UNIVERSIDADE DE LISBOA

FACULDADE DE MEDICINA

Prevalence and determinants of uncontrolled asthma in Portugal: a national population-based study
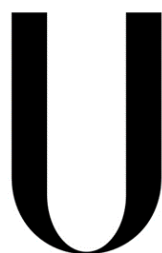
Catarina de Paraíso Camarinha

Master's Thesis Advisors: Cristina Bárbara, PhD, MD

Paulo Jorge Nicola, MSc, MD

Dissertation developed to obtain the degree of Master in Epidemiology.

2019

UNIVERSIDADE DE LISBOA

FACULDADE DE MEDICINA

Prevalence and determinants of uncontrolled asthma in Portugal: a national population-based study

Catarina de Paraíso Camarinha

Master's Thesis Advisors: Cristina Bárbara, PhD, MD

Paulo Jorge Nicola, MSc, MD

Dissertation developed to obtain the degree of Master in Epidemiology.

2019

José Agostinho Camarinha

José Bentes Camarinha

In memoriam

Acknowledgments

Thanks to the coordinators and teachers of the Master degree in Epidemiology for the transmission of such a precious knowledge.

Thank you my fellow students for sharing experiences, skills and friendship.

To my mentors to their guidance: Professor Cristina Bárbara for the wise knowledge on the topic. Dr. Paulo Nicola for the scientific thoroughness and availability to support in the accomplishment of this work

Thank you Dr. Mario Morais de Almeida for the incentive and opportunity for this complementation on my academic education.

Thank you, colleagues at the Centro de Alergia of the Hospital Cuf Descobertas for the companionship and friendship. I consider myself to be fortunate to work on such a team.

Finally, I thank my grandparents, my parents and my sister for always being present and to Pedro for showing me strength and determination.

Abstract

Background: Asthma is a chronic disease that affects people worldwide with potentially negative effect on quality of life and in healthcare systems. Asthma control represents a main goal for the management of asthma disease. Notwithstanding the provided recommendations, international studies revealed low levels of disease control. Moreover, modifiable and non-modifiable factors have been identified as related to poor asthma control level.

Aim: In this study we assessed the level of asthma control by individual's perspective, in Portugal, and the determinants associated with uncontrolled asthma.

Methods: 557 active asthmatic patients were identified by random phone number in households and 400 individuals (327 adults and 73 children) completed a questionnaire during 2011 to 2012. Asthma control was assessed based on Global Initiative for Asthma (GINA) guidelines recommendations. In adults, besides the evaluation of GINA based symptom control, we additionally determined the self-perception of control and the level of control according to Asthma Control Test^{TM} (ACT).

Results: The fulfilment of the GINA criteria was accomplished only in 3.5% of the individuals. The presence of asthma symptoms in the previous four weeks was reported by 52.1%, and the occurrence of an acute episode in the past twelve months by 70% individuals. Life activity limitations caused by asthma disease was the main criteria reported as failure (78.8%).

93.9% of adults perceived asthma as being completely, well or somewhat controlled, which didn't match the objective assessment of control. 35.2% had uncontrolled asthma, 64.8% partially controlled and none of the individuals had totally control of asthma assessed by ACT test. Factors significantly associated with poor asthma control scores were: age (OR 1.02 per year of age; 95% CI: 1.01-1.03), female sex (OR 1.87; 95% CI: 1.15-3.04), educational level (OR 0.5; 95% CI: 0.28-0.89 at high school level or more), occupation (OR 4.92; 95% CI: 2.12-11.42 if looking for a first job or being unemployed) (OR 2.51; 95% CI: 1.35-4.65 if being retired), income (OR 0.23; 95% CI: 0.07-0.72 if >619 euros), BMI (OR 1.09 per BMI unit; 95% CI: 1.03-1.14), having rhinitis symptoms (OR 4.40; 95% CI: 2.56-7.58) and using inhaled corticosteroids (OR 0.44; 95 %CI: 0.24-0.82 if used in the past or never used).

Looking for a first job or being unemployed, BMI and having rhinitis symptoms were the determinants remaining significant after multivariate adjustments.

Conclusions: This study reveals that the state of asthma management in Portugal is far from the long-term goals as stipulated by GINA guidelines. Also, there is an overestimation of asthma control through patient perception. Uncontrolled asthma was associated with several

determinants (age, sex, educational level, occupation, income, BMI, having rhinitis symptoms and the use of inhaled corticosteroids as part of treatment plan), from which their identification can contribute to improve the strategies of care on these patients.

Keywords: asthma; control; uncontrolled; determinants

Resumo Alargado

Introdução: A asma é uma doença crónica caracterizada pela ocorrência de sintomas respiratórios que afeta indivíduos de qualquer idade e etnia em todo o mundo. Esta patologia resulta num efeito potencialmente negativo, quer na qualidade de vida dos indivíduos, quer ao nível dos sistemas de saúde. O Global Initiative for Asthma (GINA) foi criado em 1993 com o objetivo de melhorar a qualidade na prestação de cuidados de saúde aos doentes asmáticos. Contudo, apesar da existência de recomendações, inúmeros indivíduos com asma permanecem subtratados, em risco de ocorrência de exacerbações e com baixos níveis de controlo da doença. O controlo da doença asmática constitui um dos principais pilares da terapêutica desta patologia. A nível mundial são perdidos mais de 23 milhões de anos de vida ajustados à incapacidade (DALYs) resultantes da doença asmática. O custo de um doente asmático não controlado poderá chegar aos 2281€ por ano, face aos 509€ de um doente asmático controlado. Estes valores resultam não só dos custos diretos associados (ex: tratamentos, hospitalizações) mas também dos custos indiretos implicados (ex: faltas ao trabalho). Os estudos do *Asthma Insights and Reality* (AIR) foram realizados em vários países ao longo dos últimos anos para avaliar o controlo da asma e o cumprimento das orientações do GINA. Fatores modificáveis e não modificáveis (idade, sexo, comorbidades, aspetos psicológicos e determinantes socioeconómicos) têm sido estudados e identificados como associados ao baixo nível de controlo da doença.

Objetivos: Neste estudo avaliamos a adesão às orientações para a gestão da doença asmática e para o nível de controlo da doença, segundo a perspetiva do indivíduo, em Portugal. Foram investigados também, nos adultos, os determinantes associados ao não controlo da asma.

Métodos: O *Asthma Insights and Reality in Portugal* (AIR-P) é um estudo transversal realizado a nível nacional (entre março de 2011 e março de 2012), com adaptação da metodologia utilizada no *Asthma Insights and Reality in Europe* (AIRE). Uma amostra probabilística de indivíduos com asma ''ativa'' foi identificada através de contato telefónico com número aleatório fixo ou móvel. O questionário aplicado avaliou as seguintes dimensões gerais: características sociodemográficas; controlo da asma e limitações relacionadas com a doença; a utilização de cuidados de saúde relacionados com a asma; terapêuticas e adesão; e conhecimentos e crenças em relação à asma. A avaliação de controlo foi efetuada com base nas recomendações do Global Initiative for Asthma (GINA). Adicionalmente, nos adultos foi avaliado o controlo sintomatológico baseado no GINA, o controlo auto percecionado e o nível do controlo através do Asthma Control Test™ (ACT).

Resultados: Num total de 5242 contactos de agregados familiares elegíveis foram identificados 557 indivíduos com asma ''ativa''. 400 indivíduos (327 adultos e 73 crianças) identificados completaram o questionário para avaliação da doença asmática. 18,3% da população estudada eram crianças (<16 anos). O cumprimento dos critérios GINA avaliados verificou-se em 3,5% (95% CI: 2-6%) dos indivíduos inquiridos. A presença de sintomas de asma, nas últimas quatro semanas, foi reportado por 54,7% dos adultos. A presença de sintomas diurnos e noturnos esteve presente em 36,7% e 32,7% dos adultos, respetivamente. Nas crianças, a presença de sintomas de asma, nas últimas quatro semanas, foi de 41,1%. 70% dos indivíduos referiu a ocorrência de, pelo menos, um episódio de exacerbação no período de 12 meses e 32,3% recorreu à utilização de medicação de alívio mais de duas vezes por semana nas últimas quatro semanas. 29,7% dos adultos e 24,7% das crianças necessitaram de recorrer ao serviço de urgência por causa da asma nos 12 meses prévios. O principal objetivo referido nas recomendações que não foi cumprido foi a ocorrência de limitações nas atividades da vida diária causadas pela asma (78,8%). 30,3% dos adultos e 38,4% das crianças reportaram nunca ter realizado um teste de função respiratória e 82,8% dos inquiridos referiram nunca ter utilizado um debitómetro. Verificaram-se sobreposições dos critérios GINA não cumpridos, com 63,6% dos indivíduos inquiridos a reportarem três ou mais critérios. 93,9% dos adultos consideraram que a sua asma se encontrava completamente, bem, ou mais ou menos controlada, não correspondendo à avaliação pelo questionário ACT do nível de controlo. Dos 327 adultos, 18% apresentaram asma não controlada, 47,7% parcialmente não controlada e 34,3% totalmente controlada segundo a avaliação do controlo sintomatológico do GINA. 35,2% dos indivíduos apresentou asma não controlada, 64,8% parcialmente controlada e nenhum individuo registou pontuação total que corresponde a asma completamente controlada pelo questionário ACT. Dos indivíduos avaliados com asma não controlada pelo ACT 39,2% percecionaram a sua doença como bem ou completamente controlada. Na análise univariada os determinantes registados como significativamente associados a asma não controlada foram: a idade (OR 1,02 por ano de idade; IC 95%: 1,01-1,03), o sexo feminino (OR 1,87; IC 95%: 1,15-3,04), nível de escolaridade (OR 0,5; IC 95%: 0,28-0,89 se nível secundário ou superior), ocupação (OR 4,92; IC 95%: 2,12-11,42 à procura do primeiro emprego ou desempregado) (OR 2,51; CI 95%: 1,35-4,65 na reforma), rendimento (OR 0,23; 95% IC: 0,07-0,72 se > 619 euros), índice de massa corporal (IMC) (OR 1,09 por unidade de IMC; IC 95%: 1,03-1,14), ter sintomas de rinite (OR 4,40; IC 95%: 2,56-7,58), e a utilização de corticoides inalados (OR 0,44; IC 95%: 0,24-0,82 se utilizou no passado corticosteroides inalados ou nunca utilizou). Os determinantes que permanecem com significado estatístico associados a um não controlo da doença asmática, após o ajuste

multivariado foram: estar à procura do primeiro emprego ou ser desempregado, o IMC e a presença de sintomas compatíveis com rinite. Indivíduos obesos apresentaram um risco atribuível populacional associado ao não controlo da asma de 23,5%. Registou-se uma elevada frequência na presença de sintomas nasais na população adulta estudada, sendo que o risco atribuível populacional associado à presença de sintomas de rinite foi de 65,9%.

Conclusões: O estado do controlo da asma em Portugal (2011-2012) está ainda distante dos objetivos estipulados pelas *guidelines* do GINA. Observou-se uma sobrestimação do controlo da asma segundo a perceção do próprio individuo. Educação para a asma, com o objetivo de melhorar a perceção dos pacientes face à doença e o tratamento, deverá ser promovida. Indivíduos asmáticos devem estar ativamente envolvidos na gestão da sua doença e ter expetativas adequadas sobre o que pode ser obtido com o tratamento relativamente aos sintomas e à qualidade de vida. Juntamente com programas direcionados a médicos para otimizar a monitorização sistemática da patologia, a implementação de planos escritos para a asma e uma melhor integração dos cuidados nos diferentes níveis do sistema de saúde podem trazer benefícios nos cuidados prestados aos doentes asmáticos.

