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EPI-ASTHMA study protocol - a population-based multicentre stepwise study on the prevalence and characterisation of patients with asthma according to disease severity in Portugal

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ABSTRACT

Introduction: In Portugal as in other countries, data on the epidemiology of asthma are mainly grounded in questionnaire studies. Additionally, the detailed characterisation of asthma in terms of disease severity, control and phenotypes remain scarce. Studies assessing the prevalence of asthma and its sub-groups using accurate methods are needed. This study aims to determine the prevalence of asthma, difficult-to-treat and severe asthma, and to evaluate sociodemographic and clinical characteristics of those patients, in mainland Portugal.

Methods and analysis: A population-based nationwide study with a multicentre stepwise approach will be conducted between 2021-2023 in 38 primary care centres of the Portuguese National Health Service. The stepwise approach will comprise 4 Stages: Stage 0-telephone call invitation to adult subjects (≥18 years) randomly selected (n~15000); Stage 1-telephone screening interview assessing the participants' respiratory symptoms (n~7500); Stage 2- diagnostic visit, including physical examination, diagnostic tests (e.g., spirometry, fraction of exhaled nitric oxide, blood eosinophil count), and patient-reported outcome measures for diagnostic confirmation of those identified with possible asthma at Stage 1 (n~1800); Stage 3-further evaluation of patients with asthma and of patients with difficult-to-treat asthma and severe asthma, after 3 months (n~460). At Stage 3, data will be collected from a review of the patient's electronic health records, a follow-up telephone call and the CARATm app database. The prevalence of asthma, difficult-to-treat and severe asthma will be determined as the percentage of patients with asthma confirmed from the overall population (Stage 1). For the analysis of factors associated with asthma, difficult-to-treat and severe asthma, logistic regression models will be explored.

Ethics and dissemination: Ethical approvals for the study were obtained from the ethics committee of the local health unit of Matosinhos, Porto (38/CES/JAS), Alto Minho

(38/2021/CES) and the regional health administration of Lisbon-Vale do Tejo (035/CES/INV/2021). Results will be published in peer-reviewed journals.

Trial registration: ClinicalTrials.gov, NCT051696198. Registered at 27th December 2022.

Strengths and limitations of this study

- EPI-ASTHMA is the first national population-based study with a multicentre stepwise approach to determine the prevalence of asthma, difficult-to-treat and severe asthma In Portugal.
- The outcome measures will enable a more comprehensive characterisation of patients with asthma and a better understanding of their disease characteristics, treatment patterns and use of healthcare resources.
- The knowledge generated by this study has great potential to inform health policies and to improve the clinical outcomes of patients with asthma in Portugal.
- Time limited follow-up with lack of optimised management might be a source of error in the estimation of the prevalence of asthma sub-groups.
- Heterogeneity in data collection across the country conveniently select regions may prove challenging and a source of bias.

Keywords: disease severity, severe asthma, difficult-to-treat asthma, epidemiology

Introduction

Asthma is a common chronic disease affecting all age groups. Worldwide, it is estimated that about 5 to 10% of people have asthma [1], with a significant wide variation across regions and countries [2]. To date, epidemiological data on prevalence have used heterogeneous methodologies due to difficulties in defining and diagnosing asthma, leading to highly variable estimates of asthma prevalence [3]. Some studies used non-standardised questionnaires, others included participants based on the assessment of lung function or responsiveness to bronchodilators. In Portugal, the 2011 National Asthma Survey was based on telephone interviews and indicated a prevalence of 6.8% [4]. Yet, previous studies have estimated a prevalence between 3.3 and 15% [5]. Furthermore, similarly to the USA and Denmark Asthma Surveys, the 2005-2006 Portuguese Health Survey, suggested that there is an underdiagnosis of asthma, particularly in the male population and in the country's southern regions [5]. The Portuguese National Program for Respiratory Diseases maintains strategic research objectives in epidemiological surveillance both in asthma prevalence and its underdiagnosis [6], which is in line with the recommendations from the Global Initiative for Asthma (GINA) [7].

Additionally, national data on the characterisation of patients with asthma, in terms of severity and control, remain lacking [8]. Worldwide, it is estimated that up to 17% of patients have difficult-to-treat and 3.7% have severe asthma [9], which are more likely to experience life-threatening exacerbations and consume additional healthcare resources. It is important to differentiate these severity groups, as difficult-to-treat asthma might be manageable in primary health care, eventually with concomitant support from a secondary care specialist, whereas severe asthma requires a specialised second or tertiary care approach [10]. Knowledge on the distribution of severity and characteristics of patients in each group will better support clinical management of the disease and will

inform personalised health policies for a future and smarter allocation of healthcare resources.

The primary aim of this study is to determine the prevalence of asthma, difficult-to-treat and severe asthma in Portugal. The secondary aims are to evaluate the sociodemographic and clinical characteristics of patients with asthma.

METHODS AND ANALYSIS

Patient and Public Involvement

No patient involved

Study Design

EPI-ASTHMA is a population-based, nationwide, cross-sectional, prevalence study. This study will be conducted between 2021 and 2023, and will involve 38 primary care centres (PCC) of the Portuguese National Health Service (NHS), geographically distributed across all mainland Portugal Health Regions (North, Centre, Lisbon Metropolitan Area, Alentejo and Algarve). EPI-ASTHMA will be first piloted in one local health unit located in the North region, where all study procedures will be tested; after that, it will follow the order of approval of the ethics committee from each local health unit and regional health administrations. The study will be conducted using a stepwise approach parallel to a clinical practice diagnostic methodology. Firstly, subjects will be invited for a screening telephone interview to report respiratory symptoms, those who fulfil the eligible criteria will be invited for a clinical assessment in a mobile outpatient clinic. A sub-group of participants with confirmed asthma diagnosis will have a follow-up after 3 months for characterization of their asthma profile, symptoms patterns, clinical features, and treatment patterns. This study protocol is described according to STROBE (The Strengthening the Reporting of Observational Studies in Epidemiology Statement: guidelines for reporting observational studies)[11].

