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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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Manuscripts

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4 1 **EPI-ASTHMA study protocol - a population-based multicentre stepwise study on**
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6 2 **the prevalence and characterisation of patients with asthma according to**
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8 3 **disease severity in Portugal**

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56 **ABSTRACT**
7

8 **Introduction:** In Portugal as in other countries, data on the epidemiology of asthma are
9
10 mainly grounded in questionnaire studies. Additionally, the detailed characterisation of
11
12 asthma in terms of disease severity, control and phenotypes remain scarce. Studies
13
14 assessing the prevalence of asthma and its sub-groups using accurate methods are
15
16 needed. This study aims to determine the prevalence of asthma, difficult-to-treat and
17
18 severe asthma, and to evaluate sociodemographic and clinical characteristics of those
19
20 patients, in mainland Portugal.
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22

23 **Methods and analysis:** A population-based nationwide study with a multicentre
24
25 stepwise approach will be conducted between 2021-2023 in 38 primary care centres of
26
27 the Portuguese National Health Service. The stepwise approach will comprise 4 Stages:
28
29 Stage 0-telephone call invitation to adult subjects (≥ 18 years) randomly selected
30
31 ($n \sim 15000$); Stage 1-telephone screening interview assessing the participants' respiratory
32
33 symptoms ($n \sim 7500$); Stage 2- diagnostic visit, including physical examination, diagnostic
34
35 tests (e.g., spirometry, fraction of exhaled nitric oxide, blood eosinophil count), and
36
37 patient-reported outcome measures for diagnostic confirmation of those identified with
38
39 possible asthma at Stage 1 ($n \sim 1800$); Stage 3-further evaluation of patients with asthma
40
41 and of patients with difficult-to-treat asthma and severe asthma, after 3 months ($n \sim 460$).
42
43 At Stage 3, data will be collected from a review of the patient's electronic health records,
44
45 a follow-up telephone call and the CARATm app database. The prevalence of asthma,
46
47 difficult-to-treat and severe asthma will be determined as the percentage of patients with
48
49 asthma confirmed from the overall population (Stage 1). For the analysis of factors
50
51 associated with asthma, difficult-to-treat and severe asthma, logistic regression models
52
53 will be explored.
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56
57 **Ethics and dissemination:** Ethical approvals for the study were obtained from the
58
59 ethics committee of the local health unit of Matosinhos, Porto (38/CES/JAS), Alto Minho
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3 52 (38/2021/CES) and the regional health administration of Lisbon-Vale do Tejo
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5 53 (035/CES/INV/2021). Results will be published in peer-reviewed journals.
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9 55 Trial registration: ClinicalTrials.gov, NCT051696198. Registered at 27th December 2022.
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13 56

14 57 Strengths and limitations of this study

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17 58 - EPI-ASTHMA is the first national population-based study with a multicentre stepwise
18
19 59 approach to determine the prevalence of asthma, difficult-to-treat and severe asthma In
20
21 60 Portugal.

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23
24 61 - The outcome measures will enable a more comprehensive characterisation of patients
25
26 62 with asthma and a better understanding of their disease characteristics, treatment
27
28 63 patterns and use of healthcare resources.

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30
31 64 - The knowledge generated by this study has great potential to inform health policies and
32
33 65 to improve the clinical outcomes of patients with asthma in Portugal.

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35
36 66 - Time limited follow-up with lack of optimised management might be a source of error
37
38 67 in the estimation of the prevalence of asthma sub-groups.

39
40
41 68 - Heterogeneity in data collection across the country conveniently select regions may
42
43 69 prove challenging and a source of bias.

44
45 70 **Keywords:** disease severity, severe asthma, difficult-to-treat asthma, epidemiology
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75 Introduction

76
77 Asthma is a common chronic disease affecting all age groups. Worldwide, it is estimated
78 that about 5 to 10% of people have asthma [1], with a significant wide variation across
79 regions and countries [2]. To date, epidemiological data on prevalence have used
80 heterogeneous methodologies due to difficulties in defining and diagnosing asthma,
81 leading to highly variable estimates of asthma prevalence [3]. Some studies used non-
82 standardised questionnaires, others included participants based on the assessment of
83 lung function or responsiveness to bronchodilators. In Portugal, the 2011 National
84 Asthma Survey was based on telephone interviews and indicated a prevalence of 6.8%
85 [4]. Yet, previous studies have estimated a prevalence between 3.3 and 15% [5].
86 Furthermore, similarly to the USA and Denmark Asthma Surveys, the 2005-2006
87 Portuguese Health Survey, suggested that there is an underdiagnosis of asthma,
88 particularly in the male population and in the country's southern regions [5]. The
89 Portuguese National Program for Respiratory Diseases maintains strategic research
90 objectives in epidemiological surveillance both in asthma prevalence and its
91 underdiagnosis [6], which is in line with the recommendations from the Global Initiative
92 for Asthma (GINA) [7].

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

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3 102 inform personalised health policies for a future and smarter allocation of healthcare
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5 103 resources.

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8 104 The primary aim of this study is to determine the prevalence of asthma, difficult-to-treat
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10 105 and severe asthma in Portugal. The secondary aims are to evaluate the
11
12 106 sociodemographic and clinical characteristics of patients with asthma.

