EpiReumaPt Protocol – Portuguese epidemiologic study of the rheumatic diseases

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Abstract

Rheumatic diseases (RDs) are among the most common diseases. In the developed world, they are the leading cause of disability and consume a large amount of health and social resources. Therefore, it is crucial to assess the impact of RDs on the general population in what refers to their prevalence, and repercussion on quality of life and function. However, no nationwide epidemiological studies on RDs have ever been performed in Portugal. With this research project we aim to estimate the prevalence of different RDs in Portugal, as well as to determine the burden of RDs, more specifically their impact on quality of life and functional and work capacity. A cross-sectional study will be performed, using a random sample of the Portuguese population. RDs will be screened through a structured interview, and subjects with a positive screening will be examined by a trained rheumatologist to establish the final diagnosis. The knowledge of the prevalence of RDs will contribute to the development of specific health plans for the current and future management of these diseases.

Keywords: Rheumatic Diseases; Prevalence; Epidemiologic Studies; Cost of Illness.

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Background

Rheumatic diseases (RDs) can be defined as systemic diseases affecting the connective tissue (including joint components) and other medical disorders of the musculoskeletal system. Clinically, they are characterized by pain and/or stiffness and disability, and in some cases, inflammation. They may or may not be accompanied by involvement of other organs and systems. RDs are among the most common diseases managed at the primary health care level, as well as the leading cause of disability in the developed world, and consume a large amount of health and social resources[1-3].

Prevalence of RDs needs to be assigned to specific populations, as different populations with different genetic and environmental backgrounds show different rates. Furthermore, in the context of increasing treatment costs, economic constraints and managed care, specific local data on the prevalence and local major determinants of different diseases might help healthcare systems develop specific plans for the care of a given disease. At a national level, knowledge of the most important RDs and their consequences is essential for planning the needs of healthcare professionals, infrastructures, and resources. In Portugal, the prevalence of RDs is ill-defined. A nationwide epidemiological study is the only way to fulfill this need, and it is also a specific objective of the National Program Against Rheumatic Diseases ("Programa Nacional Contra as Doenças Reumáticas"). Furthermore, the knowledge of the burden of RDs will raise public awareness on their importance and impact in our society.

Well-designed and consistent RDs epidemiological studies have not been performed in Portugal, as opposed to what has happened in several other European countries, such as Spain and Greece[4, 5]. No population-based studies have been done on the prevalence of any of the rheumatic symptoms or RDs in the Portuguese population. Furthermo-

re, the impact of RDs on quality of life and on function has never been assessed at a population level, despite the fact that quality of life is the most important indicator of the burden of this group of diseases[6]. Thus, it is crucial to assess the impact of rheumatic diseases on the general population in terms of their prevalence, effect on quality of life, and function.

An epidemiologic study of RDs has long been necessary in Portugal, but it has been repeatedly postponed due to financial constraints. Herein we are presenting a project where we hope to have finally met all the minimum requirements to develop and undertake an epidemiological study determinant for the future of Portuguese rheumatology and of patients with RDs.

Objectives

Primary Objective

Estimate the prevalence of the different RDs in Portugal;

Secondary Objectives:

1. Estimate the prevalence of the different RDs according to socio-demographic characteristics;
2. Identify socio-demographic and clinical variables associated with the diagnosis of some RDs;
3. Estimate the frequency of previously undiagnosed RDs;
4. Determine the impact of RDs on quality of life and on functional and work capacity;
5. Investigate the access to healthcare of patients with RD;
6. Compare the burden of RDs in Portugal with the reality from other countries;
7. Define two cohorts, one with and another without RD, to be followed prospectively.

Methodology

Study design

A cross-sectional study will be performed.

