THE BURDEN OF CHRONIC LOW BACK PAIN IN THE ADULT PORTUGUESE POPULATION: AN EPIDEMIOLOGICAL POPULATION-BASED STUDY UNDER THE SCOPE OF EPIREUMAPT

NÉLIA SOFIA AUGUSTO GOUVEIA

Tese para obtenção do grau de Doutor em Ciências da Saúde
na Especialidade em Investigação Clínica
na Faculdade de Ciências Médicas da Universidade Nova de Lisboa

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Nélia Sofia Augusto Gouveia

Orientador: Professor Doutor Jaime da Cunha Branco

Professor Catedrático de Medicina/Reumatologia da

NOVA Medical School, Universidade Nova de Lisboa

Co-Orientadora: Professora Doutora Helena Canhão

Professora Auxiliar Convidada de Reumatologia da

Faculdade de Medicina da Universidade de Lisboa

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“Ter um destino é não caber no berço onde o corpo nasceu, é transpor as fronteiras, uma a uma, e morrer sem nenhuma”

Miguel Torga

À minha Mãe,

ao meu Pai,

à minha Irmã

e ao Guilherme

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LIST OF ACRONYMS AND ABBREVIATIONS

ACP	American College of Physicians
ANA	Antinuclear Antibodies
Anti-CCP	Antibodies against Cyclic Citrullinated Peptides
Anti-dsDNA	Antibodies against double stranded DNA
Anti-TNFs	Anti-tumor necrosis factors
APS	American Pain Society
ARA	Regions of Azores
ARM	Regions of Madeira
AS	Ankylosing Spondylitis
ASAS	Assesment of SpondyloArthritis International Society
BMA	Bone microanalysis
BMD	Bone mineral density
BMI	Body Mass Index
CAPI	Computer Assisted Personal Interview
CESOP	*Centro de Estudos e Sondagens de Opinião*
CI	Confidence interval
CINDI	Countrywide Noncommunicable Disease Intervention
CLBP	Chronic Low Back Pain
COPCORD	Community Oriented Program of Control of Rheumatic Diseases
COX-1	Cyclooxygenase 1
COX-2	Cyclooxygenase 2
CT	Computerized tomography
DALYs	Disability-adjusted life years
DAS28	Disease Activity Score 28
DEXA	Axial dual Energy X-ray Absorptiometry
EpiReumaPt	Portuguese Epidemiologic Study of Rheumatic Diseases
EQ5D	European Quality of life Questionnaire
ESR	Erythrocyte Sedimentation Rate
FM	Fibromyalgia
GABA	Gamma-AminoButyric Acid
GBD	Global Burden of Disease
HADS	Hospital Anxiety and Depression Scale
HAQ	Health Assessement Questionnaire
HIV	Human Immunodeficiency Virus
HLA-B27	Human Leukocyte Antigen-B27
HOOS	Hip injury and Osteoarthritis Oucome Score
HPA	Hypothalamic-Pituitary-Adrenocortical
IMM	*Instituto de Medicina Molecular*
KOOS	Knee injury and Osteoarthritis Outcome Score
LBP	Low Back Pain
MCV	Mean Corpuscular Volume
MRI	Magnetic Ressonance Image

LIST OF ACRONYMS AND ABBREVIATIONS (cont.)

MSK	Musculoskeletal
NRS	Numeric Rating Scale
NSAIDs	Non-steroid anti-inflammatory drugs
NUTS II	Administrative Territorial Units
OA	Osteoarthritis
OP	Osteoporosis
OR	*Odds-Ratio*
PD	Periarticular Disease
PMR	Polymyalgia Rheumatica
PNCDR	Program Against Rheumatic Diseases
QoL	Quality of Life
RA	Rheumatoid Arthritis
RMD	Rheumatic and Musculoskeletal Diseases
SD	Standard Deviation
SF36	Short form (36) form health survey
SLE	Systemic Lupus Erythematosus
SpA	Spondyloarthritis
SPR	Sociedade Portuguesa de Reumatologia
UCP	Universidade Católica Portuguesa
UK	United Kingdom
USA	United States of America
WHO	World Health Organization
Y.O.	Years Old
YLDs	Years Lived with Disability

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No final desta longa epopeia todas as palavras serão poucas para transmitir o que significa a sua concretização. Ainda assim, deixo neste texto as minhas palavras de agradecimento às pessoas que mais contribuíram para o seu sucesso.

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ABSTRACT

Low Back Pain (LBP) is the most prevalent of musculoskeletal condition in developed countries. When it becomes chronic, LBP causes an enormous economic burden on individuals and society - it is one of the leading causes of loss of productivity and economic independence through absenteeism (time off work), presenteeism (lost productivity because of diminished capacity while at work) and work disability (permanent, partial or complete disablement for work purposes). In Portugal the prevalence and burden of LBP and chronic LBP (CLBP) were poorly defined. Until now no large population-based studies have focused on this.

The main aim of this thesis was to determine the prevalence of LBP and CLBP, and also to assess the burden of CLBP in the adult Portuguese population.

The research work was developed under the scope of EpiReumaPt (the Portuguese Epidemiologic Study of Rheumatic Diseases). EpiReumaPt was the first national large population-based and prevalence study of rheumatic and musculoskeletal diseases (RMD). It was performed among a randomized and representative sample of 10,661 adult Portuguese subjects recruited in Mainland, Azores and Madeira Islands, from September 2011 to December 2013.

The first section of this thesis included detailed issues regarding the development and management of EpiReumaPt, and provided a practical guide on how to set-up a large population-based study in Portugal. The detailed methodology of EpiReumaPt, including its objectives, study design, recruitment features, and data preparation for analyses were also described. The main results from EpiReumaPt study were provided in this section and showed that LBP was the musculoskeletal condition with highest prevalence among Portuguese population.

The second section of this thesis estimated the prevalence of active CLBP among adult Portuguese population, and assessed the social burden of this condition. Active CLBP was defined based on self-reported pain on the day of the interview, and for most of the time for

at least 90 days (independently from cause). LBP was defined as pain in the back area from the lower margin of the twelfth ribs to the lower gluteal folds, with or without pain referred to the lower limbs. Social burden was measured taking into account the following outcomes: quality of life, function, healthcare resources consumption, analgesic and other pain relief drugs intake, anxiety and depression symptoms. Results showed that the healthcare consumption and social burden of CLBP among adult Portuguese population were enormous, and the disability caused by CLBP among subjects in a working age provides high rates of absenteeism (work loss) and poor quality of life, with a consequent socioeconomic burden.

This thesis also concluded that analgesic and other pain relief drugs intake among adult Portuguese population with active CLBP was very low. Most of the subjects with active CLBP did not take any analgesic drug regardless pain severity. Even when subjects self-reported severe pain, only 24.0% were in the 1st step of the analgesic ladder, 2.3% used weak analgesic opioids and 0.03% used strong opioids (2nd and 3rd step of WHO analgesic ladder, respectively) to control pain.

The research work also confirmed that the prevalence of anxiety and depression symptoms among adult Portuguese subjects with active CLBP was high. Regarding pharmacological therapy, the intake of analgesic and other pain relief drugs was higher among subjects with anxiety and/or depression symptoms, when compared with subjects without these psychological symptoms. Anxiolytics, sedatives and hypnotics, antidepressants and NSAIDs intake had higher usage rates among these subjects. The pain severity mean was also higher among this subjects and function and health status was worse. Regarding healthcare resources consumption, significant differences between the two populations were found. Subjects with active CLBP and concomitant psychological symptoms had a higher number of psychiatrist and other physician visits. They also needed more home care in the previous 12 months. Factors associated with isolated symptoms of anxiety, depression, and concomitant anxiety and depression symptoms were also identified.

Summarizing, we concluded that CLBP is a common health problem among adult Portuguese population contributing to disability and affecting labor performance, and the well being of

subjects. It is also responsible for considerable healthcare resource consumption. Anxiety and depression symptoms are common among subjects with CLBP and provided an additional burden among them.

Key words: epidemiologic study; population-based study; prevalence study; low back pain; chronic low back pain; burden of disease; analgesic and pain relief drugs; anxiety and depression symptoms

RESUMO

Nos países desenvolvidos a lombalgia é a condição músculo-esquelética mais prevalente. Quando evolui para um quadro crónico é responsável por um encargo económico bastante considerável, não só em relação aos indivíduos, mas também para a sociedade. A lombalgia crónica é por isso uma das principais causas de perda de produtividade e de perda de independência económica, nomeadamente através do absenteísmo (ausência do trabalho), do presenteísmo (perda de produtividade no trabalho, devido à capacidade diminuída provocada pela lombalgia) e da incapacidade para trabalhar (invalidez permanente, total ou parcial). Até à data, em Portugal, a prevalência e carga social da lombalgia crónica eram desconhecidas. Até agora não existiam estudos populacionais de grande dimensão sobre este tema.

O objetivo principal desta tese foi determinar a prevalência de lombalgia crónica, e também avaliar a carga social que esta tem na população adulta Portuguesa.

O trabalho de investigação foi desenvolvido no âmbito do Estudo Epidemiológico de Doenças Reumáticas em Portugal (EpiReumaPt). Este foi o primeiro estudo de larga escala e de base populacional, que determinou a prevalência de doenças reumáticas e músculo-esqueléticas na população adulta portuguesa. Foi realizado numa amostra aleatória e representativa, de 10.661 indivíduos do Continente, da Região Autónoma dos Açores e da Região Autónoma da Madeira, entre Setembro de 2011 e Dezembro de 2013.

Esta tese foi dividida em duas secções. A primeira secção incluiu o detalhe das questões relativas ao desenvolvimento e gestão do EpiReumaPt, constituindo-se como um guia prático sobre como realizar um estudo de base populacional de larga escala, em Portugal. A metodologia detalhada do EpiReumaPt foi também descrita nesta secção e incluiu os objectivos, o desenho do estudo, as características de recrutamento e a preparação de dados para análise. Nesta secção foram ainda descritos os principais resultados do EpiReumaPt. Estes evidenciaram que a lombalgia foi a condição músculo-esquelética com maior prevalência na população adulta portuguesa.

A segunda secção desta tese estimou a prevalência da lombalgia crónica ativa na população adulta Portuguesa, e avaliou a carga social desta condição. A lombalgia ativa foi definida com base na dor auto-relatada no dia da entrevista e que persistia há pelo menos 90 dias (independentemente da causa). A lombalgia foi definida como dor na área definida entre a margem inferior das décimas segundas costelas até às pregas glúteas inferiores, com ou sem dor nos membros inferiores. A carga social foi medida tendo em conta os seguintes parâmetros: qualidade de vida, função, consumo de recursos de saúde, consumo de analgésicos e outros fármacos usados no alívio da dor, sintomas de ansiedade e sintomas de depressão.

Os resultados mostraram que o consumo de recursos em saúde e a carga social da lombalgia crónica na população adulta Português é significativa. Também a incapacidade causada pela lombalgia crónica, nos indivíduos com idade ativa, é responsável por elevadas taxas de absenteísmo e má qualidade de vida, aos quais acresce o consequente ónus socioeconómico.

Esta tese também concluiu que o consumo de analgésicos e outros medicamentos para alívio da dor, na população adulta portuguesa com lombalgia crónica ativa, é relativamente baixa. A maioria destes indivíduos não tomava nenhum medicamento analgésico, independentemente da intensidade da dor. Mesmo os indivíduos que reportaram dor intensa, apenas 24.0% estavam no primeiro degrau da escada analgésica da Organização Mundial de Saúde; 2.3% usavam opióides fracos e 0.03% usavam opióides fortes para controlar a dor (segundo e terceiro degrau da escada analgésica da Organização Mundial da Saúde).

O trabalho de investigação também confirmou que a prevalência de sintomas de ansiedade e depressão entre os indivíduos adultos portugueses com lombalgia crónica ativa é elevada. Nestes indivíduos, registou-se um consumo mais elevado de analgésicos e outros medicamentos para alívio da dor, quando comparados com os indivíduos com lombalgia crónica activa sem esses sintomas psicológicos. Os grupos terapêuticos mais utilizados foram os ansiolíticos, sedativos e hipnóticos, os antidepressivos e os anti-inflamatórios não esteróides. A intensidade média da dor reportada foi também maior entre os indivíduos com lombalgia ativa e sintomas de ansiedade e/ou depressão. Também nestes, foi reportada pior função e pior estado de saúde. Em relação ao consumo de recursos de saúde foram

encontradas diferenças significativas entre as duas populações: os indivíduos com lombalgia ativa e sintomas psicológicos concomitantes registaram maior número de consultas de psiquiatra e de outras especialidades médicas, assim como precisaram de mais apoio domiciliário nos 12 meses prévios à entrevista do EpiReumaPt. Foram também identificados os fatores associados a sintomas isolados de ansiedade, a sintomas isolados de depressão e a sintomas de ansiedade e depressão.

Resumindo, esta tese permitiu concluir que a lombalgia crónica é um problema de saúde comum na população adulta portuguesa, contribuindo para um elevado grau de incapacidade e que consequentemente afeta o desempenho laboral e o bem-estar dos indivíduos. A lombalgia crónica é também responsável por um consumo considerável de recursos de saúde. Acresce ainda que os sintomas de ansiedade e depressão são comuns, entre os indivíduos com lombalgia crónica, contribuindo com uma carga social adicional.

Palavras-chave: estudo epidemiológico; estudo de base populacional; estudo de prevalência; lombalgia; lombalgia crónica; carga da doença; analgésicos e outros fármacos para alívio da dor; sintomas de ansiedade e depressão

SCOPE AND CONTEXT

This thesis results from a great opportunity that the EpiReumaPt research team gave to me.

I started as manager of the EpiReumaPt study, in March 2011. The study had just been founded and it was possible to start the fieldwork organization and planning. I was already attending the PhD course, in NOVA Medical School, and I was looking for an opportunity to develop the research work. EpiReumaPt gave me that chance.

From March 2011 until now, I followed all the baby steps of this project and developed all the management issues regarding to it. I'm very thankful to the EpiReumaPt Research Team for this opportunity. I appreciate the possibility to develop my thesis under the scope of this large national study.

THESIS OUTLINE

The present thesis is divided into six main chapters, enumerated with Roman numbers, whose content is summarized below.

Chapter I is a general introduction to the thesis, summarizing the most relevant topics of literature in etiology, treatment, prevalence and burden of low back pain and chronic low back pain.

Chapter II addressed the general and specific research aims.

Chapter III contains a brief description of the general methods used during the research work.

Chapter IV presents two distinct sections with the results of this thesis, published or submitted to international peer-reviewed journals. **Section I** comprises three papers describing the development and management of this large epidemiologic population study; and also the detailed methodology and main results of EpiReumaPt. In the latter, it was possible to determine the prevalence of self-reported LBP among adult Portuguese population. **Section II** included a set of studies that aimed to determine the prevalence and social burden of CLBP in adult Portuguese population. Social burden was measured taking into account the following outcomes: quality of life, function, healthcare resources consumption, analgesic and other pain relief drugs intake, anxiety and depression symptoms.

Chapter V comprises a discussion of the main results and limitations of research work.

Chapter VI provides the main conclusions and perspectives for the future research.

CHAPTER I - Introduction

Rheumatic and musculoskeletal diseases

Rheumatic and musculoskeletal diseases (RMD) have a high prevalence in the population, and are a major cause of disability, particularly in developed countries [1] [2] [3]. Given the current lifestyles and increasing life expectancy, RMD assume an increasingly important role in resource consumption, leading to a significant socioeconomic impact [4] [5] [6] [7] (figure 1).

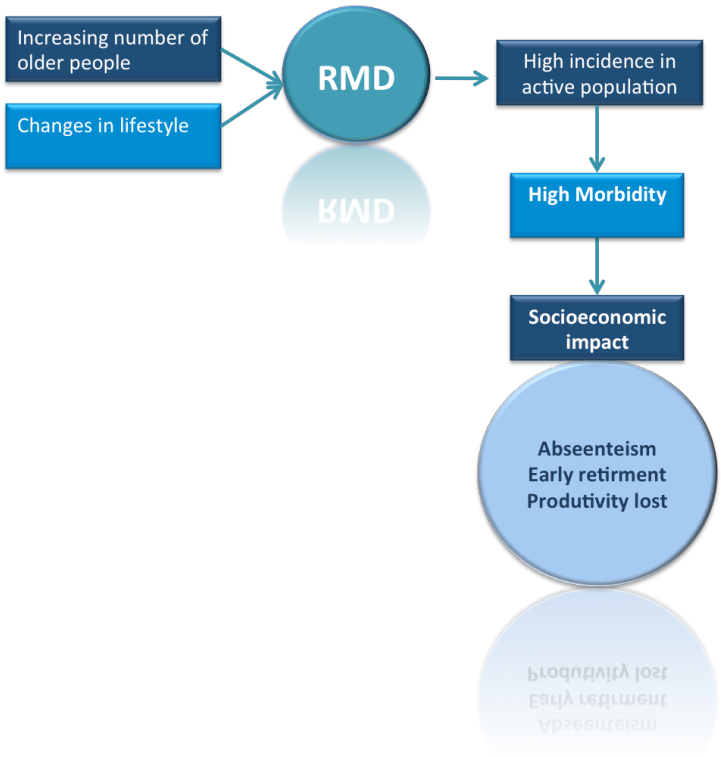

Figure 1: Burden of rheumatic and musculoskeletal diseases

RMD affect subjects by limiting their activities and restricting their participation and affect society by work loss, disability pensions, early retirement and increasing need for social

support [8] [9]. RMD impair social functioning and emotional well-being, seriously affecting quality of life [10] [11] [12] [13].

RMD are not considered to be fatal [14] but it's burden was very large among society. Production of representative national data on RMD may help national Authorities to priorize public health strategies and convince them of the need to consider focusing on musculoskeletal conditions to improve population health and quality of life [8] [15].

Epidemiologic Studies of RMD in the World

Epidemiologic prevalence studies profile the distribution and frequency of a given disease, in a pre-defined human population [16] [17]. This type of studies is the most effective way to adjust social and economic contexts, resources and consumption, to the prevalence of the diseases and, therefore, it assumes a particular relevance on strategic health care planning [18].

In developed countries several epidemiological studies were performed in order to draw the territorial profile of RMD. Greece [10], Spain [19] and Portugal [4] developed their own protocols to study the prevalence of RMD. Moreover, many other countries conducted epidemiological studies of specific pathologies (or group of pathology), which in many cases were useful to define the prevalence based on previously validated diagnostic criteria: gout [20] [21], psoriatic arthritis [22] spondilarthropathy [22] [23] [24, 25] rheumatoid arthritis [26] [27] [28] [29] fibromyalgia [30] and other RMD [3] [31].

In relation to this, the World Health Organization (WHO) and the International League of Associations for Rheumatic Diseases, launched in 1981, a program for the control of RMD - Community Oriented Program of Control of Rheumatic Diseases - COPCORD - which has been implemented in many countries (especially in underdeveloped countries) [7].

In Portugal RMD epidemiologic studies were scarce and critically focused on specific pathology (5), or they were developed in delimited geographic areas [32] [33]. Programme CINDI (Countrywide Noncommunicable Disease Intervention) was developed in Portugal, in the eighties, sponsored by WHO. Its main focus was cardiovascular disease and its risk factors. This study also included the prevalence of RMD in the Setúbal *peninsula*. Here a

randomized population of 1381 individuals of both genders was observed by a rheumatologist. This work was developed for over 20 years and, until 2011, it was the one that involved the largest sample in Portugal [34] [35].

The development of the National Program Against Rheumatic Diseases (2004-2010) (a governmental programme) allowed the planning and implementation of the first Portuguese Epidemiologic Study of Rheumatic Diseases (EpiReumaPt) [4] [36] from September 2011 to December 2013. EpiReumaPt was the first large-scale project studying RMD in the adult Portuguese population (≥18 years old), designed to determine the prevalence of RMD covered by the Program: hand, knee and hip osteoarthritis, low back pain (LBP), rheumatoid arthritis, fibromyalgia, gout, spondyloarthritis, periarticular disease, systemic lupus erythematosus, polymyalgia rheumatica and osteoporosis [34]. It also aimed at assessing the impact of RMD in relation to quality of life, function, use of healthcare resources and abseenteism [4]. EpiReumaPt protocol was developed after reviewing other international studies and adapted to the Portuguese context [10] [19] [37] [38] [39]. Details regarding EpiReumaPt management, methodology and main results are described later in this text.

Low Back Pain

Prevalence and incidence

In the 2010 WHO Global Burden of Disease study, prevalence of LBP was estimated to be 9.4% (95% confidence interval (CI) 9.0%-9.8%) [40]. The prevalence of LBP tends to be higher in women than in men [41] [42] [43, 44].

Recurrent episodes are very common in people who have had an episode of LBP. The recurrence at 1 year ranges from 24 to 80% [41]. Furthermore, it is estimated that, in developed countries, 2-5% of people suffering from chronic LBP, and many of those are permanently disabled [41].

There is great heterogeneity among epidemiological studies of LBP, which limits data comparison [41]. Studies vary widely in terms of methodology, particularly in case definition

and prevalence periods, as well as on the nature and measures taken to minimize biases [45].

Until now prevalence data about LBP among Portuguese population did not exist.

Low back pain – brief concepts

Rachialgia or pain in the spine is a highly prevalent symptom. Cervical and lumbar segments most often affect mobility [34]. In this study we will focus on pain in the lower back, namely LBP.

Although LBP is not a life-threatening situation it constitutes a major public health problem (as classified by WHO) in industrialized societies [40] [46] [47] affecting a substantial proportion of the working age population and leading to significant absenteeism and labor productivity break [34] [40] [47]. Consequently, the socio-economic burden of disability due to LBP has increased exponentially in these countries. Most significant costs are attributed to its chronicity [34] [40].

Causes of low back pain

In clinical practice, LBP is a symptom, not a disease. It is believed that LBP is caused by multiple factors, often categorized as physical, psychosocial, and lifestyle [48] [49]. In addition, LBP involved several anatomical structures: bones, intervertebral discs, joints, ligaments, muscles, neural structures, and blood vessels [41]. It is usually defined as pain in the back area from the lower margin of the twelfth ribs to the lower gluteal folds, with or without pain referred to the lower limbs [50] [5] [40]. The pain is often persistent during the episode and gets worse with long walking, standing and sitting, which limit patient mobility. Pain can also affect sleep [5] [51] [52].

LBP classification depending on the duration is defining as acute (<3 months) or chronic (≥3 months) [50]. The chronic form represents only 7% of LBP, but it is estimated to be responsible for over 75% of LBP health costs [34] [5].

Most of the times LBP has a mechanical cause based on the changes of intervertebral discs or interapophyseal joints [49] – non-specific LBP. Just a few cases are caused by a serious primary cause, as spine injuries with risk to the patient's life: cancer (0.7% of the cases), infection (0.01%), *cauda equina* syndrome (12:04%), compression fracture (4%), ankylosing spondylitis (0.3-5%), spinal stenosis (3%) or herniated discs with radiculopathy (4%) [53] [54]. Some of these specific causes require urgent evaluation since they may lead to serious or permanent complications (including paralysis or permanent loss function). The LBP can also be a symptom associated with visceral disturbs (pancreatitis, nephrolithiasis, aortic aneurysm, or systemic diseases such as endocarditis or viral syndromes) [49].

Diagnosis & Clinic

The American Pain Society (APS) and the American College of Physicians (ACP) published in 2007 a guideline for the diagnosis and treatment of LBP, according to the degree of evidence [54] [53]. This approach is similar to the recommendations of the European Cooperation in the Field of Scientific and Technical Research (COST) Action B13 guideline. LBP evaluation has two main objectives:

. determining a specific condition as LBP cause

. determining the presence and severity of neurologic involvement

This approach helps to divide LBP into 3 categories:

. non-specific LBP

. LBP potentially associated with radiculopathy or spinal stenosis

. LBP potentially associated with another specific spinal cause.

Differential diagnosis is very important to exclude other causes before settling in the diagnosis of nonspecific LBP. In order to achieve this, a careful history and physical examination are generally needed to diagnosis atypical LBP [49].

Differential diagnosis is critical to exclude other major serious causes of LBP: tumor, infection and fracture. Pain should be well characterized in clinical history: location, irradiation, start date, factors that can affect the pain (relieve or exacerbate it), concomitant

symptoms (fever, health status changes), and personal history, including similar episodes and other diseases. Laboratory blood tests are also required (sedimentation rate, blood count and protein electrophoresis). Other analytical parameters or other examinations are only asked for if there is a suspicion of unusual LBP cases [49]. Certain imaging tests can be required: radiography (X-ray), magnetic resonance imaging (MRI), and/or computerized tomography (CT) (Fig 1).

Recent studies show that imaging tests don´t contribute to improved treatment of adults under 50 years old with no signs or symptoms of systemic disease. For adults over 50, or those where findings suggest narrowing interdiscal space, osteophytes or sclerosis, an examination of X-rays and lab tests suffice to confirm diagnosis (Fig 1). Good practice advises that imaging tests should be reserved for patients considered for surgery or those in which there is a very high diagnostic hypothesis of a systemic disease [55] [56].

Since it is difficult to determine the primary cause of most cases of LBP, many of them are classified as non-specific LBP. However the following specific differential diagnoses for serious conditions is mandatory: infection, inflammatory disease and cancer. The latter are not usually monitored in primary care and require referral to a specialized center for specific treatment [57]. It has been recommended that primary healthcare evaluation should include screening to possible severe causes using red flag questions [57].

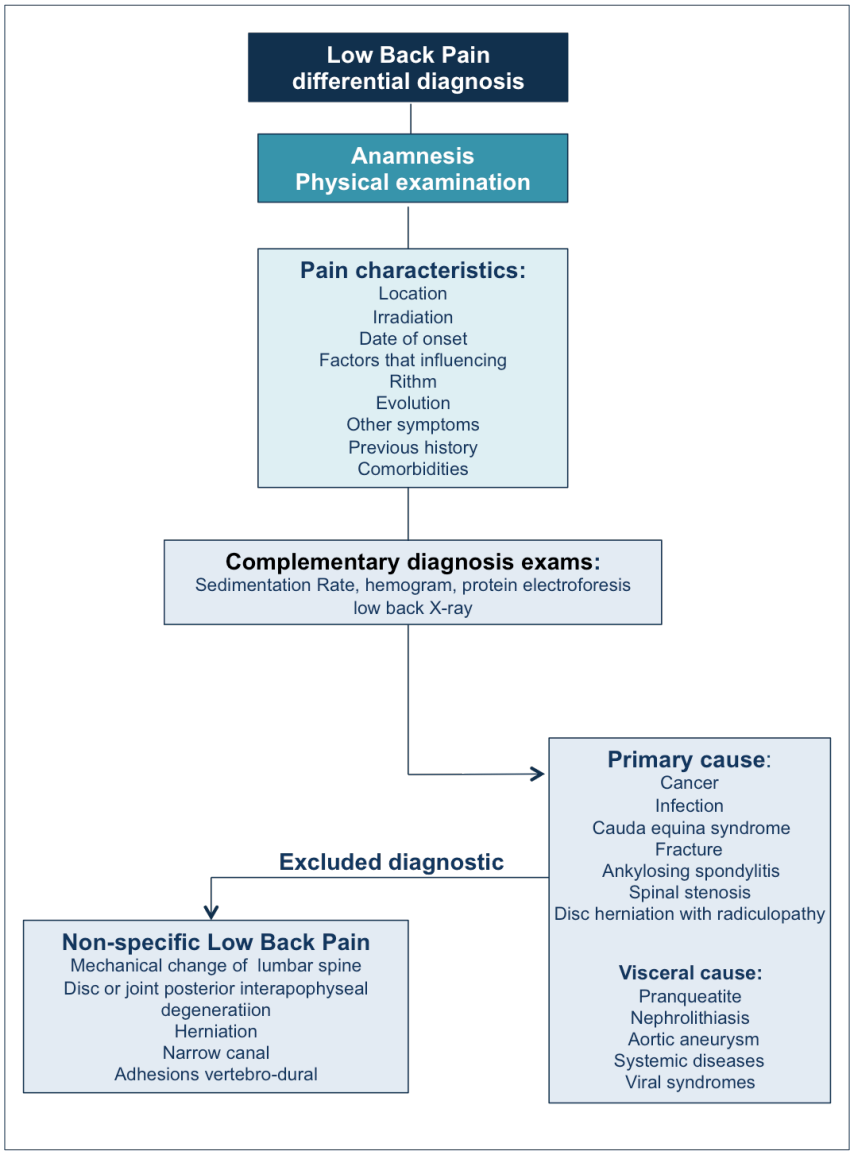

Figure 2 - Low back pain differential diagnosis

Primary causes of low back pain

The inflammatory LBP generally arises before 45 years of age and is characterized by intense pain, low location (buttock), inflammatory rhythm, spinal rigidity and high sedimentation rate. Infectious etiology should be excluded, particularly if LBP appears severe, with an insidious onset, with high sedimentation rate, fever, disc narrowing and

erosions of the adjacent endplates (X-ray images) (table 1). The study by CT is relevant and the diagnosis is usually confirmed by biopsy [49].

Tumor, as primary cause of LBP, should be suspected if LBP has a progressive evolution, severe pain, not yielding to analgesics and non-steroid anti-inflammatory drugs (NSAIDs), and is accompanied by changes in the general condition. Primary vertebral cancer is rare and most commonly is myeloma disease or metastatic lesions. They occur more frequently over 60 years old and the primary location of the tumor should be searched for.

Vertebral osteoporosis can be a valid suspected diagnosis in women over 60 years old, with acute pain.

LBP can also have a non-vertebral origin: visceral LBP due to a renal (renal ptosis, gallstones, infection, tumor), or uterus-ovarian cause. Pregnancy can also cause LBP by a hyperlordosis and overload of the posterior arch.

Table 1: Symptoms of low back pain presenting a primary cause

Symptoms of low back pain presenting a primary cause	. Insidious and progressive onset without other cause, in subjects over 50 years old and with no history of low back pain . Pain with an atypical rhythm . Increasing pain severity . Stiffness of the lumbar segment . Changes in general condition, such as asthenia, anorexia, weight loss or fever . Suspicious past history (tumors, infectious disease or drug addiction)

(***source:*** *DGS 2004*)

Nonspecific low back pain

Nonspecific LBP is a diagnosis of exclusion. It is mostly carried out on the basis of lack of history or clinical features that can suggest a specific condition [49].

Non-specific LBP is in most cases a mechanical change in the lumbar spine. It is defined as a pain due to overload or excessive use of an anatomical structure; or secondary to trauma or deformity [49].

Disc deterioration due to water loss, proteoglycans and collagen fibers leads to the loss of inability to support loads, with consequent irregularity and damage in the disk, leakage of

nuclear material through the fissures causing protrusion or herniated disc. As a result of disc fragility there is a height loss and change of the posterior arch structures: ligament and muscle tension, loss of parallelism of the articular surfaces of the posterior interapophyseal joints and consequent regenerative phenomena [49].

There are other causes of mechanical LBP: herniated disc, narrow canal, vertebro-dural adhesions. The radicular pain under the common LBP may have other causes beyond the disc herniation: osteoarthritis interapohysaria, synovitis and synovial cyst. [49].

Non-specific LBP may also relate to psychological factors. Excessive emotional and amplification of pain perception are important factors in the genesis of LBP [58] [59].

Risk factors of low back pain

There are factors that predispose individuals to develop LBP. Current studies converge to identify predisposing factors and to demonstrate the association between some of them and the likelihood of developing LBP:

. physical, manual and repetitive work and long periods in a sitting position [48]

. ergonomics at work: fast pace of work, patterned movements, insufficient recovery time, awkward postures (dynamic or static), low temperatures [60] [61].

. psychosocial factors: anxiety, depression, emotional instability and reaction to pain, labor dissatisfaction [5] [41], stress, overwork [41] [48].

. characteristics of initial episode, of the pain, co-morbidities and opioids [62] [60].

. other personal characteristics of the individual: age, body mass index (BMI), physical fitness, smoking [5], heredity (a major factor in disc degeneration) and heavy work [5] [60]. Some studies show that people with high BMI are more likely to have LBP. A meta-analysis including 33 studies shows that obesity is associated with increased prevalence of LBP in the previous 12 months, seeking care for LBP, and chronic LBP (CLBP) [5] [63].

Chronic low back pain

Most episodes of LBP are solved within a few weeks, but many have a recurrent course, with acute episodes affecting 20-40% of patients and recurrences above 85% [64]. As we said before, literature defines CLBP as pain lasting more than 3 months [50].

The development of CLBP and consequent disability depends more on individual questions and related work than with clinical or physical issues [47]. Supporting this assumption is the fact that pain chronicity can provide secondary mental disorders and cognitive behavior changes (including anxiety and depression). This issue will be discussed later in this text.

Therapy of non-specific low back pain

To treat non-specific LBP means treating the main symptom - pain. The current treatment for LBP focuses on controlling pain, maintaining function and preventing exacerbations. The main objective is always to increase the functional capacity and prevent recurrence and chronicity.

LBP treatment approach includes [49]:

a. Rest

b. Pharmacological treatment

c. Rehabilitation

d. Local treatment

e. Percutaneous treatment

f. Surgery

The evidence supporting the use of different options varies according to each patient's response, duration and severity of symptoms, response to previous treatment, presence of co-morbidities and cost [54] [49].

Pharmacological treatment is limited to reduce inflammation and to control pain. It is prescribe based on the intensity of pain and functional status. Beyond that, treatment may also include musculoskeletal manipulation (physiotherapy). In some cases heat and cold,

electrotherapy and ultrasounds, may increase treatment success. Other specific approaches may be relevant, such as behavioral therapy [56]. Surgery has restricted indications [49].

Pharmacological therapy

Analgesics such as acetaminophen, NSAIDs, weak opioids, centrally acting muscle relaxants, are used to control LBP. We summarized each of them in the following paragraphs.

Acetaminophen

Acetaminophen is an analgesic and antipyretic with no significant anti-inflammatory properties. APS/ACP guidelines recommend it as a first-line drug therapy for LBP. This recommendation is mainly based on safety considerations. Although acetaminophen is considered a weaker analgesic when compared with NSAIDs, it is better tolerated, in particular in relation to myocardial infarction and gastrointestinal bleeding. Hepatotoxicity is the most serious adverse event associated with acetaminophen and can occur with the recommended maximum dose (4g/day) [65]. It should be avoided in patients with liver disease or those who are alcohol addicts. Overdosing is another possible effect that can occur in patients who are taking concomitant medication containing acetaminophen.

Non-steroid anti-inflammatory drugs (NSAIDs)

NSAIDs have anti-inflammatory and analgesic properties. They treat pain mainly by blocking cyclooxygenase 2 (COX-2) mostly in the central nervous system, but not much in the rest of the body. As acetaminophen, NSAIDs are also recommended as first-line therapy for LBP (acute and chronic) [66] [53]. A systematic review of randomized trials corroborates this fact showing that NSAIDs are effective for short-term symptom relief when compared with placebo in acute and chronic pain [67].

All NSAIDs are associated with gastrointestinal and renal side effects. Gastrointestinal adverse events can be severe such as gastrointestinal bleeding and ulcers. Non-selective NSAIDs (which block COX-1 and COX-2 enzymes) increase this risk because COX-1 helps to protect stomach mucosa from acid production [54].

A meta-analysis of 138 randomized trials, published and unpublished, indicates that both classes of NSAIDs (non-selective and selective) are also associated with an increased risk of myocardial infarction. Naproxen (a non-selective NSAID) is the exception [68]. Naproxen and aspirin should be most appropriate in patients with a high cardiovascular risk, particularly due to its anti-platelet effect [69]. To minimize potential adverse effects, cardiovascular and gastrointestinal risks should be assessed before prescribing NSAIDs and should be given the lowest effective dose for the shortest time possible. The American Geriatrics Society does not recommend the use of NSAIDs for chronic pain in adults over the age of 75 years due to these potential adverse effects [70]. However, the extended use of alternative analgesics, such as opioids, is associated with serious effects related to abuse, addiction and other side effects. The decision to use NSAIDs or alternative therapy should be individualized, since the risk associated with different alternatives varies from patient to patient. To reduce gastrointestinal effects the physician may prescribe NSAID together with a proton pump inhibitor or, alternatively, a selective NSAID [71].

Opioids

Analgesic opioids have similar properties to the opium from which they are derived. They act binding to opioid receptors and can be administered by several routes (the most common ones are oral and transdermal). Opioids have a narrow therapeutic index associated with serious effects including respiratory depression, and uncomfortable side effects such as constipation, drowsiness, and nausea [54]. For these reasons, the guidelines of the APS/ACP recommend a controlled use in limited time in patients with non-specific LBP, non-responders to acetaminophen and NSAIDs [70] [69] [53]. Opioids are recognized as being the most potent analgesics for severe acute pain. The use of long-term opioids for persistent pain should be restricted and based on initial response rate and continuous assessment of use signs, abuse and adverse effects. Opioids are commonly associated with adverse effects, including constipation, nausea, drowsiness, pruritus and myoclonus.

The APS and the American Academy of Pain Medicine published guidelines in 2009 on use of opioids for chronic non-cancer pain that can help guide clinical decision-making regarding this class of drugs [72]. For chronic pain, in general, systematic reviews consistently indicate

a moderate effectiveness of opioids for pain relief when compared to placebo [73] [74].

In LBP the evidence of benefit about the use of opioids is limited: two clinical trials indicate a moderately more effective action than placebo [75] [76]. For CLBP, one meta-analysis found that tramadol was minimally more effective than placebo for improving function and moderately more effective for pain relief in three trials [77].

Antidepressants

Currently it is well accepted that some antidepressants (in particular those which inhibit noradrenaline uptake) may have an effect on pain modulation [78].
However antidepressants are associated with a high risk of adverse effects (drowsiness, dry mouth, dizziness) when compared to placebo. Tricyclic are also associated with increased frequency of arrhythmias, and prolonged QRS line. However these risks are smaller among therapies that use low doses, like pain relief [54].