Study population and sample size

Sample size was estimated using Cochran's formula [12]:

$$n = \frac{Z^2 P(1-P)}{d^2} \quad (1)$$

Where *n* is the sample size, *Z* is the statistic corresponding to level of confidence, *P* is expected prevalence of Severe Asthma, and *d* is the desired level of precision (i.e. the margin of error). Applying a Z = 1.96 (i.e. 95% confidence interval), an estimated prevalence in the population of P = 0.42% and a margin of error of 0.15% the estimated sample size is 7141. In order to obtain 7500 participants on screening we consider a stepwise approach with a 50% dropout on invitation. Therefore, around 15000 adults will be randomly selected from the Portuguese NHS database to be contacted and invited to enrol in the study. In Portugal, the majority of the population (including Portuguese nationals and legal residents) is registered in a PCC, therefore the NHS database includes almost the entire resident population in the local administrative entity (i.e., Nomenclature of Territorial Units for Statistics-NUTS). The sample stratification was based on demographic stratification NUTS III, small regions for specific diagnoses as per EUROSTAT classification. For each NUTS III, the PCC were selected according to the feasibility of implementing the study (in total 38 PCC, 31 are part of the regional health administrations and 7 of local health units). The number of participants will be randomly selected according to the proportional allocation of each PCC. The distribution of an estimated stratified sample by NUTS III and the correspondent study Stages is presented in Table 1. The study will include male or female subjects with at least 18 years old, registered in the NHS database, who give voluntary consent. Subjects with any specific physical and/or cognitive disabilities that prevented them from cooperating with the study procedures (e.g., lung function tests) and/or understanding/answering self-reported questionnaires will be excluded.

Table 1 – Distribution of the estimated stratified sample [13].

NUTS III	Population	Primary care centres	Stage 0 (0.15%)	Stage 1 (50%)	Stage 2 (24%)	Stage 3 (25%)
Alto Minho/Cávado	637305	2	975	488	118	30
Ave	414763	2	635	317	77	19
Área Metropolitana do Porto	1719362	6	2631	1316	319	81
Alto Tâmega/Douro/Terras de Trás-os-Montes	389151	2	596	298	72	18
Tâmega e Sousa	419811	2	643	321	78	20
Oeste	357868	2	548	274	66	17
Região de Aveiro	363424	2	556	278	67	17
Região de Coimbra	438228	2	671	335	81	21
Região de Leiria	287040	1	439	220	53	13
Viseu Dão Lafões/Beiras/Serra da Estrela/Beira Baixa	555628	2	850	425	103	26
Médio Tejo/Lezíria do Tejo	474802	2	727	363	88	22
Área Metropolitana de Lisboa	2827514	9	4328	2164	525	133
Alentejo Litoral/Baixo Alentejo/Alto Alentejo/ Alentejo Central	475674	2	728	364	88	22
Algarve	440543	2	674	337	82	21
Total	**9801113**	**38**	**15000**	**7500**	**1819**	**460**

NUTS - Nomenclature of Territorial Units for Statistics.

Study procedures

EPI-ASTHMA will use a stepwise approach, sequentially comprising the evaluation of symptoms patterns, clinical features, and tests for diagnosis confirmation, that includes the following stages (Figure 1):

- **Stage 0- Study enrolment**: Telephone call invitation to enrol participants;

- **Stage 1- Screening interview:** Telephone call interview to assess respiratory symptoms;
- **Stage 2- Diagnostic visit:** Clinical assessment, diagnostic confirmation and patient characterization;
- **Stage 3- Sub-group asthma characterization:** follow-up of patients with asthma (sub-group) and of patients with difficult-to-treat asthma and severe asthma, after 3 months.

Stage 0- Study enrolment

Around 15,000 randomised subjects 18 years or above will receive a telephone call invitation for enrolment in the study, to secure a sample size of 7500 participants for the next stage (assuming an acceptance of 50%)[14]. If needed, a second round of telephone calls will also be made to complete the number of patients in each region. Trained clinical secretaries will conduct this stage by following a semi-structured guide during the telephone call. A screening log of potential eligible participants will be completed to document the main reasons for participants not entering the study. Subjects who fulfil the study eligibility criteria and give their oral consent will be contacted in Stage 1.

Stage 1- Screening interview

A computer-assisted telephone screening interview will be performed to 7500 participants. The interview will include validated patient-reported outcome measures for screening asthma [15] and chronic obstructive pulmonary disease (COPD) [16], dyspnoea [17] and assessment of physical activity [18,19], among other questions formulated by the researchers (Table 2). At this stage participants will be considered eligible and invited to participate in Stage 2 if they have, at least, one positive response in the Adult Asthma Score (A2 Score) [15], i.e., medical history of asthma or asthma medication intake or asthma symptoms. For quality control, 5% of not eligible participants (with a negative score) will also be invited to participate in Stage 2. Interviews will be

performed by a centralised team of trained and experienced interviewers. Each participant will be contacted for at least ten attempts during different occasions before being considered excluded. Prior to any question, participants will be asked to reinforce their oral consent to participate. A pilot study with 12 individuals was conducted to assess the clarity and feasibility of the screening interview before starting the data collection [20]. The duration of each interview was no longer than 17 minutes.

Stage 2 – Diagnostic visit

The diagnostic visit will be conducted in a mobile outpatient clinic, located, whenever possible, in the close vicinity of each PCC. At this stage, participants will give a written informed consent before any study-related procedures. Stage 2 is expected to include 1800 participants, about 20% of participants from Stage 1 who fulfil the eligibility criteria, plus 5% of participants for quality control. A detailed clinical assessment will be performed, including clinical history, physical examination, lung function tests, blood count and inflammatory biomarkers testing and patient-reported outcome measures (Table 2). The clinical assessment will be carried out by a physician and the diagnostic tests by an experienced team to assure the quality and the harmonisation of procedures. All patients will be provided with a letter addressed to their primary care physician, containing the results of their clinical evaluation. Patients with asthma will also be invited to install and use the CARATm app ("Caracteristicas Auto-reportadas de Asma em Tecnologias Móveis") in their daily life. CARATm is a Portuguese health mobile app developed to collect clinical data from patients with asthma, such as asthma control and medication adherence, which is also interoperable with the Portuguese Severe Asthma Registry (asmagrave.pt).

Stage 3- Sub-group asthma characterization

This stage is expected to include 460 participants: a randomised sample of patients with asthma, and all patients identified with difficult-to-treat or severe asthma. Patients with

difficult-to-treat and severe asthma will be defined according to GINA[21]. This stage takes place 3-months after the diagnostic visit and consists of a review of patients' electronic health records, a follow-up telephone call to the patient, and extraction of CARATm app data. The review of patients' electronic health records by a physician of their PCC will ensure an asthma control assessment on two different time points, and will confirm the treatment profile for an adequate GINA severity classification [7] (Table 2).

Table 2. Summary of the data collection per study´s stage.