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16 17 108 **METHODS AND ANALYSIS**

18 19 109 **Patient and Public Involvement**

20
21 110 No patient involved

22 23 111 **Study Design**

24
25 112 EPI-ASTHMA is a population-based, nationwide, cross-sectional, prevalence study. This
26
27 113 study will be conducted between 2021 and 2023, and will involve 38 primary care centres
28
29 114 (PCC) of the Portuguese National Health Service (NHS), geographically distributed
30
31 115 across all mainland Portugal Health Regions (North, Centre, Lisbon Metropolitan Area,
32
33 116 Alentejo and Algarve). EPI-ASTHMA will be first piloted in one local health unit located
34
35 117 in the North region, where all study procedures will be tested; after that, it will follow the
36
37 118 order of approval of the ethics committee from each local health unit and regional health
38
39 119 administrations. The study will be conducted using a stepwise approach parallel to a
40
41 120 clinical practice diagnostic methodology. Firstly, subjects will be invited for a screening
42
43 121 telephone interview to report respiratory symptoms, those who fulfil the eligible criteria
44
45 122 will be invited for a clinical assessment in a mobile outpatient clinic. A sub-group of
46
47 123 participants with confirmed asthma diagnosis will have a follow-up after 3 months for
48
49 124 characterization of their asthma profile, symptoms patterns, clinical features, and
50
51 125 treatment patterns. This study protocol is described according to STROBE (The
52
53 126 Strengthening the Reporting of Observational Studies in Epidemiology Statement:
54
55 127 guidelines for reporting observational studies)[11].
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128 **Study population and sample size**

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

$$130 \quad n = \frac{Z^2 P(1-P)}{d^2} \quad (1)$$

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

153

154 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	555628	2	850	425	103	26
Lafões/Beiras/Serra da Estrela/Beira Baixa						
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

155 NUTS - Nomenclature of Territorial Units for Statistics.

156 **Study procedures**

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

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

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3 161 ● **Stage 1- Screening interview:** Telephone call interview to assess respiratory
4 symptoms;
5 162
6
7 163 ● **Stage 2- Diagnostic visit:** Clinical assessment, diagnostic confirmation and
8 patient characterization;
9 164
10
11 165 ● **Stage 3- Sub-group asthma characterization:** follow-up of patients with
12 asthma (sub-group) and of patients with difficult-to-treat asthma and severe
13 asthma, after 3 months.
14 166
15 167

168 **Stage 0- Study enrolment**

169 Around 15,000 randomised subjects 18 years or above will receive a telephone call
170 invitation for enrolment in the study, to secure a sample size of 7500 participants for the
171 next stage (assuming an acceptance of 50%)[14]. If needed, a second round of
172 telephone calls will also be made to complete the number of patients in each region.
173 Trained clinical secretaries will conduct this stage by following a semi-structured guide
174 during the telephone call. A screening log of potential eligible participants will be
175 completed to document the main reasons for participants not entering the study. Subjects
176 who fulfil the study eligibility criteria and give their oral consent will be contacted in Stage
177 1.

178 **Stage 1- Screening interview**

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

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3 188 performed by a centralised team of trained and experienced interviewers. Each
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5 189 participant will be contacted for at least ten attempts during different occasions before
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7 190 being considered excluded. Prior to any question, participants will be asked to reinforce
8
9 191 their oral consent to participate. A pilot study with 12 individuals was conducted to assess
10
11 192 the clarity and feasibility of the screening interview before starting the data collection
12
13 193 [20]. The duration of each interview was no longer than 17 minutes.

16 194 **Stage 2 – Diagnostic visit**

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19 195 The diagnostic visit will be conducted in a mobile outpatient clinic, located, whenever
20
21 196 possible, in the close vicinity of each PCC. At this stage, participants will give a written
22
23 197 informed consent before any study-related procedures. Stage 2 is expected to include
24
25 198 1800 participants, about 20% of participants from Stage 1 who fulfil the eligibility criteria,
26
27 199 plus 5% of participants for quality control. A detailed clinical assessment will be
28
29 200 performed, including clinical history, physical examination, lung function tests, blood
30
31 201 count and inflammatory biomarkers testing and patient-reported outcome measures
32
33 202 (Table 2). The clinical assessment will be carried out by a physician and the diagnostic
34
35 203 tests by an experienced team to assure the quality and the harmonisation of procedures.
36
37 204 All patients will be provided with a letter addressed to their primary care physician,
38
39 205 containing the results of their clinical evaluation. Patients with asthma will also be invited
40
41 206 to install and use the CARATm app (“Características Auto-reportadas de Asma em
42
43 207 Tecnologias Móveis”) in their daily life. CARATm is a Portuguese health mobile app
44
45 208 developed to collect clinical data from patients with asthma, such as asthma control and
46
47 209 medication adherence, which is also interoperable with the Portuguese Severe Asthma
48
49 210 Registry (asmagrave.pt).

52 211

54 212 **Stage 3- Sub-group asthma characterization**

57 213 This stage is expected to include 460 participants: a randomised sample of patients with
58
59 214 asthma, and all patients identified with difficult-to-treat or severe asthma. Patients with
60

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3 215 difficult-to-treat and severe asthma will be defined according to GINA[21]. This stage
4
5 216 takes place 3-months after the diagnostic visit and consists of a review of patients'
6
7 217 electronic health records, a follow-up telephone call to the patient, and extraction of
8
9 218 CARATm app data. The review of patients' electronic health records by a physician of
10
11 219 their PCC will ensure an asthma control assessment on two different time points, and
12
13 220 will confirm the treatment profile for an adequate GINA severity classification [7] (Table
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16 221 2).

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

224

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

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

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.

225

226 Data storage, blinding and statistical analysis plan

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

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

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2
3 240 subgroups. Associations between two quantitative variables will be calculated using the
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5 241 Pearson's correlation coefficient or Spearman correlation coefficient, in case of normality
6
7 242 assumption are not verified. Association of two categorical variables will be determined
8
9 243 using the Chi-Square test or Fisher Exact test. Continuous variables between two groups
10
11 244 will be compared with a t-test for independent samples or Mann-Whitney test, whereas
12
13 245 for comparisons among 3 or more groups an ANOVA or Kruskal-Wallis test will be used.
14
15 246 Null-hypothesis statistical testing will also be applied in an exploratory manner to identify
16
17 247 any relationship patterns among variables. Subgroup analysis per each asthma control
18
19 248 level, GINA treatment step, Short-Acting Beta Agonists (SABA) overuse among others,
20
21 249 will also be conducted. Measurements of effect size will be presented and confidence
22
23 250 intervals at 95% will be estimated to account for the uncertainty of the sample estimates.
24
25 251 Interim analysis will be conducted per region after all stages are completed.