Tricyclic antidepressants may also be an option for CLBP, although not recommended as first-line therapy, since its beneficial effects are still questionable and they are known for their adverse effects [53]. Some meta-analysis evaluating the efficacy of antidepressants vs placebo, as short-term therapy in nonspecific CLBP, reported little concordant results [79] [80].

Selective serotonin reuptake inhibitors and trazodone didn't prove to be effective in LBP [79] [74] [80]. Venlafaxine and milnacipran demonstrated benefit in certain types of chronic pain [81], but have not been studied for LBP, with and without neuropathic component.

Even if antidepressants are not first-line therapy in the treatment of LBP, depression is common in patients with this condition, and its use should also be considered and evaluated [54].

Centrally acting muscle relaxants

A systematic review of 30 trials showed moderately higher effectiveness of centrally acting muscle relaxants compared to placebo in relieving acute pain [82] [53]. This therapeutic group is an option for non-specific acute LBP, but it is not recommended as first-line therapy

because of the high frequency of central nervous system adverse events (sedation) [54]. The evidence is limited and scarce to determine if muscle relaxants are effective in chronic LBP, with exception to tizanidine [82].

It is well accepted that centrally acting muscle relaxants in addition with acetaminophen or NSAID may be more effective than analgesic or NSAIDs alone. Three trials found that combination therapy was superior to mono- therapy with acetaminophen or an NSAID for short-term pain relief [83] [84] [85].

However, more than expected, this concomitant use also increases the risk of sedation and other adverse effects related to the central nervous system [82] [54].

Benzodiazepines

Benzodiazepines are a class of drugs acting on GABA A receptors, and have sedative, anxiolytic and antiepileptic therapeutic effects. They are often used as muscle relaxants although not approved by the Food and Drug Administration neither by European Medicines Agency. Benzodiazepines may be considered as an alternative therapy to CLBP but with limited evidence on efficacy and potential for abuse [53]. Short use and therapeutic monitoring are recommended to minimize the risk of abuse and addiction [54].

Anticonvulsants

There is lack of evidence to recommend anticonvulsants in the treatment of nonspecific LBP [54]. A randomized population of patients with chronic LBP (with and without radiculopathy) had proven the efficacy of topiramate slightly superior to placebo in relieving pain, and with a slight increase of function [86] [87].

Other studies with anticonvulsants (gabapentin and topiramate) in patients with radiculopathy and spinal stenosis do not show large benefits in the use of these drugs in pain relief [88] [87].

Other drugs

Treatment with anti-tumor necrosis factors (anti-TNFs), which are used primarily to treat inflammatory RMD and inflammatory bowel disease, has been studied in LBP without great results [89]. Tanezumab is the first drug in a class of anti-nerve growth factor antibody, assessed by clinical trial among LBP patients, in a phase II study that shows that a single intravenous infusion tanezumab is superior to naproxen and placebo in pain relief, after 12 weeks. However it is also associated with increased risk of peripheral effects (paresthesia, hiperastesias or diastesias), possibly related to nerve injury [90]. High costs of anti-TNFs can be also a strong limitation to use them to relieve LBP.

World Health Organization Analgesic Ladder:

The WHO analgesic ladder updated in 1997 to help controlling pain in cancer patients still remains useful in chronic pain management (including LBP) [91]. It was used to classify drug combinations:

. step 1: non-opioids analgesic, with or without adjuvant

. step 2: opioid for mild to moderate pain, with or without non-opioid, with or without adjuvant

. step 3: opioid for moderate to severe pain, with or without non-opioids, with or without adjuvant.

Adjuvants comprised: antidepressants; anxiolytics, sedatives and hypnotics; anticonvulsants, corticoids and psychotropic.

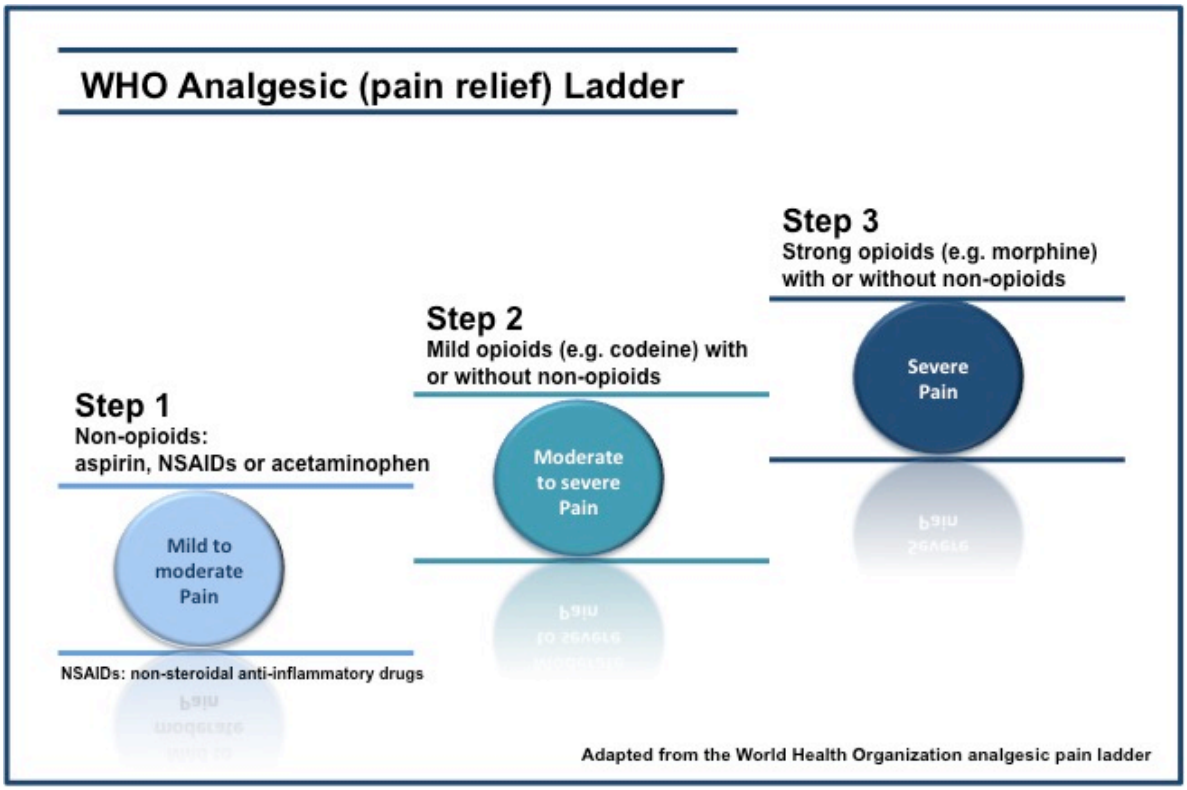

Figure 3: WHO analgesic ladder

Other therapeutic strategies

Physiatry and Rehabilitation:

The main aim of rehabilitation treatments is to improve monitoring mobility, positioning and re-education of muscular properties (relaxation, elasticity, strength, vigilance). It also aims at preventing the recurrence of LBP [49].

Surgical treatment and other recent treatments:

Surgery is the last-line therapy but often fails in permanent pain relief [56]. Surgery to solve intervertebral hernia and disc degeneration is based on mechanical prostheses that have a moderate success and relatively high re-operation rates. The intradiscal injections of

steroids and glucocorticoids have also been used to treat discogenic reducing inflammation or pain on the disk. But the injections can be potentially dangerous and cause infections (discitis and spondylodiscitis) [56].

Neuroreflexotherapy:

It is defined by the temporary implantation of epidermal devices trigger points, to desensitize neurons involved in persistent pain, neurogenic inflammation, and muscle contracture. This technique is performed without anesthesia in a regular physician visit. In a systematic review recognized by European Guideline for the Management of Chronic Non-Specific LBP this therapy proved to be substantially more effective pain relief in 30 to 45 days [92].

Implants:

They are used to bridge the shortcomings of intervertebral discs. Implants reinforce the affected area and prevents the side hernias. However, the material of the implants is not long lasting. Other best materials are under investigation [93].

New therapeutic lines:

Currently the treatments for LBP only offer palliative care helping to reduce the symptoms of pain and helping mobility. No new therapies have been developed in order to prevent, stop or reverse progression of LBP. However, there are some new technologies and devices as well as advances in therapy with stem cells that may offer new hope and approaches in treating this condition [56].

Intervertebral disk degeneration is a good example of recent approaches in the repair and regeneration biology of intervertebral discs, which are under investigation. It includes cell transplantation, administration of growth factors, and gene therapy. Mesenchyme cells can also be candidates for cell therapy and tissue engineering because of their high proliferation potential and differentiation rate [56] [72].

LBP has been associated in many cases with degenerative pathology of the discs. In these cases, new treatments have been made to normalize disc cellular homeostasis and restore full function [56]. Conventional surgery to repair discs is very traumatic and prostheses used wear out with time. The innovative therapeutic approaches gather engineering tissue for disc regeneration and are focused on restoring the disc function by the introduction of the functional cells and biomaterials that enhance or replace the degenerated disc [94].

One of the features of disc degeneration is the loss of matrix in the nucleus pulposus. There are several strategies under investigation for restoring the function of this structure (injections of a shock absorbing hydrogel and matrix producing cells and molecules that will stimulate endogenous cells to replace the lost array). Therapeutic strategies depend on the severity of degeneration [95] [96].

Socio-economic burden of chronic low back pain

LBP is the most prevalent of musculoskeletal condition and affects almost everyone at some stage of life [5] [41]. In the recent Global Burden of Disease (GBD) 2010 Study, LBP was the leading cause of years lived with disability (YLDs) in Western/industrialized countries [97] [5] [48] and was the most prevalent of musculoskeletal conditions [98]. It is one of major occupational problems contributing to a considerable absenteeism and disability among subjects aged less than 65 years old [24] [48] [34] [45]. The Expert Group of GBD showed that LBP is among the top ten highest burden diseases and injuries, with an average DALYs (disability-adjusted life years) higher than that of people suffering from HIV (human immunodeficiency virus), traffic injuries, tuberculosis, lung cancer, chronic obstructive pulmonary disease and preterm birth complications [56]. When it becomes chronic, LBP causes an enormous economic burden on individuals, families, communities, industry and governments – it is one of the leading causes of loss of productivity and economic independence through absenteeism (time off work), presenteeism (lost productivity because of diminished capacity while at work) and work disability (permanent, partial or complete disablement for work purposes) [99]. Most costs are associated with their impact on activities of daily living, in particular on productive work, as well as restrictions on social activities and others with substantial impact on lifestyle [99] [46]. For society, LBP means loss of working days; for a subject with LBP it means low productivity and a reduction in quality of life as a result of disability [100].

LBP is a leading cause of medical appointments (only preceded by respiratory infections), hospitalizations, and other health care consumption (occupational therapy, physiotherapy) [5]. The increase in direct costs with LBP in the United States of America is estimated between 100 and 200 billion dollars annually, two thirds of which are due to productivity breaks [64] [53]. Indirect costs related to lost working days are substantial. Most of patients have episodes of short-term LBP for which they do not seek medical care. But usually, in the following months, these individuals have new episodes of LBP with increased disability. Usually CLBP prevalence is not very high (5%) but disability provided by this condition contributes to 75% of the healthcare costs associated with it [53]. CLBP causes significant

costs and financial impact because it includes the costs of medical care, lost productivity, reformulations of new staff, administrative expenses, etc [41] [45]. Early retirement costs have increased exponentially [34] [57].

In Portugal the prevalence and burden of CLBP were poorly defined. Until now no large population-based studies have focused on this.

Chronic low back pain and mental disorders (anxiety and depression)

The role of psychosocial factors in disability related to pain have been increasingly valued and recognized. Chronic pain is now regarded as a phenomenon in which psychological, biological and social factors interact dynamically with each other [101]. The relation between musculoskeletal pain and anxiety and depression provided a hot topic on research field [102]. Among population-based studies it is not uncommon to find patients who reported pain associated with RMD together with symptoms of anxiety and depression [59]. It has been accepted that psychiatric diseases interfere enough with the successful rehabilitation of these patients. It is starting to be recognized that chronic LBP can be a standard complex psychophysiological behavior. Psychological factors have been explored (behavior, cognitive, and affective) and it has become increasingly evident that chronic LBP disability can be associated with high rates of psychological disorders states. Psychosocial factors can increase the intensity of disability and pain contributing to perpetuate pain related disorders [103]. This issue highlights the importance of identifying psychopathological conditions in patients with CLBP. The concomitant management of CLBP and psychological symptoms can increase the successful rehabilitation of these patients [101].

CHAPTER II – General and Specific Aims

CHAPTER II – General and Specific Aims

This study aimed to assess the burden of active CLBP in the Portuguese population.

Principal objectives

. To estimate the prevalence of self-reported LBP among adult Portuguese population

. To determine the prevalence of self-reported active CLBP, in the adult Portuguese population.

. To identify relevant associations between active CLBP and quality of life, health consumption, absenteeism, early retirement, drug consumption and psychological symptoms.

Specific objectives

. To estimate prevalence of self-reported active CLBP by NUTS II.

. To assess quality of life and function of subjects with active CLBP, and to compare them with subjects without active CLBP.

. To characterize the socio-economic and healthcare resources consumption profile of subjects with active CLBP, and to compare with subjects without active CLBP.

. To describe analgesic and other pain relief drugs intake profile subjects with active CLBP, and to compare with subjects without active CLBP.

. To estimates the prevalence of anxiety and depression symptoms among subjects with active CLBP.

. To identify relevant factors associated with active CLBP

. To identify relevant associations between anxiety and depression symptoms and active CLBP

CHAPTER III – Brief Methodology

CHAPTER III - Brief methodology

The research work presenting in the next chapter included a **Section I** with three papers describing the development and management of this large epidemiologic population study; and also the detailed methodology and main results of EpiReumaPt. In the latter, it was possible to determine the prevalence of self-reported LBP among adult Portuguese population.

In order to assess if CLBP was a common occupational problem among adult Portuguese population, **Section II** included a set of studies that aimed to determine the prevalence and social burden of CLBP. Social burden was measured taking into account the following outcomes: quality of life, function, healthcare resources consumption, analgesic and other pain relief drugs intake, anxiety and depression symptoms.

Although each study includes a detailed description of its methodology, this chapter summarizes the common aspects regarding to the data source, population of interest, inclusion an exclusion criteria, and ethic issues.

Data source and study population:

The research work of this thesis was developed under the scope of EpiReumaPt which was the first Portuguese prevalence study of RMD. It was performed among a randomized and representative sample of adult Portuguese population recruited in Mainland, Azores and Madeira Islands, between September 2011 and December 2013. EpiReumaPt had a three stages approach: in the 1st phase (RMD screening), households were selected by random route methodology. A survey was applied through a face-to-face interview to characterize the Portuguese adult population (≥18 years old) and to identify potential subjects with RMD. In the 2nd phase (RMD diagnosis) a rheumatologist visit was performed to all subjects that were screened positive for at least one RMD during the 1st phase, as well as to 20% randomly selected individuals with no rheumatic complaints. Procedures included a standardized physical examination and appropriate laboratory and imaging tests. In the 3rd

phase (RMD diagnostic revision) a team of 3 experienced rheumatologists conducted the revision of all clinical data from each participant, including laboratory and imaging results, while considering previously validated criteria for the different RMD.

The **population of interest** of the Section II was defined based on the following **inclusion criteria:**

. adult subjects (≥18 years old) who were non-institutionalized and living in private households in Portugal, (Mainland and Madeira and Açores Islands) that self-reported active CLBP (*see case definition*).

Exclusion criteria comprises the following conditions:

. Subjects with diagnosis from other pain in the spine (neck pain, back pain)

. subjects with LBP <90 days.

Case definitions:

. **LBP** was defined as pain in the back area, from the lower margin of the twelfth ribs to the lower gluteal folds, with or without referred pain to the lower limbs.

. **Active CLBP** was defined as self-reported LBP, present on the day of the interview, and that was present in most of time for at least 90 days (independently from cause).

Figure 4 shows the study design.

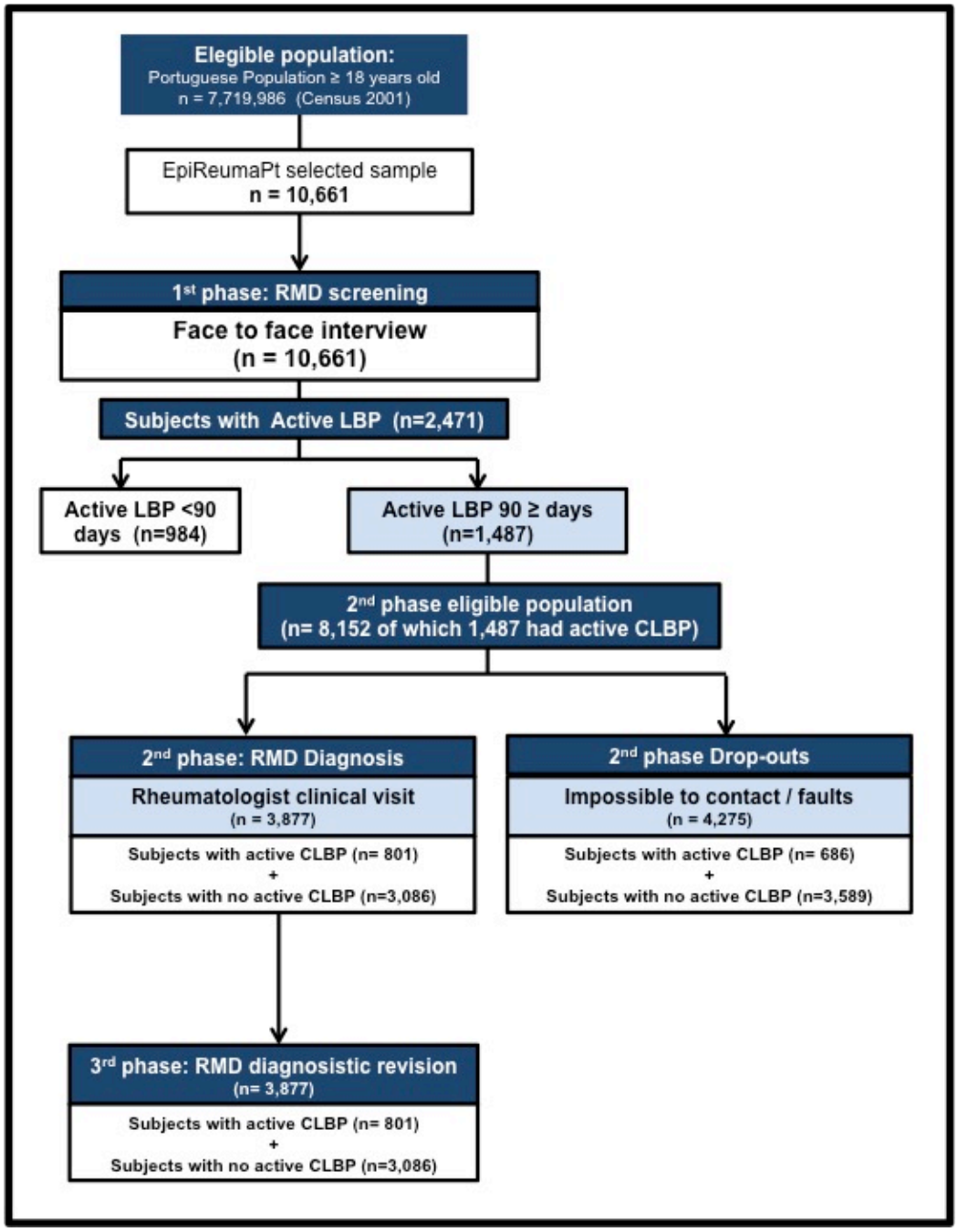

Figure 4: Study design flowchart

Measurements, assessment and instruments

Active CLBP was assessed using self-reported data described in table 2.

Table 2: Data collected in EpiReumaPt study to assess active chronic low back pain

Type of data	Measurements, assessment and instruments
Socio-demographic data	Age, gender, ethnicity, education level, marital status
Socioeconomic profile	Household income, current professional status, number of work hours per week
Life styles habits	Smoking, alcohol and coffee intake, physical exercise
Work disability data	Absenteeism, presenteeism, early retirement, and unemployment due to work disability
Health consumption data	Number and type of outpatient clinic appointment, specialty care, hospitalizations, homecare assistance and other healthcare service needs (physiotherapy, alternative treatments, psychology), in the previous 12 months. Outpatient clinic visits included General Practitioners, Rheumatologists, Orthopedics, and Physiatrists. Other outpatient specialties care provided in Emergency Care, Internal Medicine, Neurology, Cardiology, Nephrology, Surgery, Psychiatry, Urology, ophthalmology, was aggregated into "others".
Quality of life	EuroQol (EQ-5D-3L), validated to the Portuguese population [104] [105]
Physical function	Health Assessment Questionnaire (HAQ) [106], which measures the difficulty in performing the activities of daily living
Anxiety and depression symptoms	Hospital Anxiety and Depression Scale (HADS) Portuguese validated version [107]. This scale has 2 sub-scales to anxiety and to depression. To each one the cut off used for positive symptoms was ≥11 [107]. Subjects were included in the group "population with anxiety and/or depression symptoms" if they had a HADS score ≥11 to anxiety symptoms, or depression symptoms, or concomitant anxiety and depression symptoms. Portuguese validated versions of all these instruments were used.
Characteristics of CLBP	"red flag" questions [57]
Anthropometric data	Weight, height and body mass index (BMI)
Self-reported chronic diseases	Weight, height and body mass index (BMI) high cholesterol level, high blood pressure, allergy, gastrointestinal disease, mental disease, cardiac disease, diabetes, thyroid and parathyroid disease, renal colic, pulmonary disease, hyperuricemia, cancer, neurologic disease, hypogonadism
Characteristics of active CLBP	Red flag questions to screen other etiologies (cancer, infection, fracture) Visual analogic scale (VAS) provided pain severity reported by subjects on the interview day
Pharmacological therapy	Current analgesic and other pain relief medication intake [108]: **Analgesics and antipyretics** (including not only the acetylsalicylate lysine, salicylic acid, clonidine, but also combined therapies, such paracetamol & codeine) **NSAIDs** (aceclofenac, diclofenac, ibuprofen, naproxen, etodolac, indomethacin, meloxicam, piroxicam, nimesulide, celexoxib, etoricoxib) **Analgesic drugs** (weak and strong opioids: tramadol, buprenorphine, fentanyl; this therapeutic group also includes the association tramadol & paracetamol) Central Muscle Relaxants (which includes thiocolchicoside and the association, paracetamol & thiocolchicoside) **Anxiolytics, sedatives and hypnotics** (including drugs such as benzodiazepines) **Antidepressants** **Anticonvulsants** **Corticosteroids**

Statistics analysis:

Each paper presented in the next chapter described the details regarding to statistics analysis. In brief, active CLBP, analgesic and other pain relief drugs intake, anxiety and depression symptoms prevalence were estimated taking into consideration the study design [13] [15]. Prevalence estimates and confidence intervals were weighted and were obtained with STATA survey procedure.

Multivariable regressions were used to assess differences between groups (subjects with and without active CLBP (Part I), and subjects with and without anxiety and depression symptoms (Part III)). To assess factors independently associated with active CLBP (part I), and associated with anxiety and/or depression symptoms (Part II) multivariable regressions were also performed. All the comparisons were adjusted for the clinical relevant variables. Models were obtained using bidirectional elimination, a combination of the backward elimination and forward selection, testing at each step for variables to be included or excluded. The cut-off value for significance was considered to be $p<0.05$. All analyses were weighted and performed using STATA IC version 12 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

Data Protection and Ethics:

EpiReumaPt was performed according to the principles established by the Declaration of Helsinki, revised in 2013 in Fortaleza (Brazil) and according to the Portuguese law at the time the study begun (Law n. 46/2004, of 24th August). In addition to the Declaration of Helsinki, EpiReumaPt complied with the following laws and standards: Protection of Personal Information (Law n.67/98 of 26th of October and CNPD deliberation n.227/2007); and Genetic, clinical and health personal information (Law n.12/2005, of 26th January).

As an observational study it was reviewed and approved by competent Portuguese authorities: NOVA Medical School Ethics Committee and National Committee for Data Protection. The study was also reviewed and approved by the Ethical Committees of Regional Health Authorities. All the study procedures (interviews, clinical visits, laboratory

tests and imaging examinations) were implemented with the concern to minimize any potential inconveniences in the participants' daily life.

Informed Consent

Informed consent for the EpiReumaPt study was mandatory and collected by interviewers in the 1st phase. Additional consents for Biobanco-IMM and Cohort study (additional studies under the scope of EpiReumaPt) were also mandatory and collected by the Rheumatologist during the 2nd phase. Subjects not invited for observation in the 2nd phase signed the informed consent to participate in the cohort study already in 1st phase. All participants received clear information in lay terms about the research being undertaken (verbal information and a specific leaflet – main study, cohort study and Biobanco-IMM), and they were given the opportunity to ask questions and enough time to decide whether to participate in the study. Subjects were only asked to sign the consent form after the research team was assured that the patient had fully understood the study objectives and procedures. For each signed consent form, one copy was given to the participant while the other copy was archived by the site coordinator.

CHAPTER IV – Research work: Results

CHAPTER IV – Research work: Results

In agreement with the Decreto-Lei 388/70, art. 8º, the results presented and discussed in this thesis were published/submitted in the following scientific peer-reviewed journals:

Section I

Part I	**Gouveia N**, Rodrigues A, Ramiro S, et al. EpiReumaPt: how to perform a national population based study – a practical guide. 2015. Acta Reumat. Port. 40:128-136.
Part II	Rodrigues A, **Gouveia N,** Costa LP, et al. EpiReumaPt- the study of Rheumatic and Musculoskeletal diseases in Portugal: a detail view of the methodology. *2015.* Acta Reumat. Port. 40:110-124.
Part III	Branco JC, Rodrigues A, **Gouveia N**, et al. Prevalence and physical and mental health patterns of rheumatic and musculoskeletal diseases in Portugal: results from EpiReumaPt, a national health survey *submitted.* 2015.

Section II

Part IV	**Gouveia N**, Rodrigues A, Eusébio M, et al. Prevalence & social burden of active chronic low back pain in the adult Portuguese population – results from a national survey (EpiReumaPt). *submitted.* 2015.
Part V	**Gouveia N**, Rodrigues A, Ramiro S, et al. Chronic low back pain: intake of analgesic and other pain relief drugs in a southern Europe country. *submitted.* 2015.
Part VI	**Gouveia N**, Eusébio M, Canhão H, Branco JC. Anxiety and depression symptoms: an additional burden among a population with chronic low back pain? – results from a national survey (EpiReumaPt). *submitted.* 2015.

Section I – Part I

EpiReumaPt: how to perform a national population based study – a practical guide

Gouveia N, Rodrigues A, Ramiro S, et al. EpiReumaPt: how to perform a national population based study – a practical guide. 2015. Acta Reumat. Port. 40:128-136.

ARTIGO ORIGINAL

EpiReumaPt: how to perform a national population based study – a practical guide

Nélia Gouveia[1,2,3], Ana M Rodrigues[1,3,4,5], Sofia Ramiro[1,3,6], Pedro Machado[1,7,8], Leonor Pereira da Costa[9], Ana Filipa Mourão[1,3,10], Inês Silva[1,10], Tânia Rego[1], Pedro Laires[11], Rui André[12], Luís Mauricio[13], José C Romeu[13], Viviana Tavares[14,15], Jorge Cerol[9], Helena Canhão[1,3,4,5,9], Jaime C Branco[1,2,3,10,16] on behalf of the EpiReumaPt study group*

ACTA REUMATOL PORT. 2015;40:128-136

ABSTRACT

Background: The aim of this article was to describe and discuss several strategies and standard operating procedures undertaken in the EpiReumaPt study – which was the first Portuguese, national, cross-sectional population-based study of Rheumatic and Musculoskeletal Diseases (RMD).

Methods: The technical procedures, legal issues, management and practical questions were studied, analyzed and discussed with relevant stakeholders. During the 1st phase of EpiReumaPt the coordination team and Centro de Estudos de Sondagens e Opinião (CESOP) worked to recruit and interview 10,661 subjects. The 2nd phase involved the participation of a multidisciplinary team, several local authorities, a specialized vehicle ("mobile unit") and a specific software program for the clinical appointments. The development of specific recruitment strategies improved the participation rate. Blood samples were collected and sent to Biobanco-IMM and to a central lab for immediate measurements. In the 3rd phase the RMD diagnosis were validated by a team of three experienced rheumatologists - clinical data, imaging and lab test results were revised according to previously published classification criteria.

Conclusion: EpiReumaPt was a nationwide project successfully conducted, which followed critical logistic/coordination and research strategies. EpiReumaPt methodology and coordination could be used as an example for other epidemiologic endeavors and public health policies.

1. Equipa de Investigação EpiReumaPt - Sociedade Portuguesa de Reumatologia, Lisboa, Portugal
2. Centro de Estudos de Doenças Crónicas (CEDOC) da NOVA Medical School, Universidade Nova de Lisboa (NMS/UNL), Lisboa, Portugal
3. Unidade EpiDoc – Unidade de Epidemiologia em Doenças Crónicas (CEDOC, NMS/UNL), Lisboa, Portugal
4. Unidade de Investigação em Reumatologia, Instituto de Medicina Molecular, Lisboa, Portugal
5. Faculdade de Medicina da Universidade de Lisboa, Lisboa, Portugal
6. Leiden University Medical Center, Leiden, the Netherlands
7. Clínica Universitária de Reumatologia, Faculdade de Medicina da Universidade de Coimbra, Coimbra, Portugal
8. MRC Centre for Neuromuscular Diseases, University College London, London, United Kingdom
9. Universidade Católica Portuguesa - Centro de Estudos e Sondagens de Opinião (CESOP-CATÓLICA), Lisboa, Portugal
10. Serviço de Reumatologia do Hospital Egas Moniz - Centro Hospitalar Lisboa Ocidental (CHLO- E.P.E.), Lisboa, Portugal
11. Serviço de Reumatologia do Hospital Beatriz Ângelo, Loures, Portugal
12. Hospital Divino Espírito Santo-Ponta Delgada
13. Serviço de Reumatologia do Hospital de Santa Maria – Centro Hospitalar Lisboa Norte (CHLN-E.P.E), Lisboa, Portugal
14. Serviço de Reumatologia do Hospital Garcia de Orta – Almada, Portugal
15. APOROS - Associação Nacional contra a Osteoporose, Lisboa, Portugal
16. Programa Nacional Contra as Doenças Reumáticas (2004-2014), Direcção Geral da Saúde. Lisboa, Portugal

***EpiReumaPt study group**
SOCIEDADE PORTUGUESA REUMATOLOGIA:
Alexandra Bernardo, Alexandre Sepriano, Ana Filipa Mourão, Ana Maria Rodrigues, Ana Raposo, Ana Sofia Roxo, Anabela Barcelos, António Vilar, Armando Malcata, Augusto Faustino, Cândida Silva, Carlos Vaz, Carmo Afonso, Carolina Furtado, Catarina Ambrósio, Cátia Duarte, Célia Ribeiro, Cláudia Miguel, Cláudia Vaz, Cristina Catita, Cristina Ponte, Daniela Peixoto, Diana Gonçalves, Domingos Araújo, Elsa Sousa, Eva Mariz, Fátima Codinho, Fernando Pimentel, Filipa Ramos, Filipa Teixeira, Filipe Araújo, Filipe Barcelos, Georgina Terroso, Graça Sequeira, Guilherme Figueiredo, Helena Canhão, Herberto Jesus, Inês Cunha, Inês Gonçalves, Inês Silva, J. António P. da Silva, Jaime Branco, Joana Abelha, Joana Ferreira, João Dias, João Eurico Fonseca, João Ramos, João Rovisco, Joaquim Pereira, Jorge Silva, José Carlos Romeu, José Costa, José Melo Gomes, José Pimentão, Lúcia Costa, Luís Inês, Luís Mauricio, Luís Miranda, M. João Gonçalves, Margarida Coutinho, Margarida Cruz, Margarida Oliveira, Maria João Salvador, Maria José Santos, Mariana Santiago, Mário Rodrigues, Maura Couto, Miguel Bernardes, Miguel Sousa, Mónica Bogas, Patrícia Pinto, Paula Araújo, Paula Valente, Paulo Coelho, Paulo Monteiro, Pedro Madureira, Raquel Roque, Renata Aguiar, Ricardo G. Figueira, Rita Barros, Rita Fonseca, Romana Vieira, Rui André, Rui Leitão, Sandra Falcão, Sara Serra, Sílvia Fernandes, Sofia Pimenta, Sofia Ramiro, Susana Capela, Taciana Videira, Teresa Laura Pinto, Teresa Nóvoa, Viviana Tavares

Keywords: Epidemiologic studies; Population-based study; Rheumatic Diseases; Epidemiology; Cross-sectional study; Study management

INTRODUCTION

Large-scale observational epidemiologic studies are scarce in Portugal. The Portuguese Epidemiologic Study of Rheumatic Diseases (EpiReumaPt) was a challenging project, as the first national, cross-sectional, population-based study of Rheumatic and Musculoskeletal Diseases (RMDs). The EpiReumaPt study had a pioneering design in Portugal. The protocol was developed after reviewing other international studies and adapted to the Portuguese context[1-5]. The EpiReumaPt protocol was published before the work field. EpiReumaPt covered mainland Portugal, *Região Autónoma dos Açores* (Azores) and *Região Autónoma da Madeira* (Madeira). The technical procedures, legal issues, management and practical questions were studied, analyzed and discussed with all relevant stakeholders, Authorities and partners who contributed to the EpiReumaPt project.

The aim of this article is to describe and discuss all standard operating procedures, strategies and challenges related to the development of the Portuguese large-scale epidemiologic study, EpiReumaPt. An article focusing on the EpiReumaPt methodology (rather than management issues) is also published in this issue of Acta Reumatológica Portuguesa: *EpiReumaPT-the study of Rheumatic and Musculoskeletal diseases in Portugal: a detailed view of the methodology.*

EPIREUMAPT: CONCEPT AND CONTEXT

The prevalence of Portuguese RMDs was poorly defined. The National Program Against Rheumatic Diseases (2004-2014), promoted by the Directorate-General of Health and part of the National Health Plan for 2004/2010, aimed to promote a comprehensive and articulated approach of health services, in order to reduce the risk of developing RMDs among the Portuguese population, and to provide suitable treatment and rehabilitation for those with RMDs[7]. One of the specific goals was to determine the prevalence of the RMDs covered by the Program: hand, knee and hip osteoarthritis (OA), low back pain (LBP), rheumatoid arthritis (RA), fibromyalgia (FM), gout, spondyloarthritis (SpA), periarticular disease (PD), systemic lupus erythematosus (SLE), polymyalgia rheumatica (PMR) and osteoporosis (OP)[7]. EpiReumaPt was the first large-scale project studying RMDs in the Portuguese population, designed to achieve this specific goal. It also aimed to assess the impact of RMDs in relation to quality of life, function, use of healthcare resources and work participation[8]. The main promotor of EpiReumaPt was the Portuguese Society of Rheumatology (SPR). This project was also supported by the Directorate-General of Health and Nova Medical School (NOVA University of Lisbon) in collaboration with the Portuguese Catholic University.

FUNDING, INSTITUTIONAL AND SCIENTIFIC SUPPORT

The first steps to develop EpiReumaPt began in 2005 after the National Program Against Rheumatic Diseases was published. In October 2010 EpiReumaPt was awarded with a Directorate-General of Health competitive award. This was the key funding to start the working process. EpiReumaPt was budgeted in 1.5 million euros and in addition to the primary grant from the Directorate-General of Health (which covered 50% of the estimated cost) it was necessary to find other sponsors. Unrestricted grants were awarded by the following entities or companies: Calouste Gulbenkian Foundation, Pfizer, Merck Sharp & Dohme, Abbvie, Roche, Bial, Servier, Astra Zeneca Foundation, as well as individual support by some rheumatologists. Other institutions supported the study by providing goods or lowering the prices of services and products (*Galp Energia, Germano de Sousa-Centro de Medicina Laboratorial, Açoreana Seguros, HappyBrands, Clínica Médica da Praia, CAL-Clínica*). Scientific endorsement was given by the promoters and by three other Portuguese Medical Schools: *Faculdade de Medicina da Universidade de Lisboa* (Lisbon, Portugal), *Faculdade de Medicina da Universidade do Porto* (Porto, Portugal) and *Faculdade de Medicina da Universidade de Coimbra* (Coimbra, Portugal). Institutional endorsement was given by the President of the Portuguese Republic (*Alto Patrocínio da Presidência da República*), by the Regional Government of Azores, by the Regional Government of Madeira, and by the Regional Health Administrations of *Norte, Centro, Alentejo, Algarve*, and *Lisboa e Vale do Tejo*. Other institutions and national associations also gave their endorsement (*Centro Hospitalar do Médio Tejo, Hospital de S. João, Câmara Municipal de Lisboa, Associação Nacional de Freguesias*). Patient Associations with RMDs were also included as social partners.

RESEARCH TEAM

The EpiReumaPt study protocol was developed by the

core research team and was published in the end of 2010[6]. Later when EpiReumaPt was awarded the grant from the Directorate-General of Health, other investigators joined the research team. The Coordination Team, including the Principal Investigator, the Co-Principal Investigator and the Study Manager, was established in March 2011. This small Coordination Team was responsible for the executive, financial and logistical decisions, and held weekly meetings since March 2011. National and international experts were invited as external advisors, especially in the area of epidemiology.

STUDY DESIGN AND METHODOLOGY

EpiReumaPt was an epidemiologic, observational and cross-sectional population-based study. The recruitment took place from the 19th September 2011 to the 20th December 2013, and involved a three-stage approach (Figure 1)[6]. The 1st phase (RMD screening) started with a face-to-face interview performed at subjects' households, which were selected by a random route methodology[6,8]. In the 2nd phase (RMD diagnosis) all subjects who screened positive for at least one RMD during the 1st phase, and also a random 20% sample of individuals without positive screening for rheumatic complaints, were invited to be observed by a rheumatologist. Finally, in the 3rd phase, RMD diagnoses were validated after revision of the clinical data by a team of three experienced rheumatologists.