	Stage 1	Stage 2	Stage 3
Sociodemographic and anthropometric characteristics	×		
Brief PA assessment	×	×	
Respiratory symptoms (wheeze, breathlessness)	×	×	×
CAPTURE	×		
mMRC	×		
Diagnosis of chronic respiratory disease	×	×	×
Comorbidities and allergies	×	×	×
Smoking habits and ETS	×	×	
A2 Score	×		
Family history of asthma	×	×	
Age of asthma onset		×	
Inhaler prescription/use	×		
Mini-AQLQ		×	
EQ-5D		×	
Signs of asthma		×	
CARAT		×	×
Asthma control (according to GINA)		×	×
Asthma pharmacological treatment		×	×*
Inhalation technique		×	
Adherence to inhaled medication		×	×*
Other treatments		×	×
Number of exacerbations		×	×*
Number of visits to emergency room		×	×*

Number of hospital admissions and length of hospital stay		×	×*
Number of unscheduled consultations		×	×*
Number of consultations primary care team		×	×*
Referral for specialist care		×	×*
Standard measurements (blood pressure, height, weight)		×	
Pre-BD and post-BD lung function		×	
Pulmonary diagnostic tests (previously performed)			×
FeNO		×	
Peripheral blood eosinophil and neutrophil counts		×	
Use of health and fitness apps	×	×	
CARATm app use and opinion			×

A2 Score= A2 adult asthma score[15]; CAPTURE= COPD Assessment in Primary Care to Identify Undiagnosed Respiratory Disease and Exacerbation Risk [16]; mMRC=Modified British Medical Research Council [17];PA = Brief physical activity assessment [18,19]; Mini-AQLQ=Mini Asthma Quality of Life Questionnaire[22,23]; EQ-5D=European Quality of Life Five Dimension [24];CARAT=Control of Allergic Rhinitis and Asthma Test [25]; pre-BD and post-BD=Spirometry pre- and post-bronchodilator [26]; FeNO=Fractional exhaled nitric oxide [27]; || *In the previous 3 and 12 months.

Data storage, blinding and statistical analysis plan

Participants will be anonymized with a unique subject ID and their data will be anonymously stored in an appropriately secured server. In order to minimise diagnostic bias, researchers, data collectors and participants will be blinded to patient eligibility throughout data collection during Stage 2. Over the stages, data will be collected for a specific electronic case report form (e-CRF) by using blended data (primary and secondary data).

Statistical analysis will allow the characterization of the study population and the estimation of each study´s endpoints. The prevalence of asthma, difficult-to-treat and severe asthma with the respective 95% confidence intervals (95% CI) will be calculated in relation to the entire study population (Stage 1). Descriptive statistics such as i) central tendency (e.g. mode, median or mean); ii) localisation (e.g. percentile); iii) dispersion (e.g. interquartile range, standard deviation) and iv) distribution (e.g. skewness, kurtosis) will be used, depending on the type of each variable, to characterise the total sample or

subgroups. Associations between two quantitative variables will be calculated using the Pearson's correlation coefficient or Spearman correlation coefficient, in case of normality assumption are not verified. Association of two categorical variables will be determined using the Chi-Square test or Fisher Exact test. Continuous variables between two groups will be compared with a t-test for independent samples or Mann-Whitney test, whereas for comparisons among 3 or more groups an ANOVA or Kruskall-Wallis test will be used. Null-hypothesis statistical testing will also be applied in an exploratory manner to identify any relationship patterns among variables. Subgroup analysis per each asthma control level, GINA treatment step, Short-Acting Beta Agonists (SABA) overuse among others, will also be conducted. Measurements of effect size will be presented and confidence intervals at 95% will be estimated to account for the uncertainty of the sample estimates. Interim analysis will be conducted per region after all stages are completed.

For the analysis of factors associated with asthma, difficult-to-treat asthma and severe asthma, logistic regression models will be explored, taking into consideration these as dependent variables and sociodemographic, clinical, among other variables, as independent variables. The variables to be included in the multivariate model will be selected from the univariate analyses, when p-value <0.100, those that do not meet these criteria, but are considered clinically relevant, will also be possible candidates. The final model will be analysed from two perspectives: 1) the calibration using the Hosmer-Lemeshow goodness of fit test, and 2) the discrimination, using ROC curves and the respective area under the curve. All results will be considered statistically significant when p-value <0.05.

DISCUSSION

The EPI-ASTHMA study will address knowledge gaps in the epidemiology and characterisation of asthma in mainland Portugal, using a multicentre approach that combines different data collection methods, including a mHealth solution. Furthermore, it will provide a more complete picture of the prevalence of difficult-to-treat and severe asthma in Portugal, and will allow a better understanding of these patients' characteristics, treatment profile and healthcare resource use. Further knowledge on the distribution of severity and characteristics of patients in each group will better support clinical management of the disease and inform personalised health policies for a smarter allocation of the needed healthcare resources. This ambitious study is aligned with the global need of epidemiological studies to monitor the trends in the prevalence of asthma, which is vital to ensure that health policies fit the populations' needs [2,28,29].

The study design is one of its strengths. The combination of standardised questionnaires with a standardised clinical evaluation, including lung function tests will allow a more accurate diagnosis and characterisation of asthma. However, few limitations and potential risks must be acknowledged. The definition of difficult-to-treat and severe asthma will be based on the GINA treatment steps (4-5) and the assessment of asthma control during the study Stages 2 and 3, which is only 3-months apart. An optimised management during the follow-up period was not included, which is also part of the GINA criteria to distinguish these asthma subgroups. This will probably be a source of error in the estimation of the prevalence of these sub-groups, linked to the observational nature of this study. The 38 PCC will be conveniently selected, which can be seen as a source of bias. Yet, we considered the geographic areas and population distribution of each Portuguese region as well as their interest to participate and willingness to collect data and not only based on previous asthma research experience which will preserve the study real-world nature. Clinical secretaries (Stage 0) and physicians (Stage 2 and 3) will collaborate across different country's regions, which may introduce some heterogeneity in data collection. Nevertheless, both clinical secretaries and physicians

will be previously trained and continuously motivated by the management team, which will be available to clarify doubts on a 24/7 basis. To deal with possible risks, the study´s steering committee will supervise the execution and will take academic responsibility for the study. Another limitation is the need for this multicentre study to be approved by the ethics committees responsible for each regional health administration/local health unit. Although all applications will be similar in their content, they will differ in a number of aspects to comply with each institution's formal requirements, resulting in additional complexity and may hinder the compliance with the study timeline. To mitigate these risks, an experienced contracted research organisation that knows the specificities of each administration/health unit is supporting us through all the process.

EPI-ASTHMA will be managed combining traditional management methodologies with an "agile" approach [30] using the SCRUM framework on Jira software. This combination is expected to fulfil the need to make the study adaptable and to anticipate future needs that are important and can be forgotten due to the dimension of the study.