Verificou-se que o nível de asma não controlada estava associado a vários determinantes: idade, sexo, nível de escolaridade, ocupação, rendimento, IMC, sintomas de rinite e a utilização de corticosteroides inalados. O reconhecimento e a identificação de fatores que podem interferir no nível de controlo da doença asmática poderá auxiliar os prestadores de cuidados de saúde a reconhecer indivíduos mais suscetíveis a um menor nível de controlo e otimizar sua prevenção e vigilância. Do ponto de vista da saúde pública e do planeamento em saúde, estratégias de intervenção direcionadas aos fatores modificáveis podem igualmente trazer benefícios para os cuidados associados aos doentes asmáticos. Para projetos de investigação futuros outros fatores como doença pulmonar obstrutiva crónica, doença do refluxo gastroesofágico e aspetos psicológicos deverão ser inquiridos e estudados. Igualmente será importante padronizar uma ferramenta para avaliação do controlo da asma que possa ser transversal à prática clínica e à aplicação ao nível dos estudos epidemiológicos.

Palavras-chave: asma; controlo; não controlo; determinantes

List of Abbreviations and Acronyms

ACQ : Asthma Control Questionnaire

ACT : Asthma Control Test

AIR : Asthma Insights and Reality

AIRE : Asthma Insights and Reality in Europe

AIR-P : Asthma Insights and Reality in Portugal

BMI : body mass index

CARAT : Control of Allergic Rhinitis and Asthma Test

CATI : computer assisted telephone interviewing

CI : confidence interval

COPD : Chronic Obstructive Pulmonary Disease

DALYs : Disability-Adjusted Life Years

DGS : Direção-Geral da Saúde

ECRHS : European Community Respiratory Health Survey

FEV_1 : Forced expiratory volume in 1 second

FVC : Forced vital capacity

GERD : gastroesophageal reflux disease

GINA : Global Initiative for Asthma

OECD : Organisation for Economic Co-operation and Development

OR : odds ratio

SPAN : Search Partition Analysis

PAR% : population attributable risk percentage

List of Tables

List of Figures

Index

Chapter I – General Introduction

The word "asthma", originated from Greek, at the beginning only meant being with shortness of breath (1). The term was mentioned as medical word for the first time by Hippocrates and his school in *Corpus Hippocraticum* (460-360 B.C.) (2). It is by the end of the 19th century that is described by Henry Hyde Salter as: "paroxysmal dyspnea of peculiar character, with intervals of healthy breathing between the attacks" (3).

Throughout the years, the concept of asthma was updated and changed: initially the pathology was centered on symptomatology, by the year of 1960 the concept of bronchial hyperreactivity was introduced, later the contribution of the inflammatory process was emphasized and most recently the awareness of remodeling of the airways has been considered (4).

Nowadays, it is known that asthma is a disease that could manifest in different extensions and requires a complex approach, not only regarding treatment options but also considering other factors that could imply the disease manifestation and progression (5).

It has been estimated that asthma prevalence ranges between 1 and 18% in the worldwide population (6). Asthma is a public health problem with the presence of high levels of underdiagnosed and undertreated patients worldwide, creating a substantial burden in healthcare costs and results in 1% of the total global burden of disease (6).

It has been a challenge to the international organizations, such as Global Initiative for Asthma (GINA), to implement guidelines that fit in the different health care systems from all countries around the world. In order to ensure the best care, it is important to understand the specific needs from the populations and implement more adjusted health programs.

Regarding this issue, the present dissertation is inserted in the project entitled: "*Asthma Insights and Reality in Portugal (AIR-P)*", a study developed and based on the methodology from Asthma Insights and Reality in Europe (AIRE) (7), the first multinational study evaluating the degree of asthma control from GINA recommendations.

My role in this project started by answering the research team aims of reporting the findings of asthma control in Portugal, similar to the original study from Rabe et al (7). In addition, I aimed to examine modifiable and non-modifiable factors that could interfere with the level of asthma control. The database used in this thesis was already collected by AIR-P and the interviews were not conducted in the context of this work. In methods a description of the survey methodology is detailed.

I was responsible for the formulation and development of the research question, the respective literature search and review, the data analysis strategy and execution, presentation and discussion of the results and writing of the thesis in a format for publication.

The structure of the dissertation is divided in four main parts: in a first chapter, the theme is introduced; in the second and third chapters the main research is presented, in article format (two articles), with introduction, methodology, results, discussion and conclusions; finally, in the last part I present the final conclusions, future perspectives and final considerations.

The article format was chosen because we intend to submit each of the two chapters for publication. This format leads to some duplication in each chapter especially in introductions and in methods sections.

Chapter II - Article 1 "Prevalence and patterns of uncontrolled asthma in Portugal: a national population-based study"

Introduction

Asthma is a chronic disease defined by the occurrence of respiratory symptoms (wheeze, chest tightness, shortness of breath, and cough) which can oscillate over time and intensity, along with the presence of variable expiratory flow limitation (1). It is a heterogeneous disease commonly characterized by chronic inflammation of the airways (1). Asthma affects millions of people of all ages and ethnicities in all parts of the world (2). The estimated prevalence is around 315 million people worldwide (3) and it is responsible for about 250.000 deaths annually (2). In Portugal, a prevalence of 6.8% was estimated (4).

Despite the existence of treatment guidelines, countless individuals with asthma stay undertreated and remain at risk of exacerbations (5). Consequently, there is an increase of work and school absences, increase in the use of health care services and a decline in overall life quality (5). Due to asthma, more than 23 million Disability-Adjusted Life Years (DALYs) worldwide are lost annually (6).

Asthma represents a significant burden not only in terms of quality of life, but also in terms of health costs (7). These include direct costs, treatments and hospitalizations, as well as indirect costs, due to work absences and premature death (2).

The Global Initiative for Asthma (GINA) was created to improve the quality of asthma patient's care (1). According to GINA guidelines, the goals for long-term asthma management are to achieve symptom control, maintain normal activity levels, minimize exacerbations, minimize the risk of persistent airflow limitation and minimize adverse effects from asthma treatments (1).

Asthma control represents a main goal for the management of the disease (1). The Asthma Insights and Reality (AIR) studies were conducted in several countries throughout the last years in order to assess variations in management and asthma control from the patient's perspective, and evaluate the fulfilment of GINA goals.

This study intended to evaluate the accomplishment of GINA goals and the disease control level from individual's perspective in the Portuguese asthmatic population.

Methods

A cross-sectional study at national level (Portugal), was carried out from March 2011 to March 2012, based on the methodology applied in the Asthma Insights and Reality in Europe (AIRE) study (8). The AIRE was the first multinational study, involving Western European countries, to evaluate the degree of asthma control from the perspective of the patient and to analyse the degree of compliance with the GINA recommendations.

Selection of subjects and telephone interviews

A probabilistic sample of individuals diagnosed with asthma was identified through telephone numbers and a structured telephone interview was applied. The households were selected by random generation of the telephone number, which assured the chance of selecting listed and unlisted numbers, included landline (using proportionally stratification by district residents) and mobile phone numbers.

In order to select only individuals with "active asthma" as participants in the study, it was asked to an adult in each household the following questions: *"Did ever a physician diagnose any family member in your home as having asthma?"*. Participants were included as having active asthma if they answered positively at least to one of the following questions: *"Do any of those individuals diagnosed with asthma take any medication for their asthma?"* and "*Did any of those individuals diagnosed with asthma have any asthma crises or asthma symptoms in the last year*?"". If more than one household member with asthma was qualified, a respondent was randomly selected for interview. If the individual selected as the respondent was less than 16 years old, the interview was conducted with an adult who was well-informed about the child's pathology and treatments (a parent or an educational guardian).

The interview was performed by trained interviewers and data was entered directly into a computer assisted telephone interviewing (CATI) software program, which allows real-time input and verification.

Questionnaire

The questionnaire used was based on the AIRE (8) study. The structured interviews to asthmatic patients addressed the following dimensions: socio-demographic characteristics; asthma control and limitations; use of asthma related health care; asthma medications use and adherence; asthma knowledge and beliefs.

Asthma control assessment

Asthma control was evaluated based on GINA guidelines recommendations for symptom control. Characterization of activities limitations and unfavourable outcomes were investigated (acute episodes, asthma exacerbations related visits and pulmonary function assessment).

Additionally in adult individuals control was evaluated through individual self-perception of control and with the Asthma Control Test™ (ACT). ACT consists in 5 questions concerning the impact of asthma on a daily basis, in relation to shortness of breath, use of rescue medication, nocturnal asthma symptoms and self-evaluation of asthma control (5). ACT scores equal or below 19 points were considered "uncontrolled" and scores of at least 20 points were classified as "controlled" (5).

Ethical approval and consent

Authorization from the Ethics Committee of the Lisbon Faculty of Medicine and permission from the Portuguese Protection Data Authority were obtained. All participants were made aware of the voluntary nature and the confidentiality of the study and expressed their oral informed consent to be part of the study.

Statistical Analysis

Descriptive statistics were described as absolute frequency and proportion for categorical variables and continuous variables were represented as mean (standard deviation) for normally distributed variables and as median (interquartile range) for non-normally distributed variables. The scaled rectangle diagram was produced in the Search Partition Analysis (SPAN) software (9) with approximation to proportional frequencies of the co-occurrence criteria.

Cohen's kappa test was used to determine the level of agreement between control evaluations.

For all tests performed, the level of statistical significance was set at 0.05. All analyses were conducted using SPSS version 23 (IBM Corp., Armonk, N.Y., USA).

Results

Sample population

From a total of 5242 eligible households, 557 individuals were identified as having active asthma and 400 full interviews were completed. 18.3% of the study population were children and they were represented by proxy. A detailed description of participant's sociodemographic and asthma related variables is presented in table 1.1.

TABLE 1.1. Characteristics of participants		
	Adults (n=327)	Children (n=73)
Age, median (IQR)	44 (27-58)	11 (8-14)
Female, n (%)	203 (62.1)	27 (37)
Age at diagnosis of asthma, median (IQR)	15 (5-36)	3 (2-6)
Duration of asthma in years, median (IQR)	20 (10-30)	6 (3-9)
Smoking Habits	n=315	
Non-smoker, n (%)	199 (63.2)	ND
Current Smoker, n (%)	49 (15.6)	ND
Former smokers, n (%)	67 (21.3)	ND
Weight	n=310	n=66
Normal weight, n (%)	138 (44.5)	35 (53)
Underweight, n (%)	10 (3.2)	0
Overweight, n (%)	115 (37.1)	15 (22.7)
Obese, n (%)	47 (15.2)	16 (24.2)

IQR: interquartile range; ND: not determined; BMI: Body mass index

Underweight: BMI (kg/m^2) <18.5 in adults and <5th percentile in children; Overweight: 25.0≥ BMI (kg/m^2) <30.0 in adults and ≥85th percentile in children; Obesity: BMI (kg/m^2) ≥30.0 in adults and ≥95th percentile in children

Asthma Control

The frequency of asthma control items, based on GINA recommendations, is presented in table 1.2.

