EpiReumaPt – the study of Rheumatic and Musculoskeletal diseases in Portugal: a detailed view of the methodology

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ABSTRACT

Rheumatic and musculoskeletal diseases (RMD) are prevalent and a leading cause of disability and consumption of healthcare and social resources. EpiReumaPt is a national population-based survey developed by the Portuguese Society of Rheumatology that aimed to estimate the prevalence of RMDs and determine their impact on function, quality of life, mental health and use of healthcare resources.

This article describes in detail the design, methodology and planned analyses of EpiReumaPt.

Recruitment started in September 2011 and finished in December 2013. This study involved a three-stage approach. The first step was a face-to-face survey performed by trained interviewers at the household of

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10,661 subjects, who where randomly selected by a stratified multistage sampling. A highly sensitive screening questionnaire for RMDs was used. Secondly, participants who screened positive (64%) for at least one RMD, as well as 20% of individuals with a negative screening, were invited for assessment by a rheumatologist. In total, 3,877 subjects participated in this second phase, where they were also invited to donate a blood sample to be stored at the Biobanco-IMM. History and physical examination, followed by appropriate laboratory and imaging tests were performed. At the end of the visit, the rheumatologist established a diagnosis. Finally, a team of three experienced rheumatologists reviewed all the clinical data and defined the diagnoses according to previously validated criteria.

The EpiReumaPt dataset, containing data from several questionnaires, various clinical measurements and information from laboratory and imaging tests, comprises an invaluable asset for research. The large amount of information collected from each participant and the large number of participants, with a wide age range covering and being representative of the adult population from the entire country, makes EpiReumaPt the largest study of RMDs performed in Portugal.

Keywords: EpiReumaPt; Epidemiology; Rheumatic diseases; Methodology; Portugal; Study design.

INTRODUCTION

Rheumatic and Musculoskeletal diseases (RMDs) are among the most common diseases managed at the primary health care level. They are leading causes of disability in developed countries and consume a large amount of health and social resources [1-3].

As opposed to several other European countries, the prevalence of RMDs in Portugal is poor-defined due to the lack of well-designed and consistent epidemiologic studies[1-7]. A nationwide epidemiological study was the way to fulfill this unmet need, and it was also a specific objective of the National Program Against Rheumatic Diseases (PNCDR) (2004-2014)[8]. This program was part of the National Health Plan for 2004/2010 and a contribution of the Portuguese Government to the international "Bone and Joint Decade 2000/2010", an initiative of the United Nations, supported by the World Health Organization[9].

The Portuguese Society of Rheumatology (SPR) is a scientific society that has the mission to increase the knowledge and awareness of RMDs in Portugal. SPR combines its scientific expertise with excellent relationships with other stakeholders, including governmental and regulatory authorities and the pharmaceutical industry[10]. As a result, during the last few years, SPR has attained major achievements as a scientific society, for instance, with the development of national health registries, data collection and analyses of large databases[7,11]. SPR had previously recognized that an epidemiologic study of RMDs was an unmet need in Portugal, but it had been repeatedly postponed due to financial constraints. In 2011, the joint efforts of SPR, governmental entities, the pharmaceutical industry and the commitment of the investigators of the study allowed the development of the first large epidemiologic and population-based study of RMDs in Portugal (EpiReumaPt). The main aim of EpiReumaPt was to estimate the prevalence of RMDs, namely hand, knee and hip osteoarthritis (OA), low back pain (LBP), rheumatoid arthritis (RA), fibromyalgia (FM), gout, spondyloarthritis (SpA), periarticular diseases (PD), systemic lupus erythematosus (SLE), polymyalgia rheumatica (PMR), and osteoporosis (OP) in the adult Portuguese population. The secondary aims were to determine the impact of RMDs on function, quality of life, mental health, work status and use of health care resources, in line with the objectives of the PNCDR. The rigorous methodology and large scale of the study were unprecedented in Portugal represents an important contribution of rheumatology as a specialty moving towards excellence standards of epidemiological and clinical research in Portugal.

This paper describes in detail the methodology of EpiReumaPt, including its objectives and study design, how recruitment was conducted, and gives the first insight into study participation and data preparation for analyses. Specific practical issues and management strategies of EpiReumaPt are addressed in another article published in the same issue of this Journal[12].

GEOGRAPHICAL SETTING OF EPIREUMAPT

Portugal is a Southwestern European country that includes the mainland and the two archipelagos, Madeira and Azores. According to the 2011 census, Portugal has a resident population of 10,562,178 inhabitants, of which 8 million are adults (4,072,122 men and 4,585,118 women)[13]. As in other European countries, the age gap between young and older people increased in the last decade. In fact, according to Portuguese CENSUS the percentage of young adults (18-29 years-

FIGURE 1. Portuguese population density distribution according to NUTS II
NUTS II- Nomenclature of Territorial Units for Statistics (Norte, Centro, Alentejo, Algarve, Lisboa, Madeira and the Azores)

old) decreased from 16% in 2001 to 5.1% in 2011. Among the elderly population (>65 years-old) the opposite trend was observed, rising from 16% in 2001 to 19% in 2011[13].

Portugal is divided in 7 regions according to the Nomenclature of Territorial Units for Statistics II (NUTS II) - *Norte, Centro, Lisboa e Vale do Tejo, Alentejo, Algarve, Região Autónoma dos Açores* (the Azores) *and Região Autónoma da Madeira* (Madeira). At the NUTS II level, the *Norte* region has the largest population density (34.7 %) followed by *Lisboa e Vale do Tejo* (26.6%) and *Centro* (22.4%) (Figure 1). The others NUTS II regions (*Alentejo, Algarve, the* Azores and Madeira) encompass small towns and villages with a lower population density and higher desertification rates.

MATERIALS AND METHODS

STUDY POPULATION

The study population was composed by non-institutionalized adults (≥18 years-old) living in private households in Portugal (Mainland and the Islands - Madeira and the Azores).