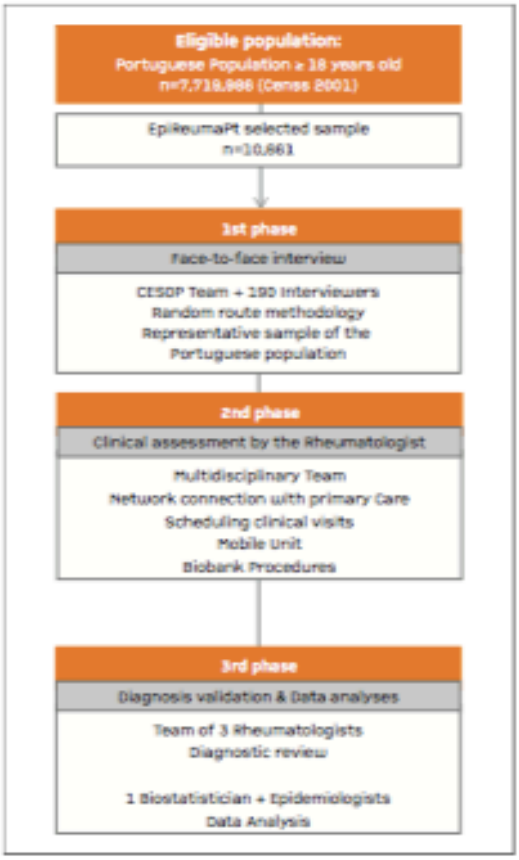

FIGURE 1. EpiReumaPt study design
CESOP: Centro de Estudos e Sondagens de Opinião da Universidade Católica Portuguesa

PLANNING AND DEVELOPMENT OF THE 1ST PHASE OF THE STUDY: FACE TO FACE INTERVIEW

The 1st phase of EpiReumaPt was performed with the collaboration of the expert national center in large-scale population studies located in the Catholic Portuguese University - *Centro de Estudos e Sondagens de Opinião* (CESOP). The CESOP team had a coordination board that was responsible for organizing the fieldwork and three sub-coordinators that were responsible for organizing the data collection of the 1st study phase.

The team that conducted the 1st phase survey was composed by 190 interviewers, non-physicians, who were recruited by the CESOP coordination board through a selection process composed of 2 stages: interview selection plus a theoretical and practical training session. This training session included topics related to: study design, study features, logistics, clinical issues related with RMDs, ethical and legal issues, random-route methodology (sample selection), interview procedures (roll-play exercises), survey and software training. Only the candidates that successfully went through the two phases were selected.

Afterwards, the team of 190 interviewers was divided into five teams (10-15 elements per team) who worked across the country during the recruitment period: Lisbon team (responsible for the recruitment in Lisbon & *Setúbal, Alentejo, Algarve, Estremadura, Ribatejo and Beira Baixa*), Coimbra team (responsible for the recruitment in *Beira Alta and Beira Litoral*), Porto team (responsible for the recruitment in *Douro Litoral, Minho, Trás-os-Montes & Alto Douro*), Azores

FIGURE 2. Portugal regions

team and Madeira team (Figure 2).

The 1st phase face to face interview was conducted with the Computer Assisted Personal Interview (CAPI) system: all interviewers had a computer with the software which provided the questionnaire applied to all subjects. The questionnaire was designed by the EpiReumaPt research team to screen for RMDs and included questions on specific rheumatic symptoms and an algorithm to screen for each RMD (OA, LBP, RA, FM, gout, SpA, PD, SLE and PMR). During the interview, subjects were also asked about socio-demographic and socio-economic factors, lifestyle, health care resources consumption, work status, functional status, quality of life, mental health status and comorbidities[6] (Figure 3). Both the survey and software performance were tested in a pilot sample of patients and healthy controls, and results validated by the EpiReumaPt research team before being used by the interviewers.

Each interviewers team worked daily on the field (week and weekend) in groups of 4/5 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. The most successful schedules were in the evenings and weekends. Quality control of the interviews was made by the team Coordinators of CESOP, by randomized phone calls among the recruited subjects.

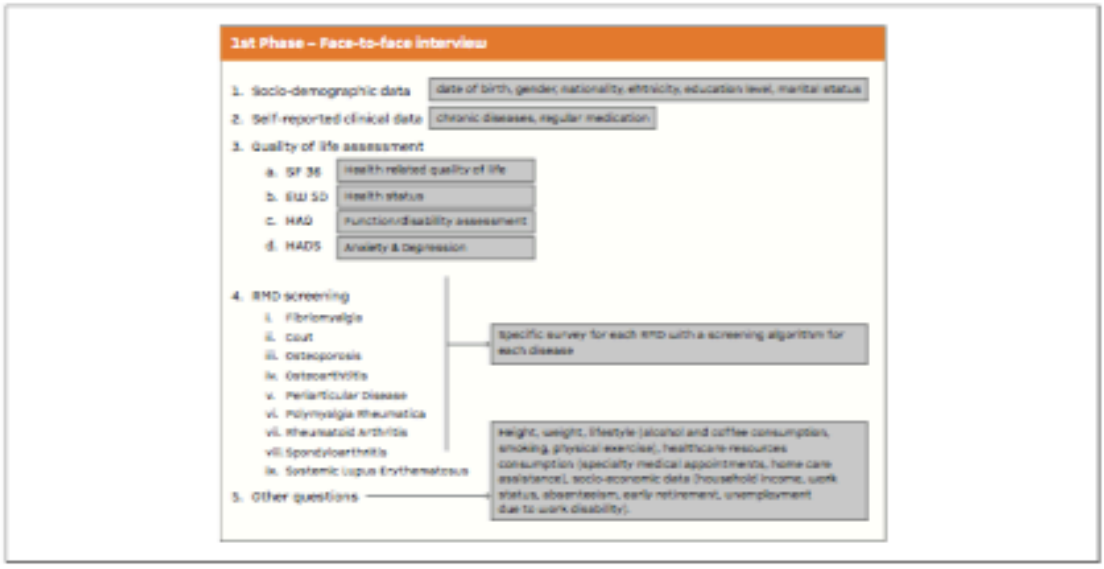

FIGURE 3. Phase 1 survey
SF36 – short form (36) form health survey; EQ5D – European Quality of life Questionnaire; HAQ – Health Assessment Questionnaire; HADS – Hospital Anxiety and depression scale

PLANNING AND DEVELOPMENT OF THE 2ND STUDY PHASE: CLINICAL ASSESSMENT BY A RHEUMATOLOGIST

IDENTIFICATION OF PRIMARY CARE CENTERS FOR CLINICAL VISITS

The 2nd phase clinical visits were performed at the Primary Care Centers of the participant's area of residence. In each region, the EpiReumaPt Coordination Team identified the Primary Care Centers, taking into account the localities where subjects were recruited. All Primary Care Centers were contacted in order to plan and schedule the days of clinical visits and to ensure that all needs were fulfilled: 1 or 2 rooms for clinical visits and an electricity source for the mobile unit. In Azores and Madeira Islands an extra consultation office was required to collect blood samples and to perform the peripheral dual energy X-ray absorptiometry (since the mobile unit was not available). All Regional Health Administrations (*Lisboa e Vale do Tejo, Alentejo, Algarve, Centro, Norte,* Regional Governments of Azores and Madeira) were previously contacted and committed to liaise with all Primary Care Centers.

SCHEDULING VISITS FOR THE 2ND PHASE

As mentioned before, CESOP interviewers identified, through the RMD screening survey, the subjects that were selected for the 2nd phase. This information was weekly sent by the CESOP Staff Coordinator to the Coordination Team of EpiReumaPt. All the identified subjects were contacted by telephone to be scheduled for the observation by the rheumatologist. The time between the CESOP interview and the clinical visit was less than 1 month.

Clinical visits were usually scheduled twice a week, but sometimes it was necessary to schedule more days. For instance, in some areas (*Trás-os-Montes*, Azores - *S. Miguel, Terceira and Faial Islands, and* Madeira Island), clinical visits were scheduled during the entire week in order to optimize journeys of the research team.

CLINICAL ASSESSMENT PERFORMED BY A MULTIDISCIPLINARY TEAM

A multidisciplinary team with rheumatologists, radiology technician, a nurse and a staff coordinator (in the Mainland Portugal also the driver of the mobile unit was included in the team) performed or assisted the clinical visits across the country. The EpiReumaPt Coordination Team was responsible for assembling this team and planning their work every week, according to their area of residence and availability. This strategy required a pool of 7 nurses, 3 radiology technicians, 5 drivers and 3 staff coordinators, and 95 experienced rheumatologists (EpiReumaPt study group), who graciously and voluntarily accepted to participate in the study. To promote the crucial participation of rheumatologists in this global effort, local rheumatology teams were invited according to the region recruited. Monthly newsletters and letters with the EpiReumaPt schedule were also sent. Rheumatologists of the research team were also scheduled - they were responsible by almost half (47%) of the total number of clinical visits.

To standardize the clinical assessment procedures a training handbook/protocol was provided to all rheumatologists and other clinical assistants (nurses and radiology technicians). Moreover, the staff coordinator provided a short summary of all study procedures and supported the rheumatologists with information and details regarding the software for data collection and the logistical issues in every clinical appointment journey.

The interviews and subsequent examinations followed a standard protocol that included: clinical history, physical examination, guidance about imaging and laboratory investigations (if necessary) and written informed consent. Computed assisted software specifically designed for the study was used to support the management of clinical visits and data collection during the 2nd phase. After the rheumatologist collected the clinical history and decided the differential diagnosis, the hypothetical RMD were selected in the software and specific questions related to validated classification criteria had to be answered. This software was tested and validated by the research team prior to the beginning of the study.

Finally, appropriate laboratory or imaging investigations were requested in order to achieve a definitive diagnosis. In Mainland Portugal, imaging investigations were performed at the mobile unit that supported all clinical visits (see below). In Azores and Madeira, the support of local hospitals or clinics was required to provide these tests.

The rheumatologist also invited all the subjects to sign 2 additional informed consents: to store blood samples in a biobank and to participate in the Portuguese Cohort Study of Rheumatic Diseases[9].

MOBILE UNIT TO SUPPORT THE CLINICAL ASSESSMENT

A mobile unit (adapted vehicle) was built and fully

FIGURE 4. Mobile Unit

equipped as required (Figure 4) before the start of the study and was equipped to assist the clinical assessment by the rheumatologist, enabling him to perform the required imaging and laboratory tests: X-ray of the affected body segments, peripheral dual energy X-ray absorptiometry and blood collection.

BIOBANK PROCEDURES

Guidelines for the collection, identification and transport of samples to the biobank were provided to standardize sample collection as well as the identification of samples and transportation procedures. The nurse drew the blood samples in the mobile unit just after the clinical visit with the rheumatologist; serum was separated by centrifuging at the screening site and immediately placed in a refrigerator. On the same day, or within two days, the samples were sent in a cooler to a central diagnostic laboratory in Lisbon, transported by a dedicated company. Serum analyses were performed in fresh blood samples, and the remaining serum and clot stored in the biobank at *Instituto de Medicina Molecular* (Biobanco-IMM).

3RD PHASE - DIAGNOSIS VALIDATION & DATA ANALYSES: PLANNING AND WORK FIELD

In order to refine and validate the 2nd phase diagnostic decisions, a team of three rheumatologists reviewed all the clinical data from each participant, including the imaging and laboratorial test results. A specific protocol was developed to support this task.

The 3rd phase was developed during the 1st semester of 2014[8] and after this, the clinical database was cleaned and merged with the 1st phase database to provide a single EpiReumaPt database. A multidisciplinary team including a biostatistician and epidemiologists was set-up to perform data cleaning and support data analyses.

STUDY AWARENESS AMONG THE PORTUGUESE POPULATION

In Portugal, large-scale epidemiological studies are not common. At the beginning of EpiReumaPt the project was advertised among the Portuguese population, clarifying certain aspects:

1. The study did not aim to screen all the "Portuguese population" for RMDs, but selected random subjects.
2. The ultimate goal of this kind of study was the general public health, rather than any individual or institutional benefits.

To improve the recruitment rate other aspects had to be taken into account:

Lack of confidence and uncertainties among certain population subgroups (eg. the elderly population) –

strategic partnerships were established, namely with the National Association of Local Councils, to promote and disseminate EpiReumaPt among the population. We also liaised with the police and other public security authorities, with the Church, and with the local councils and other local authorities, to explain the study's methodology (especially the phase 1 interview) in order to gain the trust of the population improving its compliance.

The relative lack of availability of the active population to participate in the study (especially in larger cities), led CESOP to plan the work field during the weekends, during the week and during the evenings. A promotional event of EpiReumaPt with a press release was held on 9th September'2011, before starting recruitment. A website was also developed and updated throughout the EpiReumaPt recruitment (http://www.reumacensus.org/)[10] as well as a monthly newsletter that was sent to a large mailing list, which included national and local authorities (health and social authorities), media, sponsors, rheumatologists and other health care professionals, among others.

DATA PROTECTION AND ETHICS

EpiReumaPt was performed according to the principles established by the Declaration of Helsinki, revised in 2013 in Fortaleza (Brazil)[11] and according to the Portuguese law at the time the study begun (Law n. 46/2004, of 24th August). As an observational study it was reviewed and approved by competent Portuguese authorities: NOVA Medical School Ethics Committee and National Committee for Data Protection. The study was also reviewed and approved by the Ethical Committees of Regional Health Authorities. In addition to the Declaration of Helsinki, EpiReumaPt complied with the following laws and standards: Protection of Personal Information (Law n.67/98 of 26th of October[12] and CNPD deliberation n.227/2007[13]); and Genetic, clinical and health personal information (Law n.12/2005, of 26th January[14]).

Data protection was assured by data encryption according to the Portuguese law and according to CNPD deliberation n.227/2007[14] (processing of personal data carried out under scientific clinical research). The data encryption process kept the confidentiality and anonymity of each subject: in the 1st phase, subjects were identified with a unique code (ID) that was anonymous (each subject had an ID which was the same throughout the study procedures); in the 2nd phase, personal data (ID, name, address and contact details) were only available to the rheumatologist and Technical Team (nurse and radiology technician). Data collected in both phases (1st and 2nd) were exported to a single database. Decryption was only possible with a secure password only known by the Principal Investigator. All the computers that were used during the study procedures (1st phase, 2nd phase and also 3rd phase) had restricted access with a password.

Also Biobanco-IMM samples were provided according to the Portuguese law that assures data protection of genetic information and health clinical data (Law n.67/98 of 26th of October). Blood samples were collected and coded with the subject ID. Personal data were not visible or available to professionals involved in the circuit of the blood sample (from sample collection to the storage in the Biobanco-IMM). Only the PI had access to the code allowing access to the personal, clinical and biologic data of each subject.

INFORMED CONSENT

Informed consent for the EpiReumaPt study was mandatory and collected by interviewers in the 1st phase. Additional consents for Biobanco-IMM and Cohort study were also mandatory and collected by the rheumatologist during the 2nd phase (Figure 5). Subjects not invited for observation in the 2nd phase signed the informed consent to participate in the cohort study already in 1st phase. All subjects received clear information in lay terms about the research being undertaken (verbal information and a specific leaflet – main study, cohort study and Biobanco-IMM), and they were given the opportunity to ask questions and enough time to decide whether to participate in the study. Subjects were only asked to sign the consent form after the research team was assured that the patient had fully understood the study objectives and procedures. For each signed consent form, one copy was given to the participant while the other copy was archived by the site coordinator.

DISCUSSION

EpiReumaPt was a complex large-scale project with several management challenges. Strategies had to be defined and operating procedures regarding logistic, financial and coordination-related issues had to be implemented. Previously published strategies were con-

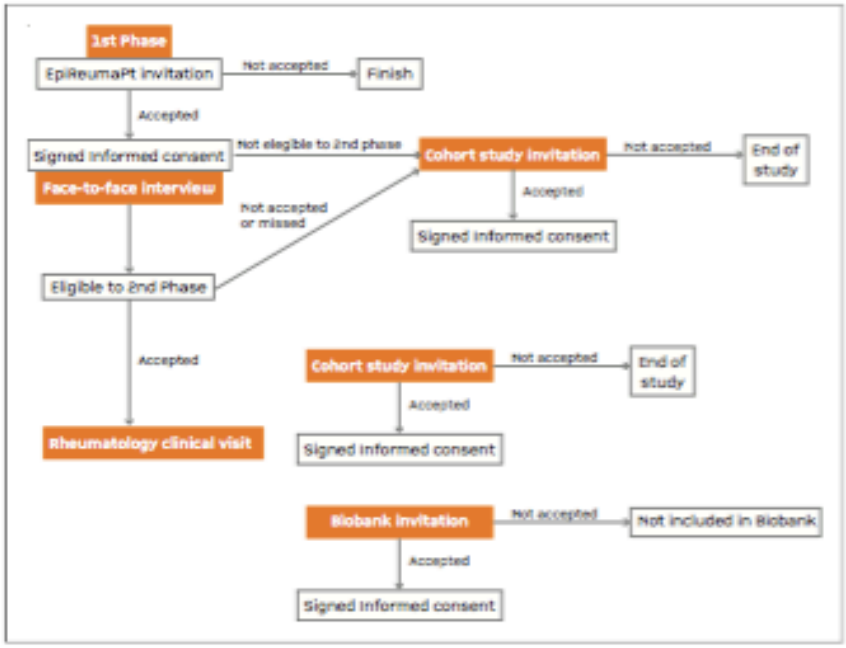

FIGURE 5. Informed consent flowchart

sidered insufficient to secure a good recruitment rate and several Country-specific actions were taken. The efforts to increase subjects' compliance were successful, particularly the measures related to raising study awareness among the general population (partnership with local authorities, the police and Church members), and to the schedule adjustment of interviews and clinical visits to the weekends and evenings. Also, Primary Care Centers were chosen as close as possible to the subjects' households.

Regarding management issues, the coordination of a multidisciplinary team over 27 months of work field, was a challenge. The very successful work field was only possible thanks to dedicated team members that gave response to all issues and unexpected situations that arose. In this context, also rheumatologists' commitment was determinant to the success of the project. The involvement of the local teams was a good strategy to maintain the work progress in the field and the existence of a core medical team of EpiReumaPt was crucial to be able to fulfill the planned schedule with no productivity losses.

Another main challenge was also the management of blood samples transportation to the Biobanco-IMM and to the central laboratories (both located in Lisbon), especially in the regions far from Lisbon. An accurate coordination between teams was necessary, as well as with the transportation company to ensure the quality of the samples. This issue was even more important in Azores and Madeira because it was necessary to coordinate all the previous factors with flights schedules.

In conclusion, as a result of detailed planning and standard operating procedures, EpiReumaPt was a nationwide project successfully conducted, which followed critical logistic/coordination and research strategies. EpiReumaPt methodology and coordination could be used as an example for other epidemiologic endeavors and public health policies.

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CORRESPONDENCE TO

Nelia Sofia Augusto Gouveia
Rua Quirino da Fonseca nº5, 2º
1000-250 Lisboa
E-mail: neliagou8@gmail.com

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Section I – Part II

EpiReumaPt- the study of Rheumatic and Musculoskeletal diseases in Portugal: a detail view of the methodology

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ARTIGO ORIGINAL

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

Ana M Rodrigues[1,2,3,4], Nélia Gouveia[1,2,4], Leonor Pereira da Costa[5], Mónica Eusébio[7], Sofia Ramiro[1,2,8], Pedro Machado[1,9], Ana Filipa Mourão[1,2,4,10], Inês Silva[1,10], Pedro Laires[1,11], Alexandre Sepriano[1,2,12], Filipe Araújo[13,14,15], Pedro Simões Coelho[13], Sónia Gonçalves[14,15], Ana Zhao[16], João Eurico Fonseca[1,4,16,17], JM Caldas de Almeida[1] Viviana Tavares[18,19], JAP da Silva[20], Henrique Barros[21], Jorge Cerol[1], Jorge Mendes[13], Loreto Carmona[22], Helena Canhão[1,2,4,23], Jaime C Branco[1,2,4,10,23] on behalf of the EpiReumaPt study group*

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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

1. EpiReumaPt Study Group – Sociedade Portuguesa de Reumatologia, Lisboa, Portugal
2. EpiDoc Unit – Unidade de Epidemiologia em Doenças Crónicas (CEDOC, NMS/UNL), Lisboa, Portugal
3. Unidade de Investigação em Reumatologia, Instituto de Medicina Molecular, Lisboa, Portugal
4. Faculdade de Medicina da Universidade de Lisboa, Lisboa, Portugal
5. Centro de Estudos de Doenças Crónicas (CEDOC) da NOVA Medical School, Universidade Nova de Lisboa (NMS/UNL), Lisboa, Portugal
6. Centro de Estudos e Sondagens de Opinião da Universidade Católica Portuguesa (CESOP-CATÓLICA), Lisboa, Portugal
7. Sociedade Portuguesa de Reumatologia, Lisboa, Portugal
8. Leiden University Medical Center, Leiden, The Netherlands
9. MRC Centre for Neuromuscular Diseases, University College London, London, United Kingdom
10. Serviço de Reumatologia do Hospital Egas Moniz – Centro Hospitalar Lisboa Ocidental (CHLO- E.P.E.), Lisboa, Portugal
11. Institute of Microbiology, Faculdade de Medicina da Universidade de Lisboa, Lisboa, Portugal
12. Unidade Curricular Especialidades Médico-Cirúrgicas I, NOVA Medical School, Universidade Nova de Lisboa (NMS/UNL), Lisboa, Portugal
13. NOVA IMS, Universidade Nova de Lisboa, Lisboa, Portugal
14. Instituto Piaget, Lisboa, Portugal
15. Unidade de Epidemiologia do Instituto de Medicina Preventiva e Saúde Pública da Faculdade de Medicina da Universidade de Lisboa, Lisboa, Portugal
16. Biobanco-IMM, Instituto de Medicina Molecular, Lisboa, Portugal
17. Serviço de Reumatologia do Hospital de Santa Maria – Centro Hospitalar Lisboa Norte (CHLN-E.P.E), Lisboa, Portugal
18. Hospital Garcia de Orta, EPE, Almada, Portugal
19. APOROS – Associação Nacional contra a Osteoporose, Lisboa, Portugal
20. Clínica Universitária de Reumatologia, Faculdade de Medicina e Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal
21. Departamento de Epidemiologia do Instituto de Saúde Pública da Universidade do Porto, Porto, Portugal
22. Instituto de Salud Musculoesquelética, Madrid, Spain
23. Programa Nacional Contra as Doenças Reumáticas (2006-2014), Direcção-Geral da Saúde, Lisboa, Portugal

***EpiReumaPt study group**
SOCIEDADE PORTUGUESA REUMATOLOGIA:
Alexandra Bernardo, Alexandre Sepriano, Ana Filipa Mourão, Ana Maria Rodrigues, Ana Raposo, Ana Sofia Roxo, Anabela Barcelos, António Vilar, Armando Malcata, Augusto Faustino, Cândida Silva, Carlos Vaz, Carmo Afonso, Carolina Furtado, Catarina Ambrósio, Cátia Duarte, Célia Ribeiro, Cláudia Miguel, Cláudia Vaz, Cristina Catita, Cristina Ponte, Daniela Peixoto, Diana Gonçalves, Domingos Araújo, Elsa Vieira-Sousa, Eva Mariz, Fátima Godinho, Fernando Pimentel, Filipa Ramos, Filipa Teixeira, Filipe Araújo, Filipe Barcelos, Georgina Terroso, Graça Sequeira, Guilherme Figueiredo, Helena Canhão, Herberto Jesus, Inês Cunha, Inês Gonçalves, Inês Silva, José António P. da Silva, Jaime Cunha Branco, Joana Abelha, Joana Ferreira, João Dias, João Eurico Fonseca, João Ramos, João Rovisco, Joaquim Pereira, Jorge Silva, José Carlos Romeu, José Costa, José Melo Gomes, José Pimentão, Lúcia Costa, Luís Inês, Luís Maurício, Luis Miranda, Margarida Coutinho, Margarida Cruz, Margarida Oliveira, Maria João Gonçalves, Maria João Salvador, Maria José Santos, Mariana Santiago, Mário Rodrigues, Maura Couto, Miguel Bernardes, Miguel Sousa, Mónica Bogas, Patrícia Pinto, Paula Araújo, Paula Valente, Paulo Coelho, Paulo Monteiro, Pedro Madureira, Raquel Roque, Renata Aguiar, Ricardo O. Figueira, Rita Barros, Rita Fonseca, Romana Vieira, Rui André, Rui Leitão, Sandra Falcão, Sara Serra, Sílvia Fernandes, Sofia Pimenta, Sofia Ramiro, Susana Capela, Taciana Videira, Teresa Laura Pinto, Teresa Nóvoa, Viviana Tavares

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-

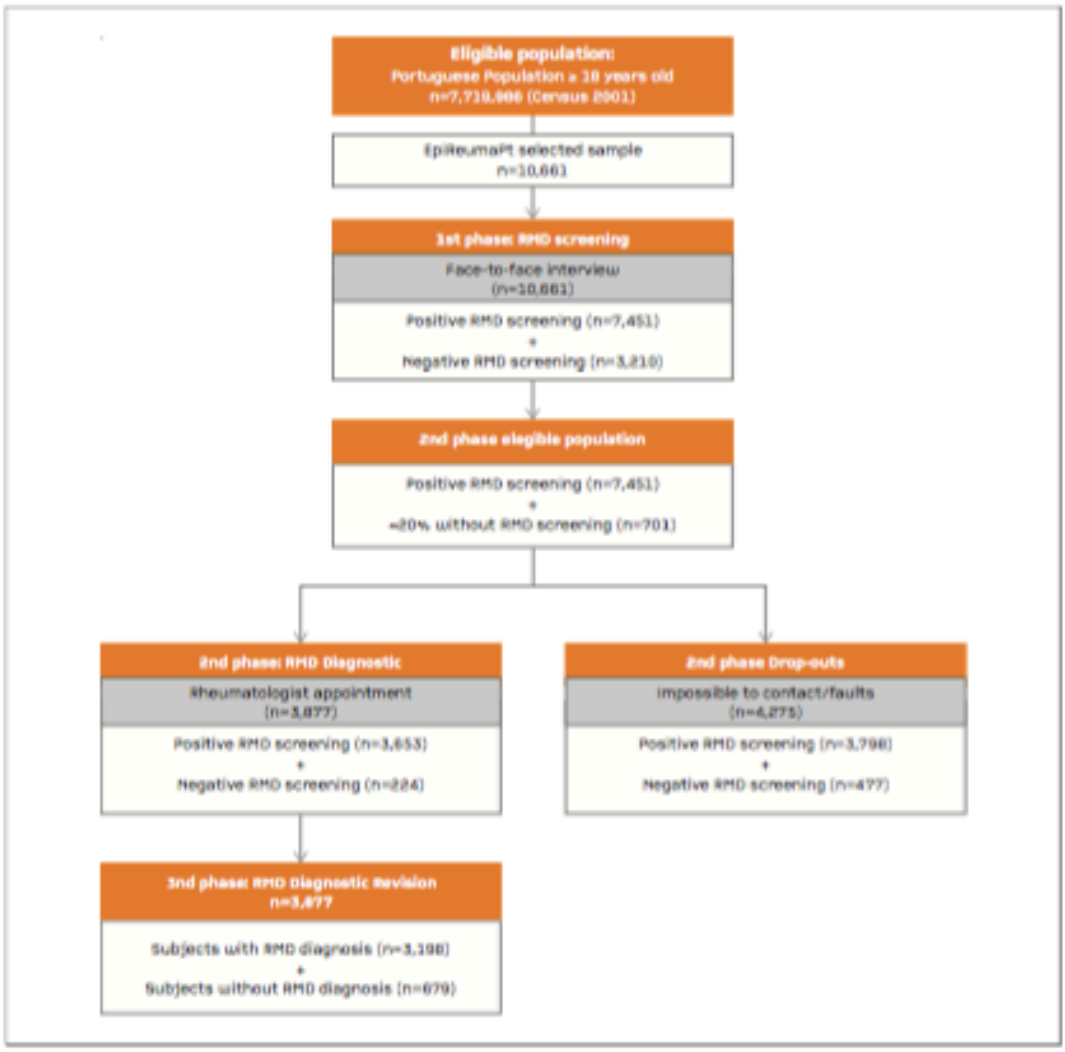

FIGURE 2. Flowchart of recruitment in the EpiReumaPt Study
RDM: Rheumatic and Musculoskeletal diseases

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)[25-27] 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	1,834 (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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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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CORRESPONDENCE TO
Ana M. Rodrigues
Unidade de Investigação em Reumatologia,
Instituto de Medicina Molecular, Lisboa, Portugal
E-mail: anamfrodrigues@gmail.com

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Section I – Part III

Prevalence and physical and mental health patterns of rheumatic and musculoskeletal diseases in Portugal: results from EpiReumaPt, a national health survey

Branco JC, Rodrigues A, **Gouveia N**, et al. Prevalence and physical and mental health patterns of rheumatic and musculoskeletal diseases in Portugal: results from EpiReumaPt, a national health survey *submitted.* 2015.

Prevalence and physical and mental health patterns of rheumatic and musculoskeletal diseases in Portugal: results from EpiReumaPt, a national health survey

Jaime Branco[1,2,3,4,5], Ana M Rodrigues[1,4,6,7], Nélia Gouveia[1,3,4], Mónica Eusébio[8], Sofia Ramiro[1,3, 10], Pedro Machado[1,12,13], Leonor Pereira da Costa,[9] Ana Filipa Mourão[1,2,3,6], Inês Silva[1,2], Pedro Laires[1,7], Alexandre Sepriano[2,3,6], Filipe Araújo[2,14,15], Sónia Gonçalves[16,17], Pedro Simões Coelho[18], Viviana Tavares[19,20], Jorge Cerol[8], Jorge Mendes[18], Loreto Carmona[21], Helena Canhão[1,4,6,7,22], on behalf of the EpiReumaPt study group*

[1] EpiReumaPt Study Group - Sociedade Portuguesa de Reumatologia, Lisboa, Portugal; [2] Serviço de Reumatologia do Hospital Egas Moniz - Centro Hospitalar Lisboa Ocidental (CHLO- E.P.E.), Lisboa, Portugal; [3] Centro de Estudos de Doenças Crónicas (CEDOC) da NOVA Medical School, Universidade Nova de Lisboa (NMS/UNL), Lisboa, Portugal; [4]EpiDoc Unit – Unidade de Epidemiologia em Doenças Crónicas (CEDOC, NMS/UNL), Lisboa, Portugal; [5] Programa Nacional Contra as Doenças Reumáticas (2006-2014), Direcção Geral da Saúde. Lisboa, Portugal; [6] Unidade de Investigação em Reumatologia, Instituto de Medicina Molecular, Lisboa, Portugal; [7] Faculdade de Medicina da Universidade de Lisboa, Lisboa, Portugal; [8] Sociedade Portuguesa de Reumatologia, Lisboa, Portugal; [9]Centro de Estudos e Sondagens de Opinião da Universidade Católica Portuguesa (CESOP-CATÓLICA), Lisboa, Portugal; [10]Leiden University Medical Center, Leiden,The Netherlands;[11] Hospital Garcia de Orta, Almada, Portugal; [12] Clínica Universitária de Reumatologia, Faculdade de Medicina da Universidade de Coimbra, Coimbra, Portugal; [13] MRC Centre for Neuromuscular Diseases, University College London, London, United Kingdom; [14] Instituto de Microbiologia, Faculdade de Medicina da Universidade de Lisboa, Lisboa, Portugal; [15] Unidade Curricular Especialidades Médico-Cirúrgicas I, NOVA Medical School, Universidade Nova de Lisboa (NMS/UNL), Lisboa, Portugal; [16] Instituto Piaget, Lisboa, Portugal; [17] Unidade de Epidemiologia do Instituto de Medicina Preventiva e Saúde Pública da Faculdade de Medicina da Universidade de Lisboa, Lisboa, Portugal; [18] NOVA IMS, Universidade Nova de Lisboa, Lisboa, Portugal; [19] Hospital Garcia de Orta, EPE, Almada, Portugal; [20] APOROS - Associação Nacional contra a Osteoporose, Lisboa, Portugal; [21] Instituto de Salud Musculoesquelética, Madrid, Spain; [22] Serviço de Reumatologia do Hospital de Santa Maria – Centro Hospitalar Lisboa Norte (CHLN-E.P.E), Lisboa, Portugal

***EpiReumaPt study group**

Sociedade Portuguesa Reumatologia:

Alexandra Bernardo, Alexandre Sepriano, Ana Filipa Mourão, Ana Maria Rodrigues, Ana Raposo, Ana Sofia Roxo, Anabela Barcelos, António Vilar, Armando Malcata, Augusto Faustino, Cândida Silva, Carlos Vaz, Carmo Afonso, Carolina Furtado, Catarina Ambrósio, Cátia Duarte, Célia Ribeiro, Cláudia Miguel, Cláudia Vaz, Cristina Catita, Cristina Ponte, Daniela Peixoto, Diana Gonçalves, Domingos Araújo, Elsa Sousa, Eva Mariz, Fátima Godinho, Fernando Pimentel, Filipa Ramos, Filipa Teixeira, Filipe Araújo, Filipe Barcelos, Georgina Terroso, Graça Sequeira, Guilherme Figueiredo, Helena Canhão, Herberto Jesus, Inês Cunha, Inês Gonçalves, Inês Silva, J. António P. da Silva, Jaime Branco, Joana Abelha, Joana Ferreira, João Dias, João Eurico Fonseca, João Ramos, João Rovisco, Joaquim Pereira, Jorge Silva, José Carlos Romeu, José Costa, José Melo Gomes, José Pimentão, Lúcia Costa, Luís Inês, Luís Maurício, Luís Miranda, M. João Gonçalves, Margarida Coutinho, Margarida Cruz, Margarida Oliveira, Maria João Salvador, Maria José Santos, Mariana Santiago, Mário Rodrigues, Maura Couto, Miguel Bernardes, Miguel Sousa, Mónica Bogas, Patrícia Pinto, Paula Araújo, Paula Valente, Paulo Coelho, Paulo Monteiro, Pedro Madureira, Raquel Roque, Renata Aguiar, Ricardo O. Figueira, Rita Barros, Rita Fonseca, Romana Vieira, Rui André, Rui Leitão, Sandra Falcão, Sara Serra, Sílvia Fernandes, Sílvia Fernandes, Sofia Pimenta, Sofia Ramiro, Susana Capela, Taciana Videira, Teresa Laura Pinto, Teresa Nóvoa, Viviana Tavares

Abstract

Objectives: To estimate the national prevalence of rheumatic and musculoskeletal diseases (RMDs) in the adult Portuguese population and to determine their impact on physical and mental health.

Methods: EpiReumaPt is a national health survey with a three-stage approach. First, 10,661 adult subjects were randomly selected. Trained interviewers undertook structured face-to-face questionnaires that included screening for RMDs and assessments of quality of life, physical function, anxiety and depression. Secondly, positive screenings for ≥1 RMD plus 20% negative screenings were invited to be evaluated by a rheumatologist. Finally, 3 rheumatologists revised all the information and confirmed the diagnoses according to validated criteria. Estimates were computed as weighted proportions, taking the sampling design into account.

Results: The disease-specific prevalence (and 95% CI) of RMDs in the adult Portuguese population was: low back pain, 26.4%(23.3%,29.5%); periarticular disease, 15.8% (13.5%; 18.0%); knee osteoarthritis (OA), 12.4% (11.0%;13.8%); osteoporosis, 10.2% (9.0%;11.3%); hand OA, 8.7% (7.5%;9.9%); hip OA, 2.9% (2.3%;3.6%); fibromyalgia, 1.7% (1.1%;2.1%); spondyloarthritis, 1.6% (1.2%;2.1%); gout, 1.3% (1.0%;1.6%); rheumatoid arthritis, 0.7% (0.5%;0.9%); systemic lupus erythematosus, 0.1% (0.1%;0.2%) and polymyalgia rheumatica, 0.1% (0.0%;0.2%). After adjustment, subjects with RMDs had significantly lower EQ5D scores (β=-0.09; $p<0.001$) and higher HAQ scores (β=0.13; $p<0.001$) than subjects without RMDs. RMDs were also significantly associated with the presence of anxiety symptoms (OR=3.5; p=0.006).

Conclusion: RMDs are highly prevalent in Portugal and are associated with significant impairment of physical and mental health.

Introduction

Rheumatic and musculoskeletal diseases (RMDs) are among the most common chronic non-communicable diseases. They are the leading cause of disability in developed countries and consume a large amount of health and social resources[1-3]. Comparative data of the impact on quality of life and mental health status of RMD are unknown[4 5]. Epidemiological data in Portugal is scarce[6-8] EpiReumaPt is a national health-survey conducted to estimate the national prevalence of hand, knee and hip osteoarthritis (OA), low back pain (LBP), rheumatoid arthritis (RA), fibromyalgia (FM), gout, spondyloarthritis (SpA), periarticular disease (PD), systemic lupus erythematosus (SLE), polymyalgia rheumatica (PMR) and osteoporosis (OP) in the adult Portuguese population. Another aim was to assess the burden of RMDs by determining their impact on physical and mental health. Both aims address the needs and objectives identified in a recent governmental initiative – the National Program Against Rheumatic diseases[9].

Methods

The study protocol has been previously published[10] as well as a separate manuscript extensively describing the methodological details of the project[11]. An outline of the methodology is presented below.

Setting

Portugal is a southwestern European country including the mainland and the Autonomous Regions of Azores and Madeira. According to the Census performed in 2011, Portugal has a resident population of 10,562,178 inhabitants[12], of which 8,657,240 are adults[13 14].

Study Population

EpiReumaPt is a national, cross-sectional and population-based study. The study population was composed by adults (≥18 years old) who were non-institutionalized and living in private households in the Mainland and the Islands (Azores and Madeira). Exclusion criteria were: residents in hospitals, nursing homes, military institutions or prisons, and individuals unable to speak Portuguese or unable to complete the questionnaires [10 13].