Conclusion

EPI-ASTHMA will be the first population-based study in Portugal to determine the prevalence of asthma, difficult-to-treat and severe asthma and to better understand the patient's disease characteristics, treatment patterns and use of healthcare resources. The knowledge generated by this nationwide robust study has great potential to inform health policies and to improve the clinical outcomes of patients with asthma in Portugal.

Ethics and dissemination:

The study will follow the tenants of the Declaration of Helsinki and the Oviedo Convention. Ethical approvals and data privacy clearance for the study were obtained by the Ethics Committee and Data Protection Officer of the local health unit of Matosinhos, Porto (ULSM; 38/CES/JAS, March 12th ,2021), Alto Minho (ULSAM; 38/2021/CES, June 17th, 2021) and the Regional Health Administration of Lisbon and

Vale do Tejo (ARSLVT; 035/CES/INV/2021; December 3rd 2021) and is under revision in the remain regional ethical committees for health administration/local health units. All participants will received both verbal and written information explaining the purpose of the study and they will have to provided verbal and written informed consent. Results will be presented at both national and international scientific meetings and published in peer-reviewed journals. Seasonal newsletters will be provided to the funders of the study as well as all the involved participants.

Statements

Patient consent for publication

Not applicable.

Authors' contributions

JCA, JAF and FB conceptualised the study. CJ wrote the statistical analysis plan and PT conducted the sample size calculation. CJ and CJO wrote the first draft of the manuscript. All authors contributed to and refined the manuscript for scientific content. All authors read and approved the final version of the manuscript.

Competing interests

JCS reports Advisory Board from Boheringer Ingelheim, personal fees and Advisory Board from GSK, grants, personal fees and Advisory Board from AstraZeneca, personal fees and Advisory Board from Bial, non-financial support from Mundipharma, personal fees from Sanofi, Advisory Board from Novartis, outside the submitted work. JAF declares grants from or research agreements with AstraZeneca, Mundipharma, Sanofi Regeneron and Novartis. Personal fees for lectures and attending advisory boards from

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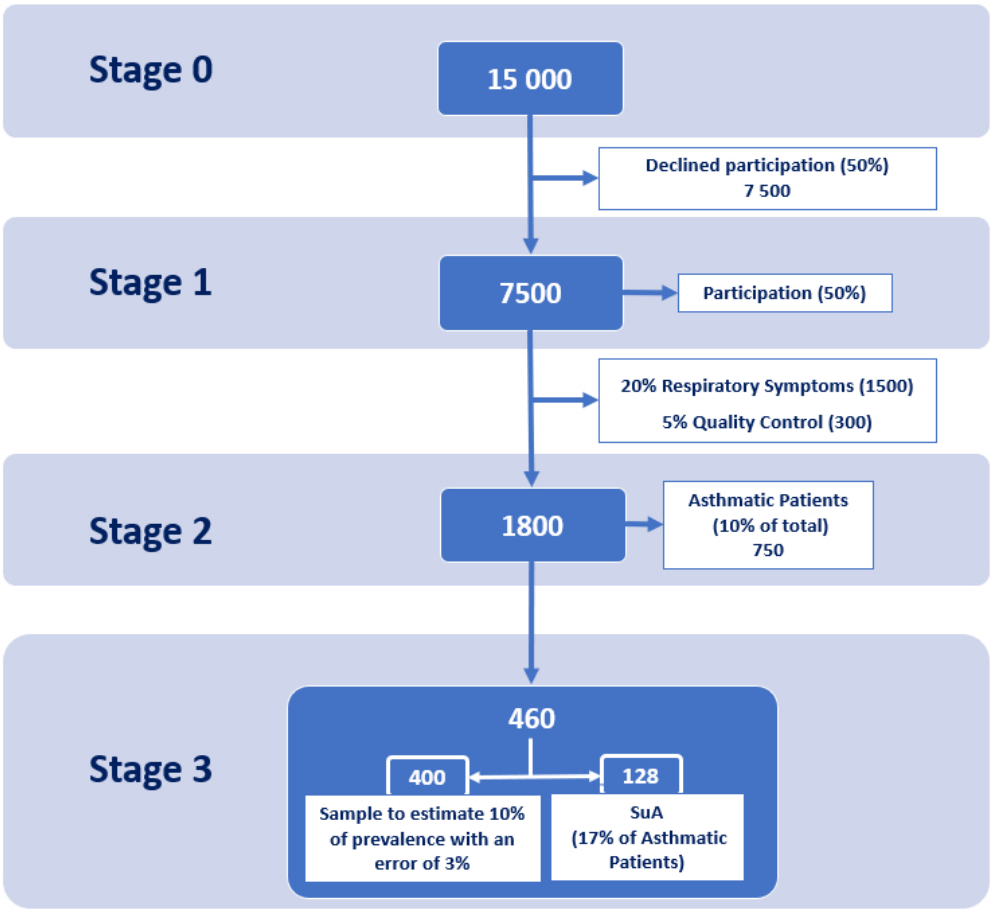
Figures

Figure 1: Flow of participants through study´s stages. SuA - severe and difficult to treat asthma.



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EPI-ASTHMA study protocol - a population-based multicentre stepwise study on the prevalence and characterisation of patients with asthma according to disease severity in Portugal

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EPI-ASTHMA study protocol - a population-based multicentre stepwise study on the prevalence and characterisation of patients with asthma according to disease severity in Portugal

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ABSTRACT

Introduction: In Portugal as in other countries, data on the epidemiology of asthma are mainly grounded in questionnaire studies. Additionally, the detailed characterisation of asthma in terms of disease severity, control and phenotypes remain scarce. Studies assessing the prevalence of asthma and its sub-groups using accurate methods are needed. This study aims to determine the prevalence of asthma, difficult-to-treat and severe asthma, and to evaluate sociodemographic and clinical characteristics of those patients, in mainland Portugal.

Methods and analysis: A population-based nationwide study with a multicentre stepwise approach will be conducted between 2021-2023 in 38 primary care centres of the Portuguese National Health Service. The stepwise approach will comprise 4 Stages: Stage 0-telephone call invitation to adult subjects (≥18 years) randomly selected (n~15000); Stage 1-telephone screening interview assessing the participants' respiratory symptoms (n~7500); Stage 2- diagnostic visit, including physical examination, diagnostic tests (e.g., spirometry, fraction of exhaled nitric oxide, blood eosinophil count), and patient-reported outcome measures for diagnostic confirmation of those identified with possible asthma at Stage 1 (n~1800); Stage 3-further evaluation of patients with asthma and of patients with difficult-to-treat asthma and severe asthma, after 3 months (n~460). At Stage 3, data will be collected from a review of the patient's electronic health records, a follow-up telephone call and the CARATm app database. The prevalence of asthma, difficult-to-treat and severe asthma will be determined as the percentage of patients with asthma confirmed from the overall population (Stage 1). For the analysis of factors associated with asthma, difficult-to-treat and severe asthma, logistic regression models will be explored.

