perspective was conducted. We measured direct and indirect costs using a
32 bottom-up approach and a human capital method, respectively, for 208 children (<18
33 years), from two national repositories. Generalised linear modelling for analysis of asthma
34 costs' determinants and sensitivity analysis to assess uncertainty were performed.

35 **Results:** The mean annualised asthma cost per child was €929.35 (95%CI, 809.65–
36 1,061.11); €698.65 (95%CI, 600.88–798.27) for direct costs, and €230.70 (95%CI,
37 197.36–263.81) for indirect costs. Extrapolations for the Portuguese children amounted to
38 €161,410,007.61 (95%CI, 140,620,769.55–184,293,968.55) for total costs. Direct costs
39 represent 75.2% with the costliest domain (51.1% of total costs) being the healthcare
40 service use: 20.7% for scheduled medical visits and 30.4% for acute asthma care – non-
41 scheduled medical visits (7.9%, €12,766,203.20), emergency department visits (11.7%,
42 €18,932,464.80) and hospitalisations (10.8%, €17,406,946.00).

43 Children with partly controlled and uncontrolled asthma had higher mean costs per year
44 (adjusted coefficients: 1.46 [95%CI, 1.12-1.90] and 2.25 [95%CI, 1.56-3.24], respectively).

45 **Conclusions:** Costs of childhood asthma are high (0.9% of the healthcare expenditures in
46 Portugal). Direct costs represented 3/4 of total costs, mainly related to the use of
47 healthcare services for acute asthma care. Policies and interventions to improve asthma

48 control and reduce acute use of healthcare services have the potential to reduce asthma
49 costs.

50 **Keywords:** burden, economics, health services research, pediatrics, pulmonary medicine

51 **Requests for offprints:**

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59 **Introduction**

60 Health economic studies are important to support decision-makers in defining health
61 priorities (1). (2,3). In light of the increasing healthcare costs and the consequent threat to
62 the sustainability of healthcare systems, focus should be put in assess the impact of
63 chronic diseases, aiming to reduce their burden (4).

64 As one of the most common chronic diseases in childhood, asthma should have reliable
65 economic data available. In childhood asthma, important direct costs (diagnostic tests,
66 medications, medical visits, hospitalisations or emergency admissions) and indirect costs
67 (mainly caregivers' loss of work days and transportation to healthcare services) are
68 relevant and can be high, especially in severe disease (5). In 2002, Druss et al have
69 quoted asthma as the 13th most expensive medical condition in USA (6). In 2011, Barnett
70 and Nurmagambetov used a regression-based method to estimate \$56 billions of
71 incremental costs in all-age asthmatic USA population, with a mean value of \$3,259 per
72 person/year (7). In the same year, Bravo et al estimated the cost of asthma in children
73 younger than 15 years old, in Spain, to be €532 million, (€1,149 person/year) (5). In the
74 same study, the costs within each category of asthma severity ranged from €403 for the
75 mildest to €5,930 for the most severe (costs person/year). Even though other asthma
76 economic studies have been conducted, there are few population based and
77 comprehensive pediatric cost-of-illness studies (8).

78 This study aimed to estimate the cost of childhood asthma in Portugal. Secondary aims
79 were: 1) to describe direct and indirect costs, 2) to determine factors associated with costs,
80 and 3) to assess costs according to the level of asthma control.

81 **Methods**

82 **Study design and setting**

83 The Cost of Childhood Asthma in Portugal (CASCAs project) was a Portuguese,
84 nationwide, population- and prevalence-based, cost-of-illness study with a societal
85 perspective. This project was reviewed and approved by the Ethics Committee of *Centro*
86 *Hospitalar de São João*, Porto, Portugal. Informed consent was obtained from parent(s) or
87 legal guardian(s).

88 **Participants and data collection**

89 Data from participants of two studies (INAsma and CED2013) was analysed. INAsma was
90 a nationwide survey, from the general population, applied by telephone interview to
91 individuals living in Portugal, in 2010 (9,10). CED2013 was a population-based survey
92 applied to children attending primary public schools in a Portuguese city (Guimarães), in
93 2013. Questionnaires were similar in the both studies, however, data on diagnostic tests
94 use and immunotherapy were only available in the CED2013 study. When the selected
95 participant was younger than 15 years old, the respondent was the usual and most
96 knowledgeable caregiver. For the CASCAs project we included 208 children with current
97 asthma (CA): 98 (0- to 17-years old) from the INAsma Study and 110 (5- to 12-years old)
98 from the CED2013 Study (Fig. S1). Participants and data collection are further described
99 in supplementary material.