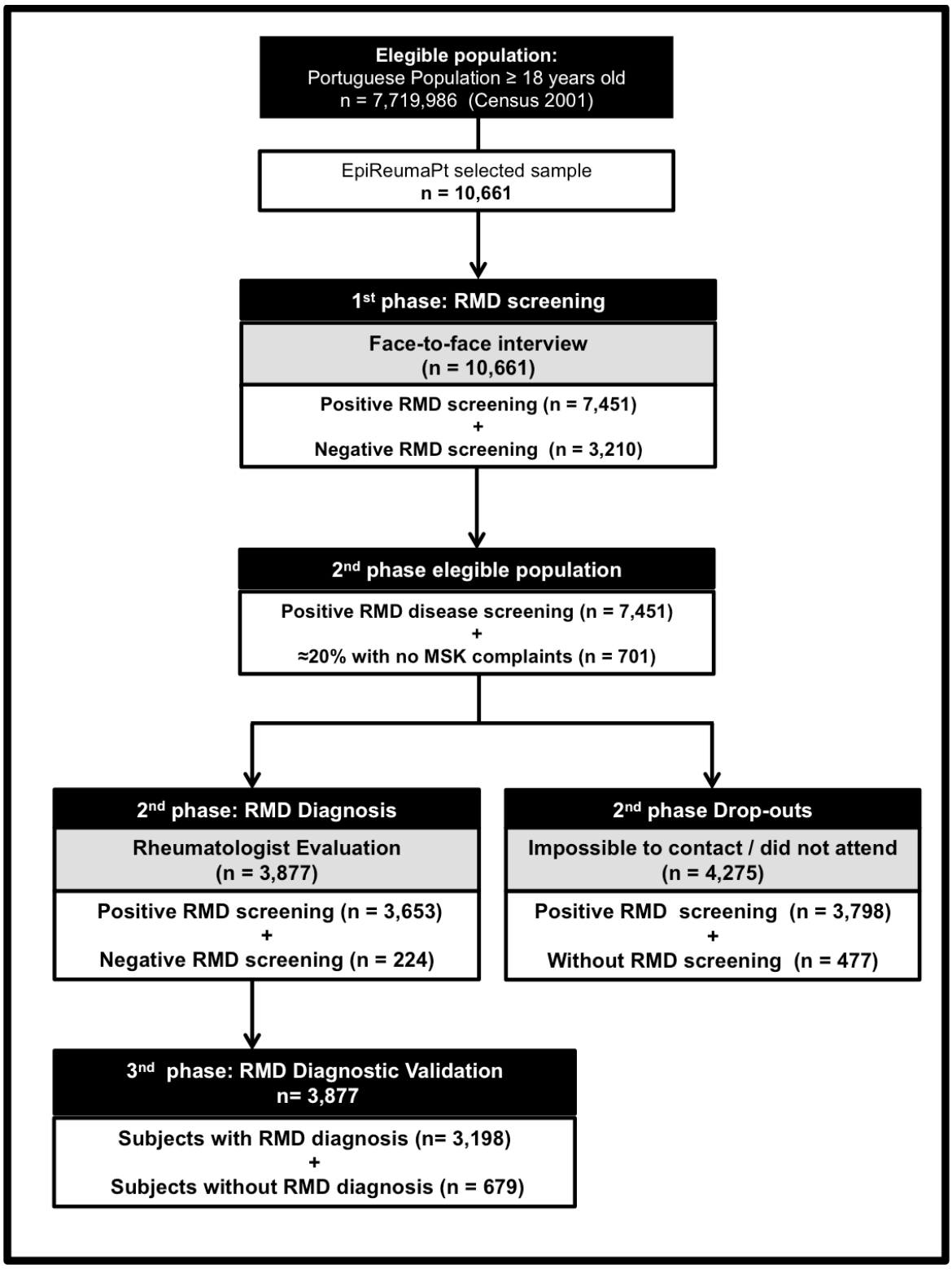
Sampling

Participants were selected through a process of multistage random sampling. The sample was stratified according to the Portuguese Nomenclature of Territorial Units for Statistics (NUTS II; seven

territorial units: Norte, Centro, Alentejo, Algarve, Lisboa e Vale do Tejo, Madeira and Azores) and the size of the population (<2,000; 2,000-9,999; 10,000-19,999; 20,000-99,999; and ≥100,000 inhabitants).

Recruitment

Recruitment took place between September 2011 and December 2013. EpiReumaPt involved a three-stage approach. First, candidate households were selected using a random route process. The adults with permanent residence in the selected household with the most recently completed birthday were recruited (one adult per household). Trained interviewers undertook structured face-to-face questionnaires in participants' households collecting a vast number of variables (socio-demographic, socio-economic, quality of life (QoL), lifestyle habits, chronic non-communicable diseases, healthcare resources utilization) and performing a screening for RMDs. Questions were asked about several rheumatic symptoms and an algorithm for the screening of each RMD was applied [14]. Secondly, all participants who screened positive for at least one RMD plus 20% of individuals with no rheumatic complaints (negative screening) were invited for a structured evaluation by a rheumatologist at the local Primary Care Center. Finally, a team of 3 experienced rheumatologists revised all the clinical, laboratorial and imaging data and confirmed the diagnoses according to validated criteria (Figure 1)[13].



RMD- Rheumatic and musculoskeletal disease; MSK- Musculoskeletal disease

Figure 1 – Flowchart of recruitment in the EpiReumaPt Study

Measurements

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, household income, current professional status) and lifestyle habits (alcohol, tobacco and coffee intake, physical exercise). Information on work atus was also collected. Healthcare resource consumption data was collected through the number and type of outpatient clinic visits, hospitalizations, homecare assistance and other needs for healthcare services in the previous 12 months.

To evaluate generic health-related QoL we used the Portuguese validated version of the European Quality of Life questionnaire, five dimensions, three levels (EQ-5D-3L)[15 16].

Functional status was assessed by the Health Assessment Questionnaire (HAQ) [17], anxiety and depression were assessed by the Portuguese validated version of the Hospital Anxiety and Depression Scale (HADS) [18]. HADS is divided into an Anxiety subscale (HADS-A) and a Depression subscale (HADS-D) both containing seven intermingled items. We also assessed anthropometric data (self-reported weight and height) and self-reported chronic diseases (high cholesterol, high blood pressure, allergies, gastrointestinal disease, mental disease, cardiac disease, diabetes, thyroid and parathyroid disease, urolithiasis, pulmonary disease, hyperuricemia, cancer, neurologic disease, hypogonadism). Information regarding pharmacological and non-pharmacological therapies was also collected.

In the 2nd phase of EpiReumaPt, a thorough history and physical examination were performed. Previous diagnosis of RMDs and current medications were also assessed [13].

Case definition

The presence of a RMD was considered if a subject, after the clinical appointment of the second phase, had a positive expert opinion combined with the fulfillment of validated classification criteria to establish a diagnosis of knee OA, hip OA, hand OA, FM, SLE, gout, RA, SpA or PMR [14]. We used the ACR classification criteria for knee OA [19], hip OA [20], hand OA [21], FM [22], SLE [23] and gout [24]; the American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR) criteria for RA [25]; the Assessment of SpondyloArthritis international Society (ASAS) criteria for axial and peripheral SpA [26-28]; and the Bird criteria for PMR [29].

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 assessment. The diagnosis was established based on expert opinion in the second phase of the study.

OP was defined by clinical decision of the rheumatologist that observed the subject in the second phase of the study based on the presence of at least one of the following: previous fragility fracture, previous OP diagnosis, current OP treatment or fulfillment of the WHO criteria [30] when axial dual energy X-ray absorptiometry (DEXA) was available. Low back pain (LBP) was defined solely by self-report and clinical history.

Statistical analysis

Prevalence estimates for RMDs were computed as weighted proportions, in order to take into account the sampling design[13].

Subjects with and without RMD were compared. Univariable analyses were first performed considering the study design. Multivariate regression models were used to assess the differences between individuals with and without RMDs, regarding: health status and function (EQ5D and HAQ), mental health (presence of symptoms of anxiety (HADS-A ≥11 vs <11), presence of symptoms of depression (HADS-D ≥11 vs <11)[18]), and health resources consumption (number of medical visits (General Practitioner, Rheumatologist, Orthopedic Surgeon and any other specialists) and, home care in the previous 12 months (yes/no), hospitalizations in the previous 12 months (yes/no), early retirement due to disease (yes/no), absence from work due to disease in the previous 12 months (yes/no) and number of days of absence). The variables significantly different in the univariable analysis were included in the multivariable model. The following variables were included in the model: age, gender, NUTS II, education level, employment status, household income, alcohol intake, current smoking, physical exercise, Body Mass Index (BMI), physical exercise, and number of comorbidities.

The burden of each RMD was assessed by investigating the association of individual RMDs with disability (HAQ), quality of life (EQ5D), presence of symptoms of anxiety and presence of symptoms of depression. For the first two outcomes, which are continuous variables, linear regression was used, and for the last two, which are dichotomous outcomes, logistic regression was performed. Multivariable models were constructed using backward section, adjusted for

potential confounders. The following potential confounders were tested: age, gender, NUTS II, years of education, work status, BMI, alcohol intake, current smoking, physical activity, and number of comorbidities. For the models with HAQ and EQ5D, the presence of symptoms of anxiety or depression was also considered as possible confounders. Possible interactions between each RMD and gender and age were tested for the four outcomes.

Significance level was set at 0.05. All analyses were weighted and performed using STATA IC version 12 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

Ethical issues

EpiReumaPt 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. All subjects provided informed consent to participate in all phases of the study [10]. Further details of ethical issues of EpiReumaPt have been described elsewhere [11].

Results

Prevalence of RMDs in the Portuguese adult Population

The EpiReumaPt population did not differ from the Portuguese population (Table 1) [12 31]. In the EpiReumaPt study, 21.2% (95% confidence interval [CI] 19.9% to 22.5%) of the Portuguese population self-reported a RMD. During the second phase of the study, we observed 3,877 subjects and detected 1,532 new RMD diagnoses. 2,670 individuals were found to have more than one RMD. Moreover, of the 3,877 subjects evaluated in the second phase, only 85 (9.6%) previously reporting a RMD had no identifiable target disease.

Table 1: Socio-demographic and health related characteristics of the adult Portuguese population: EpiReumaPt population (1st and 2nd phase) and Census 2011 population (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%)

NUTS II- Nomenclature of Territorial Units for Statistics (Norte, Centro, Alentejo, Algarve, Lisboa, Madeira and Azores)

The prevalence of each RMD, overall and stratified by gender, and the estimated number of patients in the Portuguese population is shown in Table 2. The RMD with the highest prevalence in Portugal was LBP (26.4%; 95% CI 23.3% to 29.5%) significantly more frequent in women than in men (29.6% versus 22.8%; p=0.040) (Table 2). LBP increased with age and its prevalence was highest in the 46-55 age group (27.7%; 95%CI 23.1% to 32.4%) (Figure 2). PD was also a frequent RMD with an overall prevalence of 15.8% (95%CI 13.5% to 18.0%) and women were also significantly more affected than men (19.1% versus 12.0%; p=0.005). This RMD had the highest prevalence in the working-age population (46-55 years) (21.5%; 95%CI 17.4 to 25.5%) (Figure 2). OA was also common among Portuguese individuals, particularly knee OA, with a prevalence of 12.4% (95%CI 11.0% to 13.8%). Noteworthy, gout had an overall prevalence of 1.3% (95%CI 1.0% to 1.6%) (Table 2). The age stratum with the highest gout prevalence corresponded to the elderly (>85 years old) with a 3.2% prevalence (95%CI 2.0% to 4.4%)

(Figure 2). As expected, men had the highest gout prevalence (2.6% versus 0.1% in women, p<0.001). Moreover, 22.2% (95%CI 8.2 to 36.2) of gout patients had poliarticular disease and 11.0% had chronic tophaceous gout. The mean number of gout attacks in the 12 months previous to the clinical evaluation was of 2.0 ± 1.7.

Regarding inflammatory rheumatic diseases, SpA had the highest prevalence in the adult population (1.6%; 95%CI 1.2% to 2.0%), with 51.8% of the cases being axial SpA. We found no significant gender predominance in SpA (p=0.094). Among SpA subtypes according to the classical nomenclature, undifferentiated spondyloarthritis accounted for 44.3% of cases, ankylosing spondylitis (AS) 29.6%, psoriatic arthritis 18.7% and SpA associated with inflammatory bowel disease 12.0%. Finally, the prevalence of RA was of 0.7% (95%CI 0.5% to 0.9%).

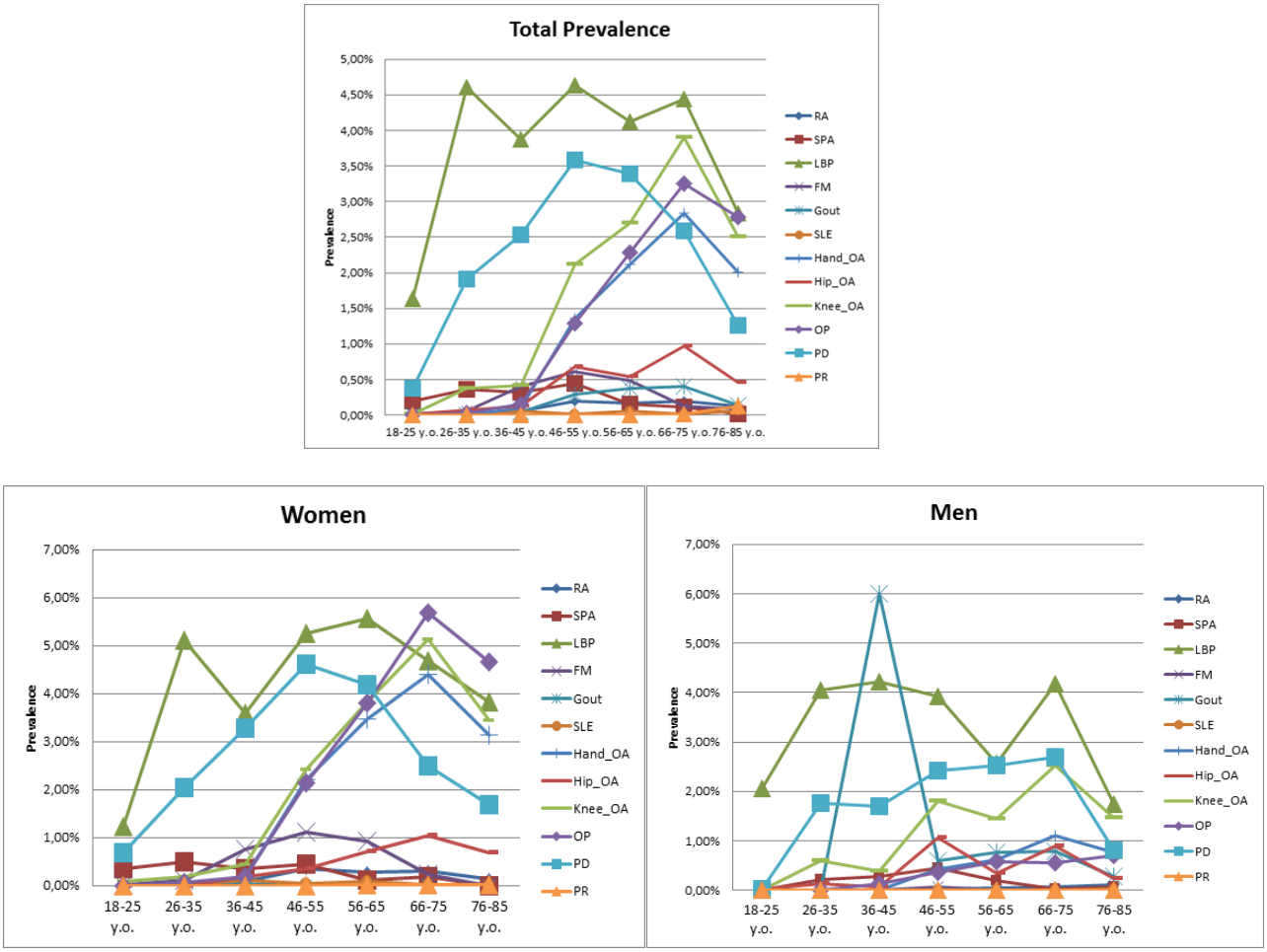


Figure 2: Prevalence of RMDs, overall and stratified by age group and gender

Subjects with RMD had significantly lower physical and mental health and consumed more healthcare resources

Regarding QoL, we found that subjects with RMD had significantly lower EQ5D scores (β=-0.09; p<0.001) when compared to subjects without RMD, adjusted for demographic factors, socio-economic factors, lifestyle and comorbidities. Furthermore, patients with RMD had significantly higher disability (HAQ score) (β=0.13; p<0.001).

We also found that in subjects with RMD there was a significantly higher prevalence of anxiety symptoms (OR=3.5; p=0.006) but no significant differences were found regarding depressive symptoms (OR= 1.9; p=0.173) (Table 3).

Table 3: Comparison of socio-demographic, socio-economic, health status and health resources consumption between subjects with and without RMD

	RMD n=3,195	Non-RMD n=682	β coef estimates/OR (as appropriate)	95% CI	Adjusted p-value
HEALTH STATUS AND FUNTION					
EQ5D (0-1)	**0.7±0.3**	**0.9±0.1**	**-0.09**	[-0.13;-0.05]	**<0.001†**
HAQ (0-3)	**0.4±0.7**	**0.1±0.2**	**0.13**	[0.08;0.17]	**<0.001†**
MENTAL HEALTH					
Anxiety (yes vs no)	**600** (16.7%)	**63** (5.3%)	**3.5**	[1.4;8.0]	**0.006†**
Depression (yes vs no)	**349** (8.3%)	**29** (1.3%)	**1.9**	[0.8;4.6]	**0.173**
HEALTHCARE CONSUMPTION					
Physician visits in the last 12 months	**2,661** (78.8%)	**502** (71.5%)	**0.5**	[0.3;0.8]	**0.010†**
General practitioners	**206** (4.6%)	**11** (1.0%)	**30.5**	[7.4;126.2]	**<0.001†**
Rheumatology visits	**475** (14.9%)	**46** (6.5%)	**3.2**	[1.3;7.8]	**0.010†**
Orthopedic visits	**1,758** (57.1%)	**347** (53.5%)	**0.9**	[0.6;1.5]	**0.825**
Other visits					
Number of physician appointments in the last 12 months	**2.5±5.9**	**4.0±19.0**	**-4.01**	[-11.37;3.34]	**0.285**
General practitioners	**0.1±0.8**	**0.0±0.1**	**0.08**	[0.05;0.11]	**<0.001†**
Rheumatology appointments	**0.4±1.4**	**0.1±0.4**	**0.27**	[0.10;0.43]	**0.002†**
Orthopedic appointments	**1.9±8.0**	**1.5±1.5**	**0.01**	[-0.47;0.50]	**0.961**
Other appointments					
Home care in the last 12 months	**100** (2.7%)	**5** (0.1%)	**13.2**	[2.7;63.6]	**0.001†**
Hospitalizations in the last 12 months	**324** (11.4%)	**53** (5.5%)	**2.5**	[1.1;5.8]	**0.027†**
Early retirement due to disease	**488** (30.9%)	**33** (22.0%)	**2.3**	[0.9;6.0]	**0.101**
Absent from work due to disease in the last 12 months	**323** (29.9%)	**76** (24.8%)	**1.7**	[0.8;3.5]	**0.163**
Number of days absent from work due to disease in the last 12 months	**31.5±83.9**	**22.5±14.1**	**14.11**	[-4.72;32.94]	**0.141**

Sample size is not constant due to missing data in RMD: EQ5D (n=3168), Early retirement due to disease (n=1419), Absent from work due to disease in the last 12 months (n=1010), Number of days absent from work due to disease in the last 12 months (n=318);
Non-RMD: EQ5D (n=678), Early retirement due to disease (n=142), Absent from work due to disease in the last 12 months (n=359), Number of days absent from work due to disease in the last 12 months (n=75).
EQ5D - European Quality of Life questionnaire five dimensions three levels; **HAQ** - Health Assessment Questionnaire.
p-values were adjusted for age, gender, for Nomenclature of Territorial Units for Statistics (North, Centre, Alentejo, Algarve, Lisbon, Madeira and the Azores), years of education, work status, household income, alcohol intake, physical exercise, Body Mass Index, and number of comorbidities. For continues variables a multivariable regression was used to assess the differences between the groups (individuals with Rheumatic Diseases, and without Rheumatic Diseases). The estimated values were obtained considering study design.
†Adjusted p-values<0.05.

Considering healthcare resources consumption (Table 3), patients with RMD had been more often hospitalized and had more homecare support needs in the previous 12 months when compared to subjects without any RMD (OR=2.5, p=0.027 and OR=13.2, p=0.001, respectively). Finally, we found no differences between the two groups regarding sick leave or early retirement due to disease (Table 4).

Disease-specific associations with worse quality of life and disability

Several RMDs were significantly and independently associated to worse QoL in the Portuguese population. By decreasing order of effect, PMR (β=-0.33; p=0.027), RA (β=-0.13; p=0.001), FM (β=-0.10; p<0.001), LBP (β=-0.07; p<0.001), knee OA (β=-0.06; p<0.001) and PD (β=-0.04; p=0.029) were associated with worse QoL. Moreover, subjects retired or in sick leave (β=-0.04; p=0.016) and with a higher number of comorbidities (β=-0.03; p<0.001) were also associated with worse QoL. The presence of anxiety and depressive symptoms (HADS≥11) were also associated with worse QoL (β=-0.14; p<0.001 and β=-0.14; p<0.001, respectively). On the other hand, alcohol consumption was significantly associated with better QoL (β=0.045; p<0.001) (Table 4). Regarding the HAQ score, and by decreasing order of effect, PMR (β=1.03; p<0.001), RA (β=0.38; p<0.001), FM (β=0.27; p=0.001), knee OA (β=0.11; p=0.002), LBP (β=0.09; p<0.001), OP (β=0.08; p=0.033) and PD (β=0.06; p=0.019) were significantly associated with disability.

Certain characteristics, such as female gender (β=0.11; p<0.001), low educational level (β=-0.01; p=0.002) and sick leave or retirement (β=0.14; p<0.001) were significantly associated with higher HAQ scores. The number of comorbidities (β=0.06; p<0.001) and symptoms of anxiety (β=0.15; p<0.001) or depression (β=0.32; p<0.001) were also significantly associated with disability. Daily or occasional alcohol intake was significantly associated with lower HAQ scores (β=-0.06; p=0.023) (Table 4).

Table 4: Impact of each rheumatic and musculoskeletal disease on quality of life (EQ5D) and function (HAQ)

	EQ5D		HAQ	
Demographic characteristics	**β coef (95% CI)**	**p-value**	**β coef (95%CI)**	**p-value**
Gender (female)	**-0.03** (-0.06; 0.00)	**0.058**	**0.11** (0.07; 0.15)	**<0.001†**
Age (years)	**0.00** (-0.0; 0.01)	**0.902**	**0.00** (-0.00; 0.00)	**0.857**
BMI				
Underweight vs Normal	**0.09**(-0.01; 0.16)	**0.021†**	**-0.02** (-0.16;0.12)	**0.802**
Overweight vs Normal	**0.03** (-0.00;0.52)	**0.067**	**-0.00** (-0.04;0.04)	**0.975**
Obese vs Normal	**0.01** (-0.02; 0.04)	**0.526**	**-0.08** (0.02;0.14)	**0.005†**
Years of education	**-0.01** (-0.0; 0.00)	**0.788**	**-0.01** (-0.02; -0.00)	**0.002†**
Employment status				
Employed vs retired or sick leave	**-0.04** (-0.09; -0.00)	**0.046†**	**0.14** (0.06; 0.21)	**<0.001†**
Employed vs unemployment	**-0.00** (-0.04; 0.05)	**0.946**	**0.04** (-0.02; 0.10)	**0.170**
NUTS II				
Norte vs Lisboa	**0.0** (-0.03; 0.04)	**0.832**	**0.03** (-0.01; 0.08)	**0.168**
Centro vs Lisboa	**0.0** (-0.03;0.04)	**0.777**	**0.04** (-0.02;0.10)	**0.167**
Alentejo vs Lisboa	**0.02** (-0.2;0.05)	**0.414**	**0.11** (0.05;0.18)	**0.001†**
Algarve vs Lisboa	**0.04** (-0.00;0.09)	**0.078**	**0.01** (-0.06;0.07)	**0.836**
Azores vs Lisboa	**0.11** (-0.03;0.05)	**0.572**	**-0.00** (-0.05;0.05)	**0.938**
Madeira vs Lisboa	**0.01** (-0.03;0.04)	**0.763**	**0.11** (0.02;0-19)	**0.011†**
Number of Comorbidities (0-15)	**-0.03** (-0.04; -0.03)	**<0.001†**	**0.06** (0.05; 0.08)	**<0.001†**
Life-style habits				
Alcohol intake (yes/no)	**0.05** (0.02; 0.07)	**0.001†**	**-0.06** (-0.10; -0.01)	**0.023†**
Regular physical exercise (yes/no)	**0.02** (-0.01; 0.05)	**0.152**	**-0.03** (-0.07; 0.01)	**0.139**
Mental Disorders				
Anxiety (yes/ no)	**-0.14** (-0.20; -0.08)	**<0.001†**	**0.15** (0.07; 0.22)	**<0.001†**
Depression (yes/ no)	**-0.14** (-0.19; -0.09)	**<0.001†**	**0.32** (0.20; 0.44)	**<0.001†**
RMD Diagnosis				
Low Back Pain (yes/ no)	**-0.07** (-0.10; -0.04)	**<0.001†**	**0.09** (0.04; 0.13)	**<0.001†**
Periarticular Disease (yes/ no)	**-0.04** (-0.08; -0.01)	**0.016†**	**0.06** (0.01;0.11)	**0.019†**
Knee Osteoarthritis (yes/ no)	**-0.06** (-0.09; -0.03)	**<0.001†**	**0.11** (0.04; 0.18)	**0.002†**
Osteoporosis (yes/ no)	**-0.01** (-0.04; 0.02)	**0.676**	**0.08** (0.01; 0.15)	**0.033†**
Hand Osteoarthritis (yes/ no)	**-0.00** (-0.04; 0.03)	**0.831**	**-0.00** (-0.08; 0.07)	**0.903**
Hip Osteoarthritis (yes/ no)	**-0.05** (-0.10; 0.01)	**0.083**	**-0.30** (-0.70; 0.10)	**0.145**
Fibromyalgia (yes/ no)	**-0.10** (-0.16; -0.05)	**<0.001†**	**0.27** (0.10; 0.43)	**0.001†**
Spondyloarthritis (yes/ no)	**-0.05** (-0.11; 0.01)	**0.120**	**0.08** (-0.35; 0.19)	**0.180**
Gout (yes/ no)	**0.05** (-0.01; 0.11)	**0.085**	**-0.06** (-0.19; 0.07)	**0.387**
Rheumatoid Arthritis (yes/ no)	**-0.13** (-0.21; -0.06)	**0.001†**	**0.38** (0.20; 0.56)	**<0.001†**
SLE (yes/ no)	**0.03** (-0.072 0.13)	**0.585**	**0.23** (-0.07; 0.53)	**0.137**
Polymyalgia Rheumatica (yes/ no)	**-0.33** (-0.63; -0.04)	**0.027†**	**1.03** (0.46; 1.60)	**<0.001†**
Hip Osteoarthritis*Age	--	**--**	**0.01** (0.00;0.01)	**0.016†**

EQ5D - European Quality of Life questionnaire five dimensions three levels; **HAQ** - Health Assessment Questionnaire; **NUTS II** - Nomenclature of Territorial Units for Statistics (North, Centre, Alentejo, Algarve, Lisbon, Madeira and the Azores); **BMI** - Body Mass Index; **SLE**- systemic lupus erythematosus

Two multivariable regression models were used: one to identify possible factors that have an impact on the quality of life, and another to identify possible factors that have an impact on the functional capacity. The estimates were obtained considering study design.

†Adjusted p-value<0.05

Disease-specific associations with depression and anxiety symptoms

Several RMDs were significantly and independently associated with the presence of anxiety (HADS-A ≥11) and depressive symptoms (HADS-D ≥11) (Table 5). By order of effect, FM (OR=3.4; p<0.001), SpA (OR=3.0; p=0.008) and LBP (OR=1.9; p=0.005) were significantly and

independently associated with the presence of anxiety symptoms (Table 6). On the other hand, PMR (OR=14.3; p=0.012), FM (OR=4.0; p=0.001) and LBP (OR=1.6; p=0.014) and Knee OA (OR=1.5; p=0.047), were significantly and independently associated with the presence of depressive symptoms. SLE was significantly associated to the absence of depressive symptoms (OR=0.1; p=0.031) (Table 5).

Table 5: Impact of each rheumatic and musculoskeletal disease on anxiety and depression symptoms (HADS)

	Anxiety		Depression	
Demographic characteristics	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**
Gender (female)	**3.1** (1.7; 5.9)	**0.001†**	**2.8** (1.6; 4.9)	**<0.001†**
Age	**0.98** (0.956; 0.997)	**0.024†**	**1.03** (1.0; 1.1)	**0.004†**
BMI				
Underweight vs Normal	**0.4**(0.1; 1.5)	**0.183**	**0.1**(0.1; 0.5)	**0.010†**
Overweight vs Normal	**0.8** (0.5;1.2)	**0.240**	**0.6** (0.4;1.0)	**0.059**
Obese vs Normal	**0.5** (0.3;0.9)	**0.026†**	**0.8** (0.5;1.3)	**0.309**
Years of education	**0.9** (0.86; 0.99)	**0.027†**	**0.9** (0.8; 0.998)	**0.044†**
Employment status				
Employed vs retired or leave	**0.9** (0.5; 1.5)	**0.602**	**0.8** (0.5; 1.5)	**0.580**
Employed vs unemployment	**2.9** (1.4; 5.9)	**0.003†**	**1.9** (0.9; 3.9)	**0.080**
NUTS II				
Norte vs Lisboa	**1.8** (1.0; 3.3)	**0.035†**	**0.9** (0.5; 1.6)	**0.820**
Centro vs Lisboa	**1.1** (0.6;1.9)	**0.739**	**0.9** (0.5;1.7)	**0.746**
Alentejo vs Lisboa	**1.1** (0.6;2.1)	**0.791**	**1.0** (0.4;2.2)	**0.972**
Algarve vs Lisboa	**1.0** (0.5;2.2)	**0.972**	**2.0** (0.5;8.0)	**0.340**
Azores vs Lisboa	**1.2** (0.7;2.2)	**0.502**	**1.0** (0.6;1.8)	**0.987**
Madeira vs Lisboa	**1.0** (0.4;2.1)	**0.922**	**0.6** (0.3;1.1)	**0.101**
Number of Comorbidities (0-15)	**1.5** (1.4; 1.7)	**<0.001†**	**1.3 (**1.2; 1.5)	**<0.001†**
Life Style Habits				
Present alcohol intake (yes/no)	**0.6** (0.3; 0.9)	**0.020†**	**0.8** (0.4; 1.5)	**0.505**
Regulat physical exercise (yes/no)	**0.7** (0.4; 1.2)	**0.182**	**0.4** (0.2; 0.6)	**0.001†**
RMD Diagnosis				
Low Back Pain (yes/ no)	**1.9** (1.2; 2.9)	**0.005†**	**1.6** (1.1; 2.4)	**0.014†**
Periarticular Disease (yes/ no)	**1.1** (0.8;1.6)	**0.599**	**0.7** (0.4; 1.1)	**0.082**
Knee Osteoarthritis (yes/ no)	**0.95** (0.6; 1.4)	**0.813**	**1.5** (1.0; 2.4)	**0.047†**
Osteoporosis (yes/ no)	**1.2** (0.8; 1.8)	**0.344**	**1.1** (0.7; 1.8)	**0.745**
Hand Osteoarthritis (yes/ no)	**0.94** (0.5; 1.6)	**0.831**	**1.0** (0.7; 1.6)	**0.903**
Hip Osteoarthritis (yes/ no)	**0.9** (0.5; 1.6)	**0.628**	**0.8** (0.4; 1.7)	**0.600**
Fibromyalgia (yes/ no)	**3.4** (1.8; 6.1)	**<0.001†**	**4.0** (1.8; 8.9)	**0.001†**
Spondyloarthritis (yes/ no)	**3.0** (1.3; 6.7)	**0.008†**	**1.7** (0.5; 5.2)	**0.365**
Gout (yes/ no)	**1.7** (0.6; 4.8)	**0.335**	**0.6** (0.1; 4.8)	**0.621**
Rheumatoid Arthritis (yes/ no)	**2.0** (0.7; 5.8)	**0.197**	**1.9** (0.8; 4.7)	**0.155**
SLE (yes/ no)	**1.6** (0.2; 11.0)	**0.608**	**0.1** (0.0; 0.8)	**0.031†**
Polymyalgia Rheumatica (yes/ no)	**3.2** (0.3; 40.1)	**0.364**	**14.3 (**1.8; 114.3)	**0.012†**

NUTS II- Nomenclature of Territorial Units for Statistics (North, Centre, Alentejo, Algarve, Lisbon, Madeira and the Azores); **BMI** -Body Mass Index; **SLE**- systemic lupus erythematosus

Two logistic regression model were used: one to identify possible factors that have an impact on the presence of anxiety symptoms, and another to identify possible factors that have an impact on presence of depression symptoms. The estimated values were obtained considering study design.

†Adjusted p-value<0.05.

Discussion

EpiReumaPt was the first large-scale epidemiological population-based study that evaluated RMDs in Portugal. In this study we determined the prevalence of 12 target diseases (LBP, FM, OP, PRD, hand, knee and hip OA, RA, SpA, SLE, gout and PMR). Moreover, we aimed to determine the impact of RMDs on physical and mental health.

We found that RMDs are highly prevalent in Portugal and that their prevalence is similar to the one reported in other European countries [32-37], namely our close neighbour Spain [38]. However, the prevalence of gout (1.3%) was higher than the estimated for Europe in the Global Burden of Disease study [39] but similar to the one in the UK [40]. This finding may relate to the increasing prevalence of metabolic syndrome in Portugal, as a result of recent dietary changes including the abandonment of the Mediterranean food pattern [41].

In the EpiReumaPt study we have used the new classification criteria of the ACR/EULAR for RA [25] and the ASAS criteria for SpA [26 28] and found a prevalence of 0.7% for RA and 1.6% For SpA with similar proportion of males and females with the disease. Global prevalence values for SpA calculated before the introduction of the ASAS criteria were reported to be ≈ 1% [42] but ranged substantially from 0.001 in Japan [43] to 2.5% in Northern Artic Natives [44]. In fact, the new ASAS classification criteria for axial SpA cover a larger disease spectrum, from no structural damage to advanced disease. Importantly, these criteria include not only radiographic but also MRI-detected abnormalities of the sacroiliac joints [26]. To our knowledge, only one study has used the ASAS classification criteria to estimate the overall prevalence of SpA [45]. Constatino *et al* used a large population-based cohort -the GAZEL cohort- to estimate SpA prevalence in the French population (0.43%). Unlike the study by Constantino *et al*, in EpiReumaPt the use of the new criteria confirmed a higher prevalence of SpA in Portugal than the one previously reported[6].

Another interesting finding of our study was the high proportion of individuals presenting with typical features of one or more RMD that did not have a previous diagnosis (1,532 subjects). This could be explained by the scarce number of rheumatologists in Portugal (1: 100000 inhabitants) [46] and by the unawareness of the population to these diseases, being frequently accepted as part of the normal aging process.

Regarding the impact of RMDs on physical and mental health of the Portuguese population, we confirmed that patients with RMD have significantly worse QoL and more disability when compared to subjects without RMD. We found that PMR, RA and FM were the conditions with the worst impact on function and QoL.

When we compared subjects with and without RMDs regarding mental distress symptoms, we found a significantly higher proportion of RMD patients with anxiety symptoms but not with depressive symptoms. This could be due to the unexpectedly low proportion of anxiety (16.7%) and depression (8.3%) symptoms among Portuguese patients with RMDs. In fact, in our study we have shown that only LBP and FM were independently associated to both anxiety and depressive symptoms. SpA was only associated with anxiety symptoms and PMR with depressive symptoms. In contrast, several other studies have shown higher prevalence of anxiety and depressive symptoms associated with several RMDs [31 47 48]. One explanation could be that many of these studies were performed in a hospital environment and were not population-based studies.

EpiReumaPt has some limitations. We had a high dropout rate from the first phase to the second phase. In order to assure that we did not over/underestimated disease prevalence due to eventual sample bias, we performed a detailed participation analysis considering several subject domains (demographic, socio-economic, lifestyle, healthcare resources consumption, RMDs screening result and self report of other chronic diseases) which is described elsewhere [14]. On the other hand, this study has also several strengths – it is the first population based study on RMDs in Portugal; RMDs were accessed and validated by a rheumatologist and captured various clinical measurements that allowed to address the burden of this diseases.

In conclusion, in the EpiReumaPt study we have demonstrated that RMDs are highly prevalent in Portugal and are associated with a significant physical and mental health impairment leading to more health resources consumption.

EpiReumaPt provided valuable data to researchers, healthcare providers and patient organizations. Results of EpiReumaPt emphasize the burden of RMDs in Portugal and the need to increase RMD awareness, being a strong argument to encourage policy makers to increase the resources allocated to the treatment of rheumatic patients.