Ethics and dissemination: Ethical approvals for the study were obtained from the ethics committee of the local health unit of Matosinhos, Porto (38/CES/JAS), Alto Minho (38/2021/CES) and the regional health administration of Lisbon-Vale do Tejo (035/CES/INV/2021). Results will be published in peer-reviewed journals.

Trial registration: ClinicalTrials.gov, NCT05169619. Registered on December 27th 2021.

Strengths and limitations of this study

- The design of this study is based on a stepwise approach, divided in 4 stages, that mimics the clinical practice diagnostic pathway for asthma.
- This study allows a reliable diagnosis and characterization of asthma patients through the use of questionnaires together with clinical examination that includes lung function assessment.
- A mHealth application to engage patients on self-management of their disease and to improve completeness of the data collection is used.
- The 3-month follow-up with lack of optimised management might be a source of error in the estimation of the prevalence of asthma sub-groups.
- Heterogeneity in data collection across the country regions may prove challenging and a possible source of bias.

Keywords: disease severity, severe asthma, difficult-to-treat asthma, epidemiology

Introduction

Asthma is a common chronic disease affecting all age groups. Worldwide, it is estimated that about 5 to 10% of people have asthma [1], with a significant wide variation across regions and countries [2]. To date, epidemiological data on prevalence have used heterogeneous methodologies due to difficulties in defining and diagnosing asthma, leading to highly variable estimates of asthma prevalence [3]. Some studies used non-standardised questionnaires, others included participants based on the assessment of lung function or responsiveness to bronchodilators. In Portugal, the 2011 National Asthma Survey was based on telephone interviews and indicated a prevalence of 6.8% [4]. Yet, previous studies have estimated a prevalence between 3.3 and 15% [5]. Furthermore, similarly to the USA and Denmark Asthma Surveys, the 2005-2006 Portuguese Health Survey, suggested that there is an underdiagnosis of asthma, particularly in the male population and in the country's southern regions [5]. The Portuguese National Program for Respiratory Diseases maintains strategic research objectives in epidemiological surveillance both in asthma prevalence and its underdiagnosis [6], which is in line with the recommendations from the Global Initiative for Asthma (GINA) [7].

Additionally, national data on the characterisation of patients with asthma, in terms of severity and control, remain lacking [8]. Worldwide, it is estimated that up to 17% of patients have difficult-to-treat and 3.7% have severe asthma [9], which are more likely to experience life-threatening exacerbations and consume additional healthcare resources. It is important to differentiate these severity groups, as difficult-to-treat asthma might be manageable in primary health care, eventually with concomitant support from a secondary care specialist, whereas severe asthma requires a specialised second or tertiary care approach [10]. Knowledge on the distribution of severity and characteristics of patients in each group will better support clinical management of the disease and will

inform personalised health policies for a future and smarter allocation of healthcare resources.

The primary aim of this study is to determine the prevalence of asthma, difficult-to-treat and severe asthma in Portugal. The secondary aims are to evaluate the sociodemographic and clinical characteristics of patients with asthma.

METHODS AND ANALYSIS

Patient and Public Involvement

No patient involved

Study Design

EPI-ASTHMA is a population-based, nationwide, cross-sectional, prevalence study. This study will be conducted between 2021 and 2023, and will involve 38 primary care centres (PCC) of the Portuguese National Health Service (NHS), geographically distributed across all mainland Portugal Health Regions (North, Centre, Lisbon Metropolitan Area, Alentejo and Algarve). The study will be conducted using a stepwise approach parallel to a clinical practice diagnostic methodology. Firstly, subjects will be invited for a screening telephone interview to report respiratory symptoms, those who fulfil the eligible criteria will be invited for a clinical assessment in a mobile outpatient clinic. A sub-group of participants with confirmed asthma diagnosis will have a follow-up after 3 months for characterization of their asthma profile, symptoms patterns, clinical features, and treatment patterns. EPI-ASTHMA was first piloted in one local health unit located in the North region from May to October 2021, where all study procedures were tested; after which, implementation is planned to follow the order of approval of the ethics committee from each local health unit and regional health administrations. Currently, the study has been concluded in 4 PCC in Northern Portugal.

This study protocol is described according to STROBE (The Strengthening the Reporting of Observational Studies in Epidemiology Statement: guidelines for reporting observational studies) statement [11].

Study population and sample size

Sample size was estimated using Cochran's formula [12]:

$$n = \frac{Z^2 P(1-P)}{d^2} \quad (1)$$

Where *n* is the sample size, *Z* is the statistic corresponding to level of confidence, *P* is expected prevalence of Severe Asthma, and *d* is the desired level of precision (i.e. the margin of error). Applying a Z = 1.96 (i.e. 95% confidence interval), an estimated prevalence in the population of P = 0.42% and a margin of error of 0.15% the estimated sample size is 7141. In order to obtain 7500 participants on screening we consider a stepwise approach with a 50% dropout on invitation. Therefore, around 15000 adults will be randomly selected from the Portuguese NHS database to be contacted and invited to enrol in the study. In Portugal, the majority of the population (including Portuguese nationals and legal residents) is registered in a PCC, therefore the NHS database includes almost the entire resident population in the local administrative entity (i.e., Nomenclature of Territorial Units for Statistics-NUTS). The sample stratification was based on demographic stratification NUTS III, small regions for specific diagnoses as per EUROSTAT classification. For each NUTS III, the PCC were selected according to the feasibility of implementing the study (in total 38 PCC, 31 are part of the regional health administrations and 7 of local health units). The number of participants will be randomly selected according to the proportional allocation of each PCC. The distribution of an estimated stratified sample by NUTS III and the correspondent study Stages is presented in Table 1. The study will include male or female subjects with at least 18 years old, registered in the NHS database, who give voluntary consent. Subjects with

any specific physical and/or cognitive disabilities that prevented them from cooperating with the study procedures (e.g., lung function tests) and/or understanding/answering self-reported questionnaires will be excluded.

Table 1 – Distribution of the estimated stratified sample [13].