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29 252 For the analysis of factors associated with asthma, difficult-to-treat asthma and severe
30
31 253 asthma, logistic regression models will be explored, taking into consideration these as
32
33 254 dependent variables and sociodemographic, clinical, among other variables, as
34
35 255 independent variables. The variables to be included in the multivariate model will be
36
37 256 selected from the univariate analyses, when p-value <0.100 , those that do not meet
38
39 257 these criteria, but are considered clinically relevant, will also be possible candidates. The
40
41 258 final model will be analysed from two perspectives: 1) the calibration using the Hosmer-
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43 259 Lemeshow goodness of fit test, and 2) the discrimination, using ROC curves and the
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45 260 respective area under the curve. All results will be considered statistically significant
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47 261 when p-value <0.05 .

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51 52 53 263 **DISCUSSION**

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3 265 The EPI-ASTHMA study will address knowledge gaps in the epidemiology and
4
5 266 characterisation of asthma in mainland Portugal, using a multicentre approach that
6
7 267 combines different data collection methods, including a mHealth solution. Furthermore,
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9 268 it will provide a more complete picture of the prevalence of difficult-to-treat and severe
10
11 269 asthma in Portugal, and will allow a better understanding of these patients'
12
13 270 characteristics, treatment profile and healthcare resource use. Further knowledge on the
14
15 271 distribution of severity and characteristics of patients in each group will better support
16
17 272 clinical management of the disease and inform personalised health policies for a smarter
18
19 273 allocation of the needed healthcare resources. This ambitious study is aligned with the
20
21 274 global need of epidemiological studies to monitor the trends in the prevalence of asthma,
22
23
24 275 which is vital to ensure that health policies fit the populations' needs [2,28,29].
25

26
27 276 The study design is one of its strengths. The combination of standardised questionnaires
28
29 277 with a standardised clinical evaluation, including lung function tests will allow a more
30
31 278 accurate diagnosis and characterisation of asthma. However, few limitations and
32
33 279 potential risks must be acknowledged. The definition of difficult-to-treat and severe
34
35 280 asthma will be based on the GINA treatment steps (4-5) and the assessment of asthma
36
37 281 control during the study Stages 2 and 3, which is only 3-months apart. An optimised
38
39 282 management during the follow-up period was not included, which is also part of the GINA
40
41 283 criteria to distinguish these asthma subgroups. This will probably be a source of error in
42
43 284 the estimation of the prevalence of these sub-groups, linked to the observational nature
44
45 285 of this study. The 38 PCC will be conveniently selected, which can be seen as a source
46
47 286 of bias. Yet, we considered the geographic areas and population distribution of each
48
49 287 Portuguese region as well as their interest to participate and willingness to collect data
50
51 288 and not only based on previous asthma research experience which will preserve the
52
53 289 study real-world nature. Clinical secretaries (Stage 0) and physicians (Stage 2 and 3)
54
55 290 will collaborate across different country's regions, which may introduce some
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57 291 heterogeneity in data collection. Nevertheless, both clinical secretaries and physicians
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3 292 will be previously trained and continuously motivated by the management team, which
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5 293 will be available to clarify doubts on a 24/7 basis. To deal with possible risks, the study's
6
7 294 steering committee will supervise the execution and will take academic responsibility for
8
9 295 the study. Another limitation is the need for this multicentre study to be approved by the
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11 296 ethics committees responsible for each regional health administration/local health unit.
12
13 297 Although all applications will be similar in their content, they will differ in a number of
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15 298 aspects to comply with each institution's formal requirements, resulting in additional
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17 299 complexity and may hinder the compliance with the study timeline. To mitigate these
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19 300 risks, an experienced contracted research organisation that knows the specificities of
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21 301 each administration/health unit is supporting us through all the process.

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24 302 EPI-ASTHMA will be managed combining traditional management methodologies with
25
26 303 an "agile" approach [30] using the SCRUM framework on Jira software. This combination
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28 304 is expected to fulfil the need to make the study adaptable and to anticipate future needs
29
30 305 that are important and can be forgotten due to the dimension of the study.

306 **Conclusion**

307
308 EPI-ASTHMA will be the first population-based study in Portugal to determine the
309
310 prevalence of asthma, difficult-to-treat and severe asthma and to better understand the
311
312 patient's disease characteristics, treatment patterns and use of healthcare resources.
313
314 The knowledge generated by this nationwide robust study has great potential to inform
315
316 health policies and to improve the clinical outcomes of patients with asthma in Portugal.

317 **Ethics and dissemination:**

318
319 The study will follow the tenants of the Declaration of Helsinki and the Oviedo
320
321 Convention. Ethical approvals and data privacy clearance for the study were obtained
322
323 by the Ethics Committee and Data Protection Officer of the local health unit of
324
325 Matosinhos, Porto (ULSM; 38/CES/JAS, March 12th ,2021), Alto Minho (ULSAM;
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327 38/2021/CES, June 17th, 2021) and the Regional Health Administration of Lisbon and
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3 319 Vale do Tejo (ARSLVT; 035/CES/INV/2021; December 3rd 2021) and is under revision
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5 320 in the remain regional ethical committees for health administration/local health units. All
6
7 321 participants will received both verbal and written information explaining the purpose of
8
9 322 the study and they will have to provided verbal and written informed consent. Results will
10
11 323 be presented at both national and international scientific meetings and published in peer-
12
13 324 reviewed journals. Seasonal newsletters will be provided to the funders of the study as
14
15 325 well as all the involved participants.
16
17
18 326

327 **Statements**

328 Patient consent for publication

329 Not applicable.
30
31 330

331 Authors' contributions

332 JCA, JAF and FB conceptualised the study. CJ wrote the statistical analysis plan and
333 PT conducted the sample size calculation. CJ and CJO wrote the first draft of the
334 manuscript. All authors contributed to and refined the manuscript for scientific content.
335 All authors read and approved the final version of the manuscript.
336

337 Competing interests

338 JCS reports Advisory Board from Boheringer Ingelheim, personal fees and Advisory
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1
2
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4
5 345 are employees of AstraZeneca, Produtos Farmacêuticos. The remaining authors declare
6
7 346 no conflicts of interest.
8

9 347

10
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13
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435 **Figures**

436 **Figure 1:** Flow of participants through study's stages. SuA - severe and difficult to treat
437 asthma.