Study population

The study population will be composed by adults (≥ 18 years old) who are non-institutionalized and living in private households in Portugal, from the Mainland and Islands (Madeira and Açores). Exclusion criteria will be: residents in hospitals, nursing homes, military barracks, or prisons, and residents unable to speak Portuguese or with a complete inability to answer the questionnaire, either directly or through a person living with him/her. The sample will be representative of the Portuguese population. Locations will be selected as the primary unit of sampling and, according to the CENSUS 2001. Excluding the islands, there are 27,960 localities in Portugal), with a total population of 7,719,986 subjects aged 18 years or older[7]. The sample size will be stratified for region and dimension of the location (< 2,000; 2,000-9,999; 10,000-19,999; 20,000-99,999; and 100,000 inhabitants). The number of questionnaires in each stratum will be proportional to the real distribution of the population. Because there is no reliable list of households in Portugal, a random selection of points in the map of each location will be performed. Addresses will be selected, and afterwards the "random-walks" will start. Interviewers will register each selected address and, if someone is at home, they will collect information on age and gender of the different people living in that address, and will give information about the study. After validation of the selected address and inhabitants, the interviews will be scheduled. In order to assure the successful data collection, up to three visits to each address (one during the weekend) will be made. Interviewers will collect 20% additional addresses in each point to compensate for possible refusals to participate. At each address, the person whose birthday is closest to the day of the visit (aged 18 years or older) will be selected for the interview and, if available, will be immediately asked to answer the questionnaire.

Primary objective and case definition

The primary objective will be the prevalence of the following rheumatic diseases: osteoarthritis (knee, hip and hand), low back pain (LBP), osteoporotic fractures (OPF), periarticular RD (PRD), fibromyalgia (FM), rheumatoid arthritis (RA), spondyloarthritis (SpA, as well as its major subtype, ankylosing spondylitis – AS), systemic lupus erythematosus (SLE), polymyalgia rheumatica (PMR), and gout (GO). A major risk of fragility fracture within 10 years will also be calculated.

Case definition: The diagnosis of RD, either active or in remission, will be based on the American College of Rheumatology (ACR, formerly the American Rheumatism Association) criteria (for RA, SLE, GO, OA, and FM)[8-17] or other internationally used criteria (for PMR, SpA and AS)[18,19].

Knee osteoarthritis will follow the ACR criteria[15]: the patient should have knee pain plus at least 3 of the following 6 clinical findings: a) age > 50 years; b) morning stiffness < 30 minutes of duration; c) crepitus on active motion; d) tenderness of the bony margins of the joint; e) bony enlargement noted on examination; e) a lack of palpable warmth of the synovium.

Hip osteoarthritis will be defined, according to the ACR criteria[13], as hip pain plus one of the following: a) hip internal rotation <15º and erythrocyte sedimentation rate (ESR) ≤45mm/hour (if ESR not available, substitute hip flexion ≤115º); b) hip internal rotation ≥15º and pain on hip internal rotation and morning stiffness of the hip ≤ 60 minutes and age > 50 years.

Hand osteoarthritis will be defined according to the ACR criteria[14]: the patient should fulfill the following 3 criteria: a) hand pain, aching, or stiffness; b) hard tissue enlargement of 2 or more of 10 selected joints; c) fewer than 3 swollen metacarpophalangeal joints; the fourth criteria corresponds to the presence of one of the following two: d) hard tissue enlargement of 2 or more DIP joints, or e) deformity of 2 or more of 10 selected joints.

LBP will be defined by self-report. The interviewers will be instructed to indicate what is understood by low back, more specifically the back area between the lower limits of the chest and the gluteal folds, and then to ask about pain in that area. In case of positive LBP, red flags will be searched, in order to detect a cause of specific LBP, namely infection, inflammatory disease and cancer[22]. The point prevalence of LBP will be estimated and, for this purpose, LBP on the day of the interview will be considered. Prevalence of LBP in the previous 6 months will also be estimated and further specified into acute LBP (less than 6 weeks), subacute LBP (between 6 weeks and 3 months) and chronic LBP (more than 3 months). Disabling acute LBP will be defined as a LBP preventing the patient from performing the activities of daily living, and with a score of at least eight, on a 0-10 pain visual analogue scale.