NUTS III	Population	Primary care centres	Stage 0 (0.15%)	Stage 1 (50%)	Stage 2 (24%)	Stage 3 (25%)
Alto Minho/Cávado	637305	2	975	488	118	30
Ave	414763	2	635	317	77	19
Área Metropolitana do Porto	1719362	6	2631	1316	319	81
Alto Tâmega/Douro/Terras de Trás-os-Montes	389151	2	596	298	72	18
Tâmega e Sousa	419811	2	643	321	78	20
Oeste	357868	2	548	274	66	17
Região de Aveiro	363424	2	556	278	67	17
Região de Coimbra	438228	2	671	335	81	21
Região de Leiria	287040	1	439	220	53	13
Viseu Dão Lafões/Beiras/Serra da Estrela/Beira Baixa	555628	2	850	425	103	26
Médio Tejo/Lezíria do Tejo	474802	2	727	363	88	22
Área Metropolitana de Lisboa	2827514	9	4328	2164	525	133
Alentejo Litoral/Baixo Alentejo/Alto Alentejo/ Alentejo Central	475674	2	728	364	88	22
Algarve	440543	2	674	337	82	21
Total	**9801113**	**38**	**15000**	**7500**	**1819**	**460**

NUTS - Nomenclature of Territorial Units for Statistics.

Study procedures

EPI-ASTHMA will use a stepwise approach, sequentially comprising the evaluation of symptoms patterns, clinical features, and tests for diagnosis confirmation, that includes the following stages (Figure 1):

- **Stage 0- Study enrolment**: Telephone call invitation to enrol participants;
- **Stage 1- Screening interview:** Telephone call interview to assess respiratory symptoms;
- **Stage 2- Diagnostic visit:** Clinical assessment, diagnostic confirmation and patient characterization;
- **Stage 3- Sub-group asthma characterization:** follow-up of patients with asthma (sub-group) and of patients with difficult-to-treat asthma and severe asthma, after 3 months.

Stage 0- Study enrolment

Around 15,000 randomised subjects 18 years or above will receive a telephone call invitation for enrolment in the study, to secure a sample size of 7500 participants for the next stage (assuming an acceptance of 50%) [14]. If needed, a second round of telephone calls will also be made to complete the number of patients in each region. Trained clinical secretaries will conduct this stage by following a semi-structured guide during the telephone call. A screening log of potential eligible participants will be completed to document the main reasons for participants not entering the study. Subjects who fulfil the study eligibility criteria and give their oral consent will be contacted in Stage 1.

Stage 1- Screening interview

A computer-assisted telephone screening interview will be performed to 7500 participants. The interview will include validated patient-reported outcome measures for screening asthma [15] and chronic obstructive pulmonary disease (COPD) [16],

dyspnoea [17] and assessment of physical activity [18,19], among other questions formulated by the researchers (Table 2). At this stage participants will be considered eligible and invited to participate in Stage 2 if they have, at least, one positive response in the Adult Asthma Score (A2 Score) [15], i.e., medical history of asthma or asthma medication intake or asthma symptoms. For quality control, 5% of not eligible participants (with a negative score) will also be invited to participate in Stage 2. Interviews will be performed by a centralised team of trained and experienced interviewers. Each participant will be contacted for at least ten attempts during different occasions before being considered excluded. Prior to any question, participants will be asked to reinforce their oral consent to participate. A pilot study with 12 individuals was conducted to assess the clarity and feasibility of the screening interview before starting the data collection [20]. The duration of each interview was no longer than 17 minutes.

Stage 2 – Diagnostic visit

The diagnostic visit will be conducted in a mobile outpatient clinic, located, whenever possible, in the close vicinity of each PCC. At this stage, participants will give a written informed consent before any study-related procedures. Stage 2 is expected to include 1800 participants, about 20% of participants from Stage 1 who fulfil the eligibility criteria, plus 5% of participants for quality control. A detailed clinical assessment will be performed, including clinical history, physical examination, lung function tests, blood count and inflammatory biomarkers testing and patient-reported outcome measures (Table 2). The clinical assessment will be carried out by a physician and the diagnostic tests by an experienced team to assure the quality and the harmonisation of procedures. All patients will be provided with a letter addressed to their primary care physician, containing the results of their clinical evaluation. Patients with asthma will also be invited to install and use the CARATm app (“Caracteristicas Auto-reportadas de Asma em Tecnologias Móveis”) in their daily life. CARATm is a Portuguese health mobile app developed to collect clinical data from patients with asthma, such as asthma control and

medication adherence, which is also interoperable with the Portuguese Severe Asthma Registry (asmagrave.pt).

Stage 3- Sub-group asthma characterization

This stage is expected to include 460 participants: a randomised sample of patients with asthma, and all patients identified with difficult-to-treat or severe asthma. Patients with difficult-to-treat and severe asthma will be defined according to GINA[21]. This stage takes place 3-months after the diagnostic visit and consists of a review of patients' electronic health records, a follow-up telephone call to the patient, and extraction of CARATm app data. The review of patients' electronic health records by a physician of their PCC will ensure an asthma control assessment on two different time points, and will confirm the treatment profile for an adequate GINA severity classification [7] (Table 2).

Table 2. Summary of the data collection per study´s stage.

	Stage 1	Stage 2	Stage 3
Sociodemographic and anthropometric characteristics	×		
Brief PA assessment	×	×	
Respiratory symptoms (wheeze, breathlessness)	×	×	×
CAPTURE	×		
mMRC	×		
Diagnosis of chronic respiratory disease	×	×	×
Comorbidities and allergies	×	×	×
Smoking habits and ETS	×	×	
A2 Score	×		
Family history of asthma	×	×	
Age of asthma onset		×	
Inhaler prescription/use	×		
Mini-AQLQ		×	
EQ-5D		×	

Signs of asthma			×	
CARAT			×	×
Asthma control (according to GINA)			×	×
Asthma pharmacological treatment			×	×*
Inhalation technique			×	
Adherence to inhaled medication			×	×*
Other treatments			×	×
Number of exacerbations			×	×*
Number of visits to emergency room			×	×*
Number of hospital admissions and length of hospital stay			×	×*
Number of unscheduled consultations			×	×*
Number of consultations primary care team			×	×*
Referral for specialist care			×	×*
Standard measurements (blood pressure, height, weight)			×	
Pre-BD and post-BD lung function			×	
Pulmonary diagnostic tests (previously performed)				×
FeNO			×	
Peripheral blood eosinophil and neutrophil counts			×	
Use of health and fitness apps		×	×	
CARATm app use and opinion				×

A2 Score = A2 adult asthma score[15]; CAPTURE = COPD Assessment in Primary Care to Identify Undiagnosed Respiratory Disease and Exacerbation Risk [16]; mMRC = Modified British Medical Research Council [17];PA = Brief physical activity assessment [18,19]; ETS = Environmental tobacco smoke; Mini-AQLQ = Mini Asthma Quality of Life Questionnaire[22,23]; EQ-5D = European Quality of Life Five Dimension [24]; CARAT = Control of Allergic Rhinitis and Asthma Test [25]; pre-BD and post-BD=Spirometry pre- and post-bronchodilator [26]; FeNO = Fractional exhaled nitric oxide [27]; || *In the previous 3 and 12 months.