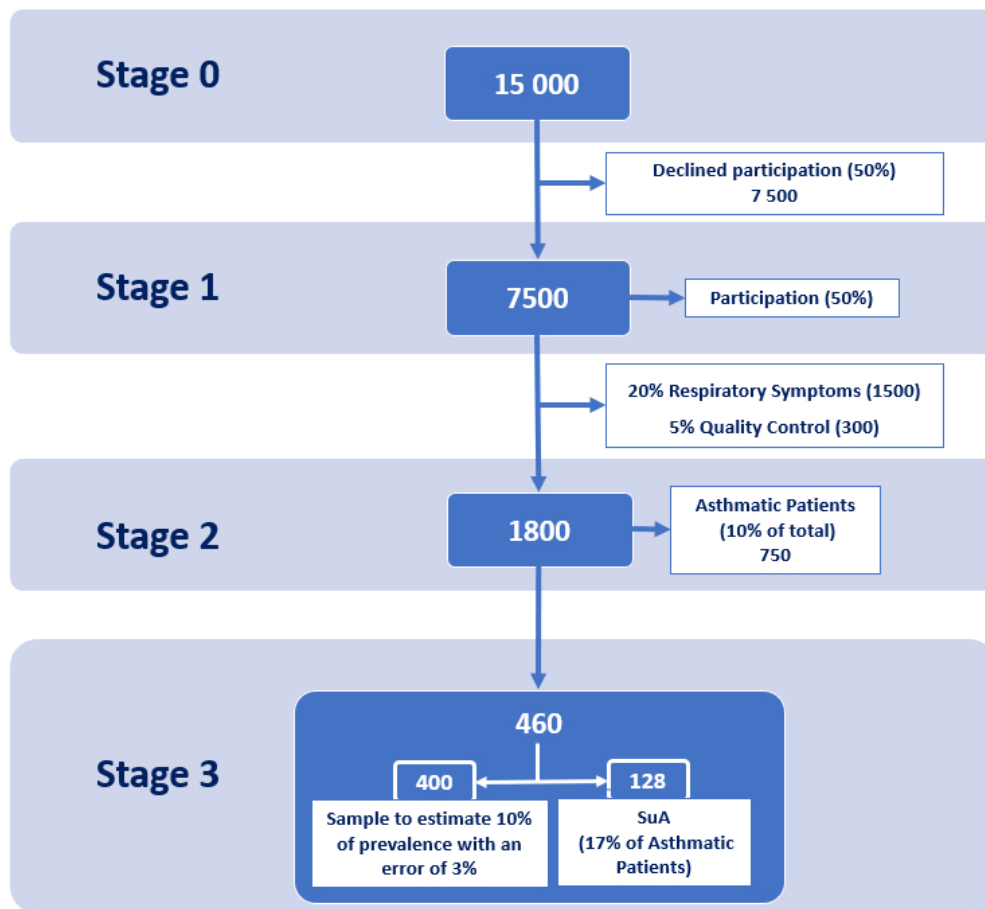


Figure 1: Flow of participants through study’s stages. SuA - severe and difficult to treat asthma.

62x57mm (300 x 300 DPI)

BMJ Open

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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Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Research methods
Keywords:	Asthma < THORACIC MEDICINE, EPIDEMIOLOGY, Chronic airways disease < THORACIC MEDICINE

SCHOLARONE™
Manuscripts

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4 **1 EPI-ASTHMA study protocol - a population-based multicentre stepwise study on**
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6 **2 the prevalence and characterisation of patients with asthma according to**
7
8 **3 disease severity in Portugal**

9
10 4 Cristina Jácome^{1,2}, Dinis Brito^{3,4}, Catarina João¹, Filipa Lopes⁵, Janete Santos¹, Liliana
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12 5 Amorim⁶, Maria João Barbosa^{3,9}, Marisa Pardal⁷, Pedro Teixeira^{3,6}, Filipa Bernardo⁷,
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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 ($n \sim 15000$); Stage 1-telephone screening interview assessing the participants' respiratory symptoms ($n \sim 7500$); 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 ($n \sim 1800$); Stage 3-further evaluation of patients with asthma and of patients with difficult-to-treat asthma and severe asthma, after 3 months ($n \sim 460$). 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.