Exclusion criteria were: residents in hospitals, nursing homes, military institutions or prisons, and individuals unable to speak Portuguese or unable to complete the questionnaire, despite being aided [7].

STUDY DESIGN

EpiReumaPt is a national, cross-sectional, population-based study conducted from September 2011 to December 2013 and involved a three-stage approach (Figure 2).

First phase (RMD disease screening): face to face interviews were performed by interviewers (non-physicians, trained for this purpose), at each participant's household. The interviews were conducted with a Computer Assisted Personal Interview (CAPI) system. A detailed and comprehensive questionnaire including a screening for RMDs symptoms was applied (available upon request). Participants were inquired about self-reported RMD and subsequently about specific rheumatic and musculoskeletal symptoms. Finally, an algorithm for the screening of specific RMD was applied. In addition, subjects were inquired about socio-demographics, socio-economics, life style, healthcare resources consumption, functional status, quality of life, mental health, work status, and other diseases.

An individual was considered to have a positive screening if the subject mentioned a previously known RMD, if any of the algorithms in the screening questionnaires was positive, or if the subject reported muscle, vertebral or peripheral joint pain in the previous 4 weeks. The overall performance of the screening algorithm was evaluated (the gold standard was considered the final diagnosis after revision, see phase 3) and the overall sensitivity of the screening questionnaire for RMD was 98%, with a specificity of 22%. The positive predictive value was 85% and the negative predictive value was 71%.

Second phase (RMD Diagnosis): In order to determine the RMD diagnosis, a clinical observation by a rheumatologist was offered to subjects who screened positive for at least one RMD and also to 20% of individuals with no rheumatic complaints, during the first phase of the study. In total, 95 rheumatologists were involved. They were blinded to the screening results and received instructions on how to conduct the history and physical examination, following a standardized protocol. They could also request for new laboratory and imaging tests during the appointment. Participants were asked to bring their previous imaging and labo-

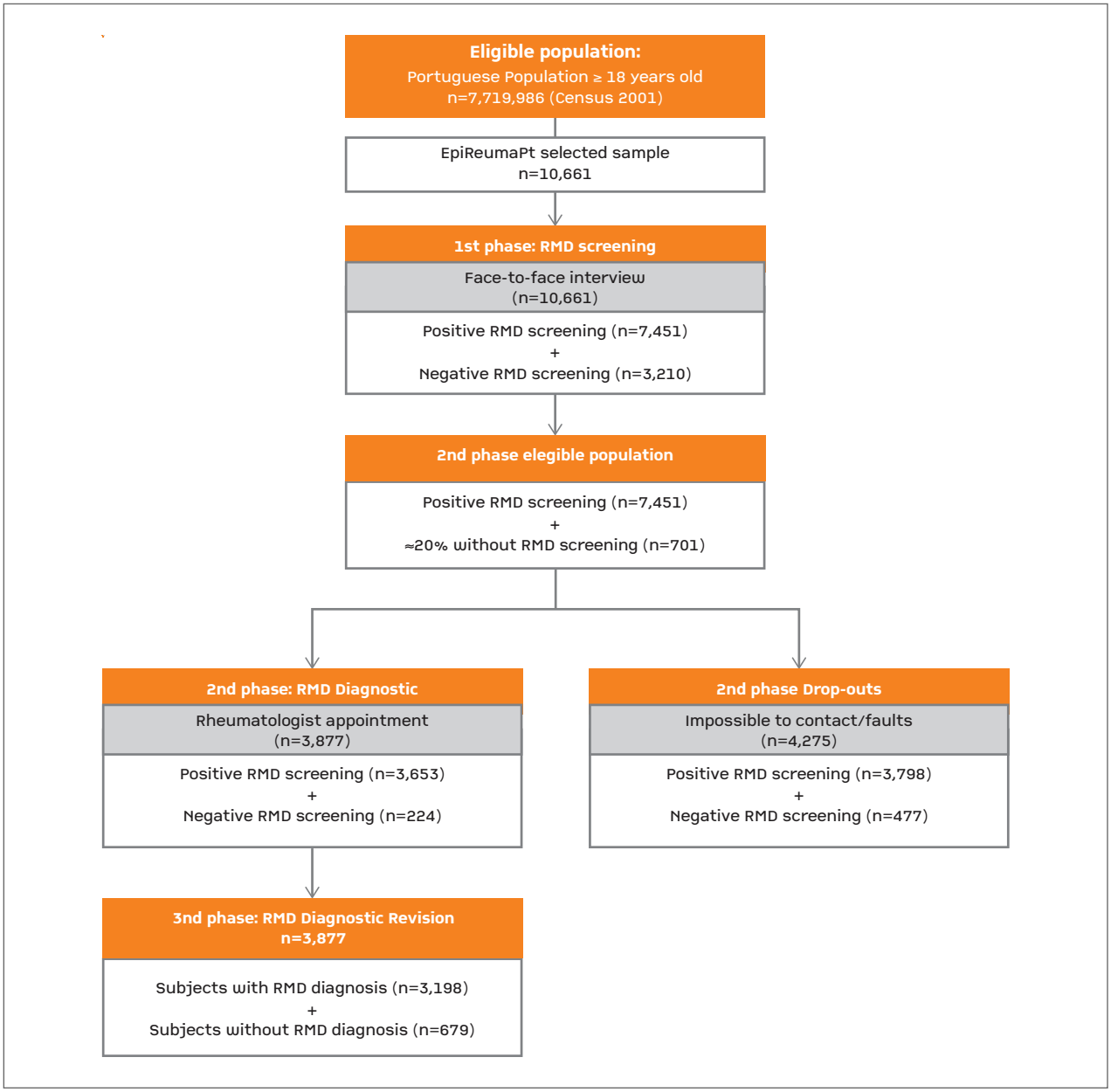

FIGURE 2. Flowchart of recruitment in the EpiReumaPt Study
RDM: Rheumatic and Musculoskeletal diseases

ratory results. Computed assisted software specifically designed for the study was used to support clinical appointment registries. First, the rheumatologist collected the clinical history in a standardized way and placed all the diagnostic hypotheses. The hypotheses where then selected in a dedicated EpiReumaPt s software and specific questions related to the possible diagnosis were asked. For each RMD that was studied in EpiReumaPt, the research team developed specific questions, including those related to validated classification criteria that should be completed, according to the diagnostic hypothesis previously selected. Finally, the physician had to go through a checklist, in order to verify if the patient fulfilled the pre-established diagnostic criteria (see case definition). If needed, laboratory testing and radiographic examinations were performed at the participant's Primary Care Center in order to confirm the diagnostic hypothesis.