Diagnosis criteria and definitions

According to GINA, uncontrolled asthma includes one or both of the following: poor symptom control and frequent exacerbations (≥2/year) requiring oral corticosteroids, or serious exacerbations (≥1/year) requiring hospitalisation [21]. In our study, poor symptom control will be based on a score less or equal than 24 in the Control of Allergic Rhinitis and Asthma Test (CARAT) [25, 28]. Data regarding exacerbations or serious exacerbations will be collected at stage 2 and 3.

Difficult-to-treat asthma is asthma that is uncontrolled despite treatment with medium or high dose inhaled corticosteroids with a second controller or with maintenance oral corticosteroids, or that requires high dose treatment to maintain symptom control and to reduce the risk of exacerbations [21]. In our study, difficult-to-treat asthma will be defined as uncontrolled asthma, despite prescription of high intensity treatment (GINA step treatment 4-5). Severe asthma is a subset of difficult-to-treat asthma, that is an uncontrolled asthma despite adherence with maximal optimised high dose ICS-LABA (inhaled corticosteroid and a long-acting β2-agonist) treatment and management of contributory factors, such as inhaler adherence and technique or asthma that worsens when high dose treatment is decreased. We will define severe asthma in the study as uncontrolled asthma despite prescription of high intensity treatment (GINA step treatment 4-5), and good treatment adherence (visual analogue scale (VAS) ≥50) [29] and good inhaler technique (number of critical errors = [0-1]) [30].

Data storage, blinding and statistical analysis plan

Participants will be anonymized with a unique subject ID and their data will be anonymously stored in an appropriately secured server. In order to minimise diagnostic bias, researchers, data collectors and participants will be blinded to patient eligibility throughout data collection during Stage 2. Over the stages, data will be collected for a specific electronic case report form (e-CRF) by using blended data (primary and secondary data).

Statistical analysis will allow the characterization of the study population and the estimation of each study´s endpoints. The prevalence of asthma, difficult-to-treat and severe asthma with the respective 95% confidence intervals (95% CI) will be calculated in relation to the entire study population (Stage 1). Descriptive statistics such as i) central tendency (e.g. mode, median or mean); ii) localisation (e.g. percentile); iii) dispersion (e.g. interquartile range, standard deviation) and iv) distribution (e.g. skewness, kurtosis) will be used, depending on the type of each variable, to characterise the total sample or

subgroups. Associations between two quantitative variables will be calculated using the Pearson's correlation coefficient or Spearman correlation coefficient, in case of normality assumption are not verified. Association of two categorical variables will be determined using the Chi-Square test or Fisher Exact test. Continuous variables between two groups will be compared with a t-test for independent samples or Mann-Whitney test, whereas for comparisons among 3 or more groups an ANOVA or Kruskall-Wallis test will be used. Null-hypothesis statistical testing will also be applied in an exploratory manner to identify any relationship patterns among variables. Subgroup analysis per each asthma control level, GINA treatment step, Short-Acting Beta Agonists (SABA) overuse among others, will also be conducted. Measurements of effect size will be presented and confidence intervals at 95% will be estimated to account for the uncertainty of the sample estimates. Interim analysis will be conducted per region after all stages are completed to monitor the safety of study procedures and completeness of data collection. This analysis may encompass potential changes in logistical, monitoring, and recruitment procedures to secure sample size.

For the analysis of factors associated with asthma, difficult-to-treat asthma and severe asthma, logistic regression models will be explored, taking into consideration these as dependent variables and sociodemographic, clinical, among other variables, as independent variables. The variables to be included in the multivariate model will be selected from the univariate analyses, when p-value <0.100, those that do not meet these criteria, but are considered clinically relevant, will also be possible candidates. The final model will be analysed from two perspectives: 1) the calibration using the Hosmer-Lemeshow goodness of fit test, and 2) the discrimination, using ROC curves and the respective area under the curve. All results will be considered statistically significant when p-value <0.05.

DISCUSSION

The EPI-ASTHMA study will address knowledge gaps in the epidemiology and characterisation of asthma in mainland Portugal, using a multicentre approach that combines different data collection methods, including a mHealth solution. Furthermore, it will provide a more complete picture of the prevalence of difficult-to-treat and severe asthma in Portugal, and will allow a better understanding of these patients' characteristics, treatment profile and healthcare resource use. Further knowledge on the distribution of severity and characteristics of patients in each group will better support clinical management of the disease and inform personalised health policies for a smarter allocation of the needed healthcare resources. This ambitious study is aligned with the global need of epidemiological studies to monitor the trends in the prevalence of asthma, which is vital to ensure that health policies fit the populations' needs [2,31,32].

The study design is one of its strengths. The combination of standardised questionnaires with a standardised clinical evaluation, including lung function tests will allow a more accurate diagnosis and characterisation of asthma. However, few limitations and potential risks must be acknowledged. The definition of difficult-to-treat and severe asthma will be based on the GINA treatment steps (4-5) and the assessment of asthma control during the study Stages 2 and 3, which is only 3-months apart. An optimised management during the follow-up period was not included, which is also part of the GINA criteria to distinguish these asthma subgroups. This will probably be a source of error in the estimation of the prevalence of these sub-groups, linked to the observational nature of this study. The 38 PCC will be conveniently selected, which can be seen as a source of bias. Yet, we considered the geographic areas and population distribution of each Portuguese region as well as their interest to participate and willingness to collect data and not only based on previous asthma research experience which will preserve the study real-world nature. Clinical secretaries (Stage 0) and physicians (Stage 2 and 3)

will collaborate across different country's regions, which may introduce some heterogeneity in data collection. Nevertheless, both clinical secretaries and physicians will be previously trained and continuously motivated by the management team, which will be available to clarify doubts on a 24/7 basis. To deal with possible risks, the study´s steering committee will supervise the execution and will take academic responsibility for the study. Another limitation is the need for this multicentre study to be approved by the ethics committees responsible for each regional health administration/local health unit. Although all applications will be similar in their content, they will differ in a number of aspects to comply with each institution's formal requirements, resulting in additional complexity and may hinder the compliance with the study timeline. To mitigate these risks, an experienced contracted research organisation that knows the specificities of each administration/health unit is supporting us through all the process.