100 Data collection of prices of healthcare services, diagnostic tests, medication, holding
101 chambers, absenteeism, transportation and subsidies were performed in different sources
102 and databases as described below and in supplementary material.

103 Cost estimation methods

104 Direct healthcare costs of childhood asthma were estimated using a bottom-up approach
105 (person-based). The cost domains included in direct costs were: 1) healthcare services
106 (scheduled medical visits, non-scheduled medical visits, emergency department visits and
107 hospitalisations); 2) diagnostic tests (blood workouts, skin prick tests, spirometries and
108 chest x-ray); and 3) treatment (asthma-specific medication, other asthma-related
109 medication and medical devices). Databases and reports from Portuguese Central
110 Administration of Health System (ACSS) (11), Ministry of Health (12) and National
111 Authority of Medicines and Health Products (INFARMED) (13) were used to achieve
112 unitary costs. A mean usage scenario for each medication was achieved by consensus, in
113 accordance with international guidelines (14), in case of parent/self-reported use of the
114 corresponding medication.

115 Indirect costs of childhood asthma were estimated using the human capital method. The
116 cost domains included in indirect costs were: 1) absenteeism; 2) transportation and 3)
117 subsidies because of asthma. Databases and reports from National Statistics Institute
118 (INE) (15) and Ministry of Social Security (16,17) were used to achieve unitary costs.

119 Each cost item was calculated for each participant by multiplying the parent/self-reported
120 amount of resources used by the unitary costs of the resources. The total cost was then
121 calculated for each participant by adding direct and indirect costs. Mean cost per patient
122 was achieved by the sum of the total cost of each participant, dividing for the total number
123 of asthmatic children in our sample. Costs were indexed to 2010 Portuguese prices in
124 euros. Cost estimation methods are further described in supplementary material.

125 Definitions

126 CA was defined as children that 'ever had asthma' plus at least one of the following:
127 wheezing, awakening with breathlessness or having an asthma attack in the previous 12

months, or taking asthma medication at the time of the interview. Asthma control was defined according to GINA (14), and categorized into 'controlled', 'partially controlled' and 'uncontrolled'. Definitions for other variables are described in supplementary material.

Statistical analysis

Statistical analysis was performed using SPSS version 23 (SPSS IBM, New York, NY, USA). General characteristics of the included participants were described using absolute and relative frequencies.

Cost variables were all annualised and presented as mean and standard deviation (SD) or 95% confidence interval (95%CI), calculated using bootstrap methods because of their skewed distributions (18,19). For each cost item and domain, extrapolated estimates for the Portuguese population were calculated. Extrapolation estimates were based on a prevalence estimate of CA from the INAsma Study (8.4% [95%CI, 6.6-10.7]), corresponding to a total weighted population of 173,681 Portuguese children with CA (9). The factors associated with costs of childhood asthma and, specifically, differences in levels of asthma control, were assessed using mixed Poisson-gamma models. A p-value of <0.05 was considered statistically significant.

We additionally used decision analytic modelling to perform univariate and multivariate deterministic sensitivity analysis, in order to evaluate how the uncertainty would impact the estimates of national annualised costs of childhood asthma in Portugal. Univariate deterministic sensitivity analysis was performed with the 95%CI of the proportion estimates of occurrence of each item in Portuguese population. The multivariate deterministic sensitivity analysis was set with two case scenarios. The best-/worst-case scenario were set, respectively, with: the lower/upper limit of the 95%CI of CA prevalence in Portuguese children; scenario of minimum/maximum use of asthma medications; and the lower/upper limit of the 95%CI for the proportion of occurrence of each item in Portuguese population.