Densitometric osteoporosis will be underestimated due to the impossibility of screening all participants with dual energy x-ray absorptiometry (DXA). For the current study, a definition of OPF will be used and considered as positive in the case of history of a low impact bone fracture or of x-ray documenting vertebral fractures in post-menopausal women or men above 50 years old. The risk of a major fracture will be defined as a Fracture Risk Assessment Tool (FRAX – http://www.shef.ac.uk/FRAX/)[23] score of >10% (with or without DXA). Furthermore, some participants (the ones that will be evaluated by a rheumatologist, as explained below) will be submitted to a wrist DXA. The criteria to perform DXA will be in accordance with the guidelines from the Portuguese Society for Rheumatology (PSR)[24]. Osteoporosis will be defined according to the definition from the World Health Organization: bone density 2.5 standard deviations below the average of the healthy adult reference range (T score < -2.5)[25].

PRDs will be 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 PRDs will be specifically searched: tenosynovitis, adhesive capsulitis of the shoulder, enthesopathy, bursitis, palmar or plantar fasciitis, and carpal or tarsal tunnel syndrome present at the time of the interview. These will be diagnosed based on the main clinical manifestations and, in some instances, on exams (eg: radiographs, ultrasounds) findings.

For *fibromyalgia*, two classification criteria will be used, namely the 1990 ACR criteria[16], as well as the new ones, recently published[17]. According to the 1990 ACR criteria[16], fibromyalgia is defined as: a) history of widespread pain (present in both sides of the body, above and below the waist) for at least 3 months; b) pain in 11 of 18 tender point sites on digital palpation. According to the 2010 ACR criteria[17], fibromyalgia is defined as: a) widespread pain index (WPI) ≥ 7 and symptom severity (SS) scale score ≥ 5 or WPI 3-6 and SS scale score ≥ 9; WPI is the number of areas in which the patient has had pain over the last week and can vary between 0 and 19; SS scale score is the sum of severity of the 3 symptoms – fatigue, waking unrefreshed, and cognitive symptoms, plus the extent of somatic symptoms in general, and the final score is between 0 and 12; b) symptoms have been present at a similar level for at least 3 months; c) the patient does not have a disorder that would otherwise explain the pain.

Similarly, new classification criteria for *RA* have been recently developed[9]. Consequently, they will also be taken into account and the prevalence of RA will be reported according to both classification criteria, the 1987 ARA revised criteria for the classification of RA[8] and the new ones. RA will be diagnosed according to the 1987 ARA criteria[8] if 4 or more

of the following are present: a) morning stiffness longer than 1h present during at least 6 weeks; b) arthritis of 3 or more joint areas (≥ 6 weeks); c) arthritis of hand joints (≥ 6 weeks); d) symmetric arthritis (≥ 6 weeks); e) rheumatoid nodules; f) serum rheumatoid factor; g) typical radiographic changes of RA on hand radiographs. The new classification criteria consist of a scoring system, according to which an individual with a score ≥6 (out of 10) is considered to have RA[9]. Furthermore, with the adaptation for populational studies, the following situations will also be considered as RA: a confirmed diagnosis of RA, deformities clearly compatible with RA or RA criteria in the past[26].

SpA will be defined according to the Assessment of SpondyloArthritis International Society (ASAS) criteria for axial SpA[19] and also for peripheral SpA[20]. A diagnosis of axial SpA will be established if a patient with back pain ≥ 3 months and age at onset ≤45 years has sacroiliitis in imaging (magnetic resonance imaging or conventional radiograph) plus one or more SpA features or HLA-B27 positive plus 2 or more other SpA features. SpA features can be any of the following: inflammatory back pain, arthritis, enthesitis, uveitis, dactylitis, psoriasis, Crohn's disease/ulcerative colitis, good response to non-steroidal anti-inflammatory drugs, family history for SpA, HLA-B27, elevated C-reactive protein. Patients with SpA fulfilling the modified New York criteria will be further specified as having Ankylosing Spondylitis (AS)[21]. Peripheral SpA will be established in the presence of arthritis or enthesitis or dactylitis plus a) one of the following SpA features: psoriasis, inflammatory bowel disease, preceding infection, HLA-B27, uveitis, and sacroiliitis on imaging; or b) two of the remaining SpA features: arthritis, enthesistis, dactylitis, inflammatory back pain in the past, and positive family history for SpA[20].