TABLE 1.2. GINA criteria for asthma control in the study population			
Control Assessment	Items	Adults (n=327) n % (95% CI)	Children (n=73) n % (95% CI)
Asthma Symptoms	Presence of Asthma Symptoms (past 4 weeks)	179 54.7% (49-60%)	30 41.1% (31-53%)
	During day (> twice a week)	120 36.7% (32-42%)	15 20.5% (13-31%)
	Night wakening	107 32.7% (28-38%)	14 19.2% (12-30%)
	During exercise/physical effort	89 27.2% (23-32%)	16 21.9% (14-33%)
Acute Episodes	Sudden severe episodes of coughing, wheezing, chest tightness or shortness of breath (past 12 months)	229 70% (65-75%)	51 69.9% (59-79%)
Need of relief medication	Use of quick relief medications > twice a week (past 4 weeks)	107 32.7% (30-40%)	22 30.1% (21-41%)
Visits for acute exacerbations of asthma	Asthma related emergency (past 12 months)	112 34.3% (29-40%)	27 37% (27-48%)
	Emergency department visit	97 29.7% (25-35%)	18 24.7% (16-36%)
	Hospitalization	9	1

TABLE 1.2. GINA criteria for asthma control in the study population		Adults (n=327) n % (95% CI)	Children (n=73) n % (95% CI)
Control Assessment	Items		
	Unscheduled care visit	2.8% (1-5%)	1.4% (0.0-7%)
		46	15
		14.1% (12-18%)	20.5% (13-31%)
Limitations on activities	Limitations caused by asthma	264	51
		80.7% (76-85%)	69.9% (59-79%)
	day to day activities	150	13
		45.9% (41-51%)	17.8% (11-28%)
	sports and recreation	159	28
		48.6% (43-54%)	38.4% (28-50%)
	choice of jobs/career (adults)	48	ND
		14.7% (11-19%)	
	social activities	47	3
		14.4% (11-19%)	4.1% (1-11%)
	sleeping	160	27
		48.9% (44-54%)	37% (27-48%)
	lifestyle	113	19
		34.6% (30-40%)	26% (17-37%)
	housekeeping chores (adults)	127	ND
		38.8% (34-44%)	
	school/work absence (past 12 months)	42	25
		12.8% (10-17%)	34.2% (24-46%)
Lung function evaluation	Pulmonary function assessment	83	27
		25.4% (21-30%)	37% (27-48%)
	Never had a lung function test	99	28
		30.3% (26-35%)	38.4% (28-50%)
	Never used a peak flowmeter	264	67
		80.7% (76-85%)	91.8% (83-96%)

ND: not determined
CI: Confidence Interval

The fulfilment of the total GINA criteria evaluated in table 1.2 for asthma control was accomplished in 14 individuals, 3.5% (95% CI: 2-6%) of the sample.

In adult individuals the presence of asthma symptoms was reported by 54.7% with 36.7% having daytime symptoms more than twice a week in the previous four weeks and 32.7% nocturnal sleep disturbance. 70% of the adults reported asthma acute exacerbation by the occurrence of sudden coughing, wheezing, chest tightness or shortness of breath.

The presence of asthma symptoms, in the past four weeks, in children was 41.1% and the occurrence of acute exacerbation in the past twelve months 69.9%.

A total of 29.7% adults and 24.7% of children needed at least one emergency department visit because of an acute episode of asthma during the past twelve months and 2.5% of all individuals required hospitalization. Also, 14.1% of adults and 20.5% of children required an unscheduled urgent care visit due to asthma during the last year.

A high level of limitations caused by asthma were reported (78.8%) specially related to sleep and sports activities. The percentage of absences from work for adults and school for children at least one day in the previous year were 12.8% and 34.2% respectively.

Despite one of the management goals of GINA is to accomplish a normal or near normal lung function, 30.3% of adults and 38.4% of children reported never having performed a lung function test. Moreover 82.8% of the inquired people reported never having used a peak flow meter.

Relief medication (e.g., β2-agonists) used more than twice a week for the past four weeks was frequent (32.3%). Also concerning therapeutics only 20.3% of the participants were taking inhaled corticosteroids for their asthma, and only 28.8% confirmed having a written asthma action plan.

The co-occurrence of non-controlled asthma GINA criteria is represented in Figure 1.1 The percentage of individuals failed 3, 4 or 5 criteria was 23.3%, 26.5% and 11.8% respectively. 2% of the total failed in all 6 criteria evaluated. In this study, limitations caused by asthma disease was the most frequent criteria reported as failure (78.8%).
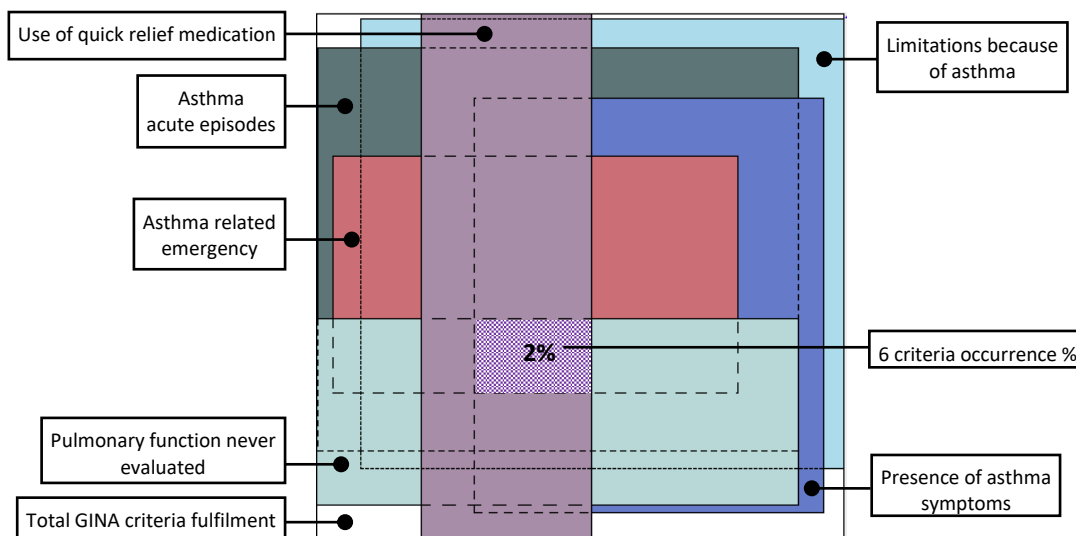

Fig 1.1. Co-occurrence of non-controlled asthma GINA criteria

Table 1.3. Asthma control assessment in adults	
ACT score	
Controlled (ACT 20-25), n (%)	212 (64.8)
Non-controlled (ACT ≤19), n (%)	115 (35.2)
Patient perceived control	
Completely controlled, n (%)	84 (25.7)
Well controlled, n (%)	145 (44.3)
Somewhat controlled, n (%)	78 (23.9)
Poorly controlled, n (%)	18 (5.5)
Not controlled at all, n (%)	2 (0.6)

A total of 307 (93.9%) of asthmatic adults perceived their asthma as being completely, well or somewhat controlled (table 1.3). However, the level of control assessed by a measure with a quantitative tool (ACT) reveals only a slight agreement with the self-perception of control evaluation K=0.20 (95% CI: 0.06-0.33) (table 1.4).

Table 1.4. Agreement between self-perception and ACT evaluation of asthma control in adults (n = 327)		ACT asthma control evaluation [b]		
		Controlled	Uncontrolled	
Perception of asthma control [a]	Controlled	211	96	K=0.20 p<0.001
	Uncontrolled	1	19	

[a] Self-perception of control

[b] Asthma Control Test™

Discussion

AIRE study, which included Western European countries, revealed that GINA's goals have only been accomplished in 5.3% of the studied population (8). In Portugal, our study revealed even lower results, with only 3.5% of the questioned population meeting all evaluated GINA criteria. The degree of overlap in Figure 1.1 shows that there are many subjects with multiple asthma non controlled GINA criteria, with more than half of the individuals (63.6%) having three or more criteria.

In the AIR studies, daytime symptoms in the past four week was reported by 56% of the subjects in Western Europe and by 74% in Central and Eastern Europe (10). The European Community Respiratory Health Survey (ECRHS), a large survey assessing asthma disease, reported in adult patients 24-52% night wakening's because of their asthma in the last twelve months (11). In the AIRE study, asthma acute episodes were reported on 57.2% of the adults and 51.5% of the children (8). These results are consistent with the findings from our study where more than half

of the individuals identified the presence of chronic symptoms (52.1%), and the occurrence of an acute episode (70%) suggesting that, despite the availability of effective asthma therapeutics, there is still a high prevalence of symptoms in asthmatic patients.

Our study revealed a high use of emergency health services with all the patients with asthma related emergency (34.8%) reporting also acute episode occurrence. Emergency department visits (29.7% in adults and 24.7% in children) were even higher than AIRE study results (11% in adults and 18% in children) (8), indicating that asthma in Portugal should be considered a high burden for the health care system, particularly for the emergency health departments. According to the Organisation for Economic Co-operation and Development (OECD), Portugal has a high proportion of emergency department utilization (above the proportion in European Union countries) mainly related to the unavailability of urgent primary care services (12). Higher cooperation between the different levels of health care system, decrease in waiting times and reduction in geographical inequalities in accesses to health care services can contribute to a better access of asthmatic patients to the primary health care level, avoiding the excessive use of emergency departments.

Regular objective measurement of lung function is recommended as follow-up for asthma, since patients and physicians have some difficulties in assessing disease symptoms severity (13-14). Insufficient monitoring with lung function tests or with peak flow meter has been verified. Nevertheless, the results of lung function assessing in our study, with 31.8% of the subjects never performing a lung function test, were not too low compared with the findings from AIRE study where 45% of adults and 60.5% of children reported having never performed a lung function test (8).

Taking quick rescue medications for symptoms relief more than twice per week is a sign of uncontrolled asthma. Although the high use of quick relief bronchodilators in our study (32.3%) comparing with the use of inhaled corticosteroids (20.3%) was half of the values stated in other Western European countries studied in which around two thirds of the individuals reported the use of quick-relief medication in the past month (8).

These findings can be explained by the improvement regarding the management of chronic diseases, such as asthma, that have been occurring in Portugal. According to the report of Health at a Glance by OECD (12), with results previous to 2013, Portugal is the second country following Italy, with fewer avoidable admissions for chronic respiratory ambulatory care (asthma and chronic obstructive pulmonary disease).

Results showed that 15.0% of adult asthmatic patients were current smokers and 20.5% ex-smokers, similar to the findings from another national study (15), but lower when compared with AIRE (8) and other similar studies (10). Regardless, knowing the importance of smoking cessation on management of asthma, all asthmatic patients should be reminded at each medical appointment about the negative effects of smoking and encouraged to stop.

Poor compliance with asthma prescribed treatments, associated with inadequate attitudes and beliefs, has been documented as contributing to suboptimal asthma management (16-17). Most of the inquired individuals (74.6%) believe that even with appropriate treatment, asthma usually causes some limitations in quality of life and 44.9% of the inquired admitted not taking medication according to physician orientations in the absence of symptoms. Ferreira et al. (18) found, in a sample of asthmatic patients that came to a follow-up visit, an association between weak therapeutic compliance and uncontrolled asthma (OR 19.5, 95% CI: 4.03 – 94.75).

A correct approach on expectations on what can be achieved with asthma treatment should be appropriately explained by physicians and an effective self-management of the disease should be promoted by health care providers. Self-management of asthma with actions such as the implementation of written asthma action plans can successfully reduce asthma related emergency visits (1).

Besides the high level of daily life limitations reported in this study there was an overestimation of asthma control through patient perception. This is in agreement with previous national studies (19-20) and investigations conducted in other parts of the world (Western European countries (8), Asia-Pacific region (21), Turkey (22), Maghreb (23), Gulf and the Near East (24), Latin American (25)). Sastre et al. (26) found in a multinational survey (Canada and Europe) that 81% of the 2003 patients inquired considered their asthma to be well or completely controlled, contrasting with only 18% controlled patients according to GINA criteria.

Asthma symptoms should be objectively analysed by the physicians routinely, since there is a tendency for asthmatic patients to poorly perceive and underestimate their symptoms, accepting lifestyle limitations as inevitable consequence of the disease (27), which can also contribute for a delay on acquiring health care assistance in these patients (28).

Strengths and limitations

A strength of this study was the identification of active asthmatic patients from general population without referral bias. It was also important to be able to use several asthma control

criteria, allowing better understanding of the effect of the criteria and comparability with other studies.