The clinical assessments were performed at the Primary Care Center of the participant's neighborhood. A mobile van, fully equipped, was used to perform imaging and laboratory tests: X-ray of the affected joint(s), peripheral dual energy X-ray and blood tests. A multidisciplinary team with a rheumatologist, an X-Ray technician, a nurse, a staff coordinator and a driver supported the clinical visits.

Third phase (RMD Diagnostic Validation): Using the results from the laboratorial and imaging tests previously requested, a team of three experienced rheumatologists reviewed all the clinical data from each participant in order to validate the diagnostic decision made in the second phase. Moreover, when a patient was referred to a rheumatology center due to a suspected inflammatory disease in the second phase, follow-up information from that center was also used. A specific protocol was developed to support these tasks. When data were insufficient to fulfill international classification criteria, a meeting with 5 rheumatologists took place in order to reach an agreement on the final diagnosis based on expert opinion. When doubts persisted regarding the final diagnosis, the opinion of the rheumatologist that performed the clinical assessment (second phase) prevailed. Diagnostic agreement between the 3 reviewers was 98.3% with a Cohen s K coefficient of 0.87 (95%CI from 0.83 to 0.91).

Sampling and recruitment

The sample size was calculated by taking into account the prevalence of RA, as described in the study protocol [7]. The participants were selected through a process of multistage random sampling. The sample was stratified according to the Portuguese statistic regions NUTS II in the 2001 Census and the size of the population (less than 2,000; 2,000-9,999; 10,000-19,999; 20,000-99,999; and ≥100,000 inhabitants). The number of participants of each stratum was proportional to the actual distribution of the population. In Madeira and the Azores we increased the sample size (oversampling) to allow separate analyses in these regions.

Candidate households were selected through a random route process: sampling points were randomly selected on the maps of each locality, where the interviewer began a systematic step count (defined for each locality according to its size), granting each household and each individual an equal probability of being chosen. Dwellings with commercial or industrial purposes, private or public institutions and visibly unoccupied buildings were considered ineligible. In the household, the individual over 18 years old with permanent residence and with the most recently completed birthday was selected. The population recruitment was led by *Centro de Estudos e Sondagens de Opinião da Universidade Católica Portuguesa* (CESOP-UCP). Each interviewers team worked daily on the field (week and weekend) in groups of 4 or 5 elements, and covering a different route. When no subject was found in a first visit of the selected household, he/she could not be replaced, unless that household had been visited in three different times, including evenings and weekends.

Quality control of interviews was performed through a random evaluation of the interviews and recheck of the participants' eligibility criteria. Specifically, each interviewer had 25% of his interviews submitted to a quality control telephone contact, in order to assess the reliability of the answers. The selection of households and the selection of respondents were also submitted to a quality control.

MEASUREMENTS AND ASSESSMENTS

Case definition

RMD diagnoses were performed according to the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA[14]; the ACR criteria for knee OA[15], hip OA[16], hand OA[17], FM[18] , SLE[19] and gout[20]; the Assessment of SpondyloArthritis international Society (ASAS) criteria for axial and peripheral SpA[21-23]; and the Bird criteria for PMR[24]. PD was defined as a regional pain syndrome affecting muscles, tendons, bursas or periarticular soft tissues, with or without evidence of joint or bone involvement. The following PDs were specifically searched: tenosynovitis, adhesive capsulitis of the shoulder, enthesopathies, bursitis, palmar or plantar fasciitis, and carpal or tarsal tunnel syndrome, present at the time of the interview. The PD diagnosis was established based on expert opinion after reviewing clinical history, physical exam, ultrasound and electromyography (when available). OP was defined by decision of the rheumatologist based on the presence of at least one of the following: previous fragility fracture, self-reported OP diagnosis, current OP treatment or fulfillment of the WHO criteria[25] when lumbar and/or femoral neck dual energy X-ray absorptiometry (DEXA) was available. Low back pain (LBP) was defined solely by self-reported symptoms.

Secondary variables description

In the 1st phase of EpiReumaPt, subjects were asked about their socio-demographic data (age, gender, ethnicity, education, marital status), socio-economic profile (measures of wealth [used to generate income quintiles], household income, work status) and life style habits (alcohol and coffee intake, current smoking and physical exercise). Work disability was evaluated by absenteeism, presenteeism, early retirement and unemployment due to work disability. Healthcare resource consumption data was collected considering the number and type of outpatient clinic visits, hospitalizations, homecare assistance and other needs for healthcare services in the previous 12 months.

Health-related quality of life was evaluated using the European Quality of Life questionnaire with five dimensions and three levels (EQ-5D-3L)[26, 27] and also the Short Form (36) Health Survey (SF-36)[28]. Physical function was assessed by the Health Assessment Questionnaire (HAQ)[29], anxiety and depression were assessed by the Hospital Anxiety and Depression Scale (HADS)[30]. We used Portuguese validated versions of all these assessment scales. Anthropometric data (self-reported weight and height) and self-reported chronic diseases (high cholesterol level, high blood pressure, allergy, gastrointestinal disease, mental disease, cardiac disease, diabetes, thyroid and parathyroid disease, urolithiasis, pulmonary disease, hyperuricemia, neoplastic disease, neurologic disease, hypogonadism) were also searched. Finally, information regarding pharmacological and non-pharmacological therapies was collected.