153 **Results**

154 Characteristics of the children included in cost-of-illness analysis are summarized in Table
 155 S3. Estimates of mean annualised costs for each cost domain are presented in Table 1.
 156 The mean annualised total costs per child were €929.35 (95%CI, 809.65–1,061.11), with
 157 €698.65 (95%CI, 600.88–798.27) for direct costs, and €230.70 (95%CI, 197.36–263.81)
 158 for indirect costs. The extrapolations for Portuguese children amount to absolute total
 159 costs of €161,410,007.61 (95%CI, 140,620,769.55–184,293,968.55), with direct costs of
 160 €121,341,498.02 (95%CI, 104,362,186.11–138,645,096.07) and indirect costs of
 161 €40,068,509.59 (95%CI, 34,276,935.33–45,819,027.76).

162 Direct costs represent 75% and indirect costs 25% of the total costs. The most expensive
 163 domain was healthcare services use (€82,519,684.10; 51% of total costs), specifically
 164 scheduled medical visits (€33,414,070.10; 21% of total costs) and those related to acute
 165 asthma care (€49,105,614.06; 30% of total costs): non-scheduled medical visits
 166 (€12,766,203.20), emergency department visits (€18,932,464.80) and hospitalisations
 167 (€17,406,946.00).

168 **Factors associated with costs of asthma**

169 We observed significant crude associations between total annualised costs of childhood
 170 asthma and nocturnal symptoms, asthma attacks and level of asthma control (Table 2).
 171 However, only asthma attacks and level of asthma control had significant and independent
 172 associations with total annualised costs of childhood asthma in the final multivariate model
 173 adjusted for age.

174 Children with asthma attacks in the previous 12 months had higher costs than those
 175 without asthma attacks (adjusted exponential model coefficients: 1.57 [95%CI, 1.22-2.02]).
 176 Children with partly controlled asthma and uncontrolled asthma had higher mean costs per
 177 year with adjusted exponential model coefficients of 1.46 [95%CI, 1.12-1.90] and 2.25

178 [95%CI, 1.56-3.24], respectively. The mean annualised costs per asthmatic child were
179 €747.63 in those with controlled asthma, €1,120.50 in partly controlled and 1,758.44 in
180 uncontrolled ($p<0.001$) (Fig. 1). Total costs and direct costs, specifically healthcare
181 services use by acute asthma care and diagnostic tests domains were significantly higher
182 in children with uncontrolled asthma (Fig. 2). Scheduled medical visits, treatment or
183 indirect costs were not different between asthma control groups.

184 **Sensitivity analysis**

185 The univariate deterministic sensitivity analysis is presented in supplementary material
186 (Table S6). The multivariate deterministic sensitivity analysis is presented in Table 3. The
187 adjusted estimates for the mean of annualised costs per child with asthma in total costs
188 varied between -35% and +53%, in direct costs between -36 and +63%, and in indirect
189 costs between -30 and +23%.

190 **Discussion**

191 We conducted a cost-of-illness analysis on Portuguese childhood asthma, with a
192 prevalence-based, societal perspective, that allowed a broad economic analysis of the
193 disease. We adopted a societal perspective, the most comprehensive approach, because
194 it uses the direct and indirect costs for all members of the society (20). From a societal
195 perspective, the childhood asthma in Portugal costs over €150 million per year,
196 corresponding to more than €900 per child with CA. Childhood asthma costs correspond to
197 0.91% of the Portuguese expenses in health in 2010. These expenditures are undertaken
198 together by the patients, by the Portuguese state and by health insurance companies,
199 depending on the type of healthcare services used. Direct costs were 3/4 of the costs, with
200 the most being related to healthcare services use and specially to acute asthma care. The
201 most important factors for higher costs were uncontrolled asthma (2.3-fold) and asthma
202 attacks in the previous 12 months (1.6-fold).

203 **Total, direct and indirect costs of childhood asthma**

204 The cost estimates for childhood asthma in Portugal were slightly lower than the Spanish
205 estimates in 2008 (€1,149 child/year) (5). Otherwise, USA estimates for 2008 prices of 5-
206 to 17-years old asthmatics were lower than ours: \$791 child/year (direct costs, \$401
207 child/year; indirect costs, \$390 child/year) (21). In that study, the authors analysed data
208 from the 1996 Medical Expenditure Panel Survey and the type of asthma-related
209 expenditures used in direct costs were not clear. In Turkey, a study performed in 2006, in
210 pediatric allergy and asthma referral centres, reported medical and non-medical costs of
211 \$1,597 per child/year (medical, \$775; non-medical, \$821), however, no formal indirect
212 costs were reported (22). The definition of medical costs was similar to our definition of
213 direct costs, and the results were also similar (assuming 1.23 exchange rate of dollar to
214 euro, in 2006). Non-medical costs included transportation (not absenteeism), but were

215 mainly driven by non-allergic household measures (\$710) like air filters, special vacuum
216 cleaners or anti-allergic bed covers, that we did not assess in our study, as the current
217 guidelines do not recommend them (14).