However, there are some limitations of this study that should be considered: 1) it is a cross-sectional study and cause-effect relationships cannot be established; 2) all the data was reported by respondents and could not be clinically confirmed; 3) only patients with active asthma were questioned, excluding undiagnosed and patients without medication and without the presence of symptoms in the last year who usually have mild degree of disease; 4) this study did not inquire for comorbidities, such as, other respiratory disease (e.g., Chronic Obstructive Pulmonary Disease), obstructive sleep apnea, gastroesophageal reflux disease, or psychological aspects), which have been associated with asthma control (29).

Conclusions

This study, as a source for understanding the state of asthma control management in Portugal (2011-2012), concluded that there is still a major gap between long-term goals of asthma management, according GINA guidelines, and clinical outcomes. Despite the level of asthma control in adults and children remained far from the main goals, Portugal showed encouraging outcomes specially regarding lung function assessing and in the use of quick relief medication.

Asthma education in order to improve patients' knowledge of the disease and treatment should be enhanced. Patients must be actively involved in managing their disease and have appropriate expectations about what can be achieved from treatment related to symptoms and quality of life. Together with programs directed to physicians to ensure systematic monitoring of these patients, implementation of written asthma action plans, and a better integration of the health system levels may bring benefits to the care of these patients.

Funding

References

1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2019. Available from: www.ginasthma.org

2. Bousquet J, Khaltaev N. Global surveillance, prevention and control of Chronic Respiratory Diseases. A comprehensive approach. Global Alliance against Chronic Respiratory Diseases. World Health Organization. ISBN 978 92 4 156346 8. 2007.

3. To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Public Health. 2012*;12(1):204.

4. Sá-Sousa A, Morais-Almeida M, Azevedo L, Carvalho R, Jacinto T, Todo-Bom A, et al. Prevalence of asthma in Portugal - The Portuguese National Asthma Survey. *Clin Transl Allergy*. 2012;2.1(1):15.

5. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the Asthma Control Test: A survey for assessing asthma control. *J Allergy Clin Immunol.* 2004;113(1):59–65.

6. The Global Asthma Report 2018. Auckland, New Zealand: Global Asthma Network, 2018

7. Nunes C, Pereira AM, Morais-Almeida M. Asthma costs and social impact. *Asthma Res Pract.* 2017;3(1):1.

8. Rabe KF, Vermeire PA, Soriano JB, Maier WC. Clinical management of asthma in 1999: The Asthma Insights and Reality in Europe (AIRE) study. *Eur Respir J.* 2000;16(5):802–7.

9. Marshall RJ. Displaying clinical data relationships using scaled rectangle diagrams. *Stat Med*. 2001;20(7):1077–88.

10. Rabe KF, Adachi M, Lai CKW, Soriano JB, Vermeire PA, Weiss KB, et al. Worldwide severity and control of asthma in children and adults: The global asthma insights and reality surveys. *J Allergy Clin Immunol*. 2004;114(1):40–7.

11. Janson C, Chinn S, Jarvis D, Burney P. Physician-diagnosed asthma and drug utilization in the European Community Respiratory Health Survey. *Eur Respir J*. 1997;10(8):1795–802.

12. OECD/EU (2016). Health at a Glance: Europe 2016 - State of Health in the EU Cycle. OECD Publishing, Paris.

13. Boulet L-P, Phillips R, O'Byrne P, Becker A. Evaluation of asthma control by physicians and patients: Comparison with current guidelines. *Can Respir J*. 2002;9(6):417–23.

14. Cowie RL, Underwood MF, Field SK. Asthma symptoms do not predict spirometry. *Can Respir J*. 2007;14(6):339–42.

15. Pereira AM, Morais-Almeida M, Sá e Sousa A, Jacinto T, Azevedo LF, Robalo Cordeiro C, et al. Prevalência da exposição ao fumo ambiental do tabaco em casa e do tabagismo na população Portuguesa - o estudo INAsma. *Rev Port Pneumol*. 2013;19(3):114–24.

16. Schmier JK, Leidy NK. The complexity of treatment adherence in adults with asthma: Challenges and opportunities. *J Asthma*. 1998;35(6):455–72.

17. Reid D, Abramson M, Raven J, Walters HE. Management and treatment perceptions among young adults with asthma in Melbourne: The Australian experience from the European Community Respiratory Health Survey. *Respirology*. 2000;5(3):281–7.

18. Ferreira MB, Alves RR, Santos AS, Carlos GP, Pedro E, Pregal AL, et al. Controlo da asma em consulta de Imunoalergologia. *Rev Port Imunoalergologia*. 2008;16(1):29–56.

19. Sá-Sousa A, Amaral R, Morais-Almeida M, Araújo L, Azevedo LF, Bugalho-Almeida A, et al. Asthma control in the Portuguese National Asthma Survey. *Rev Port Pneumol*. 2015;21(4):209–13.

20. Mendes Z, Madeira A, Costa S, Inácio S, Vaz M, Araújo AT, et al. Avaliação do controlo da asma através do Asthma Control Test TM aplicado em farmácias portuguesas. *Rev Port Imunoalergologia*. 2010;18(4):313–30.

21. Lai CKW, De Guia TS, Kim YY, Kuo SH, Mukhopadhyay A, Soriano JB, et al. Asthma control in the Asia-Pacific region: The asthma insights and reality in Asia-Pacific study. *J Allergy Clin Immunol*. 2003;111(2):263–8.

22. Sekerel BE, Gemicioglu B, Soriano JB. Asthma insights and reality in Turkey (AIRET) study. *Respir Med*. 2006;100(10):1850–4.

23. Bourdin A, Doble A, Godard P. The Asthma Insights and Reality in the Maghreb (AIRMAG) study: perspectives and lessons. *Respir Med*. 2009;103(SUPPL. 2).

24. Al-Busaidi N, Soriano JB. Asthma control in Oman: National results within the asthma insights and reality in the Gulf and the near East (AIRGNE) study. *Sultan Qaboos Univ Med J*. 2011;11(1):45–51.

25. Neffen H, Fritscher C, Schacht FC, Levy G, Chiarella P, Soriano JB, et al. Asthma control in Latin America: the Asthma Insights and Reality in Latin America (AIRLA) survey. *Rev Panam Salud Pública*. 2005;17(3):191–7.

26. Sastre J, Fabbri LM, Price D, Wahn HU, Bousquet J, Fish JE, et al. Insights, attitudes, and perceptions about asthma and its treatment: A multinational survey of patients from Europe and Canada. *World Allergy Organ J*. 2016;9(1).

27. Bellamy D, Harris T. Poor perceptions and expectations of asthma control: Results of the International Control of Asthma Symptoms (ICAS) survey of patients and general practitioners. *Prim Care Respir J*. 2005;14(5):252–8.

28. Banzett RB, Dempsey JA, O'Donnell DE, Wamboldt MZ, Kiley JP. Symptom perception and respiratory sensation in asthma. *Am J Respir Crit Care Med*. 2000;162(3 I):1178–82.

29. Boulet LP. Influence of comorbid conditions on asthma. *Eur Respir J*. 2009;33(4):897–906.

Chapter III- Article 2 "Determinants associated with uncontrolled asthma in Portugal: a national population-based study"

Introduction

Asthma is a chronic and heterogeneous disease (1) that affects people from all ages and ethnicities worldwide (2). It is estimated a global prevalence of 315 million people with asthma (3), contributing with more than 23 million of Disability-Adjusted Life Years (DALYs) (4) and asthma is also responsible for around 250.000 deaths annually (2).

Despite the existence of treatment guidelines, many individuals with asthma remain undertreated and uncontrolled, resulting in a significant burden, not only in terms of quality of life, but also in terms of health costs (2). Health cost associated with asthma could be direct costs, like treatments and hospitalizations, as well as indirect costs, due to work absences and premature death (2). In 2010, the yearly cost per an asthmatic adult patient in Europe, according to estimation from Accordini et al. (5), ranged from 509€ for a controlled asthma patient to 2281€ for uncontrolled asthma patient.

The Global Initiative for Asthma (GINA) was created in 1993 with the objective to disseminate accurate information about asthma and improve the quality of asthma patient's care worldwide (1). Presently, according to GINA guidelines achieving and maintaining asthma control represents one of the main goals for the management of the disease and consists in the evaluation of the control of symptoms and future risk of unfavourable outcomes (1).

Numerous factors such as age, gender (6), comorbidities (6-7), psychological aspects (8) and socioeconomic determinants (9) have been studied and reported as associated with asthma control. Behavioural reasons such as smoking habits (6) or therapeutics compliance also have been related to poor asthma control level (10).

A multiway and a complex causal relationship between health, education level, work and income has been reported (11). Having a chronic disease can be considered a risk factor for employment (11). In Portugal, 66294 of potential productive life years were lost due to non-communicable diseases (cardiovascular disease, diabetes, cancer and respiratory diseases) in 2013, according Organisation for Economic Co-operation and Development (OECD) (11).

The Portuguese National Asthma Survey reported a proportion of 43.1% uncontrolled disease in asthmatic Portuguese population (12). Non-modifiable factors such as age and gender were

associated with uncontrolled asthma, in a national population study (13). Other factors such as self-evaluation of uncontrolled asthma, participation on decisions related to treatment or the presence of comorbidities have been considered as important contributors for asthma control (13).

The purpose of this study was to investigate the distribution of asthma control level in Portuguese adult population, using different approaches of control level evaluation, and to examine the determinants associated with uncontrolled asthma.

Methods

Study design

A cross-sectional study at national level (Portugal) was carried out from March 2011 to March 2012, based on the methodology applied in the Asthma Insights and Reality in Europe (AIRE) (14).

A probabilistic sample of individuals diagnosed with "active asthma" was identified through telephone numbers and a structured telephone interview was applied. In order to select exclusively individuals with active asthma, it was asked to an adult in each household the following question: *"Did ever a physician diagnose any family member in your home as having asthma?"*. Participants were included as having active asthma if they answered positively at least to one of the following questions: *"Do any of those individuals diagnosed with asthma take any medication for their asthma?"* and "*Did any of those individuals diagnosed with asthma have any asthma crises or asthma symptoms in the last year?"*. If more than one household member with asthma was qualified, a respondent was randomly selected for interview.

A total of 557 individuals were identified with active asthma and 327 complete interviews were acquired in adults (≥16 years old).

Control assessment

Asthma control was evaluated in three ways: GINA based symptom control, by Asthma Control Test™ (ACT) and individual self-perception of control assessment.

The asthma symptom control, based on GINA, included four questions, regarding the past four weeks, about the frequency of daytime symptoms, night waking, relief medication needs and activity limitations due to asthma.

ACT is a quantitative self-assessment tool for asthma control, which consists in 5 simple questions that asks the interviewee to consider during the last four weeks the impact of asthma on a daily basis, in relation to shortness of breath, use of rescue medication, nocturnal asthma symptoms and self-evaluation of asthma control (15). According to *Thomas* et al. (16) ACT scores equal or below 19 are considered suitable to identify patients with poorly controlled asthma such as defined by GINA. The ACT was also used for the evaluation of determinants associated with poor asthma control. ACT score equal or below 19 points corresponded to "uncontrolled" asthma and scores of at least 20 points were classified as "controlled" (20-24 ="partially controlled; 25 ="totally controlled").

From the main questionnaire of the study, several determinants for the analysis were selected according to their relevance and consulted bibliography: age, sex, civil status, region of residence, educational level, occupation, household income, body mass index (BMI), smoking habits, rhinitis symptoms, allergies as a trigger for crises, having family doctor, assistant physician to solve asthma problems, seasonal flu vaccination, Peak Flow Meter use, conducting lung function tests, training to use the inhaler properly, written asthma action plan, forgetting to take medication, inhaled corticosteroid use and number of medications used for asthma.

Statistical Analysis

Descriptive statistics were described as absolute frequency and proportion for categorical variables and continuous variables were represented as mean (standard deviation) for normally distributed variables and as median (interquartile range) for non-normally distributed variables.