In the 2nd phase of EpiReumaPt, data concerning the medical history and physical examination were collected. Questions about previous diagnosis of RMD, medication and the need for medical visits due to RMD symptoms in the previous year were also performed. Validated instruments (eg. disease activity score 28 (DAS28) for RA and knee injury and osteoarthritis outcome score (KOOS) for knee OA) were applied by the rheumatologist according to the patient diagnosis.

Blood sampling

A blood sample was drawn whenever subjects attended the second phase of the EpiReumaPt study and signed the informed consent for the procedure. Patients with known hepatitis C, HIV infection or debilitating conditions were excluded. A 15-25 ml whole blood sample was obtained; serum was separated by centrifuging (800g, 10 minutes) the sample in the mobile van and kept kept in the fridge at 4ºC. Blood samples from 3,664 participants were sent in a cooler on the same day or within two days[12] to Biobanco-IMM. Serum and whole blood samples where aliquoted in 250µL and 2mL respectively and stored at -80ºC. DNA extraction was performed by Qiacube (Qiagen, Venlo, Netherlands) from 200µL of the whole blood. The DNA was stored at -80ºC in 100µL aliquots. The content of the EpiReumaPt biobank is described in Table III. Serum and whole blood samples were also sent to the Central Diagnostic Laboratory Germano de Sousa (Lisbon, Portugal), if deemed necessary by the rheumatologist to perform laboratory tests.

Laboratory procedures

The different laboratorial paramethers were measures according to the respective manufacturer's instructions: rheumatoid factor was measured by chemiluminescence; uric acid was quantified by a modification of uricase method first published by Bulger and Johns, modified by Kalckar; C-reactive protein was determined by immunoturbidimetric method; urea was measured by kinetic enzymatic method urease / glutamate dehydrogenase; total creatine kinase (CK) was measured by creatinine phosphate method; and complement fractions C3 and C4 were detected by turbidimetry, on an Dimension Vista 1500 Intelligent Lab System (Siemens, Erlangen, Germany), applying reagents from Siemens (Siemens, Erlangen, Germany). Thyroid stimulating hormone (TSH) and Free thyroxine (FT4) were detected by chemiluminescence, on an Advia Centaur XP (Siemens, Erlangen, Germany), applying reagents from Siemens (Siemens, Erlangen, Germany). Antibodies against Cyclic Citrullinated Peptides (anti-CCP) and antibodies against double stranded DNA (anti-dsDNA) were measured by automated fluoroimmunoassay, on an Immunocap250 (Thermo Scientific, Uppsala, Sweden), applying reagents from ELiA-Phadia (Thermo Scientific, Uppsala, Sweden). Human Leukocyte Antigen-B27 (HLA-B27) was measured flow cytometry, on a FacsCalibur (Becton Dickinson, New Jersey, USA), applying reagents from BD Bioscience (Becton Dickinson, New Jersey, USA). Antinuclear antibodies (ANA) were measured by indirect fluoroimmunoassay, applying reagents from Euroimmun (Euroimmun, Luebeck, Germany). Full blood count and erythrocyte sedimentation rate (ESR) were measured in whole blood samples. Hemoglobin was quantified by Surfactant Sodium Lauryl Sulfate Colorimetric, Mean Corpuscular Volume (MCV) was

measured by flow cytometry with hydrodynamic focusing, and leukocytes, lymphocytes and neutrophils were measured by flow cytometry with side light scatter, forward scatter and fluorescence intensity. ESR was measured by microphotometry capillary flow.

Peripheral DXA procedures

All participants who attended the second phase of the study had a wrist DXA at the mobile unit on a PIXI™ LUNAR device (a peripheral Instantaneous X-ray Imager). This procedure provided precise assessment of bone mineral density (BMD) with excellent image resolution (0.2 mm pixels). PIXI is a peripheral densitometer that allows the operator to examine both the *calcaneus* and the forearm. PIXI employs the dual-energy x-ray absorptiometry technique. A total of 3,342 participants had a forearm bone mineral density evaluation.

X- Ray procedures

Participants who attended the second phase had performed wrist and calcaneus X-ray and bone mineral assessment on a high resolution digital X-Ray machine (D3A, France) in the mobile unit, in order to assess bone microanalysis (BMA). Moreover, X-rays of the affected joint or joints were also performed on BMA high-resolution digital X-ray machine (D3A, France) as requested by the rheumatologist. The content of the EpiReumaPt imaging reservoir is described in Table III.

STATISTICAL ANALYSIS

EpiReumaPt was designed to obtain a representative sample of the Portuguese population. This population will be subject of many other future analyses. Exactly in order to guarantee its representativity, the design effect will need to be taken into account. This can be achieved by using weighted proportions that have, for this matter, been computed.

For the main sample, the initial extrapolation weights were calculated as the inverse of the inclusion probabilities, taking into account the sampling design, i.e., a stratified two-stage cluster sampling design. The stratification was based on the seven NUTS II regions and on five classes of the number of inhabitants per locality (<2,000; 2,000-9,999; 10,000-19,999; 20,000-99,999; >99,999). In each stratum, the first sampling stage consisted in the selection of localities with a probability proportional to its size (number inhabitants aged 18 years old or more), except for localities where the number of inhabitants was larger than 20,000, where all the localities were selected. In the second stage, households were selected using a pseudo-random selection procedure equivalent to the equal probability selection. These weights were submitted to a calibration process by crossing region (seven classes), size of locality (five classes), gender (two classes) and seven age categories (18-25, 26-35, 36-45, 46-55, 56-65, 66-75 and ≥76 years old). This procedure was used to reproduce the known population totals for the crossing margins of these four variables.