218 Previously published studies reported proportions of direct costs between 61-88% (8).
219 Healthcare services use in the context of asthma worsening (non-scheduled medical visits,
220 emergency and hospitalisations) were, altogether, 30% of the total costs of childhood
221 asthma in Portugal. Reducing acute asthma care costs, should be one of the major targets
222 for potential savings. Also, by reducing it other domains (e. g., indirect costs) could also be
223 lowered.

224 Indirect costs were one-fourth of the costs in childhood asthma. Other studies showed that
225 indirect costs can be as high as 50% (8). The lack of assessment of costs related to
226 presenteeism and lower salaries in Portugal may justify our proportion of indirect costs.
227 Nevertheless, more than 13 million euros were spent yearly with parental absenteeism
228 because of childhood asthma. This value can represent a potential higher burden to
229 society, as loss of parental work can further impact the overall economy.

230 **Determinants of cost variation in childhood asthma**

231 The most important determinants for higher costs were the asthma attacks in the previous
232 12 months (1.6-fold) and having uncontrolled asthma (2.3-fold). Direct costs were
233 significantly higher in children with uncontrolled asthma, specifically acute asthma care
234 and diagnostic test use. Interestingly, there were no significant differences in costs of
235 scheduled medical visits and treatment for controlled vs. uncontrolled children.

236 Considering a hypothetical scenario (data not shown) in which all Portuguese children with
237 asthma were controlled, the savings would be more than 30,000,000 € per year (20%
238 reduction). As previously reported, children with not controlled asthma had significantly

239 more unscheduled medical visits and hospitalisations (10,23); knowing that uncontrolled
240 asthma is, also, the major determinant for higher costs, effective policies should be
241 directed to improve asthma control and reduce acute care medical visits.

242 Future studies should be designed to have multinational cost-of-illness data, aiming to
243 understand differences between asthma care and to compare outcomes. Quality-of-life
244 assessment in childhood asthma should also be improved and be part of a burden of
245 disease analysis.

246 **Strengths and limitations**

247 This was the first Portuguese nationwide, population-based study on costs of childhood
248 asthma. The cost domains analysed allowed us to create a comprehensive picture of
249 childhood asthma costs in Portugal, as did the prevalence-based analysis and societal
250 perspective. We performed a univariate and multivariate deterministic sensitivity analysis,
251 aiming to understand different variations according to uncertainty. Sensitivity analysis is
252 crucial to highlight variability, to make comparisons with other data, and is recommended
253 in economic studies (24,25), but this was the first cost-of-illness study on childhood
254 asthma to report a sensitivity analysis.

255 There were some limitations regarding the participants and the reported outcomes used
256 for cost estimations. Participants were derived from INAsma and CED2013; school-age
257 children may be overrepresented in our sample, nevertheless, this is the age group with
258 the higher prevalence of asthma in our country (9). Also, differences in cost estimations
259 between the two studies were only seen in the domain of 'Treatment' and total costs were
260 not significantly different (Table S4). Data on diagnostic tests use and immunotherapy
261 were only available in the CED2013 study and then extrapolated for the entire sample. The
262 assumptions made in the treatment domain may also have masked higher cost differences
263 between asthma control groups. Specifically, medication costs were based on the reported

264 medicines used in the previous year, but we were unable to assess the number of doses
265 performed by each participant; we used a clinical consensus approach for the number of
266 doses of controller and reliever medication, based on GINA guidelines and on
267 conservative estimations of adherence. In transportation, we used an official Portuguese
268 price by kilometre, however we could not assess how many of the patients used public
269 transports or ambulances. The absenteeism costs were based on a mean Portuguese
270 daily income according to the parents' professional occupation, not with a reported
271 income; this could possibly underestimate the costs of absenteeism. Also, we couldn't
272 assess parent's absenteeism because of child's asthma.