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Section II – Part IV

Prevalence & social burden of active chronic low back pain in the adult Portuguese population – results from a national survey (EpiReumaPt)

Gouveia N, Rodrigues A, Eusébio M, et al. Prevalence & social burden of active chronic low back pain in the adult Portuguese population – results from a national survey (EpiReumaPt). *submitted.* 2015

Prevalence & social burden of active chronic low back pain in the adult Portuguese population – results from a national survey (EpiReumaPt)

Nélia Gouveia[1,2,3], Ana Rodrigues[1,3,4,5], Mónica Eusébio[6], Sofia Ramiro[1,2,7], Pedro Machado[1,8,9], Helena Canhão[1,3,4,5,10], Jaime Branco[1,2,3,11,12]

[1] Equipa de Investigação EpiReumaPt - Sociedade Portuguesa de Reumatologia, Lisboa, Portugal; [2]Centro de Estudos de Doenças Crónicas (CEDOC) da NOVA Medical School, Universidade Nova de Lisboa (NMS/UNL), Lisboa, Portugal; [3]Unidade EpiDoc – Unidade de Epidemiologia em Doenças Crónicas (CEDOC, NMS/UNL), Lisboa, Portugal; [4]Unidade de Investigação em Reumatologia, Instituto de Medicina Molecular, Lisboa, Portugal; [5]Faculdade de Medicina da Universidade de Lisboa, Lisboa, Portugal; [6]Sociedade Portuguesa de Reumatologia, Lisboa, Portugal; [7]Leiden University Medical Center, Leiden, the Netherlands; [8]Clínica Universitária de Reumatologia, Faculdade de Medicina da Universidade de Coimbra, Coimbra, Portugal; [9]MRC Centre for Neuromuscular Diseases, University College London, London, United Kingdom; [10]Serviço de Reumatologia do Hospital de Santa Maria – Centro Hospitalar Lisboa Norte (CHLN-E.P.E), Lisboa, Portugal; [11]Serviço de Reumatologia do Hospital Egas Moniz - Centro Hospitalar Lisboa Ocidental (CHLO- E.P.E.), Lisboa, Portugal; [12]Programa Nacional Contra as Doenças Reumáticas (2004-2014), Direcção Geral da Saúde. Lisboa, Portugal

Abstract

Objectives: To determine, the prevalence of active chronic low back pain (CLBP) in the adult Portuguese population; to compare the active CLBP population with the population without active CLBP, and to explore factors associated with active CLBP.

Methods: The present study was conducted under the scope of EpiReumaPt a population-based study. Active CLBP was self-reported and considered if present on the day of the interview and for ≥90 days. Prevalence estimates were calculated. Differences in quality of life, functional ability and healthcare consumption between subjects with and without active CLBP were evaluated. Factors associated with active CLBP were identified through logistic regression.

Results: The prevalence of active CLBP was 10.4% (95%CI 9.6%; 11.9%). After adjustment, active CLBP subjects had a higher likelihood for anxiety symptoms (OR=2.66), early retirement due to disease (OR=1.72), and absence from work due to disease (OR=1.86). Factors significantly and independently associated with the presence of active CLBP were: female gender (OR=1.34), presence of self-reported rheumatic musculoskeletal disease (RMD) (OR=2.82), anxiety symptoms (OR=2.47), older age, higher education level and higher number of self-reported comorbidities (OR=1.11). In turn, physical exercise (OR=0.78) was inversely associated with active CLBP.

Conclusion: Active CLBP is highly prevalent in the Portuguese population and is associated with disability and with a high consumption of healthcare resources. Female gender, older age, anxiety symptoms, educational level, the presence of other RMD and the number of comorbidities were independently associated with the presence of ACLBP. These factors should be taken into account when developing strategies to prevent the occurrence of ACLPB.

Keywords: chronic low back pain; population-based study; cross-sectional study; burden of disease; burden of low back pain

Introduction

Low Back Pain (LBP) is well documented as the leading cause of disability and work absence throughout most of the industrialized world, especially when it becomes chronic [1] [2] [3] [4]. In the recent Global Burden of Disease 2010 Study, LBP was the leading cause of years lived with disability in the world [5] and was the most prevalent rheumatic and musculoskeletal disease (RMD) [6]. Global Burden of Disease 2010 study also showed that LBP was among the top ten highest burden diseases and injuries, with an average number of disability-adjusted life years (DALYs) higher than that of people suffering from HIV, road traffic injuries, tuberculosis, lung cancer, chronic obstructive pulmonary disease and preterm birth complications [7]. The global age-standardized point prevalence of LBP in 2010 was estimated to be 9.4% (95% confidence interval (CI) 9.0%-9.8%). LBP affects nearly everyone at some moment in life and about 4-33% of the population at any given point [8] [4]. In Portugal 26.4% (CI 23.3%-29.5%) of Portuguese population self-reported LBP in the EpiReumaPt study [9].

Chronic LBP (CLBP) is one of the greatest causes of loss of productivity and economic independence through absenteeism (time off work for those in paid work), presenteeism (lost productivity because of diminished capacity while at work) and work disability (permanent, partial or complete disablement for work purposes) [10]. Most costs are associated with their impact on activities of daily living, in particular on productive work along with the need for social support rather than health-care costs [10]. Disability associated with CLBP and the impact of CLBP on the quality of life and psychological symptoms (such as depression and anxiety disturbance) have also been studied systematically in western countries [11] [12].

In Portugal the prevalence and burden of CLBP were ill-defined. EpiReumaPt was the first large-scale study investigating 12 RMD in the Portuguese population, aiming to assess impact of RMDs in terms of prevalence, quality of life, function, and use of health resources [13] [9], fulfilling the specific objective of the National Program Against Rheumatic Diseases [14]. Although, LBP was one of the specific RMD addressed in EpiReumaPt, the main objectives of the study not defined the prevalence of LBP regarding the classification of acute or chronic, active or non-active. Therefore, the aim of the present study was to determine the prevalence of active CLBP in the adult Portuguese population (according to gender, age group and by Nomenclature of Territorial Units for Statistics – NUTS II); to compare the population with and without active CLBP in terms of health care consumption, quality of life, functional capacity and anxiety symptoms, and to explore factors associated with active CLBP.

Methods

Data source and study population:

The present study is part of EpiReumaPt - a national and cross-sectional study whose recruitment occurred from September 2011 to December 2013 [15]. The EpiReumaPt sample with 10,661 subjects representative of adult Portuguese population (>18 years old) was surveyed in order to capture and characterize all cases of RMDs within the adult Portuguese population. This study has been extensively described elsewhere [16] [15]. In brief, the study included non-institutionalized subjects, living in private households in Portugal, from the Mainland and Islands (Madeira and Azores). The sample was stratified by administrative territorial units (NUTS II). Households were selected by random route methodology and the survey was applied through a face-to-face interview [13] [16] [15] [9].

The population of interest of the present study was defined based on self-reported active CLBP (see case-definition) on the day of the interview (Fig.1). Participants in the study signed an informed consent prior to participation and the study was approved by the Ethics Committee from Nova Medical School and by National Data Protection Committee [15].

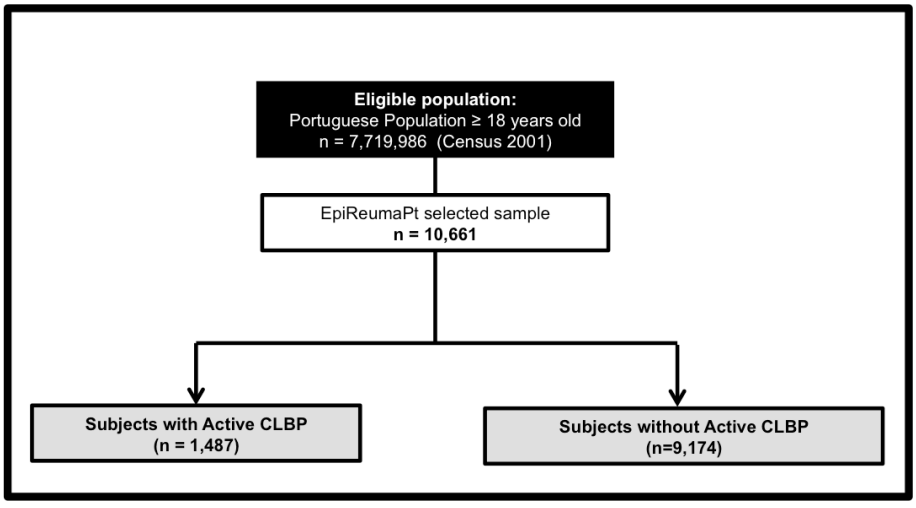

Figure 1: Flowchart of study design

Case definition:

LBP was defined as pain in the back area from the lower margin of the twelfth ribs to the lower gluteal folds, with or without pain referred to the lower limbs. Active CLBP was defined as self-reported LBP

present on the day of the interview and that was present in most of time for at least 90 days (independently from cause).

Measurements, assessment and instruments

Socio-demographic data were collected: age, gender, ethnicity, education level (0-4 years, 5-9 years, 10-12 years and >12 years), marital status; as well socio-economic features: household income without taxes, per month (<500€; 50€ to 1,500€; 1,501€ to 2,500€; 2,501€ to 4,000€; >4,000€), current work status (full-time employed, part-time employed, domestic worker, unemployed, retired, student, temporary disabled, other), number of work hours per week. Life styles habits were also inquired: smoking, alcohol and coffee intake, with the options - daily, occasionally, never. Physical exercise activities were assessed by the options yes or no. If the participant answered "yes", the type of exercise was inquired (swimming, aquarobics, walk, cycling, athletics, gym, other), as well as the average time per day and per week (minutes). The age of onset of the CLBP was recorded (years). Work disability data were collected through absenteeism data: early retirement due disease, unemployment due to work disability and absence from work due disease in the previous 12 months.

Regarding healthcare consumption data collected included the number and type of outpatient clinic visits, specialty care, hospitalizations, homecare assistance and other healthcare service needs (physiotherapy, alternative treatments, psychology), in the previous 12 months. Outpatient clinic visits included General Practitioners, Rheumatologists, Orthopedics, Physiatrists and "others".

Quality of life data were collected using the EuroQol (EQ-5D-3L) [17] [18] physical function was assessed with the Health Assessment Questionnaire (HAQ) (0-3) [19]; anxiety and depression symptoms were evaluated with the Hospital Anxiety and Depression Scale (HADS) (the cut off used for positive anxiety and depression symptoms was >11) [20]. We used Portuguese validated versions of all these instruments.

Anthropometric data were collected (weight, height and body mass index (BMI): underweight - BMI<18.5, normal – 18.5≤BMI<25, overweight - 25≤BMI<30, obese - BMI≤30)) and self-reported chronic diseases were asked: high cholesterol level, high blood pressure, allergy, gastrointestinal disease, mental disease, cardiac disease, diabetes, thyroid and parathyroid disease, renal colic, pulmonary disease, hyperuricemia, cancer, neurologic disease, hypogonadism. It were used "red flag questions" [21] to screen for systemic causes of CLBP (eg. cancer, infection, fracture); subjects recorded pain intensity on the interview day using a numeric pain rating scale (NPRS, 0-10cm).

Statistical analysis:

Details regarding to sample size calculation were previously described [13] [16]. The prevalence of active CLBP was estimated similarly to what has been described for the prevalence of the RMDs in EpiReumaPt, taking into consideration aspects of the study design [16] [9]. Prevalence estimates and confidence intervals were weighted and were obtained with STATA survey procedure.

Differences between the subjects with and without active CLBP were evaluated by univariable linear regression analysis that was performed according to study design. In a second step, the two populations were compared for the following characteristics: EQ5D, HAQ, and presence of symptoms of anxiety (HADS ≥11)(yes/no), presence of symptoms of depression (HADS ≥11)[20] (yes/no), need for physician visits (General Practitioner, Rheumatology, Orthopedic and other appointments) and number of visits, home care in the previous 12 months (yes/no), hospitalizations in the previous 12 months (yes/no), early retirement due to disease (yes/no), absence from work due to disease in the previous 12 months (yes/no), number of days of absence and complementary treatments (yes/no). Each categorical variable is presented as the absolute frequency and the correspondent proportion, adjusted for the weight to adjust for study design. The same adjustment has been done for the mean and standard deviation (SD) for each continuous variable. To assess differences between groups, a multivariable linear regression was used for continuous variables and a multivariable logistic regression for categorical variables. All the comparisons were adjusted for the differences found in the univariable analyses: age group, gender, NUTS II, education level, physical exercise, BMI, number of comorbidities and presence of self-reported RMDs.

To assess factors independently associated with active CLBP, a multivariable logistic regression model was obtained using bidirectional elimination, a combination of the backward elimination and forward selection, testing at each step for variables to be included or excluded. Dependent variable (presence of active CLBP) were tested while taking explanatory variables into account: age, gender, population size of place of residence, marital status, BMI, number of self-reported comorbidities, smoking, alcohol intake, exercise, number of physician visits, anxiety and depression symptoms. The cut-off value for significance was considered to be $p<0.05$.

All analyses were weighted and performed using STATA IC version 12 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

Results

Prevalence of active CLBP in the adult Portuguese population

The prevalence of active CLBP in the adult Portuguese population was 10.4% (CI (9.6%; 11.9%). The mean age of the active CLBP population was 58.9 (SD 17.2) years old. Active CLBP was significantly more prevalent among women (14.1% vs 6.3% in men). Regarding NUTS II regions, the highest prevalence occurred in the Centro Region and Madeira (both with 11.7%) (table 1). In the majority of NUTS II regions active CLBP was significantly more prevalent among women. The prevalence of active CLBP increased with age (table 1).

Table 1: Prevalence of active CLBP by gender, NUTS II regions and age group

	Prevalence (95% CI) n=10,661	Women (95% CI) n=6,551	Men (95% CI) n=4,110
Total **(n=10,661)**	**10.4%** (9.6%;11.9%)	**14.1%** (12.7%; 15.3%)	**6.3%** (5.4%; 7.1%)
NUTS II			
Norte **(n=3,122)**	**10.6%** (9.3%;12.0%)	**14.0%** (11.8%; 16.1%)	**6.9%** (5.3%;8.5%)
Centro **(n=1,997)**	**11.7%** (10.2%; 13.2%)	**15.2%** (13.9%; 17.5%)	**7.8%** (6.0%; 9.6%)
Lisboa & Vale do Tejo **(n=2,482)**	**8.7%** (6.9%; 10.6%)	**13.1%** (9.7%; 16.6%)	**3.8%** (2.6%; 5.1%)
Alentejo **(n=669)**	**10.9%** (8.7%; 13.1%)	**16.2%** (12.7%; 19.8%)	**5.1%** (2.6%; 7.6%)
Algarve **(n=352)**	**9.6%** (6.6%; 12.6%)	**12.0%** (7.7%; 16.3%)	**7,2%** (3.1%;11.3%)
Azores **(n=1,029)**	**10.4%** (8.6%; 12.2%)	**13.4%** (10.8%; 15.9%)	**7.4%** (4.9%;9.9%)
Madeira **(n=1,008)**	**11.7%** (9.6%; 13.7%)	**12.7%** (10.8%; 15.3%)	**10.4%** (7.2%;13.7%)
Age Group			
18-25 y.o. (n=780)	**1.9%** (1.0%;2.8%)	**0.9%** (-0.1%;1.9%)	**3.0%** (1.3%;4.6%)
26-35 y.o. (n=1,189)	**4.8%** (3.3%;6.3%)	**3.1%** (1.3%;4.8%)	**6.5%** (4.0%;9.0%)
36-45 y.o. (n=1,851)	**7.2%** (5.8%;8.5%)	**5.7%** (3.8%;7.5%)	**8.6%** (6.6%;10.6%)
46-55 y.o. (n=1,866)	**11.1%** (9.4%;12.8%)	**7.0%** (4.8%;9.1%)	**14.9%** (12.3%;17.5%)
56-65 y.o. (n=1,886)	**14.1%** (12.1%;16.1%)	**9.4%** (6.7%;12.1%)	**18.1%** (15.2%;21.0%)
66-75 y.o. (n=1,738)	**22.3%** (18.3%;26.2%)	**11.5%** (8.4%;14.7%)	**30.7%** (24.8%;36.6%)
76-85 y.o. (n=1,111)	**21.3%** (18.3%;24.4%)	**14.7%** (10.6%;18.7%)	**25.5%** (21.2%;29.8%)
> 86 y.o. (n=240)	**29.7%** (16.7%;42.7%)	**18.6%** (8.7%;28.5%)	**35.2%** (17.0%;53.3%)

NUTS II- Nomenclature of Territorial Units for Statistics (Norte, Centro, Alentejo, Algarve, Lisboa, Madeira and the Azores)

Socio-demographic and socio-economic characteristics and healthcare consumption of the population with active CLBP

A substantial proportion of the subjects (68.7%) with active CLBP were overweight or obese. The educational level of 59.8% of subjects was low (0-4 years) and subjects that lived in small towns (<2000 habitants) seemed to have a higher frequency of active CLBP (47.8%). Furthermore, 65.5% self-reported a household income ≤1500€; 50.2% were retired; and 22.3% of the patients with CLBP were retired due RMD. For those with active life, the self-reported mean time of weekly working hours was 42.7 (SD 12.16) hours. Regarding health care consumption in the previous 12 months, the use of primary care outpatient services (General Practitioners) was higher (4.4, SD 18.50) in relation with other medical specialties (Rheumatology, Orthopedics). Also, 30.6% of subjects with active CLBP had visited a doctor ≥7 times in the previous year; 14.3% was hospitalized in the last 12 months and 23.3% stated to be searching for complementary treatments. Table 2 describes socio-demographic and socio-economic characteristics and also healthcare consumption of the adult Portuguese population with active CLBP.

Table 2: Socio-demographic and socio-economic characteristics and healthcare consumption of the population with active CLBP

Demographic characteristics	Mean ± SD or n (%)
Age (years)	**58.90**±17.21
Female Gender	**1,126** (71.4%)
Ethnicity (%)	
Caucasian	**1,462** (98.2%)
Black	**16** (1.2%)
Other	**4** (0.3%)
Education level (%) (n=1,462)	
>12 years	**85** (7.8%)
10-12 years	**158** (15.3%)
5-9 years	**236** (17.2%)
0-4 years	**983** (59.8%)
Population size of the place of residence (%)	
< 2,000 habitants	**740** (47.8%)
2,000-9,999 habitants	**270** (15.3%)
10, 000 – 19, 999 habitants	**124** (7.9%)
20, 000 – 99, 999 habitants	**153** (13.6%)
≥100, 000 habitants	**200** (15.5%)
Marital Status (%)	
Single	**107** (9.9%)
Married	**889** (59.4%)
Divorced	**114** (7.9%)
Widower	**347** (20.5%)
Consensual union	**28** (2.3%)
BMI (%) (n=1,346)	
Underweight	**9** (1.1%)
Normal	**396** (30.4%)
Overweight	**522** (38.8%)
Obese	**419** (29.8%)

Socio-economic characteristics	
Household income in the last month (%)	
< 500€	**396** (21.2%)
501€ to 1,500€	**600** (43.8%)
1,501€ to 2,500€	**93** (7.9%)
2,501€ to 4,000€	**19** (1.5%)
> 4,000€	**8** (0.6%)
Employment Status (%)	
Full-time Employed	**302** (26.0%)
Part-time employed	**30** (1.7%)
Domestic worker	**121** (6.1%)
Unemployed	**115** (9.2%)
Retired	823 (50.2%)
Student	**5** (0.5%)
Temporary disabled	**44** (3.1%)
Other	**47** (3.1%)
Retirement attributable to RMD (%) (n=653)	**157** (22.3%)
Age of Retirement (years) (n=155)	**50.78**±11.01
Unemployment attributable to RMD (%) (n=102)	**15** (13.4%)
Maximum weekly working hours (hours) (n=328)	**42.68**±12.16
Health Consumptions	
Number of physician visits in the last 12 months (%)	
General practitioners visits	**4.39**±18.50
Rheumatology visits	**0.19**±1.39
Orthopedics visits	**0.57**±1.57
Rehabilitation medicine visits	**0.48**±7.93
Other visits	**2.15**±5.09
Number of physician visits in previous 12 months, independently of medical specialty	
< 7 physician visits	**1,024** (69.4%)
≥ 7 physician visits	**463** (30.6%)
Home care in the last 12 months (%) (n=1,482)	**94** (5.8%)
Hospitalizations in the last 12 months (%) (n=1,486)	**207** (14.3%)
Complementary treatments (%)	**311** (23.3%)
Number of Complementary treatments: (n=311)	
Physiotherapy exercises	**19.48**±31.46
Psychology	**0.99**±4.41
Alternative medicine (acupuncture, homeopathy, osteopaths, naturopaths, herbalists, quimiopraxia technicians, herbalists, healers and rights)	**2.46**±7.30
Other	**0.07**±0.90

Education level (n=1,462); BMI (n=1,346); Retirement attributable to MSK disease (n=653); Age of Retirement (mean) (n=155); Unemployment attributable to MSK disease (n=102); Maximum weekly working hours (mean) (n=328); Home Care in the last 12 months (n=1,482); Hospitalizations in the last 12 months (n=1,486); Number of Complementary treatments (n=311).
NUTS II- Nomenclature of Territorial Units for Statistics (North, Centre, Alentejo, Algarve, Lisbon, Madeira and the Azores)

Active CLBP features

The mean intensity of pain (NPRS) among subjects that self-reported active CLBP was 6.0 (SD 2.14), on a 0-10cm scale; in the previous 12 months, 97.5% had LBP and reported a mean of 233 days (SD 161.55) with pain, and were unable to perform daily activities among an average for 45.4 days (SD 108.49); 51.8% had persistent limitation of mobility; 60.3% of subjects referred pain irradiation and 65.5% reported progressive, slow or insidious onset; 72.2% reported relief with rest; 79.1% characterized the pain as constant and progressive; 68.9% reported progressive weakness of the legs or walking difficulties.

Among subjects with active CLBP, 62.6% sought medical care and 74.1% had already used analgesic or another pain relief drug, of which 53.3% with parenteral administration. The self-reported average treatment time was 142.3 days (SD 332.37). Other RMDs were the commonest self-reported comorbidities (58.3% of subjects), of which 22.3% self-reported a diagnosis of osteoarthritis. Furthermore, 78.9% of subjects with active CLBP reported ≥1 comorbidity. Following the self-report of RMD, high blood pressure and high cholesterol level were the most frequent self-reported comorbidities among the active CLBP population (each one with 43.1%). Regarding life-style habits, 22.3% exercised regularly, with a mean time of activity of 65 minutes. Table 3 summarizes the active CLBP features.

Table 3: Active CLBP features: diagnosis and treatment, self-reported-comorbidities and life style habits

Characteristics of active CLBP	**Active CLBP population n=1,487***
Pain severity (0-10) (n=1,416)	**6.03**±2.14
LBP is the result of a fall or a fracture (%)	**265** (16.1%)
Pain irradiation (%)	**970** (60.3%)
LBP in the last 12 months (%)	**1,447** (97.5%)
Time (days) with pain in the last 12 months (n=1,447)	**233.07**±161.55
Age of onset (years) **(n=1,352)**	**40.78**±17.31
Time not performing daily activities because of LBP in the last 12 months (days) (n=1,423)	**45.40**±108.49
Progressive, slow or insidious onset (%)(n=1,453)	**977** (65.5%)
Relief with exercise (%) (n=1,453)	**453** (32.7%)
Relief with rest (%) (n=1,453)	**1031** (72.2%)
Occurs during the night and relieves in the morning (%)(n=1,453)	**508** (31.7%)
Pain awakening in the 2nd half of the night (%)(n=1,453)	**757** (51.8%)
Morning back stiffness (%)(n=1,453)	**950** (62.7%)
Duration of morning stiffness (hours) (n=950)	**1.49**±0.58
Pain in gluteal region, alternating left and right (%)(n=1,453)	**783** (48.0%)
Previous anti-inflammatory therapy (%) (n=1,453)	**988** (70.0%)
Pain control with NSAIDs therapy within 24-48h (%) (n=998)	**642** (66.9%)
Unexplained weight loss (> 4.5 Kg in 6 months) (%)(n=1,453)	**160** (9.6%)
Constant and progressive LBP (%) (n=1,453)	**1,127** (79.1%)
Previous infection (%) (n=1,453)	**231** (13.4%)
Transplantation (%) (n=1,453)	**15** (0.8%)
Persistent limitation of mobility (%) (n=1,453)	**798** (51.8%)
Family history of Rheumatoid Arthritis or Osteoporosis (%) (n=1,453)	**615** (42.2%)
LBP with urinary retention or incontinence (%) (n=1,453)	**220** (15.0%)
Fecal incontinence (%) (n=1,453)	**109** (6.4%)
Tingling in the anal, genital region or lower limbs (%) (n=1,453)	**685** (43.5%)
Progressive weakness of the legs or walking difficulties (%) (n=1,453)	**1,045** (68.9%)
Diagnosis and treatment	**Active CLBP population n=1,487**
Seeking medical care because of LBP (%) (n=1,447)	**899** (62.6%)
Treatment of active CLBP (n=899)	**671** (74.1%)
Route of administration: (n=671)	
Injectable medication	**329** (53.3%)
Oral medication	**569** (85.6%)
Treatment duration (days) (n=618)	**142.30**±332.37
Self-reported Comorbidities	**Active CLBP population n=1,487**
Number of comorbidities (0-15) (n=1,230)	**3.18**±2.27
> 1 comorbidity (n=1,230)	**1,214** (78.9%)

Self-reported Comorbidities	
Rheumatic diseases (n=1,417)	**882** (58.3%)
High cholesterol level (%) (n=1,457)	**682** (43.1%)
High blood pressure (%) (n=1,465)	**714** (43.1%)
Gastrointestinal disease (%) (n=1,464)	**503** (32.5%)
Cancer(%) (n=1,473)	**400** (27.3%)
Allergy (n=1,469)	**418** (27.2%)
Cardiac Disease (n=1,461)	**361** (23.5%)
Diabetes (n=1,467)	**288** (18.6%)
Renal colic (n=1,452)	**227** (14.5%)
Thyroid and parathyroid disease (n=1,462)	**234** (13.3%)
Hyperuricemia (n=1,428)	**167** (11.6%)
Pulmonary disease (n=1,468)	**151** (10.1%)
Neurologic disease (n=1,466)	**106** (7.9%)
Mental disease (n=1,466)	**99** (5.5%)
Hypogonadism (n=1,430)	**18** (1.6%)
Life Style Habits	**Active CLBP population n=1,487**
Present Coffee intake (%)	
None	**580** (37.3%)
1 to 3	**822** (55.9%)
More than 3	**81** (6.7%)
Present Alcohol intake (%)	
Daily	**245** (17.5%)
Occasionally	**417** (29.2%)
Never	**824** (53.3%)
Present Smoking Habits (%)	
Daily	**148** (12.9%)
Occasionally	**24** (2.1%)
Never	**1,314** (85.0%)
Physical exercise (%)	**329** (22.3%)
Type of Physical Exercise (%)	
Swimming	**22** (1.3%)
Aquarobics	**48** (3.1%)
Walk	**198** (12.9%)
Cycling	**26** (2.2%)
Athletics	**5** (0.7%)
Gym	**49** (3.6%)
Other	**55** (4.3%)
Average time per day (minutes) (n = 328)	**64.57**±45.62
Average time per week (minutes) (n=329)	**249.05**±255.39
Age of onset (years) (n=313)	**35.96**±22.22

* Mean ± SD or n (%) - The estimated values for the characteristics were obtained considering study design.

Pain severity (NPRS) (n=1,416); Average time with pain in the last 12 months (n=1,447); Age of onset (mean) (n=1,352); Average time did not perform daily activities by LBP in the last 12 months (n=1,423); Progressive, slow or insidious onset (n=1,453); Relieves with exercise (n=1,453); Relieves with rest (n=1,453); Occurs during the night and relieves at morning (n=1,453); the pain awakens after the 2nd half of the night (n=1,453); Morning back rigid/stiffness (n=1,453); How long does the stiffness (n=950); Pain in gluteal region, alternating left and right (n=1,453); Previous anti-inflammatory therapy (n=1,453); The pain disappeared or improved with NSAIDs therapy in 24-48h (n=988); Unexplained weight loss of > 4.5 Kg in 6 months without apparent reason (n=1,453); Constant and progressive LBP (n=1,453); Previous infection (n=1,453); Transplantation (n=1,453); Persistent limitation of mobility (n=1,453); Familiar history of Rheumatoid Arthritis or Osteoporosis (n=1,453); LBP with urinary retention or incontinence (n=1,453); Fecal incontinence (n=1,453); Tingling in the anal, genital region or lower limbs (n=1,453); Legs progressive weakness or walking difficulties (n=1,453). Average time of treatment (n=618).

Number of comorbidities (n=1,230); High blood pressure (n=1,465); Diabetes (n=1,467); High cholesterol level (n=1,457); Pulmonary disease (n=1,468); Cardiac Disease (n=1,461); Gastrointestinal disease (n=1,464); Neurologic disease (n=1,466); Allergy (n=1,469); Mental disease (n=1,466); Neoplastic disease (n=1,473); Thyroid and parathyroid disease (n=1,462); Hypogonadism (n=1,430); Hyperuricemia (n=1,428); Renal colic (n=1,452); Other rheumatic diseases (n=1,417).

The burden of active CLBP among adult Portuguese population

Regarding intangible costs**,** subjects with active CLBP had significantly lower EQ5D scores (β=-0.19, p<0.001) when compared to the remaining population and also had a significantly higher HAQ score, reflecting more disability (β=0.34, p<0.001), and anxiety and depressive symptoms were significantly more prevalent (OR=2.66, p<0.001 and OR=2.02; p<0.001, respectively).

Regarding direct costs, the consumption of healthcare resources, such as visits to the rheumatology and orthopedics outpatient clinics, and also homecare assistance, among subjects with active CLBP in the previous year, was significantly higher (OR=1.56, p=0.020; OR=2.24, p<0.001; OR=2.26, p=0.011 respectively) compared with the remaining population.

Regarding indirect costs, absenteeism from work in the previous year (OR=1.86, p<0.001) and early retirement (OR=1.72; p=0.006) were significantly higher in the active CLBP population. Alternative treatments were sought more often by subjects with active CLBP (OR=1.66, p<0.001) compared to the participants without CLBP.

Table 4 shows the comparison of health status, function, healthcare resources consumption and absenteeism between the active CLBP population and the remaining population.

Table 4: Comparison of health status, function, clinical appointments consumption and absenteeism between the active CLBP population and the remaining Portuguese population

Health status and function	β estimates/Odds Ratio (as applicable)	95% CI	Adjusted p-value
EQ5D ((-1) - 1)	**-0.19**	[-0.21;-0.16]	**<0.001†**
HAQ (0-3)	**0.34**	[0.27;0.40]	**<0.001†**
Mental health			
Anxiety (HADS =>11 vs <11)	**2.66**	[2.05;3.44]	**<0.001†**
Depression (HADS =>11 vs <11)	**2.02**	[1.41;2.89]	**<0.001†**
Healthcare consumption			
Physician visits in the last 12 months			
General practitioners (yes/no)	**1.06**	[0.83;1.36]	**0.635**
Rheumatology (yes/no)	**1.56**	[1.07;2.29]	**0.020†**
Orthopedic (yes/no)	**2.24**	[1.62;3.09]	**<0.001†**
Rehabilitation medicine (yes/no)	**1.62**	[1.04;2.52]	**0.031†**
Other (yes/no)	**1.08**	[0.86;1.34]	**0.518**
Healthcare consumption			
Number of physician visits in the last 12 months		[-4.17;3.74]	**0.117**
General practitioners (yes/no)	**1.66**	[0.00;0.20]	**0.043†**
Rheumatology (yes/no)	**0.10**	[0.17;0.44]	**<0.001†**
Orthopedic Rehabilitation medicine (yes/no) Other (yes/no)	**0.30**	[-0.07;0.38]	**0.186**
	0.15	[0.00;0.61]	**0.048†**
	0.31		
Healthcare consumption			
Home care in the last 12 months (yes/no)	**2.26**	[1.21;4.24]	**0.011†**
Hospitalizations in the last 12 months (yes/no)	**1.18**	[0.83;1.69]	**0.346**
Early retirement due to disease (yes/no)	**1.72**	[1.17;2.54]	**0.006†**
Absent from work due to disease in the last 12 months (yes/no)	**1.86**	[1.33;2.61]	**<0.001†**
Absenteeism			
Number of days absent from work due to disease in the last 12 months	**3.48**	[-9.98;16.94]	**0.612**
Alternative Treatments			
Complementary Treatments	**1.66**	[1.28;2.16]	**<0.001†**

*All the comparisons were adjusted for the differences found in the univariable analyses: age group, gender, NUTS II, education level, physical exercise, BMI, number of comorbidities and presence of self-reported MSK diseases.
NUTS II - Nomenclature of Territorial Units for Statistics (North, Centre, Alentejo, Algarve, Lisbon, Madeira and the Azores); vs - versus

Factors associated with CLBP – multivariable analysis

The presence of a self-reported RMD (OR=2.82, p<0.001), anxiety symptoms (OR=2.47, p<0.001), female gender (OR=1.34, p=0.009), older age (all age groups when compared to the youngest group (18-25 y.o.)), higher education level (10-12 years vs >12 years, OR=2.04, p=0.002; 0-4 years vs >12 years, OR=1.75, p=0.042) and higher number of self-reported comorbidities (OR=1.11; p<0.001) were significantly associated with the presence of active CLBP, taking potential confounders into account (BMI, NUTS II, present alcohol intake and depression symptoms). In turn, physical exercise (OR=0.78, p=0.030) was inversely associated with active CLBP (table 5).

Table 5: Factors associated with active CLBP

Socio-demographic characteristics	OR	OR (95% CI)	p value
Gender (female)	**1.34**	**1.07; 1.66**	**0.009†**
Age group			
26-35 y.o. vs 18-25 y.o.	2.19	1.18; 4.07	**0.013†**
36-45 y.o. vs 18-25 y.o.	2.90	1.63; 5.14	**<0.001†**
46-55 y.o. vs 18-25 y.o	3.04	1.70; 5.47	**<0.001†**
56-65 y.o. vs 18-25 y.o.	3.04	1.64; 5.66	**<0.001†**
66-75 y.o. vs 18-25 y.o.	4.41	2.25; 8.64	**<0.001†**
76-85 y.o. vs 18-25 y.o.	3.39	1.75; 6.57	**<0.001†**
>86 y.o. vs 18-25 y.o	6.92	3.19; 15.02	**<0.001†**
BMI (kg/m2)			
Normal vs underweight	1.10	0.40; 3.02	0.848
Overweight vs underweight	1.28	0.47; 3.53	0.629
Obese vs underweight	1.43	0.52; 3.95	0.494
Education level			
10-12 years vs >12 years	2.04	1.29; 3.21	**0.002†**
5-9 years vs >12 years	1.58	0.99; 2.54	0.057
0-4 years vs >12 years	1.75	1.02; 2.99	**0.042†**
NUTS II			
Centro vs Norte	0.87	0.66; 1.15	0.331
Lisboa vs Norte	0.81	0.59; 1.10	0.182
Alentejo vs Norte	0.86	0.59; 1.23	0.404
Algarve vs Norte	0.67	0.40; 1.11	0.116
Açores vs Norte	0.97	0.71; 1.32	0.828
Madeira vs Norte	1.17	0.85; 1.62	0.336
Number of Comorbidities (0-15)	**1.11**	**1.05; 1.18**	**<0.001†**
Present alcohol intake (yes/no)	**0.80**	**0.62; 1.02**	**0.068**
Physical exercise (yes/no)	**0.78**	**0.62; 0.98**	**0.030†**
Anxiety symptoms (yes/no)	**2.47**	**1.88; 3.23**	**<0.001†**
Depressive symptoms (yes/no)	**1.39**	**0.93; 2.07**	**0.109**
Self-report of any RMD (yes/no)	**2.82**	**2.17; 3.69**	**<0.001†**

RMD-Rheumatic and musculoskeletal diseases; y.o. – years old; vs – versus; NUTS II - Nomenclature of Territorial Units for Statistics (North, Centre, Alentejo, Algarve, Lisbon, Madeira and the Azores)
†Adjusted p-values<0.05.

Discussion

This study has shown a high prevalence of active CLBP in the Portuguese population (10.4%, 95% CI 9.6% to 11.9%), which was similar to the global prevalence of LBP reported in the Global Burden of Disease 2010 study [1] [(9.4%, (95% CI 9.0%-9.8%)]. This finding was also consistent with results of previous studies in industrialized countries [22] [23] [24] [25]. However, it should be noted that most LBP prevalence studies did not specify the prevalence of active CLBP. Comparing the prevalence of active CLBP with previous studies is challenging due to differences in case definition, marked methodological heterogeneity across studies and difficulties in obtaining true population estimates. Also the higher prevalence in females was already reported in previous reports [22] [24] [26] and could be related to pain related to osteoporotic fractures [27], hormonal factors [28], and individual or societal influences resulting from sex differences in the likelihood of reporting somatic symptoms [29].

Several associations with CLBP have been well documented in the literature: female gender, older age groups, BMI (obesity and height), occupation, socio-economic, psychosocial status (anxiety, depression, emotional instability), pain behavior (eg. exaggerated), smoking behavior, physical fitness, occupational factors (heavy work, lifting, bending, etc, and job dissatisfaction) [8] [30] [2] [31], comorbidities [32], postural stress, education level [4] [33]. An interesting finding of the present study was the strong, significant and independent association of anxiety symptoms (OR=2.60; $p<0.001$) with the presence of active CLBP. This association was already reported by Polatin et al. in 1993 [34], in which 59.0% of 200 CLBP patients, who were starting a rehabilitation program, had diagnostic criteria for a psychiatric illness: depression 55.0% and anxiety 48.6%. A recent Korean study [12] that compared a group of patients with CLBP with a control group, also demonstrated significantly higher incidence of depression (51.5% vs 6.8%) and anxiety (42.5% vs 18.2%) among CLBP subjects. The importance of a biopsychosocial approach among treatment strategies of chronic pain has been documented in the literature [9] [35].

Although the present study did not reveal that overweight (BMI>25Kg/m^2) was a factor significantly and independently associated with active CLBP, obesity or higher BMI has been considered as an important predictor according to a meta-analysis performed by R Shiri et al. [36] and to other research studies [8] [30] [2] [31]. Moreover, obesity has been shown as a risk factor for disk degeneration and may increase the prevalence of LBP in this way [36] [37]. Also spinal mobility decreases with increasing body weight, which may interfere with disc nutrition [38]. Other studies suggested that association between overweight/obesity and CLBP could be related to differences in distribution of body fat mass or proportion of lean body mass [29]. Regarding life styles habits, in contrast with other studies [30] [8] [33] we did not find an association between smoking and active CLBP.