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3 50 **Ethics and dissemination:** Ethical approvals for the study were obtained from the ethics
4
5 51 committee of the local health unit of Matosinhos, Porto (38/CES/JAS), Alto Minho
6
7 52 (38/2021/CES) and the regional health administration of Lisbon-Vale do Tejo
8
9 53 (035/CES/INV/2021). Results will be published in peer-reviewed journals.
10

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13 55 Trial registration: ClinicalTrials.gov, NCT05169619. Registered on December 27th 2021.
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19 57 Strengths and limitations of this study

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22 58 - The design of this study is based on a stepwise approach, divided in 4 stages,
23
24 59 that mimics the clinical practice diagnostic pathway for asthma.
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26 60 - This study allows a reliable diagnosis and characterization of asthma patients
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28 61 through the use of questionnaires together with clinical examination that includes
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30 62 lung function assessment.
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32 63 - A mHealth application to engage patients on self-management of their disease
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34 64 and to improve completeness of the data collection is used.
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36 65 - The 3-month follow-up with lack of optimised management might be a source of
37
38 66 error in the estimation of the prevalence of asthma sub-groups.
39
40 67 - Heterogeneity in data collection across the country regions may prove
41
42 68 challenging and a possible source of bias.
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45 69 **Keywords:** disease severity, severe asthma, difficult-to-treat asthma, epidemiology
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75 Introduction

76

77 Asthma is a common chronic disease affecting all age groups. Worldwide, it is estimated
78 that about 5 to 10% of people have asthma [1], with a significant wide variation across
79 regions and countries [2]. To date, epidemiological data on prevalence have used
80 heterogeneous methodologies due to difficulties in defining and diagnosing asthma,
81 leading to highly variable estimates of asthma prevalence [3]. Some studies used non-
82 standardised questionnaires, others included participants based on the assessment of
83 lung function or responsiveness to bronchodilators. In Portugal, the 2011 National
84 Asthma Survey was based on telephone interviews and indicated a prevalence of 6.8%
85 [4]. Yet, previous studies have estimated a prevalence between 3.3 and 15% [5].
86 Furthermore, similarly to the USA and Denmark Asthma Surveys, the 2005-2006
87 Portuguese Health Survey, suggested that there is an underdiagnosis of asthma,
88 particularly in the male population and in the country's southern regions [5]. The
89 Portuguese National Program for Respiratory Diseases maintains strategic research
90 objectives in epidemiological surveillance both in asthma prevalence and its
91 underdiagnosis [6], which is in line with the recommendations from the Global Initiative
92 for Asthma (GINA) [7].

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

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3 102 inform personalised health policies for a future and smarter allocation of healthcare
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5 103 resources.

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8 104 The primary aim of this study is to determine the prevalence of asthma, difficult-to-treat
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10 105 and severe asthma in Portugal. The secondary aims are to evaluate the
11
12 106 sociodemographic and clinical characteristics of patients with asthma.

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16 17 108 **METHODS AND ANALYSIS**

18 19 109 **Patient and Public Involvement**

20
21 110 No patient involved

22 23 111 **Study Design**

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26
27 112 EPI-ASTHMA is a population-based, nationwide, cross-sectional, prevalence study. This
28
29 113 study will be conducted between 2021 and 2023, and will involve 38 primary care centres
30
31 114 (PCC) of the Portuguese National Health Service (NHS), geographically distributed
32
33 115 across all mainland Portugal Health Regions (North, Centre, Lisbon Metropolitan Area,
34
35 116 Alentejo and Algarve). The study will be conducted using a stepwise approach parallel
36
37 117 to a clinical practice diagnostic methodology. Firstly, subjects will be invited for a
38
39 118 screening telephone interview to report respiratory symptoms, those who fulfil the eligible
40
41 119 criteria will be invited for a clinical assessment in a mobile outpatient clinic. A sub-group
42
43 120 of participants with confirmed asthma diagnosis will have a follow-up after 3 months for
44
45 121 characterization of their asthma profile, symptoms patterns, clinical features, and
46
47 122 treatment patterns. EPI-ASTHMA was first piloted in one local health unit located in the
48
49 123 North region from May to October 2021, where all study procedures were tested; after
50
51 124 which, implementation is planned to follow the order of approval of the ethics committee
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53 125 from each local health unit and regional health administrations. Currently, the study has
54
55 126 been concluded in 4 PCC in Northern Portugal.
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3 127 This study protocol is described according to STROBE (The Strengthening the Reporting
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5 128 of Observational Studies in Epidemiology Statement: guidelines for reporting
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7 129 observational studies) statement [11].
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13 131 **Study population and sample size**

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16 132 Sample size was estimated using Cochran's formula [12]:
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19 133
$$n = \frac{Z^2 P(1-P)}{d^2} \quad (1)$$

20
21

22 134 Where n is the sample size, Z is the statistic corresponding to level of confidence, P is
23
24 135 expected prevalence of Severe Asthma, and d is the desired level of precision (i.e. the
25
26 136 margin of error). Applying a $Z = 1.96$ (i.e. 95% confidence interval), an estimated
27
28 137 prevalence in the population of $P = 0.42\%$ and a margin of error of 0.15% the estimated
29
30 138 sample size is 7141. In order to obtain 7500 participants on screening we consider a
31
32 139 stepwise approach with a 50% dropout on invitation. Therefore, around 15000 adults will
33
34 140 be randomly selected from the Portuguese NHS database to be contacted and invited to
35
36 141 enrol in the study. In Portugal, the majority of the population (including Portuguese
37
38 142 nationals and legal residents) is registered in a PCC, therefore the NHS database
39
40 143 includes almost the entire resident population in the local administrative entity (i.e.,
41
42 144 Nomenclature of Territorial Units for Statistics-NUTS). The sample stratification was
43
44 145 based on demographic stratification NUTS III, small regions for specific diagnoses as
45
46 146 per EUROSTAT classification. For each NUTS III, the PCC were selected according to
47
48 147 the feasibility of implementing the study (in total 38 PCC, 31 are part of the regional
49
50 148 health administrations and 7 of local health units). The number of participants will be
51
52 149 randomly selected according to the proportional allocation of each PCC. The distribution
53
54 150 of an estimated stratified sample by NUTS III and the correspondent study Stages is
55
56 151 presented in Table 1. The study will include male or female subjects with at least 18
57
58 152 years old, registered in the NHS database, who give voluntary consent. Subjects with
59
60

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

156

157 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	555628	2	850	425	103	26
Lafões/Beiras/Serra da Estrela/Beira Baixa						
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

158 NUTS - Nomenclature of Territorial Units for Statistics.

159 **Study procedures**

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

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

171 **Stage 0- Study enrolment**

172 Around 15,000 randomised subjects 18 years or above will receive a telephone call
173 invitation for enrolment in the study, to secure a sample size of 7500 participants for the
174 next stage (assuming an acceptance of 50%) [14]. If needed, a second round of
175 telephone calls will also be made to complete the number of patients in each region.
176 Trained clinical secretaries will conduct this stage by following a semi-structured guide
177 during the telephone call. A screening log of potential eligible participants will be
178 completed to document the main reasons for participants not entering the study. Subjects
179 who fulfil the study eligibility criteria and give their oral consent will be contacted in Stage
180 1.