273 In conclusion, childhood asthma in Portugal costs €161,410,007.61 per year,
274 corresponding to €929.35 per child with CA. The total cost estimate of childhood asthma
275 corresponds to 0.91% of the Portuguese expenses in health in 2010. Direct costs were 3/4
276 of total costs, mainly related to acute asthma care (non-scheduled visits, emergency and
277 hospitalisations). The most important factors determining higher costs were asthma
278 attacks in the previous 12 months (1.6-fold) and uncontrolled asthma (2.3-fold). A better
279 asthma control, with a consequent reduction in the acute use of healthcare services,
280 should be the major target for potential savings in this disease.

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- 345

For Peer Review

346 Legends

347 **Table 1** Annualised costs (in euros) of childhood asthma in Portugal: total costs, mean
348 cost per child with current asthma and percentage of total costs for each domain/variable.

349 **Table 2** Factors associated with annualised total costs of childhood asthma in Portugal.

350 **Table 3** Multivariate deterministic sensitivity analysis – Annualised total costs extrapolated
351 to total Portuguese children with current asthma and mean costs per patient.

352 **Fig. 1** Mean cost per child with current asthma, per year; mean cost variation according to
353 the level of asthma control. Mean costs are marked in euros and the lines represent
354 95%CI. * $p < 0.001$ between groups of asthma control.

355 **Fig. 2** Mean cost per child with current asthma, per year, in each domain. Panel A: total
356 costs. Panel B: cost variation according to the level of asthma control. * $p < 0.001$ between
357 groups of asthma control.

358 Table 1

	Total costs in Portuguese children* (95%CI ^b)	Mean cost per patient [†] (95%CI ^b)	Percentage of total costs
TOTAL COSTS	161,410,007.61 (142,367,218.84 - 181,369,857.87)	929.35 (819.71 - 1,044.27)	100%
DIRECT COSTS	121,341,498.02 (104,319,912.15 - 139,851,241.14)	698.65 (600.64 - 805.22)	75.2%
Healthcare services use	82,519,684.10 (67,027,110.46 - 99,248,305.38)	475.12 (385.92 - 571.46)	51.1%
Scheduled medical visits	33,414,070.10 (29,192,806.15 - 38,204,470.63)	192.39 (168.08 - 219.97)	20.7%
Acute asthma care	49,105,614.06 (35,070,014.88 - 64,089,678.45)	282.73 (201.92 - 369.01)	30.4%
Non-scheduled medical visits	12,766,203.20 (9,809,363.94 - 15,874,252.35)	73.50 (56.48 - 91.40)	7.9%
Emergency department visits	18,932,464.80 (13,136,536.12 - 26,300,288.04)	109.01 (75.64 - 151.43)	11.7%
Hospitalisation	17,406,946.00 (6,189,712.95 - 30,072,795.68)	100.22 (35.64 - 173.15)	10.8%
Diagnostic tests	9,128,914.10 (7,988,735.48 - 10,293,812.35)	52.56 (46.00 - 59.27)	5.7%
Blood workout	2,498,121.71 (2,056,174.62 - 3,027,259.83)	14.38 (11.84 - 17.43)	1.5%
Chest x-ray	867,148.15 (726,594.46 - 1,012,508.13)	4.99 (4.18 - 5.83)	0.5%
Pulmonary function tests	4,840,864.14 (4,047,079.93 - 5,594,160.80)	27.87 (23.30 - 32.21)	3.0%
Skin prick tests	922,780.11 (787,921.22 - 1,060,409.35)	5.31 (4.54 - 6.11)	0.6%
Treatment	29,692,899.78 (26,638,427.58 - 32,734,734.89)	170.96 (153.38 - 188.48)	18.4%
Asthma-specific medication	16,005,602.20 (14,170,511.21 - 16,552,789.28)	92.16 (81.59 - 102.71)	9.9%
Controller medication	14,731,639.10 (12,945,695.43 - 16,516,489.95)	84.82 (74.54 - 95.31)	9.1%
Reliever medication	1,273,963.08 (1,122,865.03 - 1,433,510.87)	7.34 (6.47 - 8.25)	0.8%
Other asthma medication	10,789,280.82 (8,948,166.70 - 12,786,638.37)	62.12 (51.52 - 73.62)	6.7%
Immunotherapy	7,403,386.43 (5,663,424.78 - 9,313,209.42)	42.63 (32.61 - 53.62)	4.6%
Antihistamines	1,792,454.72 (1,663,308.20 - 1,910,421.53)	10.32 (9.58 - 11.00)	1.1%
Antibiotics	1,491,836.29 (1,264,692.94 - 1,736,306.33)	8.59 (7.28 - 10.00)	0.9%
Flu vaccine	101,603.39 (n.a.)	0.59 (n.a.)	0.1%
Holding chamber	2,898,016.76 (2,659,281.90 - 3,159,830.54)	16.69 (15.31 - 18.19)	1.8%
INDIRECT COSTS	40,068,509.59 (34,117,635.12 - 46,811,024.16)	230.70 (196.44 - 269.52)	24.8%
Parental absenteeism	13,689,797.60 (10,775,047.66 - 16,906,907.47)	78.82 (62.04 - 97.34)	8.5%
Transportation	3,931,536.64 (3,397,478.25 - 4,553,290.57)	22.64 (19.56 - 26.22)	2.4%
Subsidies	22,447,175.39 (17,551,402.93 - 27,735,327.31)	129.24 (101.06 - 159.69)	13.9%