The age differences between sex was evaluated by the Mann Whitney U Test.

For additional analyses two groups of active asthma respondents were considered: controlled (ACT score≥20) and uncontrolled (ACT score≤19).

To examine the relationship between uncontrolled asthma and its determinants, an indicator of uncontrolled asthma was used as a dependent variable. The determinants were classified into the following domains, grouping conceptually related variables: demographic, socioeconomic, risk and clinical factors, clinical care and treatment. Univariate logistic regression analysis was done for all determinants. In a public health perspective and in order to measure the contribution of each determinant to the level of asthma control, the population attributable risk percentage (PAR%) was assessed, using the following formula:

$$PAR\% = [Pe \times (OR-1) / [(1 + Pe \times (OR-1)]]*100$$

(Pe = estimate of population exposure)

with OR as the inverse risk (1/OR) in the case of a protective factor (odds ratio lower than 1).

Sequential multivariable regression was performed. Variables with p<0.30 in the univariate analysis were used to build the adjusted models (Forward Likelihood Ratio method). Multivariable adjustments were performed in sequence considering variables addition concerning the different domains, where variables from a given domain were adjusted to the multivariable model, as noted in the table. Pseudo r-squared (Cox and Nagelkerke) from the originated models were calculated.

For all tests performed, the level of statistical significance was set at 0.05. All analyses were conducted using SPSS version 23 (IBM Corp., Armonk, N.Y., USA).

Results

General characteristics

A total of 327 full interviews were completed in adults with active asthma. A detailed description of the demographic and asthma related variables is summarized in table 2.1. Further socioeconomic, risk and clinical factors, as well as clinical care and treatment characteristics are described below.

TABLE 2.1. Respondent characteristics	
Age, median (IQR)	44 (27-58)
Female, n (%)	203 (62.1)
Age at diagnosis of asthma, median (IQR)	15 (5-36)
Duration of asthma in years, median (IQR)	20 (10-30)
Smoking Habits n=315	
Non-smoker, n (%)	199 (63.2)
Current Smoker, n (%)	49 (15.6)
Former smokers, n (%)	67 (21.3)
Weight n=310	
Normal weight, n (%)	138 (44.5)
Underweight, n (%)	10 (3.2)
Overweight, n (%)	115 (37.1)
Obese, n (%)	47 (15.2)

IQR: interquartile range;

BMI: Body mass index; Underweight: BMI (kg/m2) <18.5; Overweight: 25.0≥ BMI (kg/m2) <30.0; Obesity: BMI (kg/m2) ≥30.0

In the sampled population, 62.1% were female and 37.9% male. In female the median age was 46 (29-58) and in male 37.5 (26-56), without statistic significant differences. An elevated

percentage of inquired individuals was overweight or obese (52.3%) and 36.9% were ever smokers.

Asthma Control

Frequency of self-reported symptoms (in the last four weeks) is discriminated in figure 2.1.
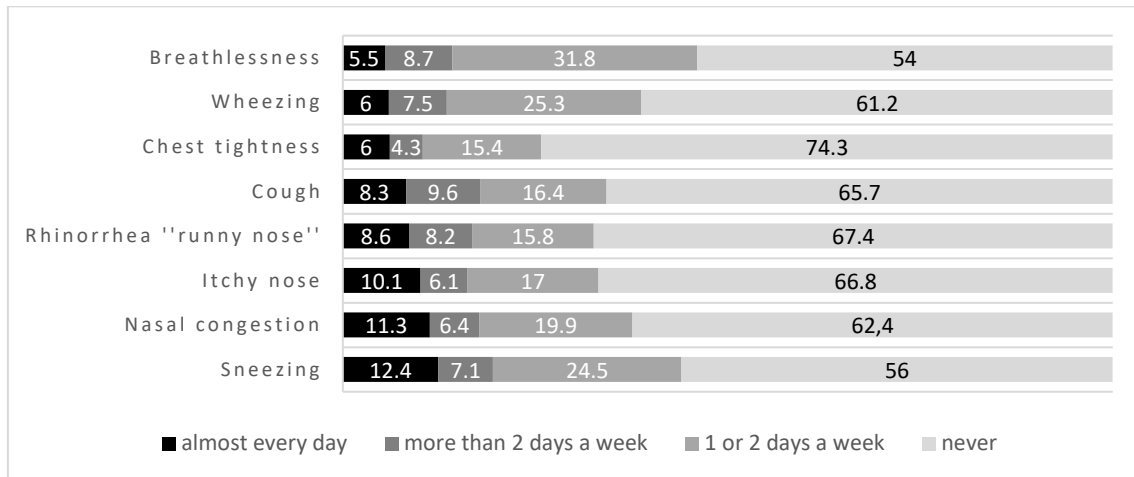
Figure 2.1. Frequency of self-reported symptoms (in the last four weeks), as cumulative percentages

Concerning GINA based symptoms control assessment, among 327 adult individuals inquired, 18% had uncontrolled, 47.7% partially controlled and 34.3% had totally controlled. Based on ACT test, 35.2% of the subjects had uncontrolled asthma, 64.8% partially controlled and none of the individuals had total control. 93.9% of the individuals perceived their asthma as completely, well or somewhat controlled and only 6.1% perceived their asthma poorly or not controlled at all (table 2.2).

Table 2.2. Asthma control assessment	
GINA based symptom control	
Controlled, n (%)	112 (34.3)
Partly controlled, n (%)	156 (47.7)
Uncontrolled, n (%)	59 (18.0)
ACT score	
Controlled asthma (ACT =25), n (%)	0
Partially controlled (ACT 20-24), n (%)	212 (64.8)
Non-controlled asthma (ACT ≤19), n (%)	115 (35.2)

Table 2.2. Asthma control assessment	
Patient perceived control	
Completely controlled, n (%)	84 (25.7)
Well controlled, n (%)	145 (44.3)
Somewhat controlled, n (%)	78 (23.9)
Poorly controlled, n (%)	18 (5.5)
Not controlled at all, n (%)	2 (0.6)

Concerning the agreement between ACT asthma control score and the participants self-perception, about 39.2% of individuals with uncontrolled asthma evaluated by ACT self-reported their asthma as completely or well controlled and only 16.5% have a self-perception that goes in concordance with objective assessment of asthma control.

Determinants for uncontrolled asthma

We, then, sought to understand which factors were associated with poor asthma control. In a univariate analysis, the factors significantly associated with poor asthma control scores (ACT score ≤ 19) were: age, female sex, educational level (<high school level), occupation (looking for a first job, being unemployed or being retired), income (<619 euros), higher BMI (obesity), having rhinitis symptoms and using inhaled corticosteroids. In contrast, civil status, region of residence, smoking habits, allergies as a trigger for the crisis, having family doctor, the assistance physician used to solve asthma problems, seasonal flu vaccine taking, peak flow meter use, lung function tests performance, training to use the inhaler properly, written asthma action plan, forgetting to take medication and number of medications used for asthma were not statistically significant determinants in the univariate analysis (table 2.3). The PAR% for the significant variables are also in table 2.3. In order to understand the relationship of significant variables in the univariate analysis a sequential multivariable adjustment analysis was performed by adding sequentially dimensions of factors (table 2.4). Occupation, BMI and having rhinitis symptoms were the factors that stayed with statistically significant results besides the sequential adjustments.

TABLE 2.3. Univariate analysis for uncontrolled asthma and Population attributable risk %					
Determinants		**N (%)**	**Uncontrolled asthma n (%)**	**Risk for uncontrolled asthma (ACT score ≤ 19)**		**Population attributable risk %**
				Crude Odds Ratio (95% CI)	**p value**	
Demographic						
Age, classes	16-25	67 (20.5%)	17 (14.8%)	ref		
	26-45	105 (32.1%)	34 (29.6%)	1.41 (0.71-2.80)	0.327	-
	46-65	109 (33.3%)	42 (36.5%)	1.84 (0.94-3.61)	0.074	-
	> 65	46 (14.1%)	22 (19.1%)	**2.70 (1.21-5.99)**	**0.015**	19.3%
Age, years		44 (27-58)[a]	47.69 (18.7)[b]	**1.02 (1.01-1.03)**	**0.005**	-
Sex	Male	124 (37.9%)	33 (28.7%)	ref	**0.012**	
	Female	203 (62.1%)	82 (71.3%)	**1.87 (1.15-3.04)**		35.1%
Civil Status	Single	106 (33%)	34 (29.8%)	ref		
	Married or Cohabited	174 (54.2%)	62 (54.4%)	1.17 (0.70-1.96)	0.543	-
	Divorced, separated or Widow (er)	41 (12.8%)	18 (15.8%)	1.66 (0.79-3.47)	0.181	-
Region of residence	Lisboa e Vale do Tejo	106 (33.3%)	38 (34.5%)	ref		
	Alentejo e Algarve	32 (10.1%)	9 (8.2%)	0.70 (0.29-1.67)	0.42	-
	Centro	63 (19.8%)	17 (15.5%)	0.66 (0.33-1.31)	0.236	-
	Açores	12 (3.8%)	4 (3.6%)	0.90 (0.25-3.17)	0.863	-
	Madeira	10 (3.1%)	6 (5.5%)	2.68 (0.71-10.11)	0.144	-
	Norte	95 (29.9%)	36 (32.7%)	1.09 (0.62-1.94)	0.764	-
Socioeconomic						
Educational level	3rd cycle of basic education or less	132 (42%)	63 (56.3%)	ref		
	High school	80 (25.5%)	25 (22.3%)	**0.50 (0.28-0.89)**	**0.019**	20.3%
	Post-secondary education or more	102 (32.5%)	24 (21.4%)	**0.34 (0.19-0.60)**	**<0.001**	38.7%
Occupation	employed	158 (51%)	44 (40%)	ref		
	student	54 (17.4%)	13 (11.8%)	0.82 (0.4-1.68)	0.59	-
	domestic	10 (3.2%)	5 (4.5%)	2.59 (0.72-9.39)	0.147	-
	looking for a first job or unemployed	29 (9.4%)	19 (17.3%)	**4.92 (2.12-11.42)**	**<0.001**	26.8%
	retired	59 (19%)	29 (26.4%)	**2.51 (1.35-4.65)**	**0.004**	22.3%