SLE will be defined according to the 1997 revised ACR criteria[11] and at least 4 of the following must be present: a) malar rash; b) discoid rash; c) photosensitivity; d) oral ulcers; e) non-erosive arthritis; f) pleuritis or pericarditis; g) renal disorder; h) neurologic disorder; i) hematologic disorder; j) immunologic disorder; k) positive antinuclear antibody.

PMR will be diagnosed, according to the criteria published by Bird *et al.*[18], in the presence of 3 of the following: a) bilateral shoulder pain or stiffness; b) onset of illness of less than 2 weeks' duration; c) initial ESR greater than 40mm/h; d) duration of morning stiffness exceeding 1 hour; e) age 65 years or more; f) depression and/or weight loss; g) bilateral tenderness in the upper arms.

Gout will be defined according to the ACR criteria[12] and will be established in the presence of 6 of the following 11 criteria: a) more than one attack of acute arthritis; b) maximum inflammation developed within 1 day; c) oligoarthritis attack; d) redness observed over joints; e) first metatarsophalangeal joint painful or swollen; f) unilateral first metatarsophalangeal joint attack; g) unilateral tarsal joint attack; h) tophus (proven or suspected); i) hyperuricemia; j) asymmetric swelling within a joint on x-ray; k) complete termination of an attack.

Secondary objectives

Secondary aims will be the evaluation of quality of life, functional and work capacity and access to health care, more specifically the comparison between participants with and without an RD.

Quality of life will be evaluated by the Short Form-36 (SF-36), which yields a continuous result in two scales, physical and mental, each ranging from 0 (worst state) to 100 (best state). This instrument has been validated for the Portuguese population[27, 28].

Functional capacity will be assessed by the Health Assessment Questionnaire (HAQ)[29], which measures difficulty in performing the activities of daily living, and ranges from 0 (no limitation) to 3 (highest limitation).

Work disability will be evaluated by absenteeism, presenteeism, early retirement, and unemployment due to work disability.

Access to health care will be evaluated by Rheumatology consultation (ever, frequent rheumatology consultations - >1 consultation/year, number of consultations in the last year) and exemption from user fees due to RD.

Study Procedures

Trained interviewers will visit the target population at their homes door-to-door. This screening involves an interview for each participant and will be based on a standardized questionnaire. Its purpose is to obtain information on 1) socio-demographic characteristics, 2) medical history, 3) identification of subjects with a potential RD, and 4) assessment of physical function (HAQ), quality of life (SF-36), work ability and access to health care. Medical history will include questions about previous diagnosis of RD, intake of a list of antirheumatic

drugs, including non-steroidal anti-inflammatory drugs (NSAIDs) for more than one month in total, and the need for medical appointments due to musculoskeletal symptoms in the previous year. In the presence of a diagnosis of RD, questions will address the examinations performed to reach that diagnosis, as well as the name of the medical speciality that established the diagnosis.

The screening questionnaire will be developed in several steps:

1. Questionnaire development: preparation of the questionnaire by a team composed by rheumatologists and epidemiologists;
2. Validation study: to assess the properties of the screening questionnaire (mainly sensitivity and specificity) a validation study will be carried out prior to the start of the study, involving participants with and without an RD. The recruitment of these cases and controls will be hospital-based, from outpatient clinics;
3. Potential refinement of the questionnaire, if necessary after the validation study;
4. Preparation of the data collection forms to be applied through Computer Assisted Personal Interviewing methods;
5. Pilot study: a pilot study will be carried out to detect possible errors in the design of the data collection forms, to assess feasibility of the recruitment, to estimate the interviews' duration, and to estimate the percentage of non-responders and the causes of non-collaboration;
6. Application of the final questionnaire.