EPI-ASTHMA will be managed combining traditional management methodologies with an "agile" approach [33] using the SCRUM framework on Jira software. This combination is expected to fulfil the need to make the study adaptable and to anticipate future needs that are important and can be forgotten due to the dimension of the study.

Conclusion

EPI-ASTHMA will be the first population-based study in Portugal to determine the prevalence of asthma, difficult-to-treat and severe asthma and to better understand the patient's disease characteristics, treatment patterns and use of healthcare resources. The knowledge generated by this nationwide robust study has great potential to inform health policies and to improve the clinical outcomes of patients with asthma in Portugal.

Ethics and dissemination:

The study will follow the tenants of the Declaration of Helsinki and the Oviedo Convention. Ethical approvals and data privacy clearance for the study were obtained by the Ethics Committee and Data Protection Officer of the local health unit of

Matosinhos, Porto (ULSM; 38/CES/JAS, March 12th ,2021), Alto Minho (ULSAM; 38/2021/CES, June 17th, 2021) and the Regional Health Administration of Lisbon and Vale do Tejo (ARSLVT; 035/CES/INV/2021; December 3rd 2021) and is under revision in the remain regional ethical committees for health administration/local health units. All participants will receive both verbal and written information explaining the purpose of the study and they will have to provide verbal and written informed consent. Results will be presented at both national and international scientific meetings and published in peer-reviewed journals. Seasonal newsletters will be provided to the funders of the study as well as all the involved participants.

Statements

Patient consent for publication

Not applicable.

Authors' contributions

Jaime Correia de Sousa, João Almeida Fonseca and Filipa Bernardo conceptualised the study. Cristina Jácome wrote the statistical analysis plan and Pedro Teixeira conducted the sample size calculation. Cristina Jácome and Catarina João wrote the first draft of the manuscript. Cristina Jácome, Dinis Brito, Catarina João, Filipa Lopes, Janete Santos, Liliana Amorim, Maria João Barbosa, Marisa Pardal, Pedro Teixeira, Filipa Bernardo, João Almeida Fonseca, Jaime Correia de Sousa contributed to and refined the manuscript for scientific content. All authors read and approved the final version of the manuscript.

Competing interests

JCS reports Advisory Board from Boheringer Ingelheim, personal fees and Advisory Board from GSK, grants, personal fees and Advisory Board from AstraZeneca, personal fees and Advisory Board from Bial, non-financial support from Mundipharma, personal fees from Sanofi, Advisory Board from Novartis, outside the submitted work. JAF declares grants from or research agreements with AstraZeneca, Mundipharma, Sanofi Regeneron and Novartis. Personal fees for lectures and attending advisory boards from AstraZeneca, GSK, Mundipharma, Novartis, Sanofi Regeneron and TEVA. MP and FB are employees of AstraZeneca, Produtos Farmacêuticos. The remaining authors declare no conflicts of interest.

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Figures

Figure 1: Flow of participants through study´s stages. SuA - severe and difficult to treat asthma.

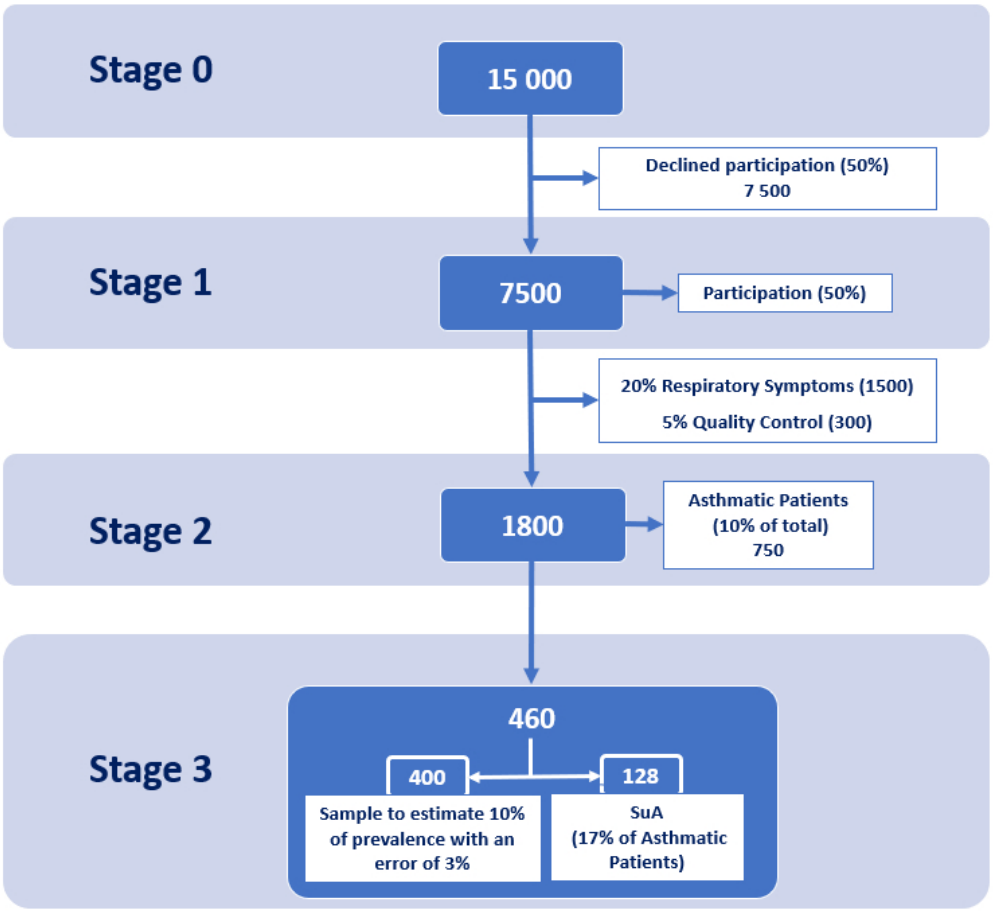

Figure 1: Flow of participants through study´s stages. SuA - severe and difficult to treat asthma.

62x57mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Item found on page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-11
Participants	6	(*a*) *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7-10
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11 and table 2
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	12 and 14
Study size	10	Explain how the study size was arrived at	6-7 and table 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	12-13
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12-13
		(*b*) Describe any methods used to examine subgroups and interactions	12-13
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	12-13
		(*e*) Describe any sensitivity analyses	NA

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	NA
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	NA
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	NA
Generalisability	21	Discuss the generalisability (external validity) of the study results	NA
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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