TABLE 2.3. Univariate analysis for uncontrolled asthma and Population attributable risk %					
Determinants		**N (%)**	**Uncontrolled asthma n (%)**	**Risk for uncontrolled asthma (ACT score ≤ 19)**		**Population attributable risk %**
				Crude Odds Ratio (95% CI)	**p value**	
Income	<340 Euros	16 (7%)	11 (12.6%)	**ref**		
	340-618 Euros	46 (20.1%)	26 (29.9%)	0.59 (0.18-1.98)	0.393	-
	619-1531 Euros	92 (40.2%)	31 (35.6%)	**0.23 (0.07-0.72)**	**0.012**	57.4%
	1532-3522 Euros	59 (25.8%)	17 (19.5%)	**0.18 (0.06-0.61)**	**0.006**	54%
	>3523 Euros	16 (7%)	2 (2.3%)	**0.07 (0.01-0.40)**	**0.003**	48.1%
Risk and clinical factors						
Body Mass Index (BMI)	Normal weight	138 (44.5%)	40 (37.4%)	**ref**		
	Underweight BMI (kg/m2) <18.50	10 (3.2%)	3 (2.8%)	1.05 (0.26-4.27)	0.946	-
	Overweight BMI (kg/m2) ≥25.0 and <30.0	115 (37.1%)	38 (35.5%)	1.21 (0.71-2.06)	0.487	-
	Obese BMI (kg/m2) ≥30.0	47 (15.2%)	26 (24.3%)	**3.03 (1.53-6.00)**	**0.001**	23.5%
Body Mass Index (BMI), kg/m^2		25.2 (22.1-28.3)[a]	26.3 (23.5-29.7)[a]	**1.09 (1.03-1.14)**	**0.001**	-
Smoking habits	current smoker	49 (15.6%)	18 (15.9%)	**ref**		
	former smokers	67 (21.3%)	19 (16.8%)	0.68 (0.31-1.50)	0.34	-
	non-smoker	199 (63.2%)	76 (67.3%)	1.06 (0.56-2.03)	0.851	-
Having rhinitis symptoms	no	118 (43.2%)	25 (22.9%)	**ref**	**<0.001**	
	at least 1 or 2 days a week	155 (56.8%)	84 (77.1%)	**4.40 (2.56-7.58)**		65.9%
Allergies as a trigger for the crisis	no	72 (22%)	29 (25.2%)	**ref**		
	yes	255 (78%)	86 (74.8%)	0.76 (0.44-1.29)	0.305	-
Clinical care						
Family doctor	having	262 (81.6%)	97 (85.1%)	**ref**	0.236	
	not having	59 (18.4%)	17 (14.9%)	0.69 (0.37-1.28)		-
Assistant physician to solve asthma problems	Family doctor/General clinic	151 (46.5%)	54 (47.8%)	**ref**		
	Pneumologist	48 (14.8%)	18 (15.9%)	1.08 (0.55-2.11)	0.827	-
	Allergologist	78 (24%)	21 (18.6%)	0.66 (0.36-1.21)	0.178	-
	Emergency Care	32 (9.8%)	15 (13.3%)	1.59 (0.73-3.42)	0.241	-
	other	16 (4.9%)	5 (4.4%)	0.82 (0.27-2.47)	0.72	-

Determinants		N (%)	Uncontrolled asthma n (%)	Risk for uncontrolled asthma (ACT score ≤ 19)		Population attributable risk %
				Crude Odds Ratio (95% CI)	p value	
Taking the seasonal flu vaccine	yes	130 (40.6%)	53 (46.1%)	ref	0.137	
	no	190 (59.4%)	62 (53.9%)	0.70 (0.44-1.12)		-
Use the Peak Flow Meter	never	264 (88.6%)	96 (91.4%)	ref	0.259	
	at least once a month or at doctor appointment/when have symptoms	34 (11.4%)	9 (8.6%)	0.63 (0.28-1.41)		-
Perform lung function tests (past 12 months)	at least every six months or at all doctor appointment	105 (43.8%)	36 (40.9%)	ref		
	only once	116 (48.3%)	46 (52.3%)	1.26 (0.73-2.18)	0.410	-
	never	19 (7.9%)	6 (6.8%)	0.89 (0.31-2.52)	0.819	-
Have training to use the inhaler properly	yes	253 (79.8%)	90 (81.1%)	ref	0.679	
	no	64 (20.2%)	21 (18.9%)	0.88 (0.49-1.58)		-
Patients having a written asthma action plan	yes	77 (24.9%)	23 (21.3%)	ref	0.281	
	no	232 (75.1%)	85 (78.7%)	1.36 (0.78-2.37)		-
Treatment						
Forgetting to take medication	yes	52 (33.3%)	19 (26.8%)	ref	0.113	
	no	104 (66.7%)	52 (73.2%)	1.74 (0.88-3.44)		-
Under inhaled corticosteroid	using	63 (31%)	31 (42.5%)	ref	**0.009**	
	used in the past or never used	140 (69%)	42 (57.5%)	**0.44 (0.24-0.82)**		46.7%
Number of asthma medication	none or one medication	162 (49.5%)	49 (42.6%)	ref	0.065	
	two or more medications	165 (50.5%)	66 (57.4%)	1.54 (0.97-2.43)		-

TABLE 2.3. Univariate analysis for uncontrolled asthma and Population attributable risk %

Data shown in this table exclude missing values and answers ''do not know/do not respond''

CI: Confidence Interval

[a] median (interquartile range)

[b] mean (standard deviation)

TABLE 2.4. Multivariable analysis for uncontrolled asthma with sequential dimensions adjustments							
Determinants		**Adjusted to A**		**Adjusted to A+B**		**Adjusted to A+B+C**	
		Adjusted OR (95% IC)	*p value*	**adjusted OR (95% IC)**	*p value*	**adjusted OR (95% IC)**	*p value*
Demographic (A)							
Age		**1.02 (1.00-1.03)**	**0.01**	/		/	
Sex	Male	Ref		/		/	
	Female	**1.77 (1.08-2.90)**	**0.023**				
Socioeconomic (B)							
Educational level	3rd cycle of basic education or less	Ref					
	High school	0.61 (0.31-1.22)	0.16	0.67 (0.33-1.34)	0.255	/	
	Post-secondary education or more	**0.38 (0.21-0.72)**	**0.003**	**0.47 (0.24-0.90)**	**0.023**		
Occupation	employed	Ref					
	student	0.92 (0.41-2.06)	0.831			0.75 (0.32-1.74)	0.498
	domestic	1.98 (0.51-7.61)	0.322	ND		5.09 (0.54-47.96)	0.155
	looking for a first job or unemployed	**4.55 (1.95-10.63)**	**<0.001**			**6.05 (2.21-16.57)**	**<0.001**
	retired	2.11 (0.90-4.93)	0.084			1.71 (0.79-3.69)	0.171
Income	<340 Euros	Ref					
	340-618 Euros	0.78 (0.23-2.68)	0.692	0.73 (0.19-2.90)	0.66	/	
	619-1531 Euros	0.35 (0.11-1.15)	0.084	0.36 (0.09-1.40)	0.14		
	1532-3522 Euros	**0.27 (0.08-0.93)**	**0.038**	0.32 (0.08-1.31)	0.112		
	>3523	**0.13 (0.02-0.87)**	**0.035**	**0.12 (0.02-0.88)**	**0.037**		
Risk and clinical factors (C)							
Body Mass Index (BMI)		**1.07 (1.02-1.13)**	**0.008**	**1.07 (1.01-1.13)**	**0.017**	**1.09 (1.02-1.16)**	**0.012**
Having rhinitis symptoms	no	Ref					
	at least 1 or 2 days a week	**4.63 (2.64-8.11)**	**<0.001**	**4.49 (2.49-8.10)**	**<0.001**	**4.71 (2.52-8.81)**	**<0.001**

TABLE 2.4. Multivariable analysis for sequential dimensions adjustments		Adjusted to A		Adjusted to A+B		Adjusted to A+B+C	
Determinants		**Adjusted OR (95% IC)**	*p value*	**adjusted OR (95% IC)**	*p value*	**adjusted OR (95% IC)**	*p value*
Treatment (E)							
Under inhaled corticosteroid	using	Ref				/	
	used in the past or never used	**0.48 (0.25-0.89)**	**0.02**	**0.49 (0.26-0.94)**	**0.032**		

CI: Confidence Interval

ND: not determinate because A+B adjustment is occupation

/: not represented because p values >0.05

A: Age and Sex; R^2 Cox=0.040 and Nagelkerke=0.055

A+B: Occupation; R^2 Cox=0.074 and Nagelkerke 0.101

A+B+C: Occupation, IMC and Having rhinitis symptoms; R^2 Cox = 0.201 and Nagelkerke = 0.272

The following adjusted models A+B+C+D and A+B+C+D+E didn't add any of the determinants considered in Clinical Care or Treatment and are not represented in this table

Individuals with more than 65 years had 2.70 (95% CI: 1.21-5.99) times higher odds for having uncontrolled asthma compared with the youngest group analysed (16-25 years) and PAR% value of 19.3%. It appears that there is a progressive increase as each year of age the chance of uncontrolled asthma increases 2%. Being female increases the odds of uncontrolled asthma by 1.87 (95% CI: 1.15-3.04). However socioeconomic determinants (occupation) seems to attenuate these associations.

Regarding socioeconomic determinants: the increase in education level decreases the odds of having uncontrolled asthma (OR 0.5 high school level or more); higher income decreases the odds of uncontrolled asthma; in concerning occupation subjects looking for a first job or unemployed had a 4.92 higher odds for uncontrolled asthma scores (95% CI: 2.12-11.42) and being retired is associated with a 2.51 odds (95% CI: 1.35-4.65) for uncontrolled asthma, when compared with employed asthmatics. The protective role of educational level and income seems to be mediated by risk and clinical factors (BMI and having rhinitis symptoms). Participants looking for a first job or been unemployed had PAR% value of 26.8% and were much like to have uncontrolled asthma regardless the various adjusted dimensions.

For each kg/m^2 increment of BMI the chance of uncontrolled asthma increased 9%, this association remained significant even with the considered dimensions adjustments. PAR% of uncontrolled asthma associated with obesity was 23.5%.

Nasal symptoms were the symptoms identified as occurring almost every day in the past four weeks (fig. 2.1). Having rhinitis symptoms increases the odds of uncontrolled asthma in 4.4 (95% CI: 2.56-7.58). These associations remained significant regardless the adjustments considered. The PAR% of uncontrolled asthma associated with rhinitis symptoms was 65.9%.

Clinical factors, as smoking habits and having allergies as a trigger for asthma crisis, were not significantly associated with uncontrolled asthma. Also, in this analysis, the determinants related to clinical care did not demonstrate significant associations. Concerning treatment determinants evaluated (forgetting to take medication, the number of medications used for asthma and the use of inhaled corticosteroids) individuals not using inhaled corticosteroids had a significant lower odds for uncontrolled asthma (OR 0.44 95% CI: 0.24-0.82), but it seems that the effect is mediated by the risk factors and the clinical aspects considered (BMI and having rhinitis symptoms).

Discussion

This study revealed that 64.8% subjects had their asthma controlled, according to the evaluation of a questionnaire for asthma control purpose, the ACT. And 35.2% of the inquired had uncontrolled asthma.

The Portuguese National Asthma Survey using Control of Allergic Rhinitis and Asthma Test (CARAT) for assessment of asthma control, reported 43.1% of uncontrolled asthma in Portuguese population (12). In 2007, a study in a central hospital in Lisbon using the ACT questionnaire to assess asthma control in the context of allergology consultation found that 23.3% of the respondents presented ACT values ≤19 (10). These results reveal lower levels of uncontrolled asthma compared to our study but that can be explained by the sample studied which corresponds to patients followed up in a specialty consultation.

Another study carried out at Portuguese pharmacies, with the application of the same questionnaire to evaluate the control, revealed higher scores for poor asthma control (61.2%) compared to our study (17).

Most of the adult patients interviewed overestimate their disease control revealing a discrepancy between patient perception of asthma control and the objective measurement, since 93.9% of the individuals perceived their asthma with some level of control. It has been described that most of these patients can tolerate their symptoms and lifestyle limitations as inevitable consequence of the disease (18). The self-perception and expectations regarding asthma disease may result in misinterpretations of control level (18).

In this study it was possible to observe that the level of control assessed can differ from the chosen asthma control tool utilized. In our study the control level was obtained by GINA based symptom control and ACT questionnaire. There are different methodologies used in epidemiological studies for collecting data regarding asthma control level such as in clinical practice for control assessment [e.g., GINA based symptom control tool (1); CARAT (19); Asthma Control Questionnaire (ACQ) (20); ACT (15)] which can make it more difficult to compare results between studies.

Regarding the studied determinants, at demographic factors, our results indicate that uncontrolled asthma was more associated with older age and with female sex. So far, age has been considered an important determinant for asthma control. Kämpe et al. (21) stated that

uncontrolled asthma was more common in older groups (≥65years); Mendes et al. (17), using a Portuguese population, found that 69% of elderly (>70 years) had uncontrolled asthma.

Asthma disease among elderly population is a special concern since most of patients are polypathological and polymedicated, which can have a negative impact on disease management (22). Besides, more difficulties on the execution of proper inhaler techniques is commonly present (22-23).