Each cost item was calculated for each participant by multiplying the parent/self-reported amount of resources used by the unitary costs of the resources. Costs were indexed to 2010 Portuguese prices in euros.

*Total costs were extrapolated to total Portuguese children with current asthma (n=173,681)(9);[#]Bootstrapped 95%CI; n.a., not applicable

[†]Mean cost per patient: sum of the total cost of each participant, dividing for the total number of asthmatic children in our sample.

363 Table 2

	Mean cost (SD)	Factors associated with childhood asthma costs			
		Crude association (95%CI)		Adjusted association* (95%CI)	
Gender					
Female	999.44 (1,155.01)	1.00	(ref)		n.i.
Male	888.99 (806.34)	0.89	(0.67-1.18)		n.i.
Age groups					
0- 5 years old	1,035.91 (1,146.11)	1.00	(ref)	1.00	(ref)
6-12 years old	969.84 (974.54)	0.94	(0.60-1.46)	0.86	(0.59 -1.26)
13-17 years old	681.33 (618.04)	0.66	(0.39-1.14)	0.64	(0.40-1.03)
Caregiver education					
No education	1,190.65 (1,311.41)	1.00	(ref)		n.i.
0-4 years (basic 1 st cycle)	1,011.55 (1,151.59)	0.85	(0.49-1.47)		n.i.
5-9 years (basic 2 nd and 3 rd cycle))	1,010.83 (1,136.31)	0.85	(0.51-1.42)		n.i.
10-12 years (secondary)	669.32 (442.65)	0.56	(0.32-1.01)		n.i.
>12 years (higher)	840.07 (477.72)	0.71	(0.41-1.21)		n.i.
Mensual income of caregiver					
< 650.00 €	1,064.76 (1,187.16)	1.00	(ref)		n.i.
650.00 – 749.99 €	1,009.69 (909.77)	0.95	(0.67-1.35)		n.i.
750.00 – 1,199.99€	839.60 (972.68)	0.79	(0.52-1.21)		n.i.
>= 1,200.00 €	755.10 (550.96)	0.71	(0.50-1.02)		n.i.
Wheezing					
No	776.19 (746.83)	1.00	(ref)		n.i.
Yes	964.25 (985.50)	1.24	(0.84-1.83)		n.i.
Nocturnal symptoms					
No	685.41 (588.66)	1.00	(ref)		n.i.
Yes	1,014.00 (1,034.80)	1.48	(1.07-2.05)		n.i.
Asthma attacks					
No	677.58 (713.02)	1.00	(ref)	1.00	(ref)
Yes	1,136.82 (1,058.60)	1.68	(1.27-2.22)	1.57	(1.22-2.02)
Asthma control					
Controlled	747.63 (562.79)	1.00	(ref)	1.00	(ref)
Partly controlled	1,120.50 (1,135.96)	1.50	(1.14-1.98)	1.46	(1.12-1.90)
Uncontrolled	1,758.44 (1,795.65)	2.35	(1.60-3.47)	2.25	(1.56-3.24)

Bold values show statistical significant differences. n.i.: not included in the model (non-significant variables)