The number of comorbidities was also independently and significantly associated (OR=1.11; p<0.001) with the presence of active CLBP in the present study. This was previously reported, suggesting that people that self-reported more diseases had a higher predisposition to develop CLBP. For example, some authors suggested that dyslipidemia plays a major role in the development of atherosclerosis in obese individuals; atherosclerosis could cause malnutrition of disc cells which may predispose to disc degeneration, so people with severe disc degeneration are more likely to have LBP [39] [40] as referred before.

Also, as reported in earlier studies about the burden of CLBP, the economic cost and financial burden of CLBP is enormous [4]. In our study we surveyed the need for outpatient clinical visits (total consumption and consumption by medical specialists care) and found that the active CLBP population had significantly greater use of primary care and of Orthopedic outpatient clinic visits than the remaining Portuguese population. The same difference had been previously shown [41] [42].

As this is an analysis within the EpiReumaPt study, the major strengths rely on the fact that the sample is representative of the adult Portuguese population [9] [15, 16]. Comparing with other studies we opted for narrowing the case definition and analyzed specifically CLBP that was active on the interview's day, to avoid recall bias. Our study also has limitations: 1) Since LBP is a multifactorial condition it is difficult to identify and measure all the factors involved; as this study was part of EpiReumaPt (that aimed to determine the prevalence of 12 RMD) the study was not specifically designed to collect specific information about active CLBP. 2) Occupation/job was not available; the lack of this information is an important limitation in some analyses since the type of occupation/job has been described as associated with LBP. 3) EpiReumaPt questions regarding abseenteism and early retirement due disease were not specific about active CLBP; conclusions about these topics must be analyzed with caution. 4) In the majority of previous studies, quality of life was analyzed through SF-12 or SF-36 questionnaire, instead of EQ5D, which limits comparability.

In conclusion, the present study confirmed that active CLBP in Portugal was not only very prevalent, but was associated with an important burden, including significant disability. Also was significantly associated with high level of healthcare resources consumption. Female gender, age group, anxiety symptoms, educational level, the presence of other RMD and the number of comorbidities were independently associated with the presence of active CLBP.

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Section II – Part V

Chronic low back pain: intake of analgesic and other pain relief drugs in a southern Europe country

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Chronic low back pain: intake of analgesic and other pain relief drugs in a Southern European country

Nélia Gouveia[1,2], Ana Rodrigues[1,2,4,5], Sofia Ramiro[1,2,6], Mónica Eusébio[1], Pedro Machado[1,8,9], Helena Canhão[1,2,4,5,10], Jaime Branco[1,2,11]

[1]EpiReumaPt Study Group - Sociedade Portuguesa de Reumatologia, Lisboa, Portugal; [2]EpiDoc Unit – Unidade de Epidemiologia em Doenças Crónicas, Centro de Estudos de Doenças Crónicas (CEDOC) da NOVA Medical School, Universidade Nova de Lisboa (NMS/UNL), Lisboa, Portugal; [4]Unidade de Investigação em Reumatologia, Instituto de Medicina Molecular, Lisboa, Portugal; [5]Faculdade de Medicina da Universidade de Lisboa, Lisboa, Portugal; [6]Leiden University Medical Center, Leiden, the Netherlands; [8]Clínica Universitária de Reumatologia, Faculdade de Medicina da Universidade de Coimbra, Coimbra, Portugal; [9]MRC Centre for Neuromuscular Diseases, University College London, London, United Kingdom; [10]Serviço de Reumatologia do Hospital de Santa Maria – Centro Hospitalar Lisboa Norte (CHLN-E.P.E), Lisboa, Portugal Portugal; [11]Serviço de Reumatologia do Hospital Egas Moniz - Centro Hospitalar Lisboa Ocidental (CHLO- E.P.E.), Lisboa

Abstract

Objectives: To analyze and characterize the intake profile of pain relief drugs among an adult population of a southern European country with active chronic low back pain (CLBP).

Methods: EpiReumaPt was a cross-sectional Portuguese population-based study (10,661 subjects). Self-reported active CLBP was considered in those presenting LBP on the day of enrollment and for ≥90 days. Estimated prevalence of analgesic and other pain relief drugs intake were calculated among those who self-reported active CLBP. The intake profile of these drugs was also characterized, taking into account the severity of pain and the WHO analgesic ladder. It was also assessed if the presence of active CLBP was a factor independently associated with the intake of pain relief drugs.

Results: Among 1487 subjects with active CLBP only 18.73% were using analgesic or other pain relief drugs. Estimated prevalence of drug intake were: anxiolytics, 14.10%; NSAIDs, 12.32%; antidepressants, 10.11%; analgesic antipyretic, 6.58%; anticonvulsants, 3,41%; central muscle relaxants, 2.57%; analgesic opioids, 1.57%. Subjects medicated with analgesic opioids reported the worst quality of life (mean EQ5D 0.39), followed by centrally acting muscle relaxants (mean EQ5D 0.42) and anticonvulsants (mean EQ5D 0.44). Most subjects that self-reported severe pain was in the 1st step of WHO analgesic ladder: NSAIDs plus anxiolytics (4.64%); NSAIDs plus antidepressants (3.24%); NSAIDs plus centrally acting muscle relaxants (2.50%). The intake of all therapeutic groups was higher among subjects with ACLBP when compared with the remaining population, especially: centrally acting muscle relaxants (OR=15.57; p<0.001), anticonvulsants (OR=12.87; p<0.001), and analgesic, antipyretics (OR=7.94; p<0.001).

Conclusion: Analgesic and other pain relief drugs intake in patients with active CLBP was very low, even for those who self-reported severe pain. The WHO analgesic ladder was respected with an extremely conservative use of analgesic opioids even for those who report severe pain.

Introduction

Pain is one of the most common causes of disability and social burden among people with musculoskeletal (MSK) complaints in the developed world [1] [2]. Physical disability and loss of functional capacity resulting from pain, affect social functioning and mental health [3], reduce quality of life and increase morbidity risk [4]. MSK complaints are also the dominant cause of chronic pain worldwide [5] with low back pain (LBP) being the most prevalent MSK condition [6]. The Global Burden of Disease Study 2010 showed that LBP is among the top ten high burden diseases and injuries [4].

Treatment of LBP continues to be a significant medical and financial burden [1] and aims at relieving pain, improving functional ability, and preventing recurrence and chronicity. European Guidelines for the Management of Chronic non-specific LBP provides guidance for diagnosis and treatment [7]. Analgesics are currently LBP standard treatment with rehabilitation being also prescribed alternatively/additionally. Disc surgery remains the last option when all other strategies have failed [4]. Pharmacological treatments (analgesics such as acetaminophen, nonsteroidal anti-inflammatory drugs (NSAID) or weak opioids) are prescribed based on the pain intensity and functional status. The World Health Organization (WHO) supports that oral medicines are among the key components of pain management. WHO also appeals to recognition that therapeutic regimes need to be individualized and combined with psychological support [8]. Managing chronic pain is challenging due to the long term safety profile of most drugs [4]. Successful management of LBP depends not only on the delivery of appropriate interventions during the initial episode but also on an accurate identification and treatment of patients at higher risk of recurrence [9]. The WHO analgesic ladder [10] developed in 1986 (and updated in 1997) to help controlling pain in cancer patients still remains useful in chronic pain management (including LBP).

EpiReumaPt was the first large national project studying rheumatic and musculoskeletal diseases (RMD) in adult Portuguese population [11] [12] [13], and allowed to estimate the prevalence of LBP (26.4% (95% CI 23.3%; 29.5%) [14]) and active chronic LBP (CLBP) (10.4% (95% CI 9.6% to 11.9%) [15]). Active CLBP was defined as self-reported pain in the back area from the lower margin of the twelfth ribs to the lower gluteal folds, with or without pain, referred to the lower limbs, present in the day of the interview and for at least 90 days (independently from cause).

It was significantly associated with disability and with a high level of health care resources consumption. Anxiety symptoms, presence of other RMD and the number of comorbidities were factors also significantly and independently associated with this chronic pain condition [15].

This paper aims at characterizing analgesic and other pain relief drugs intake profile among adult Portuguese population with active CLBP, taking into account the WHO analgesic ladder and pain severity. The analgesic drugs intake profile in the population with active CLBP was also compared with the remaining Portuguese population in the study.

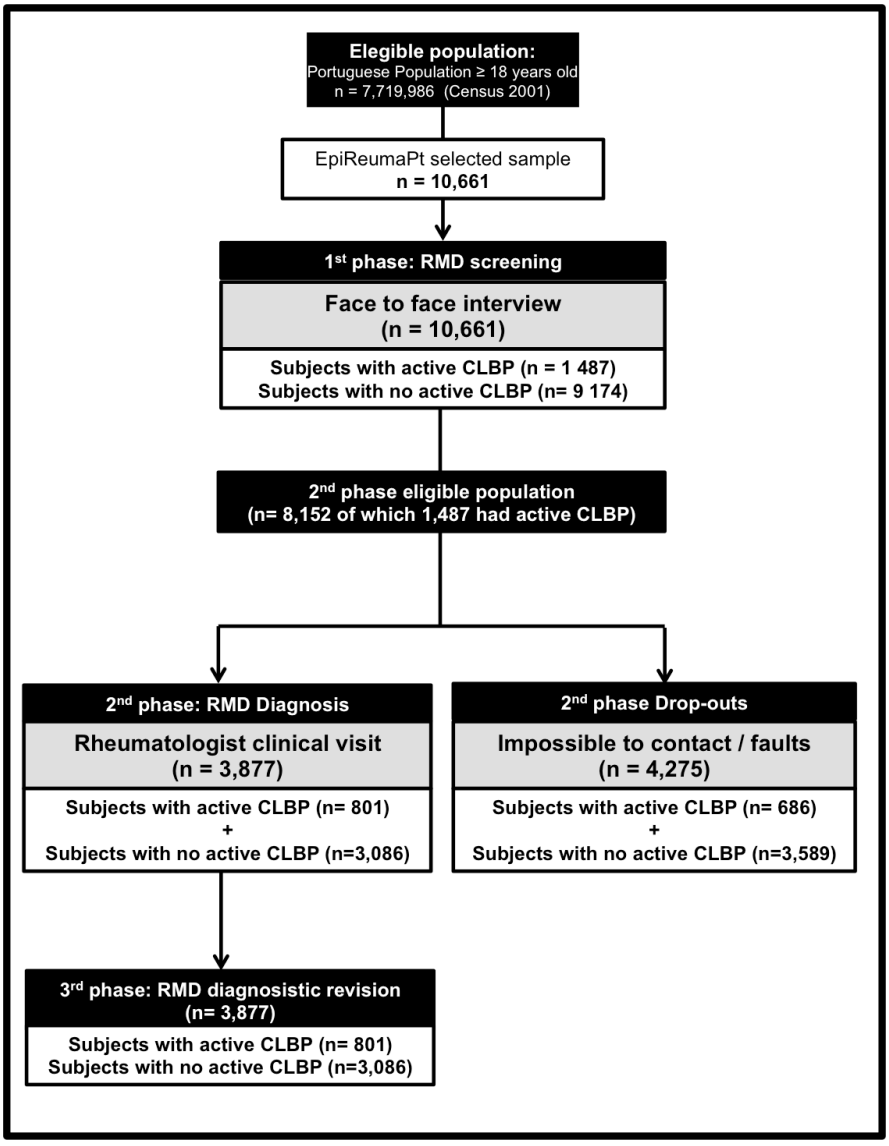
Material and Methods

Data source & Study population:

This study was developed under the scope of EpiReumaPt - a national and cross-sectional study conducted in Portugal from September 2011 to December 2013. The major objective of EpiReumaPt was to estimate the prevalence of twelve RMD [11], including LBP. A representative sample of the adult Portuguese population (>18 years old) (10,661 inhabitants) was surveyed in order to capture and characterize all cases of RMD.

EpiReumaPt methodology had been extensively described in previous papers and consisted on a three-stage approach [11] [12] [13]. In short, the study included non-institutionalized subjects, living in private households in Portugal, from the Mainland and Islands (Madeira and Açores) and the sample was stratified by administrative territorial units (NUTS II) (Norte, Centro, Lisboa & Vale do Tejo, Alentejo, Algarve, Açores Islands (Azores) and Madeira Islands (Madeira)). In the 1st phase (RMD screening), households were selected by random route methodology [13] and a survey was applied through a face-to-face interview [11] [12]. The 1st phase objectives were to characterize the Portuguese adult population and to identify potential subjects with RMD. In the 2nd phase (RMD diagnosis) a rheumatologist visit was performed to all subjects that were screened positive for at least one RMD during the 1st phase, as well as to 20% randomly selected individuals with no rheumatic complaints. Procedures included a standardized physical examination and appropriate laboratory and imaging tests [11] [12] [13]. In the 3rd phase (RMD diagnostic revision) a team of 3 experienced rheumatologists conducted the revision of all clinical data from each participant, including laboratory and imaging results, while considering previously validated criteria for the different RMD [12] [13].

The population of interest of the present study was defined based on self-reported active CLBP (see case definition) collected in the 1st phase. Second and 3rd phase data were used to analyze concomitant RMD diagnoses (Fig.1).



RMD: Rheumatic and musculoskeletal diseases; CLBP: Chronic Low Back Pain
Figure 1: Flowchart of study design

Case definition:

LBP was defined as pain in the back area from the lower margin of the twelfth ribs to the lower gluteal folds, with or without pain referred to the lower limbs. Active CLBP was defined as self-reported LBP present in the day of the interview and for at least 90 days (independently from cause).

Measurement, assessment and instruments:

Socio-demographic data were also collected, like age, gender, ethnicity, education level, marital status; monthly net household income, current work status. Anthropometric data were also collected (weight, height and body mass index (BMI)) and presence of other chronic diseases was assessed by self-report (high cholesterol level, high blood pressure, allergy, gastrointestinal disease, mental disease, cardiac disease, diabetes, thyroid and parathyroid disease, renal colic, pulmonary disease, hyperuricemia, cancer, neurologic disease, hypogonadism). Regarding active CLBP's characteristics, the red flag questions [16] were applied to screen other etiologies (cancer, infection, fracture). A numeric rating scale (NRS) (0-10 scale) provided self-reported pain severity on the interview day (1st phase). Pain severity was classified as [17]: no pain, NRS =0; mild pain, 1≤NRS≤3; moderate pain, 4≤NRS≤6; severe pain, 7≤NRS≤10.

Quality of life (EQ-5D-3L) was assessed by EQ5D, validated to the Portuguese population [18] [19]. To evaluate anxiety and depression symptoms the Hospital Anxiety and Depression Scale (HADS) Portuguese validated version was used [20], and a cut-off of >11 was used to identify positive cases of anxiety and positive cases of depression symptoms [20].

Information regarding analgesic and other pain relief drugs was collected and organized according to INFARMED classification [21]: **analgesics and antipyretics** (including not only the acetylsalicylate lysine, salicylic acid, clonidine, metamizol, but also combined therapies, such acetaminopheno & codeine); **NSAIDs** (aceclofenac, diclofenac, ibuprofen, naproxen, etodolac, indomethacin, meloxicam, piroxicam, nimesulide, celexoxib, etoricoxib); **analgesic opioids** (weak and strong opioids: tramadol, buprenorphine, fentanyl and the tramadol & acetaminopheno association); **central muscle relaxants** (baclofen, cyclobenzaprine, thiocolchicoside and acetaminopheno & thiocolchicoside association); **anxiolytics, sedatives and hypnotics** (benzodiazepines, zolpidem, buspirone); **antidepressants** (moclobemide pirlindole, fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram, mirtrazapine); **anticonvulsants** (eslicarbazepine acetate, valproic acid, carbamazepine, clonazepam, fenitoina, phenobarbital, gabapentin, lamotrigine, oscarbazepine, pregabalin, primidone, rufinamide, tiagabine, topiramate, valproic acid, vigabatrin).

The World Health Organization (WHO) analgesic ladder [10] was used to classify drug combinations: step 1 – non-opioids analgesic with or without adjuvant; step 2 – opioid for mild to moderate pain with or without non-opioid, with or without adjuvant; step 3 – opioid for moderate to severe pain with or without non-opioids, with or without adjuvant. Adjuvants comprised: antidepressants; anxiolytics, sedatives and hypnotics; anticonvulsants. Corticoids and psychotropic were not included in this analysis, as they are not commonly used as adjuvants in pain relief among clinical practice.

Statistical analysis:

Details regarding EpiReumaPt sample size calculation were previously described [11] [12]. The analgesic and other pain relief drugs intake prevalence was estimated similarly to what has been described for the prevalence of the RMDs in EpiReumaPt, taking into consideration aspects of the study design [12] [14] [15]. Prevalence estimates and confidence intervals were weighted and were obtained with STATA survey procedure. Confidence intervals (CI) calculation and the weight procedure were detailed in the manuscript that described methodology of EpiReumaPt [14].

In the present study, all the analyses were performed, taking into account the study design (weight procedure). First, a descriptive analysis aimed to characterize analgesic and other pain relief drugs intake profile among adult Portuguese population with active CLBP.

After, we assessed if the presence of active CLBP was a factor associated with the intake of each therapeutic group. Among subjects who went to rheumatologist visits (2nd phase), and which diagnosis were reviewed (3rd phase) (population previously described by Branco JC et al [14]), we performed a multivariable analysis to each therapeutic group (anxiolytics, sedatives & hypnotics; NSAIDs, antidepressants, analgesics, antipyretics, anticonvulsants, analgesic opioids, central muscle relaxants). Potential confounders were adjusted: active CLBP, age group, gender, NUTS II, education level, number of comorbidities, diagnosis of RMD (rheumatoid arthritis, spondyloarthritis, fibromyalgia, gout, systemic lupus erythematosus, hip OA, knee OA, hand OA, osteoporosis, periarticular disease, polymyalgia rheumatica). Other specific factors were adjusted to some therapeutic groups: anxiolytics, sedatives & hypnotics, antidepressants and anticonvulsants: anxiety symptoms and depression symptoms; NSAIDs and analgesics, antipyretics: heart disease and gastrointestinal diseases. The cut-off value for significance was considered to be $p<0.05$. All analyses were weighted and performed using STATA IC version 12 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

The present study was an analysis conducted within EpiReumaPt that was reviewed and approved by Portuguese legal and ethics authorities. Ethical Committees of Regional Health Authorities also reviewed and approved the study [13].

Results

Study population was described in detail by Gouveia N, et al [15] where the prevalence of active CLBP in adult Portuguese population was estimated (10.4 (CI (9.56%; 11.9%)). Table 1 resumes the main socio-demographic and socio-economic characteristics of this population selected in the 1st phase, as well as the remaining population.

Table 1: Socio-demographic, socio-economic characteristics of populations with and without active CLBP

Demographic characteristics	Population with active CLBP (n=1,487) Mean ± SD or n (%)	Population without active CLBP (n=9,174) Mean ± SD or n (%)
Age (years)	**58.90**±17.21	**45.14±**17.73
Female Gender	**1,126** (71.4%)	**5,425** (50.41%)
Ethnicity (%)		
Caucasian	**1,462** (98.2%)	**8,880** (95.66%)
Black	**16** (1.2%)	**205** (3.63%)
Other	**4** (0.3%)	**62** (0.71%)
Education level (%) (n=1,462)		
>12 years	**85** (7.8%)	**1,679** (21.82%)
10-12 years	**158** (15.3%)	**1,762** (24.78%)
5-9 years	**236** (17.2%)	**1,939** (23.26%)
0-4 years	**983** (59.8%)	**3,743** (30.14%)
Population size of the place of residence (%)		
< 2,000 habitants	**740** (47.8%)	**3,892** (38.83%)
2,000-9,999 habitants	**270** (15.3%)	**1,722** (16.13%)
10, 000 – 19, 999 habitants	**124** (7.9%)	**904** (8.94%)
20, 000 – 99, 999 habitants	**153** (13.6%)	**1,258** (17.05%)
≥100, 000 habitants	**200** (15.5%)	**1,398** (19.05%)
Marital Status (%)		
Single	**107** (9.9%)	**1,828** (31.71%)
Married	**889** (59.4%)	**5,222** (49.11%)
Divorced	**114** (7.9%)	**696** (7.37%)
Widower	**347** (20.5%)	**1,067** (6.74%)
Consensual union	**28** (2.3%)	**354** (5.07%)
BMI (%) (n=1,346)		
Underweight	**9** (1.1%)	**158** (2.37%)
Normal	**396** (30.4%)	**3,667** (47.20%)
Overweight	**522** (38.8%)	**3,227** (34.73%)
Obese	**419** (29.8%)	**1,661** (15.70%)
Employment Status (%)		
Full-time Employed	**302** (26.0%)	**3,691** (44.90%)
Part-time employed	**30** (1.7%)	**315** (5.01%)
Domestic worker	**121** (6.1%)	**539** (3.61%)
Unemployed	**115** (9.2%)	**972** (12.39%)
Retired	823 (50.2%)	**2,935** (22.09%)
Student	**5** (0.5%)	**423** (9.35%)
Temporary disabled	**44** (3.1%)	**116** (0.94%)
Other	**47** (3.1%)	**126** (1.71%)
Household income in the last month (%)		
< 500€	**396** (21.2%)	**1,598** (18.80%)
501€ a 1500€	**600** (43.8%)	**3,516** (57.56%)
1501€ a 2500€	**93** (7.9%)	**943** (16.48%)
2501€ a 4000€	**19** (1.5%)	**349** (5.13%)
> 4000€	**8** (0.6%)	**91** (2.03%)
EQ5D n=1470	**0.55**±0.30	**0.86±**0.21
Depression Symptoms (HADS>11)	**309 (21.83%)**	**527** (4.17%)
Anxiety Symptoms (HADS>11)	**424 (27.71%)**	**988** (8.64%)

Population with active CLBP:

Education level (n=1,462); BMI (n=1,346); Retirement attributable to MSK disease (n=653); Age of Retirement (mean) (n=155); Unemployment attributable to MSK disease (n=102); Maximum weekly working hours (mean) (n=328)

Population without active CLBP:

Education level (n=9,123); Marital Status (n=9,167); BMI (n=8,763); Employment status (n=9,117); Household income in the last month (n=6,497); EQ5D (n=9,127); Comorbidities (n=8,371); >1 Comorbidity (n=8,371).

NUTS II- Nomenclature of Territorial Units for Statistics (North, Centre, Alentejo, Algarve, Lisbon, Madeira and the Azores); **EQ5D** – European Quality of life Questionnaire; **NRS** – Numeric Rating Scale; **HADS:** Hospitalar Anxiety and Depression Scale

Active CLBP characteristics that were self-reported were reported in table 2. In brief, the mean intensity of pain (NRS) among subjects that self-reported active CLBP was 6.0 (SD 2.14); in the previous 12 months, 97.5% had LBP, and reported a mean of 233 days (SD 161.55) with pain; 51.8% had persistent mobility limitation; 60.3% referred pain irradiation; 72.2% reported relief with rest; 79.1% characterized the pain as constant and progressive.

Table 2: Active CLBP characteristics of the population with active CLBP

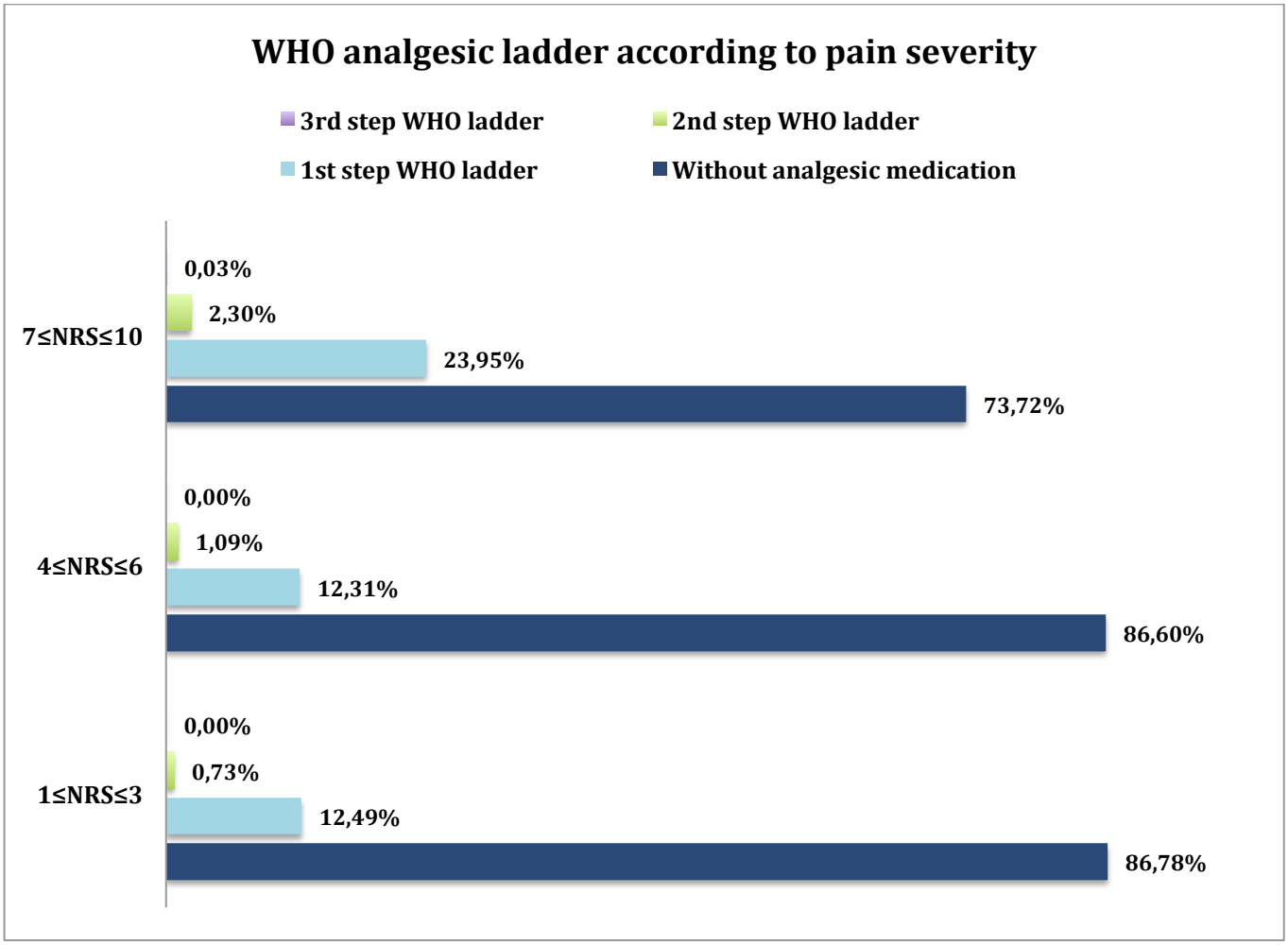
Self-reported comorbidities	Active CLBP population n=1,487
Number of comorbidities (0-15) (n=1,230)	**3.18**±2.27
> 1 comorbidity (n=1,230)	**1,214** (78.9%)
Characteristics of active CLBP	**Active CLBP population n=1,487***
Pain severity (0-10) (n=1,416)	**6.03**±2.14
LBP is the result of a fall or a fracture (%)	**265** (16.1%)
Pain irradiation (%)	**970** (60.3%)
LBP in the last 12 months (%)	**1,447** (97.5%)
Time (days) with pain in the last 12 months (n=1,447)	**233.07**±161.55
Age of onset (years) (n=1,352)	**40.78**±17.31
Time not performing daily activities because of LBP in the last 12 months (days) (n=1,423)	**45.40**±108.49
Progressive, slow or insidious onset (%)(n=1,453)	**977** (65.5%)
Relief with exercise (%) (n=1,453)	**453** (32.7%)
Relief with rest (%) (n=1,453)	**1031** (72.2%)
Occurs during the night and relieves in the morning (%)(n=1,453)	**508** (31.7%)
Pain awakening in the 2nd half of the night (%)(n=1,453)	**757** (51.8%)
Morning back stiffness (%)(n=1,453)	**950** (62.7%)
Duration of morning stiffness (hours) (n=950)	**1.49**±0.58
Pain in gluteal region, alternating left and right (%)(n=1,453)	**783** (48.0%)
Previous anti-inflammatory therapy (%) (n=1,453)	**988** (70.0%)
Pain control with NSAIDs therapy within 24-48h (%) (n=998)	**642** (66.9%)
Unexplained weight loss (> 4.5 Kg in 6 months) (%)(n=1,453)	**160** (9.6%)
Constant and progressive LBP (%) (n=1,453)	**1,127** (79.1%)
Previous infection (%) (n=1,453)	**231** (13.4%)
Transplantation (%) (n=1,453)	**15** (0.8%)
Persistent limitation of mobility (%) (n=1,453)	**798** (51.8%)
Family history of Rheumatoid Arthritis or Osteoporosis (%) (n=1,453)	**615** (42.2%)
LBP with urinary retention or incontinence (%) (n=1,453)	**220** (15.0%)
Fecal incontinence (%) (n=1,453)	**109** (6.4%)
Tingling in the anal, genital region or lower limbs (%) (n=1,453)	**685** (43.5%)
Progressive weakness of the legs or walking difficulties (%) (n=1,453)	**1,045** (68.9%)

WHO analgesic ladder and pain severity

Only 18.73% of subjects that self-reported active CLBP used analgesic or other pain relief drugs. Regarding WHO analgesic ladder, 17.16% (CI (14.09%; 20.23%)) of the subjects were in the 1st step, 1.56% (CI (0.92%; 2.21%)) in the 2nd, and 0.01% (CI ((-0.01%;0.04%) in the 3rd step.

According to pain severity, 17.22% of subjects with active CLBP reported the intake of drugs to control severe pain (7≥NRS≥10), 2.01% to moderate pain (4≤NRS≤6) and 2.12% to mild pain (1≤NRS≤3).

Additionally a drug intake was analyzed within each level of pain severity, taking into account the WHO analgesic ladder. It was confirmed that most of subjects with active CLBP didn't take any analgesic drug regardless pain severity (Fig.2); even when subjects self-reported severe pain (7≥NRS≥10), only 23,95% were in the 1st step of the analgesic ladder, 2,30% used weak analgesic opioids and 0,03% used strong opioids (2nd and 3rd step of WHO analgesic ladder, respectively) to control pain.



NRS: Numeric rating scale; WHO: World Health Organization

Figure 2: WHO analgesic ladder according to pain severity

Analgesic and other pain relief drug intake according to therapeutic group

When inquired about therapeutic groups of analgesic and other pain relief drug intake, 12.32% (CI:10.20%; 14.44%) of subjects with active CLBP referred the use of NSAIDs and 6.58% (CI: 3.95%; 9.20%) reported analgesic antipyretics. Only 2.57% (CI: 1.59%; 3.55%) reported use of centrally acting muscle relaxants. Moreover, anxiolytics, sedatives and hypnotics, which include benzodiazepines, was the most reported therapeutic group among subjects with active CLBP (14.10%) (CI: 11.50%; 16.70%)(Fig. 3a).

In the total population with active CLBP, the intake of analgesic and other pain relief drugs increased with age, especially between 46-76 year-old (y.o.) age groups (Fig.3b); NSAID intake increased with age and had higher values in the 56-75 y.o. age groups (17.46%) (Fig.3b). Among women, the intake of anxiolytics, sedatives and hypnotics, and antidepressants had also high prevalence, especially among 46-55 y.o. and 56-65 y.o. age groups (21.11% and 19.28%, respectively). Young women (26-35 y.o. group) self-reported higher intake of analgesic, antipyretic drugs (21.13%). From 36-45 y.o. age group, the intake of NSAIDs increased among women, reaching its highest at 56-65 y.o. group (21.18%) (Fig.3c). Among men, the higher intake of NSAIDs between 46-55 y.o. age groups was even more striking (20.69%); the analgesic antipyretics consumption increased in the 46-55 y.o. age group and remained stable until 66-75 y.o. age group (Fig.3d).

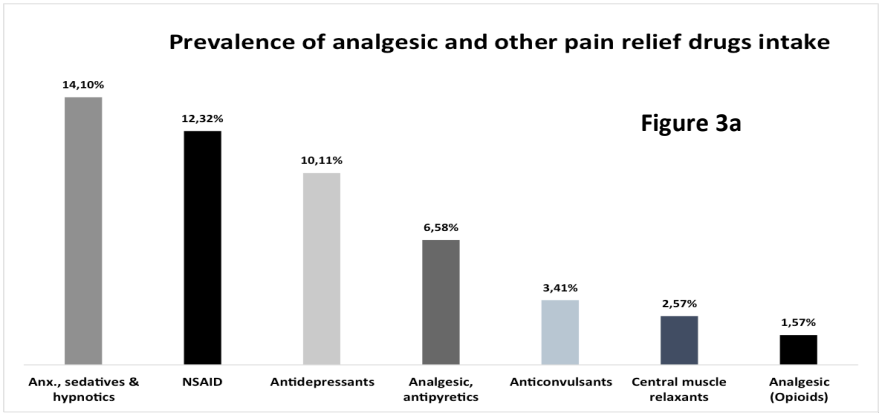


Figure 3a

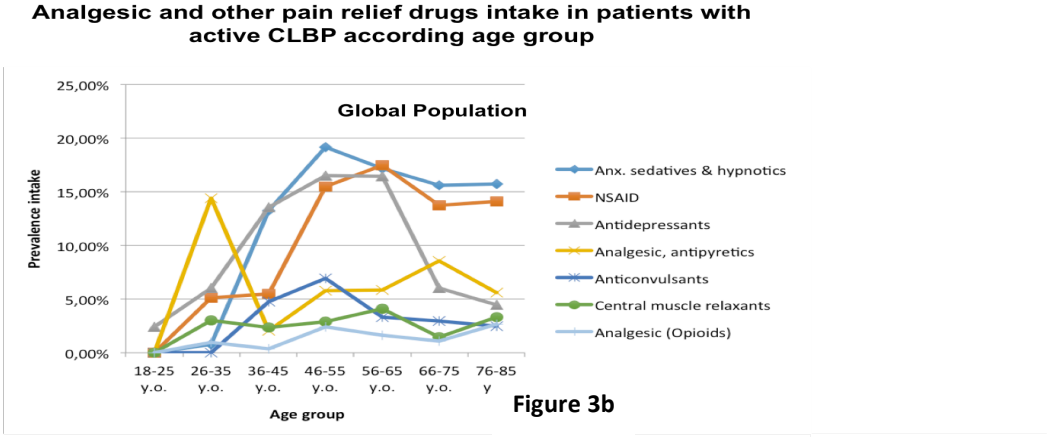


Figure 3b

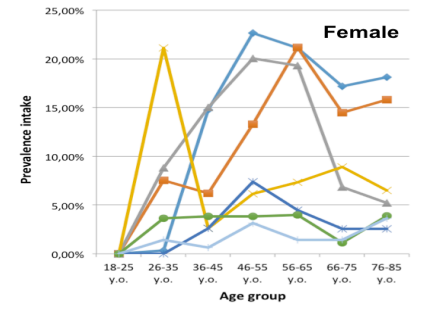


Figure 3c

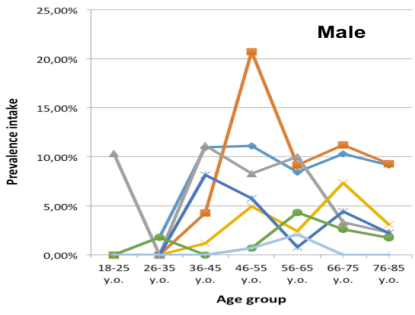


Figure 3d

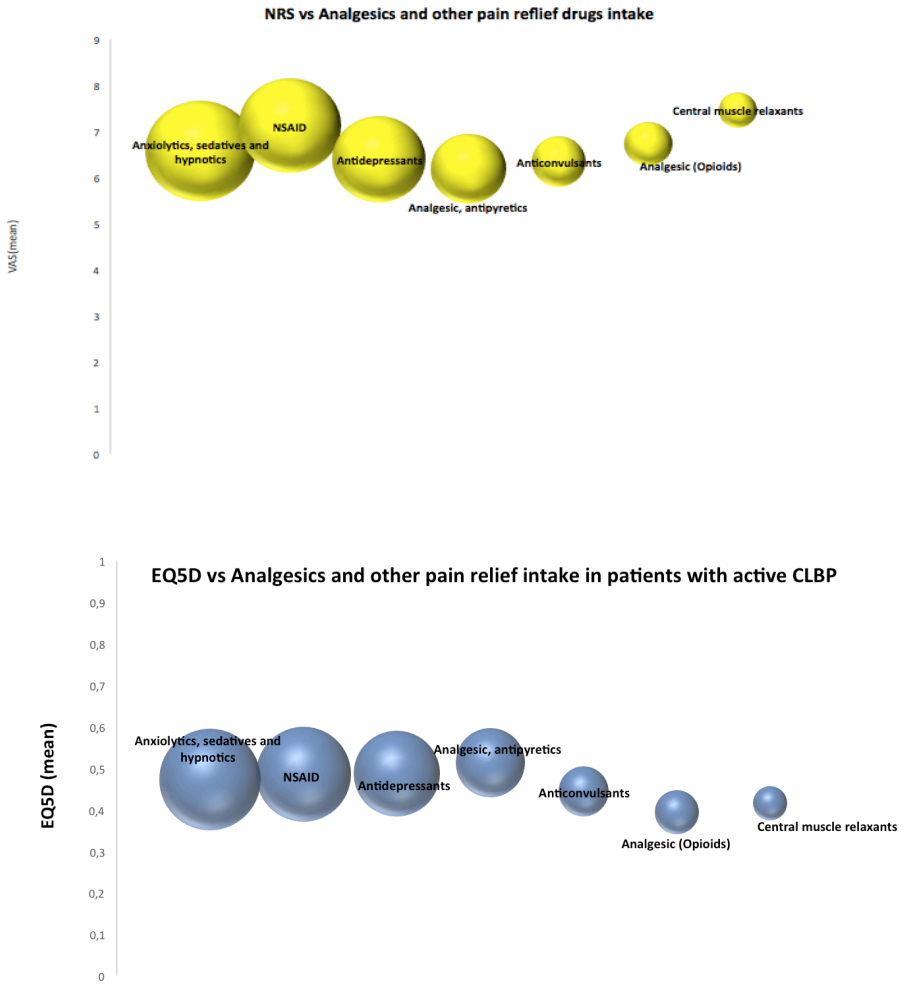
NSAIDs: nonsteroidal anti-inflammatory drugs; y.o.: years-old

Figure 3: Prevalence of analgesic and other pain relief drugs intake in patients with active CLBP: global and according age group

Figure 4 shows the analgesic and other pain relief drug intake according to pain severity self-reported by subjects with active CLBP. Ball size expresses the prevalence of drug intake according to each therapeutic

group. Drug intake was higher for values of NRS≥6 (mean NRS 6.19). Analgesic opioids (mean NRS 6.73) were used among subjects that self-reported moderated pain, as well as anxiolytics, sedatives & hypnotics (mean NRS 6.57), antidepressants (mean NRS 6.40), analgesic and antipyretics (mean NRS 6.19) and anticonvulsants (mean NRS 6.34). NSAIDs (mean NRS 7.12) and centrally acting muscle relaxants intake (mean NRS 7.46) were observed among subjects that self-reported severe pain.