Our results observing the association between sex and poor asthma control, are in agreement with other studies (17,21,24), with female been associated with poor scores in asthma control. Usually women perceive asthma differently from men, reporting higher levels of symptoms and more limitations on day-to-day life (25-26). Also, women have been associated with higher incidence of later asthma onset and a higher prevalence of non-allergic asthma phenotype, favouring a less effective response to corticosteroid treatments (1,27-28). Temprano et al. (29) in a number of short-term and long-term measures of control demonstrated that women had poor asthma control compared with men.

In this study, socioeconomic determinants, especially occupation reveal a considerable association with poor control score of asthma as well as greater influence on other important determinants. The PAR% for being looking for a first job or being unemployed was 26.8%, suggesting a very significant contribution for poor asthma control. Moreover studies identified that the severity of asthma (30), the frequency of asthma symptoms and night awakenings because of asthma can contribute to work disability and unemployment (31).

The inverse association between income (32) and education (21) with poor controlled asthma outcomes has been documented. The PAR% register for having at least post-secondary education was 38.7% suggesting a contribution for preventing worse levels of control in asthma. The same positive contribution was verified for higher levels of income.

Asthma expenses related to medical treatments are usually high, which can be a significant burden for low-income families (33-34), and in turn can compromise treatment adherence. In the way of reducing the burden of asthma in lower socioeconomic strata, implementation of higher co-participation on asthma treatments and in ambulatory care assistance can be beneficial for the clinical outcomes in these subjects.

Individuals with higher levels of education can have a better understanding of the prescribed therapeutics and may have more tendency in adhering to treatment regime (21). Furthermore,

there are work environments associated with trigger agents exposure (e.g., diisocyanates, acrylates or cleaning agents) (35) of which individuals with higher education levels are less likely to be exposed (21).

Higher BMI revealed being associated with uncontrolled level in asthma, as have been stated before: Lessard et al. (36) found that regardless similar perception of symptoms, obese individuals had poorer asthma control than nonobese asthmatics; Lavoie et al. (37) on 382 adults study found that patients with higher BMI had poor asthma control (scored higher in ACQuestionnaire) independent of their age, sex and asthma severity; with an odds ratio of 2.99 (95% CI 1.14-7.08) Ferreira et al (10) reported that obesity is a factor associated with a non-control of asthma.

Obesity has a negative impact on overall breathing mechanisms, decreasing chest wall compliance and increasing the work of breathing (38). This comorbidity has been reported not only as a risk factor for the development of asthma but also for increasing the severity, the risk of exacerbations and hospitalizations (39). The pro-inflammatory that characterizes obesity with excessive production of inflammatory cytokines can induce more difficulties in asthma control, secondary to a reduction in the response to corticosteroids (40).

In this way, nutritional education promoting a diet modification and weight loss in obese asthmatic patients must be implemented, in order to improve the general health status and achievement of better asthma control scores (41). According to our results a considerable number of individuals (PAR%=23.5%) with uncontrolled asthma could be spare if obesity was not present.

Findings from studies (10,42-44) conclude that rhinitis is an important contributor to a non-optimal asthma control level, as also was supported by our results. Bousquet et al. (45) in a multivariate analysis found that patients with simultaneous asthma and allergic rhinitis are associated with higher levels of acute exacerbations (OR 1.35, 95% CI: 1.03-1.77) with more emergency visits (OR 2.35, 95% CI: 1.12-4.80).

Consequently, in asthmatic patients it is important to evaluate the upper airways and the lower airways in patients with rhinitis, but most important it is necessary to optimize the treatment of both diseases in patients with a concomitant diagnosis (46). Since the PAR% register for having rhinitis symptoms in our study (65.9%) suggests that controlling nasal symptoms could contribute positively in preventing worse levels of control in asthma disease.

The presence of smoking habits was not observed to be a determinant associated with a poor asthma control in our study, as otherwise has been stated (24,47). In this regard, other studies also did not identify smoking as an independent risk factor for uncontrolled asthma (10) or for decline in lung function in asthmatic patients (48) which could be related to a healthy smoker effect (49), underestimating the effect of tobacco at pulmonary level.

It was not also found an association with determinants of poor asthma control that have been reported in other studies, such as patients having a written asthma action plan (50) and therapeutic compliance (10). Besides a higher number of individuals have reported allergies as a trigger for asthma crises (78%), it was not detected a significant association with uncontrolled asthma, similar to what was been reported by other investigations (10,47).

Lung function assessment with peak flow meter or lung function tests were not significant determinants for asthma control in our study. However minimizing airflow limitation is one of the main goals for these patients and has been stated the importance of these exams on diagnosis and follow-up of asthma (1): peak flow measurement is considered beneficial, particularly in patients with severe asthma on detecting variations that can suggest the increased risk of exacerbations (1,51); Forced Expiratory Volume in 1 second (FEV_1) measurement has been reported to be related to the future risk of exacerbations (52-53); self-reported indicators of disease control, in a 500 individuals study, did not show direct relationships with lung function values ($FEV_1\%$ or FEV_1/Forced vital capacity (FVC) ratio), revealing the difficulty for patients to accurately assess disease symptoms severity (54). In this way, lung function evaluations can be important in recognizing objectively lung function status and can be a beneficial contribute for the clinical management of the disease (1).

The use of inhaled corticosteroid plays an important role in asthma treatment plan (1). Though Rabe et al. (14) reported that the use of inhaled corticosteroids was low even in patients with severe persistent symptoms. In our study, the use of these medications was associated with lower ACT scores, which represents worse control outcomes. This association with the level of control could be explained by the relation of treatment plan with disease severity. For example, patients with mild asthma degree and well controlled symptoms could only be at step 1 of treatment plan and only be doing a reliever inhaler as needed, as was defined before 2019 GINA guidelines (1).

Strength and limitations

There are some limitations of this study that should be considered: 1) it is a cross-sectional study and cause-effect relationships cannot be established; 2) all the data was reported by respondents and could not be clinically confirmed; 3) only patients with active asthma were questioned, excluding undiagnosed individuals, patients without the presence of symptoms and without medication in the last year who usually have mild degree of disease; 4) this study did not inquire for comorbidities, such as other respiratory disease [(eg., Chronic Obstructive Pulmonary Disease (COPD)], obstructive sleep apnea, gastroesophageal reflux disease (GERD), or psychological aspects, which have been associated to asthma control (55); 5) the degree of asthma severity, according to GINA guidelines, was not assessed.

A strength of this study was the identification of active asthmatic patients from the general population without referral bias. It was also important to evaluate different methods to access data from the level of asthma control and the analysis of multiple factors and dimensions that could have influence the level of control of this important chronic disease.

Conclusions

In this study uncontrolled asthma was associated with several factors: age, sex, educational level, occupation, income, BMI, having rhinitis symptoms and use of inhaled corticosteroids as part of treatment plan. Some of these factors remain associated after full adjustment, notably occupation, BMI and having rhinitis symptoms, which are important modifiable factors.

The recognition and identification of factors that may interfere with asthma control can help physicians to recognize patients that are more susceptible to a lower level of control and optimize their surveillance.

The values of PAR% for unemployment, obesity and rhinitis symptoms were relatively high (respectively 26.8%, 23.5% and 65.9%). Since these are modifiable factors from the point of view of public health and health planning, intervention strategies more directed to these concerns can promote benefits for asthmatic patients and consequently for other health problems. Similarly, their identification by physicians could contribute to a better therapeutic asthma approach.

In future research longitudinal studies should be made to confirm these associations and other comorbidities, such as COPD or GERD and physiological factors should also be inquired. It is also important to standardize a tool for asthma control evaluation that can be used in epidemiological studies and that can promote reliable comparison between studies.

Funding

References

1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2019. Available from: www.ginasthma.org.

2. Bousquet J, Khaltaev N. Global surveillance, prevention and control of Chronic Respiratory Diseases. A comprehensive approach. Global Alliance against Chronic Respiratory Diseases. World Health Organization. ISBN 978 92 4 156346 8. 2007.

3. To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Public Health*. 2012;12(1):204.

4. The Global Asthma Report 2018. Auckland, New Zealand: Global Asthma Network, 2018.

5. Accordini S, Corsico AG, Braggion M, Gerbase MW, Gislason D, Gulsvik A, et al. The Cost of Persistent Asthma in Europe: An International Population-Based Study in Adults. Int *Arch Allergy Immunol*. 2013;160(1):93–101.

6. Braido F, Brusselle G, Guastalla D, Ingrassia E, Nicolini G, Price D, et al. Determinants and impact of suboptimal asthma control in Europe: The INTERNATIONAL CROSS-SECTIONAL AND LONGITUDINAL ASSESSMENT ON ASTHMA CONTROL (LIAISON) study. *Respir Res.* 2016;17(1):51.

7. Hekking PPW, Amelink M, Wener RR, Bouvy ML, Bel EH. Comorbidities in Difficult-to-Control Asthma. *J Allergy Clin Immunol Pract*. 2017.

8. Baiardini I, Sicuro F, Balbi F, Canonica GW, Braido F. Psychological aspects in asthma: do psychological factors affect asthma management? *Asthma Res Pract*. 2015;1(1):7.

9. Azeez IA, Ladipo MMA, Ige OM. Assessment of Socioeconomic Status and Control Of Asthma In Adults. *Ann Ibadan Postgrad Med*. 2016;14(2):85–91.

10. Ferreira MB, Alves RR, Santos AS, Carlos GP, Pedro E, Pregal AL, et al. Controlo da asma em consulta de Imunoalergologia. *Rev Port Imunoalergologia*. 2008;16(1):29–56.

11. OECD/EU (2016). Health at a Glance: Europe 2016 - State of Health in the EU Cycle. OECD Publishing, Paris.

12. Sá-Sousa A, Amaral R, Morais-Almeida M, Araújo L, Azevedo LF, Bugalho-Almeida A, et al. Asthma control in the Portuguese National Asthma Survey. *Rev Port Pneumol*. 2015;21(4):209–13.

13. Sousa H. Socioeconomic and Clinical determinants of asthma control in the Portuguese Asthma Survey [master's thesis]. Faculdade de Medicina da Universidade do Porto; 2014.

14. Rabe KF, Vermeire PA, Soriano JB, Maier WC. Clinical management of asthma in 1999: The Asthma Insights and Reality in Europe (AIRE) study. *Eur Respir J*. 2000;16(5):802–7.

15. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the Asthma Control Test: A survey for assessing asthma control. *J Allergy Clin Immunol*. 2004;113(1):59–65.

16. Thomas M, Kay S, Pike J, Williams A, Carranza Rosenzweig JR, Hillyer E V., et al. The Asthma Control Test (ACT) as a predictor of GINA guideline-defined asthma control: Analysis of a multinational cross-sectional survey. *Prim Care Respir J*. 2009;18(1):41–9.

17. Mendes Z, Madeira A, Costa S, Inácio S, Vaz M, Araújo AT, et al. Avaliação do controlo da asma através do Asthma Control Test TM aplicado em farmácias portuguesas. *Rev Port Imunoalergologia*. 2010;18(4):313–30.

18. Fletcher M, Hiles D. Continuing discrepancy between patient perception of asthma control and real-world symptoms: A quantitative online survey of 1,083 adults with asthma from the UK. *Prim Care Respir J*. 2013;22(4):431–8.

19. Fonseca JA, Nogueira-Silva L, Morais-Almeida M, Azevedo L, Sa-Sousa A, Branco-Ferreira M, et al. Validation of a questionnaire (CARAT10) to assess rhinitis and asthma in patients with asthma. *Allergy Eur J Allergy Clin Immunol*. 2010;65(8):1042–8.

20. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J*. 1999;14(4):902–7.

21. Kämpe M, Lisspers K, Ställberg B, Sundh J, Montgomery S, Janson C. Determinants of uncontrolled asthma in a Swedish asthma population: cross-sectional observational study. *Eur Clin Respir J*. 2014;1:1–9.