181 **Stage 1- Screening interview**

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

1
2
3 185 dyspnoea [17] and assessment of physical activity [18,19], among other questions
4
5 186 formulated by the researchers (Table 2). At this stage participants will be considered
6
7 187 eligible and invited to participate in Stage 2 if they have, at least, one positive response
8
9 188 in the Adult Asthma Score (A2 Score) [15], i.e., medical history of asthma or asthma
10
11 189 medication intake or asthma symptoms. For quality control, 5% of not eligible participants
12
13 190 (with a negative score) will also be invited to participate in Stage 2. Interviews will be
14
15 191 performed by a centralised team of trained and experienced interviewers. Each
16
17 192 participant will be contacted for at least ten attempts during different occasions before
18
19 193 being considered excluded. Prior to any question, participants will be asked to reinforce
20
21 194 their oral consent to participate. A pilot study with 12 individuals was conducted to assess
22
23 195 the clarity and feasibility of the screening interview before starting the data collection
24
25 196 [20]. The duration of each interview was no longer than 17 minutes.

28 29 197 **Stage 2 – Diagnostic visit**

30
31 198 The diagnostic visit will be conducted in a mobile outpatient clinic, located, whenever
32
33 199 possible, in the close vicinity of each PCC. At this stage, participants will give a written
34
35 200 informed consent before any study-related procedures. Stage 2 is expected to include
36
37 201 1800 participants, about 20% of participants from Stage 1 who fulfil the eligibility criteria,
38
39 202 plus 5% of participants for quality control. A detailed clinical assessment will be
40
41 203 performed, including clinical history, physical examination, lung function tests, blood
42
43 204 count and inflammatory biomarkers testing and patient-reported outcome measures
44
45 205 (Table 2). The clinical assessment will be carried out by a physician and the diagnostic
46
47 206 tests by an experienced team to assure the quality and the harmonisation of procedures.
48
49 207 All patients will be provided with a letter addressed to their primary care physician,
50
51 208 containing the results of their clinical evaluation. Patients with asthma will also be invited
52
53 209 to install and use the CARATm app (“Características Auto-reportadas de Asma em
54
55 210 Tecnologias Móveis”) in their daily life. CARATm is a Portuguese health mobile app
56
57 211 developed to collect clinical data from patients with asthma, such as asthma control and
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212 medication adherence, which is also interoperable with the Portuguese Severe Asthma
213 Registry (asmagrave.pt).

214

215 **Stage 3- Sub-group asthma characterization**

216 This stage is expected to include 460 participants: a randomised sample of patients with
217 asthma, and all patients identified with difficult-to-treat or severe asthma. Patients with
218 difficult-to-treat and severe asthma will be defined according to GINA[21]. This stage
219 takes place 3-months after the diagnostic visit and consists of a review of patients'
220 electronic health records, a follow-up telephone call to the patient, and extraction of
221 CARATm app data. The review of patients' electronic health records by a physician of
222 their PCC will ensure an asthma control assessment on two different time points, and
223 will confirm the treatment profile for an adequate GINA severity classification [7] (Table
224 2).

225

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

227

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

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

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.

228

229 **Diagnosis criteria and definitions**

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

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3 236 Difficult-to-treat asthma is asthma that is uncontrolled despite treatment with medium or
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5 237 high dose inhaled corticosteroids with a second controller or with maintenance oral
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7 238 corticosteroids, or that requires high dose treatment to maintain symptom control and to
8
9 239 reduce the risk of exacerbations [21]. In our study, difficult-to-treat asthma will be defined
10
11 240 as uncontrolled asthma, despite prescription of high intensity treatment (GINA step
12
13 241 treatment 4-5). Severe asthma is a subset of difficult-to-treat asthma, that is an
14
15 242 uncontrolled asthma despite adherence with maximal optimised high dose ICS-LABA
16
17 243 (inhaled corticosteroid and a long-acting β 2-agonist) treatment and management of
18
19 244 contributory factors, such as inhaler adherence and technique or asthma that worsens
20
21 245 when high dose treatment is decreased. We will define severe asthma in the study as
22
23 246 uncontrolled asthma despite prescription of high intensity treatment (GINA step
24
25 247 treatment 4-5), and good treatment adherence (visual analogue scale (VAS) ≥ 50) [29]
26
27 248 and good inhaler technique (number of critical errors = [0-1]) [30].
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32 **Data storage, blinding and statistical analysis plan**