*Adjusted coefficients were calculated using multivariate mixed Poisson-gamma (Tweedie distribution family) generalised linear models. Goodness-of-fit statistics for the multivariate regression model: scaled deviance (D = 2,919.3; df = 181); scaled Pearson chi-square (v2 = 181.0; df = 181); AIC = 5,111.3; consistent AIC = 5,136.7

368 Table 3

	Costs in Portuguese childhood asthma	Multivariate sensitivity analysis	
		Best-case scenario*	Worst-case scenario [#]
TOTAL COSTS	161,410,007.61 (929.35)	79,585,960.00 (606.99)	308,018,952.55 (1,424.38)
DIRECT COSTS	121,341,498.02 (698.65)	58,535,047.13 (446.44)	246,538,052.49 (1,140.07)
Healthcare services use	82,519,684.10 (475.12)	42,595,571.35 (324.87)	138,329,936.99 (639.68)
Scheduled medical visits	33,414,070.10 (192.39)	23,171,710.16 (176.73)	44,989,758.82 (208.05)
Acute asthma care	49,105,614.00 (282.73)	19,423,861.19 (148.14)	93,340,178.17 (431.63)
Non-scheduled medical visits	12,766,203.20 (73.50)	6,167,963.51 (47.04)	20,981,450.09 (97.02)
Emergency department visits	18,932,464.80 (109.01)	10,627,732.56 (81.06)	29,012,394.70 (134.16)
Hospitalisation	17,406,946.00 (100.22)	2,628,165.12 (20.04)	43,346,333.38 (200.45)
Diagnostic tests	9,128,914.10 (52.56)	5,000,033.78 (38.13)	14,486,032.35 (66.99)
Blood workout	2,498,121.71 (14.38)	1,305,608.05 (9.96)	4,067,419.36 (18.81)
Chest x-ray	867,148.15 (4.99)	458,238.33 (3.49)	1,403,577.64 (6.49)
Pulmonary function tests	4,840,864.14 (27.87)	2,626,641.61 (20.03)	7,722,475.88 (35.71)
Skin prick tests	922,780.11 (5.31)	609,545.80 (4.65)	1,292,559.47 (5.98)
Treatment	29,692,899.78 (170.96)	10,939,442.00 (83.43)	93,722,083.15 (433.40)
Asthma-specific medication	16,005,602.20 (92.16)	3,225,956.01 (24.60)	67,162,295.84 (310.58)
Controller medication	14,731,639.10 (84.82)	2,883,526.64 (21.99)	63,387,483.49 (293.12)
Reliever medication	1,273,963.08 (7.34)	342,429.37 (2.61)	3,774,812.35 (17.46)
Other asthma medication	10,789,280.82 (62.12)	5,819,598.60 (44.39)	22,412,953.76 (103.64)
Immunotherapy	7,403,386.43 (42.63)	4,017,060.24 (30.64)	16,754,942.43 (77.48)
Antihistamines	1,792,454.72 (10.32)	1,127,631.03 (8.60)	2,603,722.95 (12.04)
Antibiotics	1,491,836.29 (8.59)	636,556.20 (4.85)	2,826,579.23 (13.07)
Flu vaccine	101,603.39 (0.59)	38,351.14 (0.29)	227,709.14 (1.05)
Holding chamber	2,898,016.76 (16.69)	1,893,887.38 (14.44)	4,146,833.55 (19.18)
INDIRECT COSTS	40,068,509.59 (230.70)	21,050,912.88 (160.55)	61,480,900.06 (284.31)
Parental absenteeism	13,689,797.60 (78.82)	8,312,678.55 (63.40)	20,379,882.34 (94.24)
Transportation	3,931,536.64 (22.64)	2,770,123.76 (21.13)	5,221,446.58 (24.15)
Subsidies	22,447,175.39 (129.24)	9,968,110.57 (76.03)	41,101,017.72 (190.06)

*Best-case scenario was set with: the lower limit of the 95%CI of CA prevalence in Portuguese children; scenario of minimum use of asthma medications; and the lower limit of the 95%CI for the proportion of occurrence of each variable in Portuguese population.

[#]Worst-case scenario was set with: the upper limit of the 95%CI of CA prevalence in Portuguese children; scenario of maximum use of asthma medications; and the upper limit of the 95%CI for the proportion of occurrence of each variable in Portuguese population.