A sub-sample was drawn selecting all individuals with positive screening for RMDs and 20% of those with negative screening. For this sub-sample, inclusion probabilities were calculated considering the result of the screening and adjustment for non-response. This last adjustment was used because not all individuals selected for the second phase actually attended the assessment by the rheumatologist. The basic extrapolation weights obtained from these procedures were again submitted to a calibration process by crossing two classes of region (one collecting all the mainland regions and a different one gathering the two autonomic regions), gender (2 classes), four age categories (resulting from the aggregation of the original classes in 18-35, 36-55, 56-75 and ≥76 years old) and result of the RMD screening (positive/negative) in order to reproduce the known national totals for the crossing margins of these four variables. The decision on the variables used for this second stage calibration was based on a generalized linear model (positive diagnostic for several rheumatic diseases was used as dependent variable) that identified the most important criteria related to the prevalence of RMDs. These weighted proportions will be used in several future analyses, including the estimation of the prevalence of the RMDs (study's primary objective), which will be a matter of a separate manuscript.

ETHICAL ISSUES AND PERSONAL PROTECTION

The EpiReumaPt study was performed according to the principles established by the Declaration of Helsinki. The study was reviewed and approved by the National Committee for Data Protection (*Comissão Nacional de Proteção de Dados*) and by the NOVA Medical School Ethics Committee. Ethical Committees of Regional Health Authorities (ARS) also reviewed and approved the study. According to the Portuguese law, all

subjects provided informed consented to participate in the EpiReumaPt study. Individuals also consented to give a blood sample for storage in Biobanco-IMM and to be re-contacted if needed. Data protection was assured by a data encryption process, which kept the confidentiality and anonymity of each study subject. Decryption was only possible with a secure password only known by the Principal Investigator. This study was conducted according to the good practices in research.

REPORTING OF DIAGNOSIS AND TEST RESULTS

During the assessment by the rheumatologist in phase 2, all patients with a new diagnosis of a chronic inflammatory rheumatic disease were referred to a rheumatology center for follow-up. Other non-inflammatory newly diagnosed RMDs were referred to the primary care physician. Each participant who performed laboratory tests received a letter reporting the test results. If a clinically significant abnormality was depicted in the laboratorial results or X-rays, the participant was also advised to see his/her doctor for further investigation.

RESULTS

The EpiReumaPt population is comparable to the Portuguese population, as confirmed with data from the Portuguese National Institute of Statistics (Census 2011)[13, 31] (Table I).

PARTICIPATION ANALYSIS

The EpiReumaPt study recruited 10,661 subjects and 64% had a positive screening for at least one RMD. Moreover, out of the 8,152 eligible subjects, 3,877 entered the second phase and were evaluated by a rheumatologist. Individuals who attended the observation by the rheumatologist did not differ from those who did not except for the screening diagnosis, age group, gender and residence region according to the NUTS II (Table II). These variables were considered in the weighted model used to calculate the prevalence of RMD. Furthermore, a sensitivity analysis was performed and no differences in health status (including quality of life and functional status) were found between participants and dropouts of the second phase according to age groups, NUTS II and comorbidities (data not shown).

DISCUSSION

EpiReumaPt is the first large-scale epidemiological population-based study that evaluated RMDs in Portugal. EpiReumaPt has a unique study design: the first phase with a face to face questionnaire that aimed at screening for the presence of RMD symptoms and specific RMDs; the second phase, comprising a clinical observation performed by rheumatologists in primary care units near the participants' residence in order to have the RMD diagnosis firmly established by a specialist; and the third phase, consisting of a rigorous case review that aimed to homogenize the diagnostic criteria and validate the definitive RMD diagnosis. With this study design we were able to diagnosis new RMDs, to correct the misinformation of some self-reported diagnosis and to refine RMDs with a standardized case definition.

EpiReumaPt has also unique features when compared to other studies performed in Portugal and abroad[1,2,4,32-36]: It is a population-based study, with a representative sample of the Portuguese population and it covers an extensive range of topics that go beyond rheumatology. Unlike the recruitment performed by mail as in the Spanish (Episer)[37] and the Greek studies[5, 38] that also evaluated the prevalence of RMD, recruitment in EpiReumaPt was done by a random route technique with a face to face interview, which reduced selection bias. The EpiReumaPt screening algorithm was specifically developed for this study and designed to be highly sensitive in order to capture the maximum number of RMDs cases. Finally, our case definition included the most recent classification criteria for several RMDs such as the classification criteria of the ACR/EULAR for RA[14] and the ASAS criteria for SpA[21,23]. A comparison with Census 2011 allowed the development of different weights to be applied in the samples from 1st and 2nd phases, which will improve the accuracy of further analyses and estimates.

The concerted action from research groups, health and governmental authorities, pharmaceutical companies, the SPR and the population has resulted in a very large database and has triggered extensive research activities and collaborations. EpiReumaPt has initiated collaboration with various research groups in Portugal and other European countries and in the USA. Procedures for data access are established, and a dedicated team of researchers is currently working on EpiReumaPt data covering studies within a wide range of medical topics. Moreover, the EpiReumaPt image

TABLE I. SOCIO-DEMOGRAPHIC AND HEALTH RELATED CHARACTERISTICS OF THE ADULT PORTUGUESE POPULATION: EPIREUMAPT (1ST AND 2ND PHASE POPULATIONS) AND CENSUS 2011 POPULATIONS (PORTUGUESE POPULATION)