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34 250 Participants will be anonymized with a unique subject ID and their data will be
35
36 251 anonymously stored in an appropriately secured server. In order to minimise diagnostic
37
38 252 bias, researchers, data collectors and participants will be blinded to patient eligibility
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40 253 throughout data collection during Stage 2. Over the stages, data will be collected for a
41
42 254 specific electronic case report form (e-CRF) by using blended data (primary and
43
44 255 secondary data).
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47 256 Statistical analysis will allow the characterization of the study population and the
48
49 257 estimation of each study's endpoints. The prevalence of asthma, difficult-to-treat and
50
51 258 severe asthma with the respective 95% confidence intervals (95% CI) will be calculated
52
53 259 in relation to the entire study population (Stage 1). Descriptive statistics such as i) central
54
55 260 tendency (e.g. mode, median or mean); ii) localisation (e.g. percentile); iii) dispersion
56
57 261 (e.g. interquartile range, standard deviation) and iv) distribution (e.g. skewness, kurtosis)
58
59 262 will be used, depending on the type of each variable, to characterise the total sample or
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3 263 subgroups. Associations between two quantitative variables will be calculated using the
4
5 264 Pearson's correlation coefficient or Spearman correlation coefficient, in case of normality
6
7 265 assumption are not verified. Association of two categorical variables will be determined
8
9 266 using the Chi-Square test or Fisher Exact test. Continuous variables between two groups
10
11 267 will be compared with a t-test for independent samples or Mann-Whitney test, whereas
12
13 268 for comparisons among 3 or more groups an ANOVA or Kruskal-Wallis test will be used.
14
15 269 Null-hypothesis statistical testing will also be applied in an exploratory manner to identify
16
17 270 any relationship patterns among variables. Subgroup analysis per each asthma control
18
19 271 level, GINA treatment step, Short-Acting Beta Agonists (SABA) overuse among others,
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21 272 will also be conducted. Measurements of effect size will be presented and confidence
22
23 273 intervals at 95% will be estimated to account for the uncertainty of the sample estimates.
24
25 274 Interim analysis will be conducted per region after all stages are completed to monitor
26
27 275 the safety of study procedures and completeness of data collection. This analysis may
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29 276 encompass potential changes in logistical, monitoring, and recruitment procedures to
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31 277 secure sample size.
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35 278 For the analysis of factors associated with asthma, difficult-to-treat asthma and severe
36
37 279 asthma, logistic regression models will be explored, taking into consideration these as
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39 280 dependent variables and sociodemographic, clinical, among other variables, as
40
41 281 independent variables. The variables to be included in the multivariate model will be
42
43 282 selected from the univariate analyses, when p-value <0.100, those that do not meet
44
45 283 these criteria, but are considered clinically relevant, will also be possible candidates. The
46
47 284 final model will be analysed from two perspectives: 1) the calibration using the Hosmer-
48
49 285 Lemeshow goodness of fit test, and 2) the discrimination, using ROC curves and the
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51 286 respective area under the curve. All results will be considered statistically significant
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53 287 when p-value <0.05.
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3 289 **DISCUSSION**
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8 291 The EPI-ASTHMA study will address knowledge gaps in the epidemiology and
9
10 292 characterisation of asthma in mainland Portugal, using a multicentre approach that
11
12 293 combines different data collection methods, including a mHealth solution. Furthermore,
13
14 294 it will provide a more complete picture of the prevalence of difficult-to-treat and severe
15
16 295 asthma in Portugal, and will allow a better understanding of these patients'
17
18 296 characteristics, treatment profile and healthcare resource use. Further knowledge on the
19
20 297 distribution of severity and characteristics of patients in each group will better support
21
22 298 clinical management of the disease and inform personalised health policies for a smarter
23
24 299 allocation of the needed healthcare resources. This ambitious study is aligned with the
25
26 300 global need of epidemiological studies to monitor the trends in the prevalence of asthma,
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28 301 which is vital to ensure that health policies fit the populations' needs [2,31,32].
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31 302 The study design is one of its strengths. The combination of standardised questionnaires
32
33 303 with a standardised clinical evaluation, including lung function tests will allow a more
34
35 304 accurate diagnosis and characterisation of asthma. However, few limitations and
36
37 305 potential risks must be acknowledged. The definition of difficult-to-treat and severe
38
39 306 asthma will be based on the GINA treatment steps (4-5) and the assessment of asthma
40
41 307 control during the study Stages 2 and 3, which is only 3-months apart. An optimised
42
43 308 management during the follow-up period was not included, which is also part of the GINA
44
45 309 criteria to distinguish these asthma subgroups. This will probably be a source of error in
46
47 310 the estimation of the prevalence of these sub-groups, linked to the observational nature
48
49 311 of this study. The 38 PCC will be conveniently selected, which can be seen as a source
50
51 312 of bias. Yet, we considered the geographic areas and population distribution of each
52
53 313 Portuguese region as well as their interest to participate and willingness to collect data
54
55 314 and not only based on previous asthma research experience which will preserve the
56
57 315 study real-world nature. Clinical secretaries (Stage 0) and physicians (Stage 2 and 3)
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3 316 will collaborate across different country's regions, which may introduce some
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5 317 heterogeneity in data collection. Nevertheless, both clinical secretaries and physicians
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7 318 will be previously trained and continuously motivated by the management team, which
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9 319 will be available to clarify doubts on a 24/7 basis. To deal with possible risks, the study's
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11 320 steering committee will supervise the execution and will take academic responsibility for
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13 321 the study. Another limitation is the need for this multicentre study to be approved by the
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15 322 ethics committees responsible for each regional health administration/local health unit.
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17 323 Although all applications will be similar in their content, they will differ in a number of
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19 324 aspects to comply with each institution's formal requirements, resulting in additional
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21 325 complexity and may hinder the compliance with the study timeline. To mitigate these
22
23 326 risks, an experienced contracted research organisation that knows the specificities of
24
25 327 each administration/health unit is supporting us through all the process.
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29 328 EPI-ASTHMA will be managed combining traditional management methodologies with
30
31 329 an "agile" approach [33] using the SCRUM framework on Jira software. This combination
32
33 330 is expected to fulfil the need to make the study adaptable and to anticipate future needs
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35 331 that are important and can be forgotten due to the dimension of the study.
36
37

38 **Conclusion**

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40 333
41 334 EPI-ASTHMA will be the first population-based study in Portugal to determine the
42
43 335 prevalence of asthma, difficult-to-treat and severe asthma and to better understand the
44
45 336 patient's disease characteristics, treatment patterns and use of healthcare resources.
46
47 337 The knowledge generated by this nationwide robust study has great potential to inform
48
49 338 health policies and to improve the clinical outcomes of patients with asthma in Portugal.
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52 **Ethics and dissemination:**