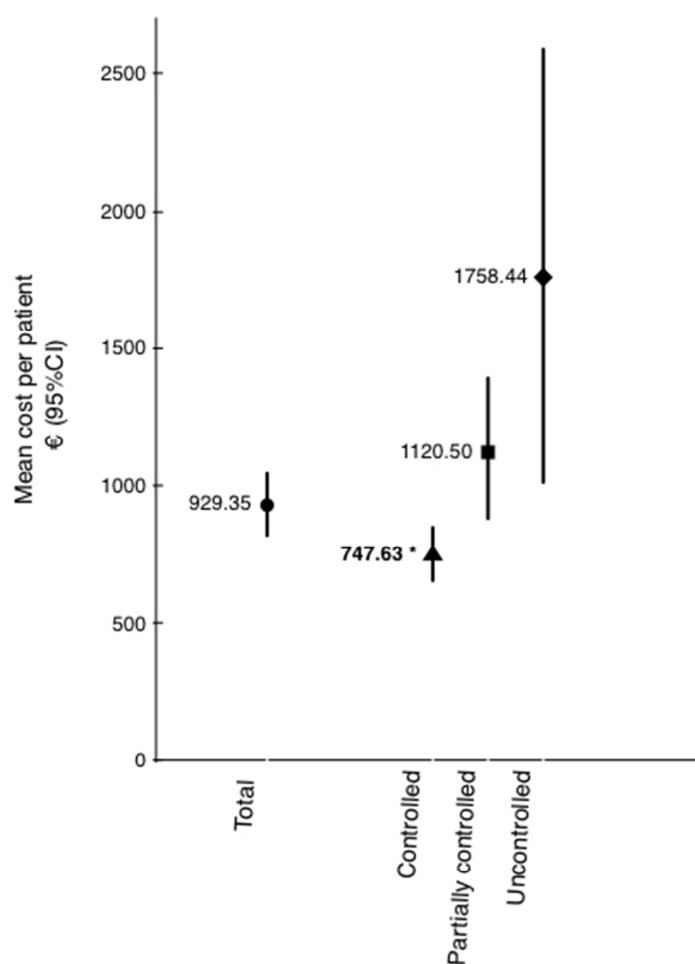


Fig. 1 Mean cost per child with current asthma, per year; mean cost variation according to the level of asthma control. Mean costs are marked in euros and the lines represent 95%CI. * $p < 0.001$ between groups of asthma control.

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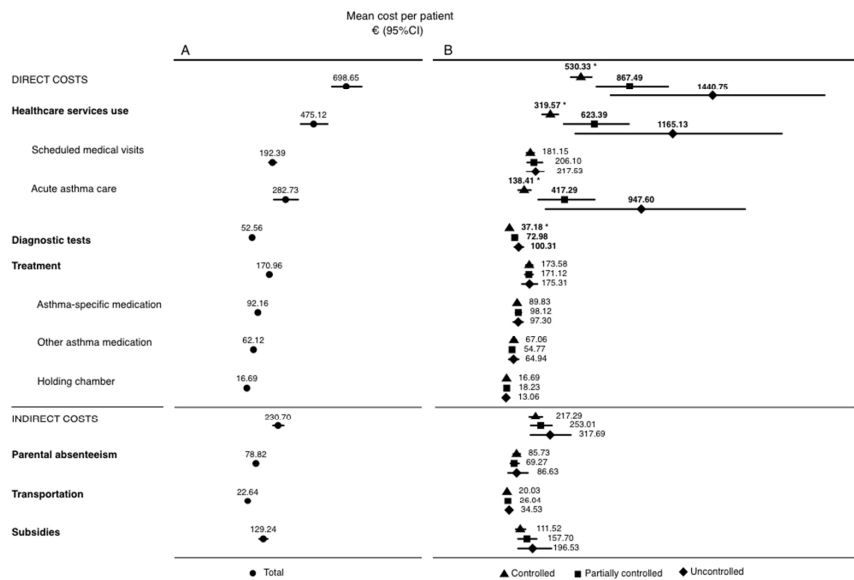


Fig. 2 Mean cost per child with current asthma, per year, in each domain. Panel A: total costs. Panel B: cost variation according to the level of asthma control. * $p<0.001$ between groups of asthma control.

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