Demographic characteristics	1st phase study population n=10,661	2nd phase study population n=3,877	CENSUS 2011
Gender (female)	**6,551** (52.6%)	**2,630** (52.5%)	**4,585,118** (53.0%)
Age group			
18-29	**1,182** (22.1%)	**190** (21.0%)	**1,470,782** (17.0%)
30-39	**1,511** (18.8%)	**403** (19.3%)	**1,598,250** (18.5%)
40-49	**1,906** (17.3%)	**680** (18.2%)	**1,543,392** (17.8%)
50-59	**1,801** (14.8%)	**818** (14.7%)	**1,400,011** (16.2%)
60-69	**1,915** (12.9%)	**914** (13.4%)	**1,186,442** (13.7%)
70-74	**849** (5.8%)	**376** (5.3%)	**496,438** (5.7%)
≥75	**1,497** (8.4%)	**496** (8.0%)	**961,925** (11.1%)
Ethnicity/Race			
Caucasian	**10,342** (96.0%)	**3,786** (93.3%)	
Black	**221** (3.4%)	**64** (6.1%)	
Asian	**8** (0.1%)	**2** (0.0%)	**No comparable data**
Gipsy	**20** (0.3%)	**3** (0.1%)	
Other	**38** (0.3%)	**13** (0.5%)	
Education level			
>12 years	**1,764** (20.4%)	**508** (21.1%)	**1,741,567** (20.1%)
10-12 years	**1,920** (23.8%)	**575** (23.2%)	**1,560,958** (18.0%)
5-9 years	**2,175** (22.6%)	**775** (22.4%)	**2,134,401** (24.6%)
0-4 years	**4,726** (33.2%)	**1,997** (33.4%)	**3,239,724** (37.4%)
NUTS II			
Norte	**3,122** (34.9%)	**1,050** (37.2%)	**3,007,823** (34.7%)
Centro	**1,997** (22.8%)	**856** (19.8%)	**1,938,815** (22.4%)
Lisboa	**2,484** (26.7%)	**708** (29.6%)	**2,300,053** (26.6%)
Alentejo	**669** (7.3%)	**273** (5.8%)	**633,691** (7.3%)
Algarve	**352** (3.8%)	**144** (3.1%)	**370,704** (4.3%)
Azores	**1,029** (2.2%)	**420** (2.3%)	**192,357** (2.2%)
Madeira	**1,008** (2.3%)	**426** (2.2%)	**213,797** (2.5%)
Marital status			
Single	**1,935** (29.4%)	**456** (32.2%)	
Married	**6,111** (50.2%)	**2,460** (49.9%)	
Divorced	**810** (7.4%)	**310** (7.3%)	**No comparable data**
Widower	**1,414** (8.2%)	**550** (7.6%)	
Consensual union	**382** (4.8%)	**99** (3.1%)	
BMI			
Underweight	**167** (2.2%)	**46** (1.1%)	
Normal	**4,063** (45.5%)	**1,234** (46.4%)	**No comparable data**
Overweight	**3,799** (35.1%)	**1,485** (34.3%)	
Obese	**2,080** (17.1%)	**924** (18.1%)	
Socio-economics			
Household income*			
<500€	**1,994** (19.9%)	**795** (21.8%)	
501€to 750€	**1,707** (21.7%)	**710** (20.4%)	
751€to 1000€	**1,268** (18.8%)	**511** (18.9%)	**No comparable data**
1001€to 1500€	**1,141** (17.2%)	**403** (15.9%)	
1501€to 2000€	**657** (9.9%)	**246** (10.3%)	

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TABLE I. SOCIO-DEMOGRAPHIC AND HEALTH RELATED CHARACTERISTICS OF THE ADULT PORTUGUESE POPULATION: EPIREUMAPT (1ST AND 2ND PHASE POPULATIONS) AND CENSUS 2011 POPULATIONS (PORTUGUESE POPULATION) – (CONTINUE)

Demographic characteristics	1st phase study population n=10,661	2nd phase study population n=3,877	CENSUS 2011
2001€to 2500€	379 (5.9%)	118 (4.7%)	
2501€to 3000€	222 (3.0%)	73 (4.7%)	
3001€to 4000€	146 (1.8%)	43 (16%)	
>4000€	99 (1.9%)	26 (1.7%)	
Employment status			
Employed full-time	3,993 (42.8%)	1,221 (42.6%)	
Employed part-time	345 (4.6%)	117 (3.5%)	
Domestic worker	660 (3.9%)	286 (3.3%)	
Unemployed	1,087 (12.0%)	390 (13.7%)	No comparable data
Student	428 (8.4%)	58 (4.8%)	
Temporally work disabled	160 (1.2%)	80 (12.5%)	
Retired	3,758 (24.9%)	1,636 (26.4%)	
Others	229 (2.2%)	89 (4.5%)	
Quality of life EQ5D Score	0.83 ± 0.23	0.81 ± 0.24	No comparable data
HAQ (0-3)	0.26 ± 0.54	0.27 ± 0.53	
Life Style Habits			
Current coffee intake			
None	3,374 (29.1%)	1,263 (30.2%)	
1 to 3	6,364 (59.1%)	2,331 (59.5%)	No comparable data
More than 3	908 (11.9%)	277 (10.4%)	
Current alcohol intake			
Daily	2,050 (20.2%)	773 (20.8%)	
Occasionally	3,967 (42.6%)	1,305 (46.0%)	No comparable data
Never	4,625 (37.1%)	1,794 (33.2%)	
Current smoking habits			
Daily	1,854 (23.2%)	526 (20.8%)	
Occasionally	246 (2.7%)	67 (2.2%)	No comparable data
Never	8,554 (74.1%)	3,282 (77.0%)	
Physical exercise	3,499 (37.0%)	1,182 (37.3%)	No comparable data
Number of comorbidities (self-reported)	1.55 ± 1.80	1.71 ± 1.83	No comparable data
High cholesterol level	3,360 (24.4%)	1,556 (25.4%)	
High blood pressure	3,369 (23.1%)	1,528 (23.2%)	
Allergy	2,287 (21.3%)	985 (23.6%)	
Gastrointestinal disease	1,837 (14.9%)	907 (17.4%)	
Mental disease	1,619 (12.9%)	764 (11.1%)	
Cardiac disease	1,366 (10.5%)	641 (11.7%)	
Diabetes	1,217 (8.3%)	539 (8.8%)	No comparable data
Thyroid and parathyroid disease	941 (7.0%)	484 (10.5%)	
Renal colic	885 (7.0%)	426 (8.8%)	
Pulmonary disease	637 (5.4%)	295 (6.0%)	
Hyperuricemia	690 (5.2%)	332 (4.7%)	
Neoplasic disease	439 (3.4%)	208 (3.6%)	
Neurologic disease	418 (3.3%)	183 (3.7%)	
Hypogonadism	90 (0.7%)	40 (0.6%)	