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54
55 340 The study will follow the tenants of the Declaration of Helsinki and the Oviedo
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57 341 Convention. Ethical approvals and data privacy clearance for the study were obtained
58
59 342 by the Ethics Committee and Data Protection Officer of the local health unit of
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3 343 Matosinhos, Porto (ULSM; 38/CES/JAS, March 12th ,2021), Alto Minho (ULSAM;
4
5 344 38/2021/CES, June 17th, 2021) and the Regional Health Administration of Lisbon and
6
7 345 Vale do Tejo (ARSLVT; 035/CES/INV/2021; December 3rd 2021) and is under revision
8
9 346 in the remain regional ethical committees for health administration/local health units. All
10
11 347 participants will receive both verbal and written information explaining the purpose of the
12
13 348 study and they will have to provide verbal and written informed consent. Results will be
14
15 349 presented at both national and international scientific meetings and published in peer-
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17 350 reviewed journals. Seasonal newsletters will be provided to the funders of the study as
18
19 351 well as all the involved participants.
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353 **Statements**

354 Patient consent for publication

355 Not applicable.

356

357 Authors' contributions

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

366

367 Competing interests

1
2
3 368 JCS reports Advisory Board from Boheringer Ingelheim, personal fees and Advisory
4
5 369 Board from GSK, grants, personal fees and Advisory Board from AstraZeneca, personal
6
7 370 fees and Advisory Board from Bial, non-financial support from Mundipharma, personal
8
9 371 fees from Sanofi, Advisory Board from Novartis, outside the submitted work. JAF
10
11 372 declares grants from or research agreements with AstraZeneca, Mundipharma, Sanofi
12
13 373 Regeneron and Novartis. Personal fees for lectures and attending advisory boards from
14
15 374 AstraZeneca, GSK, Mundipharma, Novartis, Sanofi Regeneron and TEVA. MP and FB
16
17 375 are employees of AstraZeneca, Produtos Farmacêuticos. The remaining authors declare
18
19 376 no conflicts of interest.
20
21
22 377

23 24 378 Funding

25
26
27 379 Funding for this study was provided by AstraZeneca. The funding body had no role in
28
29 380 the conducting or reporting of the study. N/A for the award/grant number.
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33 34 35 382 **REFERENCES**

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474 **Figures**

475 **Figure 1:** Flow of participants through study's stages. SuA - severe and difficult to treat
476 asthma.

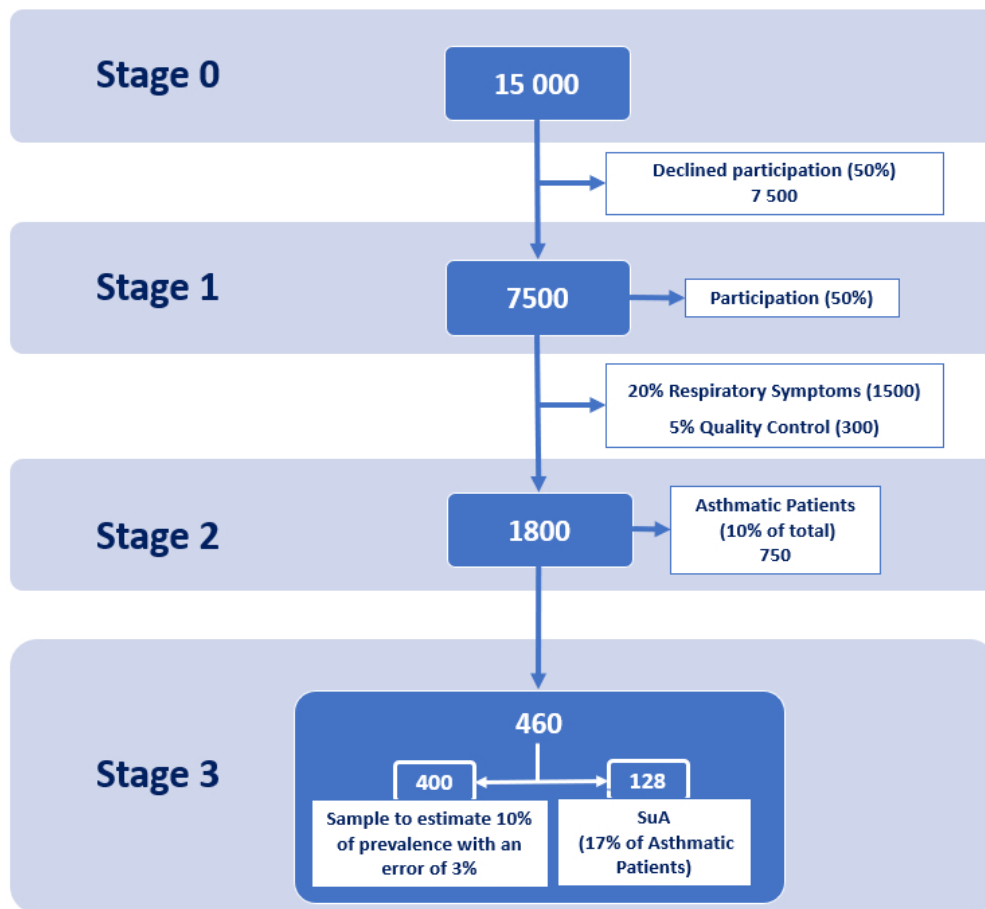


Figure 1: Flow of participants through study’s stages. SuA - severe and difficult to treat asthma.

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) <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	7-10
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed	NA
		<i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
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) <i>Cross-sectional study</i> —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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	NA
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	NA
		<i>Cross-sectional study</i> —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.