22. Melani AS. Management of asthma in the elderly patient. *Clin Interv Aging*. 2013;8:913–22.

23. Melani AS, Bonavia M, Cilenti V, Cinti C, Lodi M, Martucci P, et al. Inhaler mishandling remains common in real life and is associated with reduced disease control. *Respir Med*. 2011;105(6):930–8.

24. Laforest L, Van Ganse E, Devouassoux G, Bousquet J, Chretin S, Bauguil G, et al. Influence of patients' characteristics and disease management on asthma control. *J Allergy Clin Immunol*. 2006;117(6):1404–10.

25. Zillmer LR, Gazzotti MR, Nascimento OA, Montealegre F, Fish J, Jardim JR. Gender differences in the perception of asthma and respiratory symptoms in a population sample of asthma patients in four Brazilian cities. *J Bras Pneumol*. 2014;40(6):591–8.

26. Zein JG, Erzurum SC. Asthma is Different in Women. *Curr Allergy Asthma Rep*. 2015;15(6).

27. Van Den Berge M, Heijink HI, Van Oosterhout AJM, Postma DS. The role of female sex hormones in the development and severity of allergic and non-allergic asthma. *Clin Exp Allergy*. 2009;39(10):1477–81.

28. Sundberg R, Torén K, Franklin KA, Gislason T, Omenaas E, Svanes C, et al. Asthma in men and women: Treatment adherence, anxiety, and quality of sleep. *Respir Med*. 2010;104(3):337–44.

29. Temprano J, Mannino DM. The effect of sex on asthma control from the National Asthma Survey. *J Allergy Clin Immunol*. 2009;123(4):854–60.

30. Eisner MD, Yelin EH, Katz PP, Lactao G, Iribarren C, Blanc PD. Risk factors for work disability in severe adult asthma. *Am J Med*. 2006;119(10):884–91.

31. Taponen S, Lehtimäki L, Karvala K, Luukkonen R, Uitti J. Correlates of employment status in individuals with asthma: A cross-sectional survey. *J Occup Med Toxicol*. 2017;12(1).

32. Pavord ID, Mathieson N, Scowcroft A, Pedersini R, Isherwood G, Price D. The impact of poor asthma control among asthma patients treated with inhaled corticosteroids plus long-acting β 2-agonists in the United Kingdom: A cross-sectional analysis. *npj Prim Care Respir Med*. 2017;27(1).

33. Franco R, Nascimento HF, Cruz AA, Santos AC, Souza-Machado C, Ponte E V., et al. The economic impact of severe asthma to low-income families. *Allergy Eur J Allergy Clin Immunol*. 2009;64(3):478–83.

34. Nunes C, Pereira AM, Morais-Almeida M. Asthma costs and social impact. *Asthma Res Pract*. 2017;3(1):1.

35. Lillienberg L, Andersson E, Janson C, Dahlman-Höglund A, Forsberg B, Holm M, et al. Occupational exposure and new-onset asthma in a population-based study in northern Europe (RHINE). *Ann Occup Hyg*. 2013;57(4):482–92.

36. Lessard A, Turcotte H, Cormier Y, Boulet LP. Obesity and asthma: A specific phenotype? *Chest*. 2008;134(2):317–23.

37. Lavoie KL, Bacon SL, Labrecque M, Cartier A, Ditto B. Higher BMI is associated with worse asthma control and quality of life but not asthma severity. *Respir Med*. 2006;100(4):648–57.

38. Salome CM, King GG, Berend N. Physiology of obesity and effects on lung function. *J Appl Physiol*. 2010;108(1):206–11.

39. Peters U, Dixon AE, Forno E. Obesity and asthma. *J Allergy Clin Immunol*. 2018;141(4):1169–79.

40. Sutherland ER, Goleva E, Strand M, Beuther DA, Leung DYM. Body mass and glucocorticoid response in asthma. *Am J Respir Crit Care Med*. 2008;178(7):682–7.

41. Çelebi Sözener Z, Aydın Ö, Mungan D, Mısırlıgil Z. Obesity-asthma phenotype: Effect of weight gain on asthma control in adults. *Allergy Asthma Proc*. 2016;37(4):311–7.

42. Lin J, Su N, Liu G, Yin K, Zhou X, Shen H, et al. The impact of concomitant allergic rhinitis on asthma control: a cross-sectional nationwide survey in China. *J Asthma*. 2014;51(1):34–43.

43. Vandenplas O, Dramaix M, Joos G, Louis R, Michils A, Verleden G, et al. The impact of concomitant rhinitis on asthma-related quality of life and asthma control. *Allergy Eur J Allergy Clin Immunol*. 2010;65(10):1290–7.

44. Ohta K, Bousquet PJ, Aizawa H, Akiyama K, Adachi M, Ichinose M, et al. Prevalence and impact of rhinitis in asthma. SACRA, a cross-sectional nation-wide study in Japan. *Allergy Eur J Allergy Clin Immunol*. 2011;66(10):1287–95.

45. Bousquet J, Gaugris S, Kocevar VS, Zhang Q, Yin DD, Polos PG, et al. Increased risk of asthma attacks and emergency visits among asthma patients with allergic rhinitis: A subgroup analysis of the improving asthma control trial. *Clin Exp Allergy*. 2005;35(6).

46. Bergeron C, Hamid Q. Relationship between Asthma and Rhinitis: Epidemiologic, Pathophysiologic, and Therapeutic Aspects. Allergy asthma *Clin Immunol Off J Can Soc Allergy Clin Immunol*. 2005;1(2):81–7.

47. De Vries MP, Van Den Bemt L, Lince S, Muris JWM, Thoonen BPA, Van Schayck CP. Factors associated with asthma control. *J Asthma*. 2005;42(8):659–65.

48. Cerveri I, Cazzoletti L, Corsico AG, Marcon A, Niniano R, Grosso A, et al. The impact of cigarette smoking on asthma: A population-based international cohort study. *Int Arch Allergy Immunol*. 2012;158(2):175–83.

49. Beeklake MR, Lalloo U. The "healthy smoker": A phenomenon of health selection? *Respiration*. 1990;57(3):137–44.

50. Kaya Z, Erkan F, Ozkan M, Ozkan S, Kocaman N, Ertekin BA, et al. Self-management plans for asthma control and predictors of patient compliance. *J Asthma*. 2009;46(3):270–5.

51. Frey U, Brodbeck T, Majumdar A, Robin Taylor D, Ian Town G, Silverman M, et al. Risk of severe asthma episodes predicted from fluctuation analysis of airway function. *Nature*. 2005;438(7068):667–70.

52. Caminati M, Caimmi C, Dama A, Schiappoli M, Passalacqua G, Senna G. What lies beyond Asthma Control Test: Suggestions for clinical practice. *J Asthma*. 2016;53(6):559–62.

53. Papaioannou AI, Kostikas K, Bakakos P, Papaporfyriou A, Konstantellou E, Hillas G, et al. Predictors of future exacerbation risk in patients with asthma. *Postgrad Med*. 2016;128(7):687–92.

54. Cowie RL, Underwood MF, Field SK. Asthma symptoms do not predict spirometry. *Can Respir J*. 2007;14(6):339–42.

55. Boulet LP. Influence of comorbid conditions on asthma. *Eur Respir J*. 2009;33(4):897–906.

Chapter IV – Final Conclusions, Future Perspectives and Final Considerations

Final conclusions

From this study analysis it is possible to confirm, similar to other AIR studies results, the presence of a major gap between the long-term goals of asthma management based on GINA guidelines and clinical outcomes evaluated by self-reporting from active asthmatic patients in Portugal. It was also evidencing an important discrepancy between self-perception of asthma control level and Asthma Control Test tool measurement. Improvement in patient's asthma education and involvement in management of the disease can bring benefits and enhance expectations concerning what can be achieved from asthma treatment. Together with programs directed to physicians to ensure systematic monitoring of these patients and implementation of written asthma action plans can contribute to a better approach of this condition.

In this study uncontrolled asthma was associated with some important determinants. The recognition of factors that could interfere with asthma control can be an important support on clinical aspects by helping identifying individuals that are more prone to lower disease control levels and consequently optimize the strategies of care.

Future perspectives

Asthma prevalence has been increasing in many countries, in parallel with the development of urbanization and the adoption of modern lifestyles (8). It is estimated that by 2025 100 million of people more will have asthma worldwide (8). Aging of population especially in developed countries contributes to increasing the number of individuals living with chronic conditions. In this way health care systems must be able to support and deliver adequate assistance to meet the needs of the population, with continuous care and access to primary care.

Health policies directed for the prevention of risk factors and a better suited follow-up evaluation on asthma disease can bring important benefits for patients and improvement on health care economics related to this disease.

In 2014 the Direção-Geral da Saúde (DGS) published the Good Practices and Orientations for Control of Asthma in Adults and Children document (9), included in the National Program for Respiratory Disease.

After that, in 2016, a policy was created with the purpose of increasing the population's accessibility to primary health care regarding respiratory disease. Strategies such as the support on smoking cessation, easy access to spirometry exams, and respiratory rehabilitation treatments were stipulated with the objective of increasing the capacity of primary health care to assist patients with respiratory diseases (10).

This strategy was essentially implemented towards the early diagnosis of Chronic Obstructive Pulmonary Disease, but is expected that also asthmatic patients may benefit from it.

Because of that, nowadays Portuguese population may have results that are more positive concerning asthma control level. Assessment of the current state of asthma management care should be updated considering the results of the above implemented strategies.

Final considerations

I chose this project and theme because asthma is a pathology that is part of my professional day-to-day life. As a respiratory physiologist and working in a laboratory of pulmonary function tests, respiratory disease is a subject of great interest to me. The competency acquired in the master's degree in epidemiology enabled me to develop skills and knowledge in epidemiological investigation, statistics analysis and clinical research. These competences were important contributions for my collaboration in this project and development of my thesis. Besides this, the challenge of reporting results from a national level study and writing two articles about such an important health topic for the scientific community was a rewarding experience.

Chapter V - References

1. Holgate ST. A brief history of asthma and its mechanisms to modern concepts of disease pathogenesis. Allergy, Asthma Immunol Res. 2010;2(3):165–71.

2. Marketos SG, Ballas CN. Bronchial asthma in the medical literature of greek antiquity. J Asthma. 1982;19(4):263–9.

3. Sakula A. Henry Hyde Salter (1823-71): a biographical sketch. *Thorax*. 1985 Dec;40(12):887–8.

4. Makino S, Sagara H. Evolution of asthma concept and effect of current asthma management guidelines. *Allergy, Asthma Immunol Res*. 2010;2(3):172–6.

5. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2019. Available from: www.ginasthma.org.

6. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald M, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J.* 2008;31(1):143–78.

7. Rabe KF, Vermeire PA, Soriano JB, Maier WC. Clinical management of asthma in 1999: The Asthma Insights and Reality in Europe (AIRE) study. *Eur Respir J*. 2000;16(5):802–7.

8. Bousquet J, Bousquet PJ, Godard P, Daures J-P. The public health implications of asthma. *Bull World Health Organ*. 2005;83(7):548–54.

9. Direção Geral da Saúde. *Programa Nacional para as Doenças Respiratórias - Boas práticas e Orientações para o controlo da asma no adulto e na criança*. Direção-Geral da Saúde. 2014.

10. Gabinete do Secretário de Estado Adjunto e da Saúde. Despacho n.o 6300/2016. Vol. 92, *Diário da República*. 2016.

Chapter VI - Annexes

AIR-P study questionnaire link:

https://1drv.ms/f/s!AkBeK0JQIkPOmxSEwVymo_Jg5Wxn

Articles bibliographic references link:

https://1drv.ms/f/s!AkBeK0JQIkPOmkTBCWAEr4iTR5fU