*household income in the last month

Sample size is not constant due to missing data in: **1st Phase EpiReumaPt study:** Ethnicity (n=10,629), Education level (n=10,585), Marital status (n=10,652), BMI (n=10,109), Household income (n=7,613), EQ5D Score (n=10,596), Current coffee intake (n=10,646), Current alcohol intake (n=10,646), Current smoking habits (n=10,645), Physical exercise (n=10,654), Number of Comorbidities (n=9,601), High cholesterol level (n=10,514), High blood pressure (n=10,582), Allergy (n=10,570), Gastrointestinal disease (n=10,572), Mental disease (n=10,593),

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Continuation
Cardiac Disease (n=10,563), Diabetes (n=10,587), Thyroid and parathyroid disease (n=10,557), Renal colic (n=10,543), Pulmonary disease (n=10,594), Hyperuricemia (n=10,458), Neoplasic disease (n=10,602), Neurologic disease (n=10,581), Hypogonadism (n=10,445)
2nd phase EpiReumaPt study: Ethnicity (n=3,868), Education level (n=3,855), Marital status (n=3,875), BMI (n=3,689), Household income (n=2,925), EQ5D Score (n=3,846), Current coffee intake (n=3,871), Current alcohol intake (n=3,871), Current smoking habits (n=3,871), Physical exercise (n=3,874), Number of Comorbidities (n=3,398), High cholesterol level (n=3,825), High blood pressure (n=3,851), Allergy (n=3,845), Gastrointestinal disease (n=3,835), Mental disease (n=3,855), Cardiac Disease (n=3,833), Diabetes (n=3,840), Thyroid and parathyroid disease (n=3,834), Renal colic (n=3,835), Pulmonary disease (n=3,855), Hyperuricemia (n=3,799), Neoplasic disease (n=3,854), Neurologic disease (n=3,847), Hypogonadism (n=3,785)
The data presented in the CENSUS 2011 columns was obtained from the National Institute of Statistics.
NUTS II- Nomenclature of Territorial Units for Statistics (Norte, Centro, Alentejo, Algarve, Lisboa, Madeira and the Azores); **BMI**- Body Mass Index; **EQ5D**- European Quality of Life questionnaire five dimensions three levels; **HAQ**- Health Assessment Questionnaire
The estimated values for the characteristics were obtained considering study design.

TABLE II. COMPARISON BETWEEN EPIREUMAPT SUBJECTS INCLUDED IN PHASE 2 WITH THOSE NOT PARTICIPATING DESPITE BEING ELIGIBLE

	Second phase participants n=3,877	Second phase drop-outs n=4,275
Individuals without Rheumatic Disease (701 individuals selected to medical consultation)	**224** (31.9%)	**477** (68.0%)
Gender		
Female	**2,628** (67.8%)	**2,784** (65.1%)
Age	**57.10** (±15.48)	**55.24** (±18.95)
NUTSII		
Norte	**1,050** (27.1%)	**1,313** (30.7%)
Centro	**856** (22.1%)	**765** (17.9%)
Lisboa	**708** (18.3%)	**1,146** (26.8%)
Alentejo	**273** (7.0%)	**247** (5.8%)
Algarve	**144** (3.7%)	**132** (3.1%)
Azores	**420** (10.8%)	**335** (7.8%)
Madeira	**426** (11.0%)	**337** (7.9%)
Years of education	**6.81 (±3.94)**	**6.98 (±4.17)**
Household income		
<500€	**795** (27.2%)	**862** (28.9%)
501€to 750€	**710** (24.3%)	**674** (22.6%)
751€to 1000€	**511** (17.5%)	**463** (15.5%)
1001€to 1500€	**403** (13.8%)	**435** (14.6%)
1501€to 2000€	**246** (8.4%)	**232** (7.8%)
2001€to 2500€	**118** (4.0%)	**142** (4.8%)
2501€to 3000€	**73** (2.5%)	**81** (2.7%)
3001€to 4000€	**43** (1.5%)	**55** (1.8%)
>4000€	**26** (0.9%)	**41** (1.4%)
Employment status		
Full-time employee	**1,221** (31.8%)	**1,493** (35.2%)
Unemployed	**390** (10.2%)	**391** (9.2%)
Retired	**1,636** (42.6%)	**1,679** (39.6%)
Student	**58** (1.5%)	**149** (3.5%)
EQ5D	**0.72 (±0.27)**	**0.75 (±0.27)**
HAQ	**0.50 (±0.64)**	**0.43 (±0.65)**

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TABLE II. COMPARISON BETWEEN EPIREUMAPT SUBJECTS INCLUDED IN PHASE 2 WITH THOSE NOT PARTICIPATING DESPITE BEING ELIGIBLE (CONTINUE)