A similar analysis was made to assess quality of life (through EQ5D score) according to drug intake. EQ5D mean scores ranged between 0.39 and 0.51, which are low values to this score. Subjects that reported use of analgesic opioids reported worse quality of life (mean EQ5D 0.39), followed by those that reported the intake of central muscle relaxants (mean EQ5D 0.42) and anticonvulsants (mean EQ5D 0.44) (Fig.4).



EQ5D – European Quality of life Questionnaire; NRS: Numeric rating scale; NSAIDs – nonsteroidal anti-inflammatory drugs

Figure 4: Analgesic and other pain relief drugs intake according to severity of pain (NRS) and Quality of life (EQ5D)

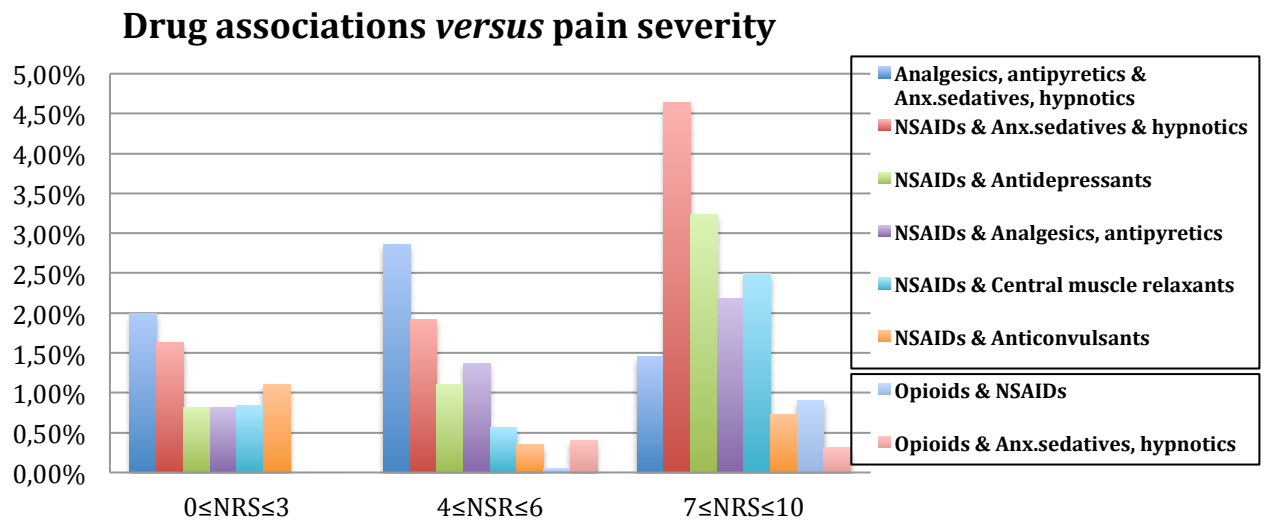
Drug associations versus pain severity

Considering pain severity, the most common combinations of therapeutic groups among subjects with CLBP were (Fig. 5):

. severe pain (7≤NRS≤10) –most used drug associations belonged to the 1st step of WHO analgesic ladder: NSAIDs + anxiolytics, sedatives and hypnotics was the most used (4.64%) followed by the association between NSAIDs + antidepressants (3.24%), and by NSAIDs + centrally acting muscle relaxants (2.50%). Regarding the 2nd step of WHO analgesic ladder, only 0.90% of these particular group of subjects combined analgesic opioids + NSAIDs; 0.31% combined analgesic opioids + anxiolytics, sedatives and hypnotics. 3rd step of WHO analgesic ladder drugs were used by 0.01% subjects, combining strong opioid (morphine) + analgesic, antipyretics + anticonvulsants.

. moderate pain (4≤NRS≤6) – drug associations most used also belonged to the 1st step of WHO analgesic ladder: analgesic, antipyretics + anxiolytics, sedatives and hypnotics (2.86%), followed by NSAIDs + anxiolytics, sedatives and hypnotics (1.92%) and by NSAIDs + analgesic and antipyretics (1.37%). The 2nd step of WHO analgesic ladder was used only by 0.40% of the subjects (combining opioids + anxiolytics, sedatives and hypnotics) and by 0.05% (opioids + NSAIDs combination). The 3rd step of WHO analgesic ladder was not used among this group of subjects.

. mild pain (0≤NRS≤3) – none of the subjects that self-reported mild pain used the 2nd and 3rd step of WHO analgesic ladder. Drug associations used belonged to the 1st step: analgesic, antipyretics + anxiolytics, sedatives and hypnotics (1.99%), followed by NSAIDs + anxiolytics, sedatives and hypnotics (1.63%).



NRS: Numeric rating scale; NSAIDs – nonsteroidal anti-inflammatory drugs

Figure 5: Drug associations versus pain severity

To compare analgesic and other pain relief drugs intake between subjects with and without active CLBP, a multivariable analysis was performed among subjects that went to rheumatologist visits (2nd phase) and which diagnosis were reviewed (3rd phase). The intake of all therapeutic groups analyzed in this paper (anxiolytics, sedatives & hypnotics; NSAIDs, antidepressants, analgesics, antipyretics, anticonvulsants, analgesic opioids, central muscle relaxants) was higher among subjects with active CLBP (table 3), especially centrally acting muscle relaxants intake (OR=15.57; p<0.001), anticonvulsants (OR=12.87; p<0.001) and analgesic antipyretics (OR=7.94; p<0.001). *p*-values were adjusted to age, gender, NUTS II, education level, number of comorbidities, diagnosis of RMD (rheumatoid arthritis, spondyloarthritis, fibromyalgia, gout, systemic lupus erythematosus, hip OA, knee OA, hand OA, osteoporosis, periarticular disease, polymyalgia rheumatica). Other specific factors were also adjusted to some therapeutic groups:

. anxiolytics, sedatives & hypnotics, antidepressants and anticonvulsants: anxiety symptoms and depression symptoms;

. NSAIDs and analgesics, antipyretics: heart disease and gastrointestinal diseases.

Table 3 – Comparison of analgesic and other pain relief drugs intake between subjects with and without active CLBP

Analgesic and other pain relief drugs	OR estimates	95% CI	Adjusted p-value
Anxiolytics, sedatives & hypnotics	**5.75**	[3.41-9.71]	**<0.001**
NSAIDs	**6.63**	[3.96-11.10]	**<0.001**
Antidepressants	**7.05**	[3.87-12.87]	**<0.001**
Analgesics, antipyretics	**7.94**	[3.55-17.73]	**<0.001**
Anticonvulsants	**12.87**	[5.47-30.28]	**<0.001**
Analgesic opioids	**5.20**	[1.84-14.72]	**0.002**
Central muscle relaxants	**15.57**	[6.47-37.45]	**<0.001**

NSAIDs – Nonsteroidal anti-inflammatory drugs; **Sample size is not constant due to missing data:** Anxiolytics, sedatives & Hypnotics (n=1031); NSAIDs (n=1050); Antidepressants (n=1027); Analgesics, antipyretics (n= 1014); Anticonvulsants (n=929); Analgesic drugs (opioids) (n= 1044); Central Muscle Relaxants (n= 995).

A logistic regression was used in order to obtain an Odds Ratio. The estimated values were obtained considering study design.

†Adjuste p-values<0.05.

Discussion

This work showed that analgesic and other pain relief drugs intake among adult Portuguese population with active CLBP was very low, even in a setting where, according to the Portuguese law [22], patients can have access to some of these drugs (NSAIDs and analgesic and antipyretic drugs) without medical prescription. This pattern of very low use of pain relief drugs was also observed in those who self-reported severe pain (7≤NRS≤10). Even though, this small portion of subjects that took pain relief medication respected the WHO analgesic ladder and was extremely conservative about the use of analgesic opioids. This finding contrasts with United States (US) context where opioid prescription for LBP has increased, and opioids are now the most commonly prescribed drug class [23]. Opioid prescription has increased worldwide, with US opioid sales quadrupling between 1999 and 2010 [24]. Rates of opioid prescription in the US and Canada are two to three times higher than in most European countries [25]. But opioids seem to have short-term analgesic efficacy for CLBP and the increasing of opioids' prescription doesn´t provide proportional effectiveness in chronic pain relief. In the other hand, given the short duration of randomized controlled trials, the long term effectiveness and safety of opioids are still unknown [24].

Like in other countries, active CLBP is one of the most common reasons for visiting a physician, but treatment patterns remain extremely variable [26] and consensus across the medical community with respect to prevention and treatment guidelines appears inconsistent [27]. The top 3 of therapeutic groups that active CLBP adult Portuguese population used to relieve pain were: anxiolytics, sedatives and hypnotic drugs (14.10%), NSAIDs (12.32%) and antidepressants (10.11%). The higher prevalence of anxiolytics, sedatives and hypnotic and antidepressants needs to be analyzed with caution in order to understand whether the use of these drugs was in fact to relieve pain. It is also well known that anxiety and depression symptoms and CLBP coexists. So, our statistical analyses were adjusted for these potential confounding factors. In fact, a preview paper [15] regarding the burden of active CLPB among Portuguese population showed a strong, significant and independent association of anxiety symptoms with the presence of active CLBP (OR=2.60; $p<0.001$). Polatin et al. already reported this interesting finding in 1993 [28], in which 59.0% of 200 CLBP patients, who were starting a rehabilitation program, filled criteria for a psychiatric diagnosis: 55.0% for depression and 48.6% for anxiety. A recent Korean study [29] comparing a group of patients with CLBP with a control group, also demonstrated significantly higher incidence of depression (51.5% vs 6.8%) and anxiety (42.5% vs 18.2%) among CLBP subjects. Also, the association between psychosocial factors and LBP have been reported [30]. So, the high intake of

anxiolytics and antidepressants could be explained by the presence of a concomitant mental disorder, and not only by the use of these drugs to pain relief. Prospective studies with a well-characterized baseline (regarding presence of CLBP and anxiety/depression) and rigorous follow-up evaluations are critical to clarify this hypothesis and the issue of direction of association.

Regarding the high prevalence of NSAIDs intake versus NSAIDs efficacy, several studies tried to clarify this topic. One systematic review including 51 randomized controlled trials comparing NSAIDs with placebo, found strong evidence that NSAIDs significantly improved pain control [31]. Additionally, three small randomized clinical trials identified by other systematic review found no significant difference in symptoms or return to work between an opioid analgesic, acetaminophen and NSAIDs [32] [33].

Although this study was performed among a large and randomized population, there were limitations that must be taken into account. Questionnaire-based drug intake was not optimal, because people can forgot or omit drugs. Questions about drugs did not provide accurate data about the reasons to take the med (due to CLBP or other disease). Also, it was not possible to define whether subjects were taking the analgesic drug according to physician's indication or by self-medication. The lack of this data limited a detailed identification of factors independently associated with each analgesic therapeutic group intake.

In conclusion, this paper showed that analgesic and other pain relief drugs intake among adult Portuguese population with active CLBP was very low, even for those who self-reported severe pain. Even though, this small proportion of subjects that took medication for pain relief respected the WHO analgesic ladder and was extremely conservative about the use of analgesic opioids. The use of all therapeutic groups analyzed in this paper was significantly higher in subjects with active CLBP when compared with the remaining Portuguese population, especially the intake of centrally acting muscle relaxants, anticonvulsants and analgesic antipyretics.

Prospective studies with rigorous follow-up evaluations are a good choice to well characterize the drug intake to pain relief and to assess the drug effectiveness in patients with active CLBP.

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Section II – Part VI

Anxiety and depression symptoms: an additional burden among a population with chronic low back pain? – results from a national survey (EpiReumaPt)

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Anxiety and depression symptoms: an additional burden among a population with chronic low back pain? – results from a national survey (EpiReumaPt)

Nélia Gouveia[1,2], Mónica Eusébio[1], Ana Rodrigues[1,2,4,5], Sofia Ramiro[1,2,6], Pedro Machado[1,8,9], Helena Canhão[1,2,4,5,10], Jaime Branco[1,2,11]

[1]EpiReumaPt Study Group - Sociedade Portuguesa de Reumatologia, Lisboa, Portugal; [2]EpiDoc Unit – Unidade de Epidemiologia em Doenças Crónicas, Centro de Estudos de Doenças Crónicas (CEDOC) da NOVA Medical School, Universidade Nova de Lisboa (NMS/UNL), Lisboa, Portugal; [4]Unidade de Investigação em Reumatologia, Instituto de Medicina Molecular, Lisboa, Portugal; [5]Faculdade de Medicina da Universidade de Lisboa, Lisboa, Portugal; [6]Leiden University Medical Center, Leiden, the Netherlands; [8]Clínica Universitária de Reumatologia, Faculdade de Medicina da Universidade de Coimbra, Coimbra, Portugal; [9]MRC Centre for Neuromuscular Diseases, University College London, London, United Kingdom; [10]Serviço de Reumatologia do Hospital de Santa Maria – Centro Hospitalar Lisboa Norte (CHLN-E.P.E), Lisboa, Portugal Portugal; [11]Serviço de Reumatologia do Hospital Egas Moniz - Centro Hospitalar Lisboa Ocidental (CHLO- E.P.E.), Lisboa

Abstract

Objectives: To determine the prevalence of psychological symptoms (anxiety and/or depression) among adult Portuguese subjects with active chronic low back pain (CLBP). Among those, to compare the populations with and without these psychological symptoms; and to explore factors associated with this symptomatology.

Methods: EpiReumaPt was a cross-sectional Portuguese population-based study (10,661 subjects). Self reported active CLBP was considered if present on the day of the interview and for ≥90 days. Prevalence of psychological symptoms was calculated. Differences in quality of life, pain severity, healthcare consumption and absenteeism between subjects with and without psychological symptoms were evaluated. Factors associated with isolated anxiety, isolated depression and concomitant anxiety and depression symptoms were identified through logistic regression.

Results: Among EpiReumaPt sample with active CLBP, 39.4% (CI (35.5%; 43.5%)) had anxiety and/or depression symptoms. Among subjects with anxiety and/or depression symptoms: health status was significantly worse (β=-0.11); the mean of pain severity was significantly higher (β=0.71), as also the need of home care in the previous 12 months (OR=3.53). **Among subjects with active CLBP: factors significantly associated: with anxiety symptoms-** education level, mental diseases (OR=2.54), cancer (OR=2.23;) smoking (OR=2.11) and severity of pain (OR=1.13). Age (OR=0.96) was inversely associated with anxiety symptoms; with **depression symptoms-** increasing age (β=1.04); neurologic diseases (OR=3.84), HAQ score (OR=2.78), and mechanical LBP (OR=2.09); **with concomitant anxiety and depression symptoms-** lower

education level (<12 years); geographic region (NUTS II); smoking (OR=2.81), severity of pain (OR=1.15), constant and progressive LBP (OR=2.85), antidepressants intake (OR=1.95) and worse quality of life (OR=0.03). Physical exercise had a protective factor against anxiety and depression symptoms (OR=0.52).

Conclusion: The prevalence of psychological symptoms among Portuguese population with active CLBP is high and among those health status was significantly worse; the mean of pain severity and healthcare resources consumption were significantly higher.

Introduction

In the recent Global Burden of Disease 2010 Study, low back pain (LBP) was the leading cause in the world of years lived with disability[1] and was the most prevalent rheumatic and musculoskeletal condition[2 3]. Chronic LBP (CLBP) is a multifactorial condition, which combines somatic, musculoskeletal and psychosocial factors[2]. Although CLBP does not contribute to mortality, it carries a significant socio-economic burden associated with increased disability, worse quality of life and poor relationship satisfaction [4 5].

Psychological symptoms like anxiety and depression have been commonly identified in patients with CLBP [6]. Previous studies suggested a positive correlation between anxiety and depression symptoms and pain severity [7 8], and with chronic musculoskeletal pain, which includes LBP [4]. An hypothesis was raised that subjects who self-reported excessive complaints were more predisposed to depression [9].

Pharmacological therapy to relief CLBP is, most of the times, not very effective and psychological symptoms tend to get worse [2]. Furthermore, CLBP and depression most likely have a bidirectional association: depression is a predictor of persistent pain and pain is a predictor of depression persistence [10 11 12]. Depression and anxiety commonly appear together and the link between pain and anxiety is equally important. Pain may cause symptoms of anxiety, which in their turn can make one more sensitive to pain, resulting in a clear chronicity loop[2 13].

In Portugal, a recent study under the scope of the Portuguese Epidemiological Study of Rheumatic Diseases (EpiReumaPt) [14 15 16] provided information about high prevalence and burden of CLBP in the adult Portuguese population. Female gender, age group, anxiety symptoms, educational level, the presence of other rheumatic and musculoskeletal diseases (RMD) and the number of comorbidities were independently associated with the presence of active CLBP [17]. Another study from the same research group provided information about analgesic and other pain relief drugs to control CLBP in Portugal and showed that anxiolytics, hypnotics and sedatives was the most widely therapeutic group used among subjects that self-reported CLBP [18].

In order to explore the role of anxiety and depression symptoms among Portuguese population with CLBP, this study was conducted aiming at: determining the prevalence of anxiety and depression symptoms among adult Portuguese subjects with active CLBP; comparing subjects with anxiety and/or depression symptoms with subjects without these symptoms; and exploring factors associated with isolated anxiety, isolated depression, and concomitant depression and anxiety symptoms.

Methods

Data source and study population:

The actual study was developed under the scope of EpiReumaPt - a national and a prevalence study of RMD (from September 2011 to December 2013) [16]. EpiReumaPt recruited 10,661 subjects, a representative sample

of adult Portuguese population (>18 years old), using a random-route methodology [16]. The sample was stratified by administrative territorial units (NUTS II) [14 15 16]. A survey was applied to the subjects, through a face-to-face interview, in order to capture and characterize all cases of RMD within the adult Portuguese population. Details regarding EpiReumaPt methodology were described previously [14 15 16].

The study population was defined based on self-reported active CLBP (see case-definition). Among those, anxiety and depression symptoms were assessed (fig.1).

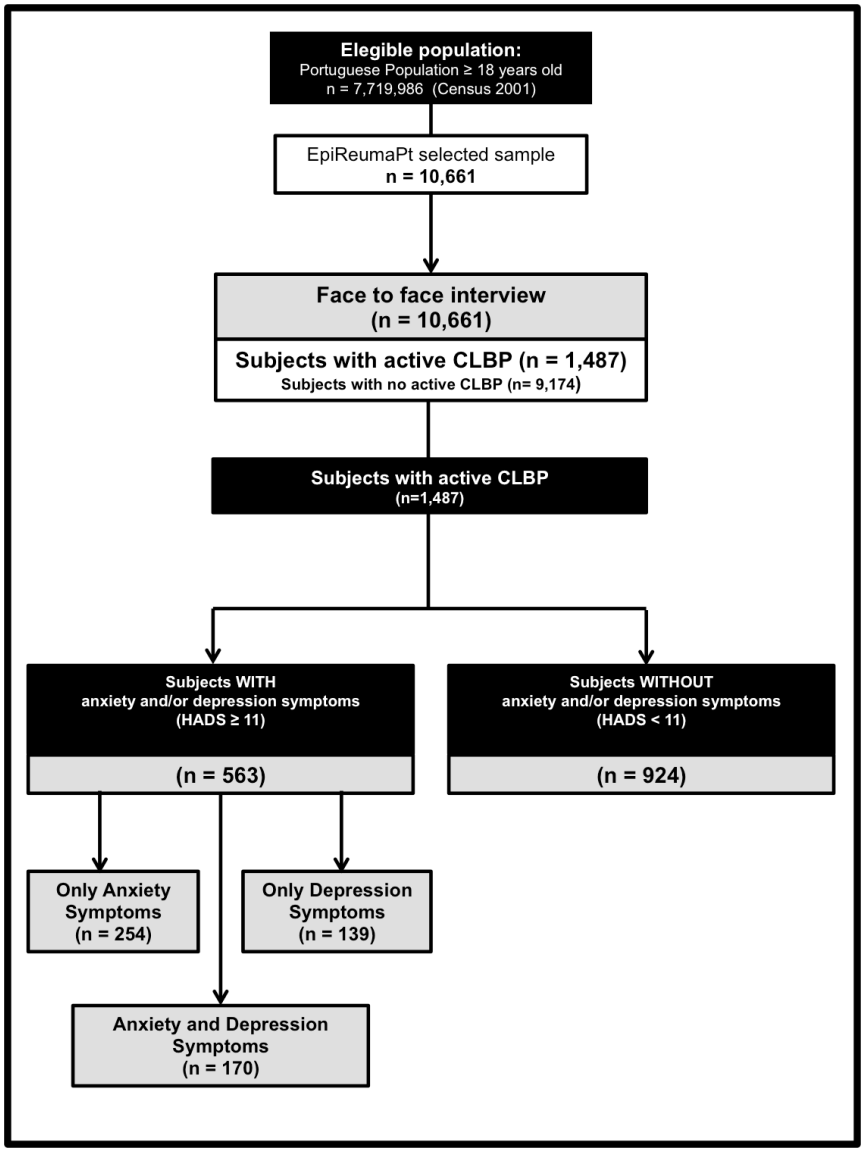

Figure 1: Flowchart of study design

Participants in the study signed an informed consent prior to participation. The study was approved by the Ethics Committee of Nova Medical School and by the National Data Protection Committee [16].

Case definition:

LBP was defined as pain in the back area, from the lower margin of the twelfth ribs to the lower gluteal folds, with or without referred pain to the lower limbs. Active CLBP was defined as self-reported LBP, present on the day of the interview, and that was present in most of time for at least 90 days (independently from cause). Anxiety and depression symptoms were assessed through the Hospital Anxiety and Depression Scale (HADS) (see *measurements, assessment and instruments*). The cut off used for positive anxiety and depression symptoms was ≥11.

Measurements, assessment and instruments:

Socio-demographic data were collected as detailed in previous studies [17] [18]: age, gender, ethnicity, education level, marital status; as well socio-economic features: household income per month, without taxes, current work status, number of work hours per week. Lifestyle habits were also inquired: smoking, alcohol and coffee intake. Work disability data were collected through absenteeism data: early retirement due to disease, unemployment due to work disability and absence from work due disease in the previous 12 months.

Anthropometric data were collected (weight, height and body mass index (BMI)) and self-reported chronic diseases were asked: high cholesterol level, high blood pressure, allergy, gastrointestinal disease, mental disease, cardiac disease, diabetes, thyroid and parathyroid disease, renal colic, pulmonary disease, hyperuricemia, cancer, neurologic disease, hypogonadism.

Healthcare consumption data collected included the number and type of outpatient clinic visits, specialty care, hospitalizations, homecare assistance and other healthcare service needs (physiotherapy, alternative treatments, psychology), in the previous 12 months. Outpatient clinic visits included General Practitioner, Rheumatologist, Orthopedic, Physiatrist, Psychiatrist and "others".

Analgesics and other pain relief drugs (pain modulators) were organized according INFARMED classification [19] and detailed in a previous study [18]: analgesics and antipyretics; NSAIDs; analgesic opioids; central muscle relaxants; anxiolytics, sedatives and hypnotics; antidepressants; anticonvulsants. World Health Organization (WHO) analgesic ladder was used [20] to classify drug combinations.

Quality of life data were collected using the EuroQol (EQ-5D-3L) [21] [22]; subjects recorded pain intensity on the interview day using a numeric pain rating scale (NPRS, 0-10cm). It were used "red flag questions" [23]

to screen causes and characteristics of active CLBP. Physical function was assessed with the Health Assessment Questionnaire (HAQ) (0-3)[24]. Anxiety and depression symptoms were assessed through the Hospital Anxiety and Depression Scale (HADS). This scale has 2 sub-scales to anxiety and to depression. To each one the cut off used for positive symptoms was ≥11 [25]. Subjects were included in the group "population with anxiety and/or depression symptoms" if they had a HADS score ≥11 to anxiety symptoms, or depression symptoms, or concomitant anxiety and depression symptoms. Portuguese validated versions of all these instruments were used.

Statistical analysis:

Sample size calculation were previously described [14] [15]. The prevalence of anxiety and depression symptoms among subjects with active CLBP was estimated taking into consideration the study design [26]. All the analyses and confidence intervals were weighted and were obtained with STATA survey procedure.

Differences between subjects with and subjects without anxiety and/or depression symptoms were evaluated by univariable linear regression analysis that was performed according to study design. After that, the two populations were compared through multivariable regressions. The following characteristics were assessed: EQ5D (mean of score), pain severity (mean of NRS), number of physician visits, home care in the previous 12 months (yes/no), hospitalizations in the previous 12 months (yes/no), early retirement due to disease (yes/no), absence from work due to disease in the previous 12 months (yes/no), number of days of absence and complementary treatments (yes/no). The comparison was adjusted according to potential confounders: age group, gender, NUTS II, education level, physical exercise, BMI, number of comorbidities and presence of self-reported RMD. Each categorical variable was presented as the absolute frequency and the correspondent proportion (adjusted for the weight, according to study design). The same adjustment has been done for the mean and standard deviation (SD) for each continuous variable.

To assess factors independently associated with psychological symptoms among subjects with active CLBP, 3 multivariable logistic regressions models were developed: Model A: isolated anxiety symptoms; Model B: isolated depression symptoms; Model C: concomitant anxiety and depression symptoms. In a 1st step, a univariable linear regression analysis was made in order to identify potential confounders. In a 2nd step, were 3 multivariable logistic regression models, using backward elimination combined with and forward selection, testing at each step for variables to be included or excluded. Variables were excluded or included again according to their significance level (p-value) and their clinical relevance. To each

model, dependent variables (isolated anxiety symptoms; isolated depression symptoms; concomitant anxiety and depression symptoms) were tested while taking explanatory variables into account: Model A: age, gender, education level, BMI, NUTS II, number of comorbidities, self-reported mental disease, self-reported cancer, smoking, pain (NRS); Model B: age, gender, BMI, education level, NUTS II, number of comorbidities, self-reported neurologic disease, mechanical pain, HAQ score; Model C: gender, age, BMI, educational level, NUTS II, regular physical exercise, smoking, pain (NRS), self-reported pain constant and progressive, antidepressants intake, EQ5D score.

The cut-off value for significance was considered to be $p<0.05$. All analyses were weighted and performed using STATA IC version 12 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

Results

Among EpiReumaPt sample who self-reported active CLBP, 39.4% (CI (35.5%; 43.5%)) had anxiety and/or depression symptoms, with 79.8% of them being women. The mean age of subjects with these psychological symptoms was 59.8 (SD 19.74) years old (y.o.). Symptoms prevalence increased with age: 43.5% among 66-75 y.o. age group; 40.5% among 76-85 y.o. age group, and 51.9% among >86 y.o. age group. Regarding NUTS II regions, the highest prevalence of anxiety and depression symptoms among subjects with active CLBP occurred in the Norte Region (38.1%) and Lisboa & Vale do Tejo (23.3%) (table 1). More than half (69.9%) of the subjects with active CLBP and concomitant anxiety and/or depression symptoms were overweight or obese; 53.4% were retired; 93.9% self-reported an household income per month <1500€. Table 1 provides detailed information about socio-demographic, socio-economic characteristics and health care consumption.

Table 1: Socio-demographic and socio-economic characteristics and healthcare consumption of the population with active CLBP with and without anxiety and/or depression symptoms

Demographic characteristics	Pop. with active CLBP WITH Anxiety and/or depression symptoms (n=563)	Pop. with active CLBP WHITHOUT Anxiety and/or depression symptoms (n=924)
Age (years)	**59.84**±19.74	**58.29**±20.03
Female Gender	**483** (79.8%)	**643** (65.9%)
Ethnicity (%)		
Caucasian	**554** (99.2%)	**908** (98.2%)
Black	**4** (0.4%)	**12** (1.7%)
Other	**2** (0.5%)	**2** (0.2%)
Education level (%)		
>12 years	**18** (3.9%)	**67** (10.2%)
10-12 years	**44** (11.7%)	**114** (17.5%)
5-9 years	**97** (19.3%)	**139** (16.0%)
0-4 years	**392** (65.1%)	**591** (56.4%)
NUTII		
Norte	**193** (38.1%)	**232** (34.4%)
Centro	**122** (26.5%)	**178** (25.3%)
Lisboa e Vale do Tejo	**94** (23.3%)	**202** (22.0%)
Alentejo	**29** (5.5%)	**74** (9.1%)
Algarve	**19** (3.2%)	**31** (3.7%)
Região Autónoma dos Açores	**49** (1.7%)	**94** (2.5%)
Região Autónoma da Madeira	**57** (1.9%)	**113** (3.0%)
Population size of the place of residence (%)		
< 2000 habitants	**288** (46.8%)	**452** (48.5%)
2000-9999 habitants	**99** (13.4%)	**171** (16.4%)
10 000 – 19 999 habitants	**44** (8.0%)	**80** (7.8%)
20 000 – 99 999 habitants	**60** (13.8%)	**93** (13.4%)
>=100 000 habitants	**72** (18.0%)	**128** (13.9%)
Marital Status (%)		
Single	**37** (8.1%)	**70** (11.1%)
Married	**314** (55.5%)	**575** (62.1%)
Divorced	**44** (7.6%)	**70** (8.1%)
Widower	**158** (27.1%)	**189** (16.2%)
Consensual union	**8** (1.8%)	**20** (2.6%)
BMI (%)		
Underweight	**4** (1.4%)	**5** (0.9%)
Normal	**150** (28.8%)	**246** (31.4%)
Overweight	**184** (36.8%)	**338** (40.1%)
Obese	**162** (33.0%)	**257** (27.7%)
Socioeconomics		
Household income in the last month (%)		
< 500€	**178** (32.0%)	**218** (26.9%)
501€ a 1500€	**197** (62.0%)	**403** (55.7%)
1501€ a 2500€	**19** (4.2%)	**74** (14.2%)
2501€ a 4000€	**4** (1.1%)	**15** (2.5%)
> 4000€	**2** (0.8%)	**6** (0.8%)
Employment Status (%)		
Full-time Employed	**96** (22.4%)	**206** (29.0%)
Part-time employed	**12** (1.6%)	**18** (1.8%)
Domestic worker	**53** (7.5%)	**68** (5.4%)
Unemployed	**47** (10.3%)	**68** (8.8%)
Retired	**315** (53.4%)	**508** (49.4%)
Student	**0**	**5** (0.9%)
Temporary disabled	**19** (3.32%)	**25** (3.0%)

Other	**8** (1.56%)	**14** (1.8%)
Retirement attributable to RMD (%)	**9** (19.0%)	**6** (9.3%)
Age of Retirement (years)	**49.79**±13.40	**51.66**±14.75
Maximum weekly working hours (hours)	**42.52**±12.69	**42.76**±12.74
Health Consumptions		
Number of physician visits in the last 12 months (%)	**488** (87.7%)	**743** (80.6%)
General practitioners visits	**46** (6.9%)	**75** (6.7%)
Rheumatology visits	**111** (26.3%)	**167** (20.4%)
Orthopedics visits	**36** (670%)	**63** (6.8%)
Rehabilitation medicine visits	**64** (11.1%)	**25** (2.4%)
Psychiatry	**324** (65.4%)	**454** (48.7%)
Other visits		
Number of physician visits in previous 12 months, independently of medical specialty		
< 7 physician visits	**348** (62.8%)	**676** (73.7%)
≥ 7 physician visits	**215** (37.2%)	**248** (26.3%)
Home care in the last 12 months (%)	**54** (9.6%)	**40** (3.36%)
Hospitalizations in the last 12 months (%)	**89** (16.4%)	**118** (13.0%)
Complementary treatments (%)	**121** (23.7%)	**190** (23.3%)
Number of Complementary treatments:		
Physiotherapy exercises	**5** (1.4%)	**13** (1.4%)
Psychology	**3** (0.5%)	**3** (0.4%)
Alternative medicine (acupuncture, homeopathy, osteopaths, naturopaths, herbalists, quimiopraxia technicians, herbalists, healers and rights)	**7** (1.3%)	**14** (2.9%)
Other	**3** (0.5%)	**1** (0.1%)

Sample size is not constant due to missing data in Population with CLBP with Anxiety or Depression symptoms: Ethnicity (n=560), Education level (n=551), Marital Status (n=561), BMI (n=500), Household income in the last month (n=400), Employment Status (n=550), Retirement attributable to RMD (n=40), Age of Retirement (years) (n=66), Unemployment attributable to RMD (n=9), Maximum weekly working hours (hours) (n=107), Home care in the last 12 months (n=560), Hospitalizations in the last 12 months (n=562), Complementary treatments (n=555), Physiotherapy exercises (n=443), Psychology (n=440), Alternative medicine (acupuncture, homeopathy, osteopaths, naturopaths, herbalists, quimiopraxia technicians, herbalists, healers and rights) (n=447), Other (n=438).
in Population with CLBP without Anxiety or Depression symptoms: Ethnicity (n=922), Education level (n=911), BMI (n=846), Household income in the last month (n=716), Employment Status (n=912), Retirement attributable to RMD (n=62), Age of Retirement (years) (n=89), Unemployment attributable to RMD (n=22), Maximum weekly working hours (hours) (n=221), Home care in the last 12 months (n=922), Complementary treatments (n=918), Physiotherapy exercises (n=748), Psychology (n=733),), Alternative medicine (acupuncture, homeopathy, osteopaths, naturopaths, herbalists, quimiopraxia technicians, herbalists, healers and rights) (n=752), Other (n=729).

Table 2 shows self-reported comorbidities and life-styles habits. RMD were self-reported by 67.4% of subjects with concomitant active CLBP and anxiety and/or depression symptoms. Regarding lifestyle habits, only 13.8% of subjects with active CLBP and concomitant anxiety and/or depression symptoms practiced physical exercise regularly. The pain severity mean was higher among these subjects (mean of NRS: 6.5 (SD 2.5)) and function was worse (mean of HAQ score: 1.1 (SD 0.89)).

Table 2: Self-reported-comorbidities and life style habits among subjects with active CLBP with and without anxiety and depression symptoms

	Pop. with active CLBP WITH Anxiety and/or depression symptoms (n=563)	Pop. with active CLBP WHITHOUT Anxiety and/or depression symptoms (n=924)
Number of comorbidities (0-15)	**3.92**±2.83	**2.77**±2.44
Self-reported Comorbidities		
Rheumatic diseases **(%)**	**362** (67.4%)	**520** (52.7%)
High cholesterol level **(%)**	**298** (47.7%)	**384** (40.2%)
High blood pressure **(%)**	**306** (48.8%)	**408** (39.4%)
Gastrointestinal disease **(%)**	**243** (40.9%)	**260** (27.1%)
Cancer **(%)**	**46** (7.2%)	**53** (4.3%)
Allergy (%)	**186** (30.6%)	**232** (25.1%)
Cardiac Disease (%)	**170** (31.2%)	**191** (18.6%)
Diabetes (%)	**147** (27.3%)	**141** (13.1%)
Renal colic (%)	**112** (18.8%)	**115** (11.9%)
Thyroid and parathyroid disease (%)	**117** (17.1%)	**117** (10.9%)
Hyperuricemia (%)	**73** (12.0%)	**94** (11.3%)
Pulmonary disease (%)	**70** (13.2%)	**81** (8.1%)
Neurologic disease (%)	**53** (12.9%)	**53** (4.6%)
Mental disease (%)	**237** (40.3%)	**163** (18.9%)
Hypogonadism (%)	**6** (1.3%)	**12** (1.8%)
Life Style Habits		
Present Coffee intake (%)		
Yes	**32** (6.5%)	**49** (6.9%)
No	**530** (93.5%)	**872** (93.1%)
Present Alcohol intake (%)		
Yes	**70** (12.9%)	**175** (20.5%)
No	**493** (87.1%)	**748** (79.5%)
Present Smoking Habits (%)		
Yes	**70** (14.4%)	**78** (11.9%)
No	**493** (85.6%)	**845** (88.1%)
Physical exercise (%)	**87** (13.8%)	**242** (27.7%)
Average time per day (minutes)	**61.35**±45.00	**65.61**±55.15
Age of onset (years)	**39.72**±25.95	**34.83**±25.59
Pain and Quality of life		
Pain (NRS)	**6.51**±2.48	**5.73**±2.41
EQ5D	**0.44**±0.28	**0.62**±0.28
HAQ	**1.11**±0.89	**0.68**±0.77

Sample size is not constant due to missing data in Population with CLBP with Anxiety or Depression symptoms: Number of comorbidities (n=433), Rheumatic diseases, (n=531), High cholesterol level (n=546), High blood pressure (n=552), Gastrointestinal disease (n=551), Cancer (558), Allergy (n=552), Cardiac Disease (n=547), Diabetes (n=553), Renal Colic (n=536), Thyroid and parathyroid disease (n=551), Hyperuricemia (n=529), Pulmonary disease (n=552), Neurologic disease (n=548), Mental disease (n=553), Hypogonadism (n=532), Present Coffee intake (n=562), Average time per day (minutes) (n=86), Average time per week (days) (n=86), Age of onset (years) (n=78), Pain (n=525), EQ5D (n=553).

in Population with CLBP without Anxiety or Depression symptoms: Number of comorbidities (n=797), Rheumatic diseases, (n=886), High cholesterol level (n=911), High blood pressure (n=913), Gastrointestinal disease (n=913), Cancer (n=915), Allergy (n=917), Cardiac disease (n=914), Diabetes (n=914), Renal colic (n=916), Thyroid and parathyroid disease (n=911), Hyperuricemia (n=899), Pulmonary disease (n=916), Neurologic disease (n=918), Mental disease (n=913), Hypogonadism (n=898), Present Coffee intake (n=921), Present Alcohol intake (n=923), Present Smoking Habits (n=923), Average time per day (minutes) (n=242), Average time per week (days) (n=239), Age of onset (years) (n=235), Pain (n=891), EQ5D (n=917).