Participants identified by this screening questionnaire as potentially having an RD, as well as some of the patients considered as not having an RD (20-30% depending on the accuracy of the questionnaires, as determined in interim analyses), will be evaluated by a rheumatologist according to a structured protocol. Participants will be evaluated in a diagnostic van, fully equipped for the purpose. The evaluation by a rheumatologist will include a medical history and physical examination and will be as closest as possible in time to the screening questionnaire. Available and appropriate laboratory test results or imaging findings will be evaluated during the diagnostic procedure. During the evaluation, blood will be drawn and kept frozen in a biobank for future research, with the patient consent. As explained before, wrist DXA will be performed to the participants evaluated by a rheumatologist and with a clinical indication for a DXA, as recommended by the PSR[24]. In cases where further laboratory investigation or radiographs are necessary, they will be performed as soon as possible (most of them can already take place inside the diagnostic van, such as conventional radiographs and blood draw for laboratory analysis). Afterwards, participants' data will be re-evaluated by a rheumatologist to reach a definite diagnosis. If necessary, the participant will be re-evaluated by a rheumatologist. Cases that pose diagnostic doubts will be discussed among a scientific committee composed by 3 rheumatologists and the principal investigator. Patients with an identified RD, not being followed by a rheumatologist but with clinical indication for will be referred to a rheumatology appointment in their referral hospital.

Non-responders will also be randomly analyzed, by means of comparison of socio-demographic characteristics, as well as clinical aspects, if available. Therefore, non-responders will be asked to answer a basic questionnaire designed specifically for this purpose. Reasons for non-participation will also be registered.

Prior to the start of the study, all participating interviewers and rheumatologists will be trained in order to standardize procedures. This training will cover the study protocol, how to conduct the interview, assessment of musculoskeletal symptoms, and standardizing the use of the RDs classification criteria. The field work will be only undertaken by interviewers with adequate skills to assure the quality of the data collection. Therefore, interviewers not achieving a reasonable level of knowledge after the training will be excluded from the process. Data collection forms will be further monitored centrally to check for missing data or inconsistencies, including potential participant telephone contact to confirm the answers.

At the end of the study, two cohorts will be defined for prospective follow-up, one composed by participants with an RD and another by participants without an RD. The aim of creating these cohorts is to investigate the evolution and outcomes of the RDs, as well as the potential appearance of an RD in the non-RD cohort.

Statistical Considerations

The prevalence of the different RDs will be estimated with 95% confidence intervals adjusted for the design of the study and standardized for age and gender, according to the total adult population of the studied areas. Comparison of demographic

and clinical characteristics between groups (eg with and without RD) will be undertaken using *t* tests for continuous normally distributed variables or Wilcoxon for continuous non-normally distributed variables. Chi-squared tests will be used for categorical variables, and Fisher's Exact test will be used for categorical variables within smaller sample sizes. Comparison between more than two groups will be performed through one-way analysis of variance (ANOVA) for continuous variables and chi-squared test for categorical variables. Factors significantly associated with any disease group will be included in a logistic regression model for further analysis. The effect of specific conditions on quality of life and function will be assessed by linear regression, univariably and then multivariably, controlling for potential confounders and also analyzing potential effect modification. A probability of $p < 0.05$ will be considered significant. All data will be analyzed with SPSS v 17.0.

Sample Size Calculation

Sample size calculation was based on the prevalence of RA, which is expected to be between 0.5 and 1%[30]. Assuming a 95% confidence interval, a 0.25% margin of error, a total population of 8,500,000 adults in Portugal, and increasing the sample size by 50% to account for the design effect and recruitment failures, a total of 9,000 participants will be required.

Ethical considerations

Confidentiality will be safeguarded by the non-existence of identifiers on the database. Contacts will only be kept for logistical reasons, in order to reach participants for posterior observation by a rheumatologist. All participants will sign an informed consent. Blood from the participants evaluated by rheumatologists will be drawn and kept frozen in a biobank for future research, as long as the patient gives his/her consent.

This project will be submitted to the National Ethics Committee from the Portuguese College of Physicians (Ordem dos Médicos), and also to the Comissão Nacional de Protecção de Dados (CNPD), the Portuguese data protection authority (in accordance with the Portuguese law number 67/98, October 26th regarding protection of personal data). The study will be conducted in accordance with the applicable laws and regulations including, but not limited to, the Guideline for Good Clinical Practice (GCP) and the ethical principles stated in the Declaration of Helsinki (amended in Edinburgh).

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Scientific patronage

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This protocol was prepared as the basis of this epidemiologic study. Nevertheless, it can be complemented by additional amendments in the future, if considered to be convenient and beneficial for the project.

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