	Second phase participants n=3,877	Second phase drop-outs n=4,275
Positive RMD screening diagnosis		
Low back pain	**648** (53.3%)	**567** (46.7%)
Inflammatory low back pain	**1,263** (55.4%)	**1,015** (44.6%)
Spondyloarthritis	**2,119** (52.5%)	**1,919** (47.5%)
Rheumatoid arthritis	**2,002** (54.2%)	**1,694** (45.8%)
Osteoarthritis	**2,660** (51.9%)	**2,465** (48.1%)
Fibromyalgia	**822** (56.9%)	**623** (43.1%)
SLE	**694** (54.2%)	**587** (45.8%)
Gout	**624** (53.6%)	**539** (46.3%)
PMR	**300** (59.3%)	**206** (40.7%)
Osteoporosis	**983** (52.4%)	**894** (47.6%)
Periarticular disease	**2,405** (53.1%)	**2,127** (46.9%)
Self-reported previous RMD diagnosis	**1,604** (43.1%)	**1,310** (31.7%)
Rheumatoid arthritis	**221** (59.1%)	**153** (40.9%)
Spondyloarthritis	**93** (60.4%)	**61** (39.6%)
Psoriatic arthritis	**14** (60.9%)	**9** (39.1%)
Osteoarthritis	**635** (54.3%)	**535** (45.7%)
Osteoporosis	**393** (54.5%)	**328** (45.5%)
Gout	**57** (65.5%)	**30** (34.5%)
Polymyalgia rheumatica	**11** (45.8%)	**13** (54.2%)
SLE	**11** (47.8%)	**12** (52.2%)
Fibromyalgia	**66** (68.0%)	**31** (32.0%)
Periarticular diseases	**224** (62.2%)	**136** (37.8%)
Comorbidities		
High cholesterol level	**1,556** (40.7%)	**1,410** (33.6%)
High blood pressure	**1,528** (39.7%)	**1,446** (34.2%)
Allergy	**985** (25.6%)	**910** (21.5%)
Gastrointestinal disease	**907** (23.6%)	**782** (18.5%)
Mental disease	**764** (19.8%)	**713** (16.8%)
Cardiac disease	**641** (16.7%)	**615** (14.5%)
Diabetes	**539** (14.0%)	**528** (12.4%)
Thyroid and parathyroid disease	**484** (12.6%)	**386** (9.1%)
Urolithiasis	**426** (11.1%)	**382** (9.1%)
Pulmonary disease	**295** (7.6%)	**259** (6.1%)
Hyperuricemia	**332** (8.7%)	**323** (7.7%)
Neoplasic disease	**208** (5.4%)	**192** (4.5%)
Neurologic disease	**183** (4.8%)	**203** (4.8%)
Hypogonadism	**40** (1.1%)	**43** (1.0%)
Rheumatic diseases	**1,604** (43.1%)	**1,310** (31.7%)
Number of Comorbidities	**2.61 ± 2.10**	**2.09 ± 1.98**

Sample size is not constant due to missing data in
Second phase Participants: Years of Education (n=3, 867), Household income (n=2,925), Employment status (n=3, 839), EQ5D (n=3,846), Self-reported previous RMD diagnosis (n=3,171), Self-reported previous RMD diagnosis per disease (n=1,604), High cholesterol level (n=3,825), High blood pressure (n=3,851), Allergy (n=3,845), Gastrointestinal disease (n=3,835), Mental disease (n=3,855), Cardiac Disease (n=3,833), Diabetes (n=3,840), Thyroid and parathyroid disease (n=3,834), Renal colic (n=3,835), Pulmonary disease (n=3,855), Hyperuricemia (n=3,799),

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Continuation
Neoplasic disease (n=3,854), Neurologic disease (n=3,847), Hypogonadism (n=3,785), Rheumatic diseases (n=3,717), Number of Comorbidities (n=3,398).
Second phase drop-outs: Years of education (n=4,253), Household income (n=2,985), Employment status (n=4,237), EQ5D (n=4,250), Self-reported previous RMD diagnosis (n=4,131), Self-reported previous RMD diagnosis per disease (n=1,307), High cholesterol level (n=4,202), High blood pressure (n=4,233), Allergy (n=4,233), Gastrointestinal disease (n=4,235), Mental disease (n=4,235), Cardiac Disease (n=4,228), Diabetes (n=4,250), Thyroid and parathyroid disease (n=4,227), Renal colic (n=4,211), Pulmonary disease (n=4,238), Hyperuricemia (n=4,172), Neoplasic disease (n=4,249), Neurologic disease (n=4,233), Hypogonadism (n=4,177), Rheumatic diseases (n=4,131), Number of Comorbidities (n=3,793).
Positive Screening Low Back Pain (n=1,215), Inflammatory Low Back Pain (n=2,278), Spondyloarthritis (n=4,038), Rheumatoid Arthritis (n=3,696), Osteoarthritis (n=5,125), Fibromyalgia (n=1,445), SLE (n=1,281), Gout (n=1,163), PMR (n=506), Osteoporosis (n=1,877), Periarticular Pathology (n=4,532).
Regarding the acronyms **NUTS II** stands for the Nomenclature of Territorial Units for Statistics (Norte, Centro, Alentejo, Algarve, Lisboa, Madeira and the Azores), **EQ5D** refers to European Quality of Life questionnaire five dimensions three levels, **HAQ** stands for Health Assessment Questionnaire, and **SLE** - systemic lupus erythematosus.

TABLE III. THE EPIREUMAPT BIOBANK AND IMAGING RESERVOIR

EpiReumaPt biobank	n	Volume per aliquot
Serum	21,219	250 µL
Whole blood	7,476	2 mL
DNA	3,608	100 µL

EpiReumaPt imaging reservoir X-ray area	n
Wrists (BMA)	2,422
Calcaneus (BMA)	2,228
Hands	438
Hips	122
Knees	479
Lumbar spine	1,265
Thoracic spine	691
Cervical spine	206

BMA: bone mineral assessment

and biobank reservoirs constitute a valuable tool to perform a comprehensive approach to the pathophysiology and outcome research of several diseases.

A fundamental premise for population-based studies is high confidence and legitimacy felt by the study population. The strategy to achieve and withhold this confidence in the Portuguese population has been successful, and resulted in high participation rates and enthusiastic public and political support for EpiReumaPt[12]. The confidence and supportive attitude from the population was the trigger to develop an ongoing cohort study with EpiReumaPt subjects[39]. The follow-up of this population goes beyond RMDs. Several other diseases and health related topics are being explored in this cohort.

In conclusion, the strict and robust methodology of EpiReumaPt allowed for a large amount of information to be collected from each participant, and the inclusion of a large number of participants with a wide age range covering an entire country adult population, making EpiReumaPt the largest study on RMDs performed in Portugal. Moreover, the follow-up of this population is ongoing and now goes beyond RMDs. EpiReumaPt will answer several health-related questions and will generate important evidence useful to support health policies in Portugal.

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