Regarding pharmacological therapy, the intake of analgesic and other pain relief drugs was higher among subjects with active CLBP and concomitant anxiety and/or depression symptoms, when compared with subjects without these psychological symptoms (Fig.2). Most of these subjects were in the 1st step of WHO analgesic ladder. Anxiolytics, sedatives and hypnotics, antidepressants and NSAIDs intake had higher prevalence among these subjects than in the other group without psychological symptoms (Fig.2).

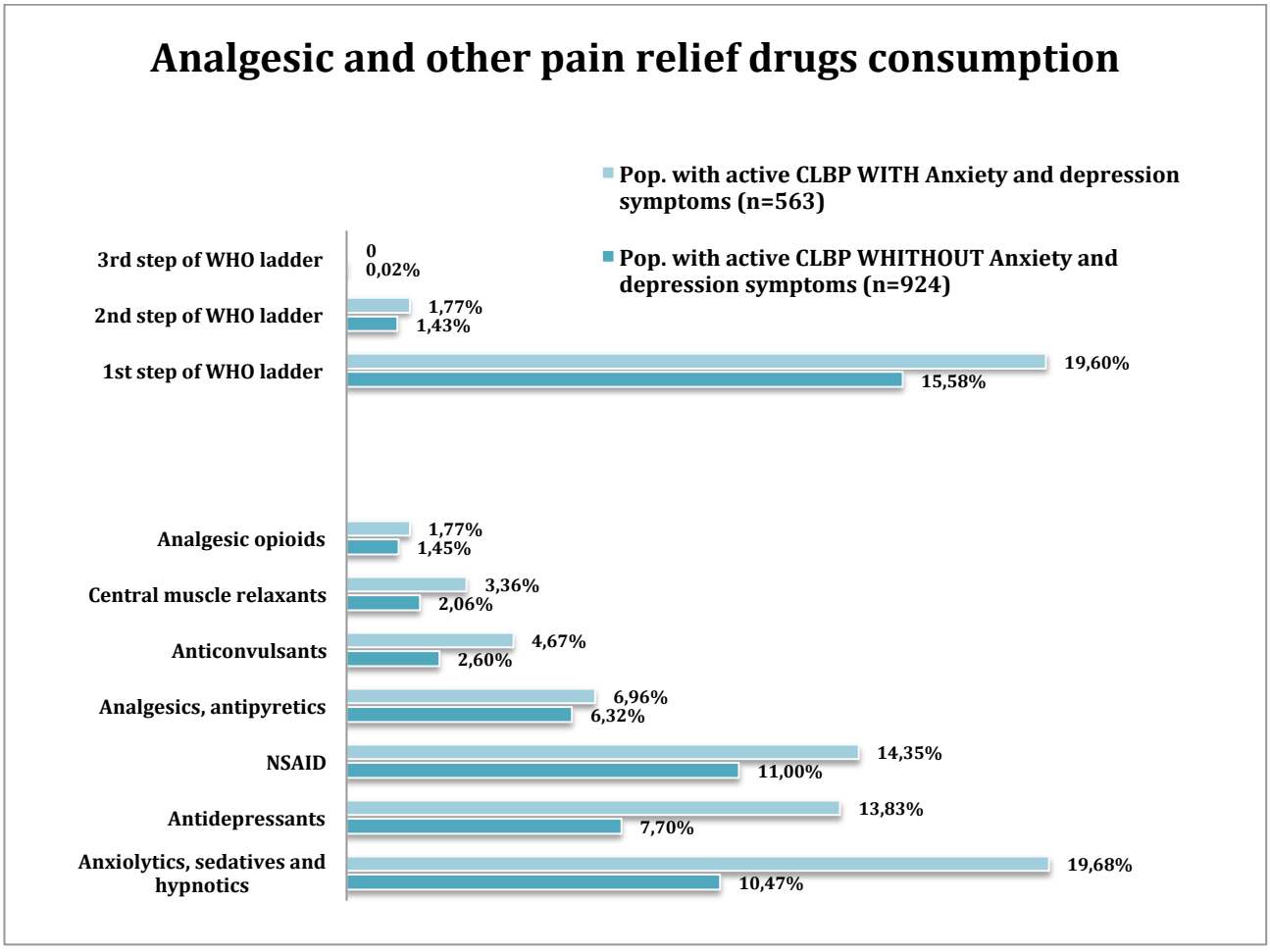

Figure 2: Analgesic and other pain relief drug consumption among subjects with active CLBP with and without anxiety and/or depression symptoms

Health status, pain severity, healthcare consumption and absenteeism were compared among subjects with anxiety and/or depression symptoms and subjects without these psychological symptoms (table 3). Health status was assessed through EQ5D score and it was significantly worse among subjects with anxiety and/or depression symptoms (β=-0.11; $p<0.001$). Also the mean of pain severity self-reported by these subjects was

significantly higher (β=0.71; p<0.001). Regarding healthcare resources consumption, significant differences between the two populations were found among the number of psychiatrists (β=0.32; p=0.003) and other physicians (β=0.95; p=0.003) visits; and among the need for home care in the previous 12 months (OR=3.53; p=0.011).

Table 3: Comparison of health status (EQ5D by dimensions), pain (NRS), healthcare consumption and absenteeism between the active CLBP Portuguese population with and without anxiety and/or depression symptoms

	β estimates/Odds Ratio (as applicable)	95% CI	Adjusted p-value
EQ5D ((-1)- 1)	**-0.11**	(-0.14;-0.07)	**<0.001†**
Pain (NRS)	**0.71**	(0.35;1.07)	**<0.001†**
Number of Physician visits in the previous 12 months (mean)			
General practitioners	**-2.35**	(-6.99;2.29)	0.320
Rheumatology	**-0.08**	(-0.24;0.09)	0.375
Orthopedic	**0.04**	(-0.16:0.24)	0.694
Rehabilitation medicine	**0.31**	(-0.36;0.98)	0.365
Psychiatry	**0.32**	(0.11;0.52)	**0.003†**
Other	**0.95**	(0.32;1.57)	**0.003†**
Healthcare consumption			
Home care in the previous 12 months (yes/no)	**3.53**	(1.34;9.29)	**0.011†**
Hospitalizations in the previous 12 months (yes/no)	**1.20**	(0.73;1.97)	0.461
Early retirement due to disease (yes/no)	**1.30**	(0.66;2.59)	0.447
Absent from work due to disease in the previous 12 months (yes/no)	**1.69**	(0.83;3.44)	0.147
Analgesic and other pain relief drugs consumption			
1st step of WHO analgesic ladder (yes/no)	**1.37**	(0.78;2.41)	0.274
2nd step of WHO analgesic ladder (yes/no)	**1.87**	(0.69;5.08)	0.219
Complementary Treatments (yes/no)	**0.99**	(0.62;1.58)	0.962
Number of days absent from work due to disease in the previous 12 months (mean)	**10.91**	(-17.02;38.84)	0.441

*All the comparisons were adjusted for the differences found in the univariable analyses: age group, gender, NUTS II, education level, physical exercise, BMI, number of comorbidities and presence of self-reported MSK diseases.
NUTS II - Nomenclature of Territorial Units for Statistics (North, Centre, Alentejo, Algarve, Lisbon, Madeira and the Azores)
†Adjusted p-values<0.05.

To assess factors associated with anxiety and/or depression symptoms, a multivariable analysis was made to each of the following hypothesis, among subjects with active CLBP: isolated anxiety symptoms; isolated depression symptoms; concomitant anxiety and depression symptoms (table 4):

Factors associated with anxiety symptoms among subjects with active CLBP: lower education level, self-reported comorbidities (mental diseases (OR=2.54; p<0.001) and cancer (OR=2.23; p=0.041)), smoking (OR=2.11; p=0.030) and severity of pain (OR=1.13; p=0.030) were risk factors significantly, independently and directly associated with the presence of anxiety symptoms among subjects with active CLBP. On the other hand, age (OR=0.96, p<0.001) was inversely associated with anxiety symptoms (table 4). Potential confounders were taken into account (gender, BMI, NUTS II, number of self-reported comorbidities).

Factors associated with depression symptoms among subjects with active CLBP: when subjects with and without depression symptoms were compared, increasing age was found to have a significant association with these symptoms (OR=1.04; p<0.001). Furthermore, *Odds-Ratio* of self-reported neurologic diseases (OR=3.84; p=0.008), of HAQ score (OR=2.78; p<0.001), and of mechanical LBP (OR=2.09; p=0.056) were higher among subjects with isolated depression symptoms.(table 4). Adjustment was performed taking into account gender, BMI, education level and NUTS II.

Factors associated with concomitant anxiety and depression symptoms among subjects with active CLBP: lower education level (<12 years); geographic region (NUTS II); smoking (OR=2.81; p=0.013), severity of pain (OR=1.15; p=0.037), constant and progressive LBP (OR=2.85; p=0.003), antidepressants intake (OR=1.95; p=0.030) and worse quality of life (OR=0.03; p<0.001) were factors significantly and independently associated with the presence of concomitant anxiety and depression symptoms among subjects with active CLBP (table 4). Physical exercise seemed to be a protective factor against psychological symptoms (OR=0.52; p=0.057). The analysis was adjusted to: gender, age and BMI.

Table 4: Factors associated with anxiety and/or depression symptoms in subjects that self-reported active CLBP

	Anxiety		Depression		Anxiety and Depression	
Demographic characteristics	**OR**	**p-value**	**OR**	**p-value**	**OR**	**p-value**
Gender (female)	**1.83** (0.97; 3.46)	0.063	**0.94** (0.39; 2.25)	0.891	**1.67** (0.82; 3.67)	0.155
Age (years)	**0.96** (0.94; 0.97)	**<0.001†**	**1.04** (1.02; 1.07)	**<0.001†**	**0.99** (0.97; 1.01)	0.326
BMI						
Underweight vs Normal	**1.47** (0.33; 6.56)	0.613				
Overweight vs Normal	**0.79** (0.46; 1.37)	0.408	**0.78** (0.33; 1.87)	0.577	**1.03** (0.53; 1.97)	0.930
Obese vs Normal	**0.59** (0.33; 1.04)	0.067	**1.23** (0.56; 2.70)	0.614	**1.33** (0.69; 2.55)	0.391
Education level						
10-12 years vs >12 years	**2.73** (1.00; 7.46)	**0.051†**	**0.30** (0.04; 2.24)	0.242	**4.75** (0.49; 45.75)	0.178
5-9 years vs >12 years	**3.55** (1.38; 9.13)	**0.008†**	**1.01** (0.16; 6.60)	0.990	**15.56** (1.93; 125.27)	**0.010†**
0-4 years vs >12 years	**3.66** (1.41; 9.48)	**0.007†**	**1.20** (0.26; 5.57)	0.814	**8.29** (1.05; 65.41)	**0.045†**
NUTS II						
Norte vs Lisboa	**1.21** (0.66; 2.21)	0.546	**0.52** (0.21; 1.30)	0.164	**3.29** (1.57; 6.92)	**0.002†**
Centro vs Lisboa	**1.06** (0.55; 2.05)	0.863	**0.67** (0.28; 1.60)	0.363	**3.20** (1.42; 7.24)	**0.005†**
Alentejo vs Lisboa	**0.87** (0.34; 2.25)	0.778	**0.61** (0.16; 2.21)	0.452	**0.84** (0.20; 3.44)	0.805
Algarve vs Lisboa	**0.27** (0.03; 2.71)	0.267	**0.66** (0.16; 2.72)	0.572	**7.05** (1.97; 25.27)	**0.003†**
Azores vs Lisboa	**0.85** (0.40; 1.81)	0.673	**0.63** (0.20; 1.99)	0.433	**2.47** (0.96; 6.36)	**0.060†**
Madeira vs Lisboa	**0.82** (0.37; 1.81)	0.627	**0.57** (0.17; 1.89)	0.357	**1.16** (0.35; 3.80)	**0.805**
Number of Comorbidities (0-15)	**1.08** (0.97; 1.20)	0.159	**0.88** (0.76; 1.00)	0.056	--	--
Mental disease (yes/no)	**2.54** (1.52; 4.24)	**<0.001†**	--	--	--	--
Cancer (yes/no)	**2.23** (1.03; 4.81)	**0.041†**	--	--	--	--
Neurologic Disease (yes/no)	--	--	**3.84** (1.42; 10.37)	**0.008†**	--	--
Life-style habits						
Alcohol intake (yes/no)	--	--	--	--	--	--
Regular physical exercise (yes/no)	--	--	--	--	**0.52** (0.27; 1.02)	**0.057†**
Smoking (yes/no)	**2.11** (1.07; 4.17)	**0.030†**	--	--	**2.81** (1.24; 6.39)	**0.013†**
Pain (NRS)	**1.13** (1.01; 1.26)	**0.030†**	--	--	**1.15** (1.01; 1.32)	**0.037†**
Mechanical pain (yes/no)	--	--	**2.09** (0.98; 4.44)	**0.056†**	--	--
Constant and progressive LBP (yes/no)	--	--	--	--	**2.85** (1.41; 5.73)	**0.003†**
HAQ (0-3)	--	--	**2.78** (1.70; 4.54)	**<0.001†**	--	--
EQ5D (0-1)	--	--	--	--	**0.03** (0.01; 0.09)	**<0.001†**
Antidepressants (yes/no)	--	--	--	--	**1.95** (1.07; 3.55)	**0.030†**

BMI – body index mass; **vs** – versus; **NUTS II** - Nomenclature of Territorial Units for Statistics (North, Centre, Alentejo, Algarve, Lisbon, Madeira and the Azores); **NRS** – Numeric Rate Scale; **EQ5D -** European Quality of Life questionnaire five dimensions three levels; **HAQ** - Health Assessment Questionnaire;

†Adjusted p-values<0.05.

Discussion

This study showed a high prevalence (39.4% (CI (35.5%; 43.5%)) of psychological symptoms among Portuguese population with active CLBP. Women were more affected than men by anxiety and/or depression, and most of them were retired. A previous study also confirmed that depression was a significant factor in chronic non-specific LBP [2]. Polatin et al [27] described in 1993 that anxiety and depression were the most prevalent psychiatric illness in CLBP patients. In that study, a sample of 200 patients with CLBP was assessed and 59% who were starting a functional rehabilitation program, met the diagnostic criteria for a psychiatric illness. A recent Korean study also showed a significantly higher incidence of depression (51.5% vs 6.8%) and anxiety (42.5% vs 18.2%) in CLBP patients [4].

The relationship between musculoskeletal pain and anxiety/depression symptoms has been a widely discussed topic nowadays [12] [28]. In our study, most of subjects with concomitant active CLBP, and psychological symptoms, self-reported moderate pain. In fact, chronic pain can be a complex pattern of psychophysiological behaviour, and a particular form of somatization, in which negative emotions are expressed through physical symptoms, including pain. Psychosocial factors can also interfere with compliance to rehabilitation programs, increasing disability and pain intensity, contributing to pain chronicity [29] [30].

In our study, quality of life of subjects with active CLBP was worse in those who had concomitant anxiety and/or depression symptoms. These findings concur with previous studies that also showed that anxiety and depression symptoms affected quality of life of CLBP patients and patients with other RMD [31]. Bener et al [32] also identified that psychological distress was associated with increased risk of LBP: significant association was observed in subjects with LBP with higher scores of anxiety, depression and somatization. Other studies also showed that subjects with LBP had significantly higher scores of depression than those without LBP [33] [34] [2]. Among different types of psychological distress, somatization was more prevalent in LBP subjects, followed by depression and then anxiety. While pain can cause concern and pessimism, depression impairs the capacity to cope with pain, leading to progressive deterioration [35].

Regarding drug consumption, a previous study showed that Portuguese population with active CLBP had a very low intake of analgesic and other pain relief drugs, even for those who self-reported severe pain. The WHO analgesic ladder was respected and subjects were extremely conservative about the use of analgesic opioids [18]. In this study we contribute to further complete

these previous results, showing that most of the subjects with active CLBP and concomitant anxiety and/or depression symptoms were also in the 1st step of the WHO analgesic ladder. Anxiolytics, sedatives and hypnotics, antidepressants and NSAIDs complete the top 3 of analgesic and other pain relief drugs intake among these subjects. Although the World Health Organization (WHO) supports that oral medicines are among the key components of pain management, WHO also appeals to recognition that therapeutic regimes need to be individualized and combined with psychological support [36]. In fact, a cognitive-behavioral therapy and complementary treatments may be useful when combined with pharmacological treatment and rehabilitation programs [37] [38].

Our study showed that more than half of the subjects with active CLBP and concomitant anxiety and/or depression symptoms were overweight or obese; Wright et al in 2010 analyzed the correlation between obesity and CLBP and found that many underlying factors such as family status, socio-demographic factors, and depression may contribute to the association between CLBP and depression[39].

Although this study was performed among a representative sample of the Portuguese population, there were limitations that must be taken into account. Since LBP is a multifactorial condition it is difficult to identify and measure all the factors involved; as this study was part of EpiReumaPt (that aimed at determining the prevalence of 12 RMD) the study was not specifically designed to collect specific information about active CLBP. Moreover, EpiReumaPt was a cross-sectional study and cannot identify which comes first: the pain disability or the psychological state. Weak mobility and function, and severity of LBP, can be potential factors to develop psychological symptoms. But, on the other hand, the opposite can also be true: anxiety/depression can also be a result of weak mobility and high severity of pain. To a better assessment of the direction of association between active CLBP and anxiety and depression symptoms, prospective studies are greatly needed with a well-characterized baseline and with rigorous follow-ups measurements.

In conclusion, our paper showed a high prevalence of psychological symptoms (anxiety and/or depression) among Portuguese population with active CLBP. Among those who had concomitant anxiety and/or depression symptoms, health status was significantly worse; the mean of pain severity and healthcare resources consumption were significantly higher. The education level, self-reported comorbidities (mental diseases and cancer), smoking and severity of pain were significantly and independently associated with the presence of isolated anxiety symptoms among subjects with active CLBP; while age was inversely associated with these symptoms. Factors associated with isolated depression symptoms among subjects with active CLBP included

increasing age, self-reported neurologic diseases, HAQ score and mechanical LBP. Moreover, factors associated with concomitant anxiety and depression symptoms were lower education level, geographic region, antidepressants intake, and worse health status. Physical exercise seemed to have a protective effect against concomitant anxiety and depression symptoms among subjects with active CLBP.

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CHAPTER V - Discussion

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Epidemiologic prevalence and population based studies are the most effective way to adjust social and economic contexts, resources and consumption, the prevalence of diseases and, therefore, it assumes a particular relevance regarding the strategic health care planning. EpiReumaPt, a Portuguese population based study that aimed at estimating RMD prevalence in Portugal showed that LBP was the most prevalent musculoskeletal condition. Like in other developed countries, LBP is one of the most common occupational problems contributing to a considerable absenteeism and disability. Chronic LBP is one of the leading causes of loss of productivity and economic independence through absenteeism (time off work for those in paid work), and work disability (permanent, partial or complete disablement for work purposes). Disability associated with chronic LBP and its impact on the quality of life and psychological symptoms (such as depression and anxiety disturbance) have also been studied systematically in western countries.

This thesis comprises two distinct sections: **Section I** that included three papers describing the development and management of a large epidemiologic population study; and also the detailed methodology and main results of EpiReumaPt; and **Section II** that included a set of studies provided under the scope of EpiReumaPt that aimed at estimating the prevalence and social burden of chronic LBP in Portuguese population.

These final chapters summarize the main results of the studies included in this thesis, and it also outlines future perspectives based on research challenges about this topic.

Section I – EpiReumaPt

Population-based studies in Portugal are scarce and prevalence of RMD was not well known. It was necessary to provide evidence to better adjust economic resources and planning strategic RMD health care policies. EpiReumaPt was developed to fulfill this lack of information identified on National Program Against Rheumatic Diseases [34]. It also aimed at assessing the impact of RMDs in quality of life, function, use of healthcare resources and work participation. The EpiReumaPt study was a pioneering design in Portugal [4]. It was an epidemiologic, observational and cross-sectional population-based

study. The recruitment took place from the 19th September 2011 to the 20th December 2013.

Section I comprises three important parts related to EpiReumaPt development:

Part I described and discussed all standard operating procedures, strategies and challenges related to the development of a large-scale epidemiologic study.

EpiReumaPt represented a complex large-scale project with several management challenges. Previously published strategies were considered insufficient to secure a good recruitment rate and several country-specific actions were taken. Part I focused on the efforts to increase participants' compliance. They were successful, particularly the measures related to raising study awareness among the general population. Regarding management issues, the coordination of a multidisciplinary team over 27 months of work field was a key factor. The involvement of the medical local teams helped keeping and boosting Rheumatologists' commitment during the duration of the study. All logistic and management issues were analyzed and solved with a high degree of accuracy, assuring the work field success.

This first paper was designed in order to be a practical guide on how to set-up a large population-based study in Portugal. This information remains useful to other clinical specialties and/or Health Authorities that want to promote similar studies.

Part II was focused on the EpiReumaPt detailed methodology, including its objectives, study design, recruitment features, and data preparation for analyses.

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 at homogenizing the diagnostic criteria and validate the definitive RMD diagnosis. EpiReumaPt has also unique features when compared to other studies performed in Portugal and abroad: 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.

The EpiReumaPt screening algorithm was specifically developed for this study and created in order to be highly sensitive to capture the maximum number of RMD cases. A comparison with the Census 2011 allowed the development of different weights to be applied in the samples from the 1st and 2nd phases, which will improve the accuracy of further analyses and estimates.

EpiReumaPt resulted in a very large database and it has allowed collaboration with various research groups in Portugal, in other European countries and also in the USA. Moreover, the EpiReumaPt image and biobank reservoirs constitute a valuable tool to perform a comprehensive approach to the pathophysiology and outcome research of several diseases.

To our knowledge, the EpiReumaPt database is the largest clinical/socioeconomic data set in Portugal and its research team is committed to promote it among the scientific community. In fact, the EpiReuma database wants to promote it, not only among Rheumatology, but also across other clinical and academic fields (economy, socio and human sciences, etc) that can use and analyze specific data.

The follow-up of EpiReumaPt population is ongoing and it currently goes beyond RMD. It will provide prospective information about health-related questions and will generate important evidence, which can be useful to support health policies in Portugal.

Part III comprises the *princeps* paper of EpiReumaPt that answers to the primary objective: to estimate the national prevalence of hand, knee and hip osteoarthritis, LBP, rheumatoid arthritis, fibromyalgia, gout, spondyloarthritis, periarticular disease systemic lupus erythematosus, polymyalgia rheumatica and osteoporosis in the adult Portuguese population. Another aim of this paper was to assess the burden of RMD by determining their impact on physical and mental health. Both were aligned with the specific objective of the National Program Against Rheumatic diseases [34].

EpiReumaPt study had demonstrated that RMD were highly prevalent in Portugal with

similar prevalence found in other European countries [40] [109] [113], namely Spain [114]. Regarding the impact of RMD on physical and mental health of the Portuguese population, it was confirmed that patients with a RMD had a significantly worse quality of life and more disability when compared to subjects without a RMD, after controlling for other important factors. In what concerns mental distress symptoms a significantly higher proportion of RMD patients with anxiety symptoms - but not with depression symptoms - was found.

In addition to other conclusions, EpiReumaPt showed that LBP was the musculoskeletal condition with highest prevalence among Portuguese population. As we said before, in Portugal (until the EpiReumaPt study was carried out) there were no available data about prevalence, burden and factors associated to LBP, and specifically to CLBP. With EpiReumaPt data, it was possible to conduct the following studies (**Section II**) in order to explore these epidemiological issues among a representative sample of adult Portuguese population.

To better define CLBP, case definition was described in the same way among papers of Section II: LBP was defined as pain in the back area from the lower margin of the twelfth ribs to the lower gluteal folds, with or without pain referred to the lower limbs. Active CLBP was defined as self-reported LBP present in the day of the interview and for at least 90 days (independently from cause).

Section II – CLBP among adult Portuguese population

Section II included three papers with a detailed analysis about the social burden of CLBP (**Part IV**), a profile of analgesic and other pain relief drug intake among adult Portuguese population with active CLBP (**Part V**), and also the analysis among those subjects of the additional burden of anxiety and depression symptoms (**Part VI**).

Part IV aimed at determining the prevalence of active CLBP in the adult Portuguese population (according to gender, age group and by NUTS II); to compare the population

with and without active chronic LBP in terms of health care consumption, quality of life, functional capacity and anxiety symptoms; and to explore factors associated with active CLBP.

This paper confirmed that active CLBP in Portugal was very prevalent (10.4%, 95% CI 9.6% to 11.9%), which was similar to the global prevalence of LBP reported in the Global Burden of Disease 2010 study [40] [(9.4%, (95% CI 9.0%-9.8%)]. Although there are differences in the case definition, this finding was also consistent with results of previous studies in industrialized countries [45] [64] [115] [116]. Female gender, age group, anxiety symptoms, educational level, the presence of other RMD and the number of comorbidities were independently associated with the presence of active CLBP.

The burden of active CLBP was assessed by intangible costs, direct costs and indirect costs. Regarding intangible costs, subjects with active CLBP had a significantly lower quality of life when compared to the remaining population. They also had a significantly worse function, reflecting more disability, and high prevalence of anxiety and depression symptoms. About direct costs, the consumption of healthcare resources, such as rheumatology and orthopedics visits, and also homecare assistance, among subjects with active CLBP in the previous year, was significantly higher when compared with the remaining Portuguese population. Indirect costs assessment showed that absenteeism from work in the previous year and early retirement was significantly higher in the active CLBP population.

This paper also found a strong, significant and independent association of anxiety symptoms with the presence of active CLBP. The latter association was detailed in **Part VI** of this thesis.

As reported in earlier studies in other countries about the burden of CLBP [41], the economic cost and financial burden of CLBP among Portuguese population seemed to be enormous. In fact, disability caused by CLBP among subjects in a working age provides high rates of absenteeism (work loss), with a consequent socioeconomic burden. Likewise when these subjects go back to work low productivity can be reported. It would be interesting to assess through a prospective study the impact of CLBP in productivity rate and accurately estimate the presenteeism issues related with this condition. Economic

analyses can also stem from this prospective study estimating how much money individuals and society spend on CLBP.

CLBP has become increasingly prevalent in society because it is dependent of factors that can be changed. Assuming that factors such as the wrong sitting postures all day at work, lack of exercise, obesity, overweight are modifiable facts, it could be interesting to promote healthier life styles habits among Portuguese population. A national prevention program could be suggested to promote ergonomic conditions, healthy life style habits (exercise, healthy eating habits) and postural behaviors, targeted not only for the general population, but also to schools (to improve good habits since young ages), employers (providing information concerning the best work ergonomic solution, and adjusting the work schedule according to the weight of the tasks), care institutions (promoting occupational advices to avoid incorrect postures and habits). A strategic and well-design prevention policy could be provided in order to prevent LBP acute episodes, and recurrences (chronicity), decreasing individual and social costs associated to this condition.

Part V was developed in order to understand and characterize the profile of analgesic and other pain relief drugs intake among adult Portuguese population with active CLBP, taking into account the WHO analgesic ladder and pain severity. The analgesic drugs intake profile in the population with active CLBP was also compared with the remaining Portuguese population in the study.

This paper concluded that analgesic and other pain relief drugs intake among adult Portuguese population with active CLBP was very low (18.8%). Most of the subjects with active CLBP didn't take any analgesic drug regardless pain severity. Even when subjects self-reported severe pain (7≥NRS≥10), only 24,0% were in the 1st step of the analgesic ladder, 2,30% used weak analgesic opioids and 0,03% used strong opioids (2nd and 3rd step of WHO analgesic ladder, respectively) to control pain.

The top 3 of therapeutic groups that adult Portuguese population with active CLBP used to relieve pain were: anxiolytics, sedatives and hypnotic drugs, NSAIDs and antidepressants. The higher prevalence of anxiolytics, sedatives and hypnotic and

antidepressants was analyzed in the following paper (**Part VI**). The intake of all therapeutic groups analyzed in this paper (anxiolytics, sedatives and hypnotics; NSAIDs, antidepressants, analgesics, antipyretics, anticonvulsants, analgesic opioids, centrally acting muscle relaxants) was higher among subjects with active CLBP, especially centrally acting muscle relaxants, anticonvulsants and analgesic antipyretics. Analgesic opioids intake had higher prevalence among subjects who self-reported moderated pain (4≤NRS≤6), as well as anxiolytics, sedatives and hypnotics, antidepressants, analgesic and antipyretics, and anticonvulsants. NSAIDs and centrally acting muscle relaxants had higher intake among subjects that self-reported severe pain (7≤NRS≤10). Subjects that reported use of analgesic opioids reported worse quality of life, followed by those that reported the intake of centrally acting muscle relaxants and anticonvulsants.

To sum it up, this paper showed that Portuguese subjects with moderate or severe active CLBP were suffering from pain and were undertreated. This fact must be linked to findings of **Part IV** related to loss of productivity and absenteeism. It seems that pain control is not effective and, in the other hand, the excessive conservative use of analgesic opioids may raise the following question: will physicians be at ease to manage this stronger therapeutic level? In fact, to control chronic pain opioids must be used with caution in order to avoid abuse or addiction. But the question remains and cannot be answered by EpiReumaPt. We surely need additional information regarding the therapeutic regimen (long term use or SOS indication), who prescribes it (physician or self-medication) and how long that drug is taken. To link this information with a well characterization of LBP is also crucial to complete the analysis.

Regarding other therapeutic groups, like analgesics, antipyretics and NSAIDs it is important in future studies to collect the information of who prescribed the drug. In Portugal patients can get these drugs without medical prescription. In our study it is not possible to well define if subjects are taking the drug by medical indication or by self-medication. Furthermore, subjects that were taking NSAIDs and centrally acting muscle relaxants self-reported higher severity of pain. It seems that the medication is not being effective. Subjects with CLBP may be more prone to accept their pain and to try managing it by self-medication, which may turn out to be an ineffective strategy. This is an

important issue that once again brings to discussion the rational use of medicines and the effectiveness of self-medication.

In future analysis under the scope of EpiReumaPt it will be interesting to conduct a similar analysis to assess if other RMD characterized by chronic pain (osteoarthritis, fibromyalgia) have the same intake pattern of analgesic and other pain relief drugs, clinical, quality of life and function outcomes. Results of this analysis can be useful for medical community to ponder the chance of a specific doctor appointment for this type of RMD, all this under the scope of Rheumatology.

Once again, a prospective study can also be very useful to access LBP evolution (acute and chronic cases) and drug effectiveness.

Part VI was developed in order to explore the findings of the last papers (Part IV and V) and to determine the prevalence of anxiety and depression symptoms among adult Portuguese subjects with active CLBP; to compare subjects with these symptoms with subjects without them; and to identify factors associated with isolated anxiety, isolated depression, and concomitant depression and anxiety symptoms.

This paper showed a high prevalence of these psychological symptoms among adult Portuguese population with active CLBP. Regarding pharmacological therapy, the intake of analgesic and other pain relief drugs was higher among subjects with anxiety and/or depression symptoms, when compared with subjects without these psychological symptoms. Most of these subjects were in the 1st step of the WHO analgesic ladder. Anxiolytics, sedatives and hypnotics, antidepressants and NSAIDs intake had higher usage rates among these subjects. The pain severity mean was also higher among this subjects and function and health status was worse. Regarding healthcare resources consumption, significant differences between the two populations were found. Subjects with active CLBP and concomitant psychological symptoms had a higher number of psychiatrist and other physician visits. They also needed more home care in the previous 12 months. The education level, self-reported comorbidities (mental diseases and cancer), smoking, and severity of pain were significantly and independently associated with the presence of isolated anxiety symptoms among subjects with active CLBP; while age was inversely

associated with these symptoms. Factors associated with isolated depression symptoms among subjects with active CLBP included increasing age, self-reported neurologic diseases, HAQ score and mechanical LBP. Moreover, factors associated with concomitant anxiety and depression symptoms were lower education level, geographic region, antidepressants intake and worse health status. Physical exercise seemed to have a protective effect against concomitant anxiety and depression symptoms among subjects with active CLBP.

These findings are important but it is interesting to clarify which comes first: pain chronicity/disability or psychological symptoms. To a better assessment of the association direction between active CLBP and anxiety and/or depression symptoms, a prospective study is warranted. A well-characterized baseline and rigorous follow-ups measurements regarding the presence or absence, and evolution of LBP and psychological symptoms will be necessary.

The relation between pain and psychological disorders has been a hot topic in research field, with somatization breaking new ground. It has been hypothesized that chronic pain could sometimes be a particular form of somatization in which negative emotions are expressed through physical symptoms, including pain [117]. The somatosensory amplification is a related concept and has been defined as an increased propensity to experience and report dysphoric symptoms, including pain [118]. The term “somatic” covers various bodily sensations that a depressed individual perceives as unpleasant or worrisome. Presented somatic symptoms may be either clearly attributed to a distinct medical disorder or be placed into several categories, which includes “symptom-only” diagnosis (e.g., low back pain, idiopathic dizziness) [119]. The concurrence of somatic and psychological symptoms amplifies their adverse effects on quality of life, occupational and social disability, and health care costs. Indeed, pain and depression are among the leading causes of lost work productivity and, when occurring together, their negative impact is synergistic. New hypothesis have been developed. In short, chronic stress evoked by chronic pain leads to a loss of negative glucocorticoid feedback in the hypothalamic-pituitary-adrenocortical (HPA) axis and down-regulation of the glucocorticoid receptors within the brain and the body periphery. During chronic pain, loss of serotonergic and noradrenergic tone in response to glucocorticoid-induced monoaminergic depletion may

lead to descending inhibitory impulses to the spinal cord to effect an enhancement of pain sensation [118]. In this context, a new therapeutic approach among subjects with CLBP would be interesting, including a multidisciplinary clinical approach with an interface with psychiatry and with psychology [120].

CHAPTER VI - Conclusion and a Perspective for Future Research

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This thesis intended to contribute to epidemiological and clinical research providing detailed information of how to develop a large epidemiological study according to the Portuguese context; as well detailed methodology and main results of EpiReumaPt. Assuming that LBP was the musculoskeletal condition with higher prevalence, the EpiReumaPt study also provides data, which allowed studying the burden of CLBP among adult Portuguese population. Some relevant topics were chosen to characterize this burden: quality of life, function, healthcare consumption; analgesic and other pain relief drugs intake profile; anxiety and depression symptoms concomitant to CLBP.

We concluded that CLBP is a common health problem among adult Portuguese population contributing to disability and affecting labor performance and the wellbeing of subjects. It is also responsible for considerable healthcare resource consumption. Anxiety and depression symptoms are common among subjects with CLBP and provided an additional burden among these subjects.

The research work was conducted under the scope of EpiReumaPt. In fact, this prevalence study was a landmark on epidemiological research in Portugal. It was the first large population-based study that allowed estimating the prevalence of RMD in adult Portuguese population. Moreover, it provided a robust and big database, with data from the real world that can be useful to clinical research beyond Rheumatology. EpiReumaPt was a cross-sectional study and allowed us to identify, validate and explore relevant clinical hypothesis. Some suggestions were also provided in the "discussion" chapter of this thesis, according to these cross-sectional results. However, finding evidences related to CLBP can be improved in future studies in order to follow these subjects and to understand pain evolution and its impact on individual (on subjects' life) and on society (economy).

Two kinds of studies will be important to continue this research strategy:

. Longitudinal and prospective study: a prospective observational study will allow estimating the incidence of LBP and CLBP. It would be interesting to know LBP incidence, and how many of those new cases evolve to chronicity. As said before in the "discussion" chapter, a prospective study will also provide the impact of LBP and CLBP on quality of

life, socioeconomic (absenteeism, presenteeism, healthcare resources consumption, occupational factors, etc.), and clinical fields. The cause-effect relation between comorbidities (including RMD), psychological symptoms/disorders and CLBP could be well depicted. Another advantage of a prospective study would be the possibility to develop a robust effectiveness study related to the use of analgesic and other pain relief intake and to better understand the self-medication profile and therapeutic regimens of subjects with LBP and CLBP.

. Interventional studies: in the "discussion" chapter, we made some suggestions that could be implemented through interventional studies in order to assess their efficacy: 1) a **national prevention program** could be suggested to promote ergonomic conditions, healthy life style habits and postural behaviors, targeted not only for the population, but also to schools, employers and care institutions. A strategic and well-design prevention policy can be provided in order to prevent LBP acute episodes and recurrences (chronicity), decreasing individual and social costs associated to this condition. 2) A pilot study considering the hypothesis of a **specific pain physician appointment for this kind of RMD**, under the scope of Rheumatology. 3) In this context, a new therapeutic approach among subjects with CLBP would be interesting, one which included an **interface with psychiatry and with psychology**.

In conclusion, this thesis added evidence that CLBP leads a social, psychological and economic burden. Since we identify and confirmed this relevant hypothesis, it will be useful to continue the journey in order to provide additional information, which would be useful in the design of future strategy health and social policies.

CHAPTER VII – References

CHAPTER VII - References

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